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Research paper

Altered amygdala circuits underlying valence processing among manic and depressed phases in bipolar adults

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ABSTRACT

Background: Disruptions in affective processing characterize mood disorders, yet the neural mechanisms underlying internal state dependency in affective processes are not well understood. The present work presents a pilot investigation into state dependency among neural circuits known to be involved in processing affective information, by examining acute manic and depressive mood phases in adults with bipolar disorder and major depressive disorder.

Methods: The present study probed affective processes with a well-validated passive picture-viewing task amongst acutely manic ($n = 8$) or acutely depressed (bipolar depression: $n = 11$; major depression: $n = 15$) mood-disordered adults during functional magnetic resonance imaging .

Results: Beta-series correlation analyses seeded from the amygdala revealed distinct neural circuits distinguished across current mood state rather than diagnostic boundaries. We delineated an amygdala-striatum pathway that distinguished depressed from manic mood phase, rather than between diagnostic boundaries, in processing valenced information. Specifically, we found differences in this neural response to negative, but not positive, images across clinical mood states.

Limitations: As a preliminary investigation of state-dependent affective processes, the current investigation is predominantly limited by the small sample size. While it provides direction and generates hypotheses for further work, future studies need to replicate and expand the reported effects with larger samples.

Conclusions: These findings demonstrate the conditions under which mood state-dependent affective processes cut cross traditional diagnostic boundaries, speaking to recent advances in transdiagnostic disease mechanisms, and can guide future work examining the neural mechanisms driving symptomatology in affective disorders.

1. Introduction

Our experiences are a function of the manner in which our internal affective states transform and provide meaning to information we encounter. Advances in the cognitive neuroscience of emotion have aimed to explain these internal states by providing clues on how brain systems might support certain evaluative processes (Cunningham et al., 2008; Kober et al., 2008). Here we consider how clinically relevant internal mood states shape neural responses to affective information across bipolar disorder (BD) and major depression (MDD) mood-disordered groups. We conducted an early investigation into the specificity or generalizability of neural circuits relevant to affective demands across different mood symptoms within the same clinical diagnosis, as well as for similar mood symptoms across different clinical diagnoses as a function of current mood phase. This work therefore serves an important step in understanding how to best characterize these psychiatric illnesses, and lays a foundation for continuing work that emphasizes transdiagnostic processes underlying clinical symptomatology, in line with recent advances in biological psychiatry (Insel et al., 2010).

1.1. Neural processes in mood state-dependent affective processes

Our investigation into BD and MDD mood disordered groups is motivated by the influence of manic and depressive mood phases on the perception and evaluation of incoming stimuli. A body of work in adults with BD has shown disturbance of both positive emotional states (Gruber, 2011), as well as the processing of affective information such as positive stimuli (Gruber et al., 2008) and rewards (Nusslock et al.,

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2012; Whitton et al., 2015). These disruptions in affective processing often lead to the behavioral phenotypes that comprise BD symptomatology (Philips and Swartz, 2014), such as increased impulsivity (Trost et al., 2014) and risk-taking (Devlin et al., 2015).

Neuroimaging work in BD further points to critical disturbances in ventral and medial prefrontal regions and subcortical regions involved in the processing of affect, including the amygdala and basal ganglia (Almeida et al., 2010; Lawrence et al., 2004; Price and Drevets, 2012; Strakowski et al., 2005). The general pattern has distinguished BD individuals from those with MDD and healthy controls via disrupted neural response to affectively charged information. For example, individuals with BD exhibit decreased connectivity between the perigenual cingulate cortex and the amygdala in processing valenced faces (Wang et al., 2009). Other work has shown that the pattern of connectivity between the amygdala and orbitofrontal cortex differs depending on the nature of the current affective information, with decreased connectivity for positive stimuli but increased connectivity for negative stimuli (Versace et al., 2010).

While much attention has been given to differences in affective processes between psychiatric diagnoses, some work has started to probe whether differences between mood symptomatology, rather than strict diagnostic boundaries, describe alterations in affective processing across clinical phases. Distinct behavioral and neural patterns have emerged from interactions between manic/depressive mood symptomatology and the kind of information processed. Individuals with MDD are well known to demonstrate biases towards negative information, which correspond to disrupted neural responses in ventral and medial prefrontal cortices (Elliot et al., 2002). Furthermore, prefrontal-subcortical circuits are involved in processing mood-congruent negative information: depressed individuals show alterations in the connectivity between the amygdala and cingulate cortex (Anand et al., 2005), as well as rostral prefrontal cortex (Kong et al., 2013), suggesting impaired prefrontal regulation of amygdala activity in response to affective demands. Manic individuals also demonstrate mood-congruent biases in processing affective information, with decreased accuracy in the recognition of negative emotions (Lembke and Ketter, 2002) and increased ventromedial prefrontal response to positive distractors (Elliot et al., 2004). This is paired with subcortical disruptions in manic mood phases with greater responses in the left amygdala during the viewing of positive pictures compared to neutral (Bermpohl et al., 2009).

It should be noted that these neural patterns reflecting mood phases-dependent responses to affective information in clinical groups are mirrored in brain responses to bottom-up information processing and goal representation in healthy individuals. Neural pathways implicated in evaluative processes regarding the affective properties of incoming stimuli involve the amygdala (LeDoux 2007) and areas of the mesolimbic reward system such as the ventral striatum (Delgado et al., 2003; Liu et al., 2011). For example, amygdala response to positive and negative features of information (Hamann and Mao, 2002) can be modulated by current goals (Cunningham et al., 2008). Critically, the neural interaction between the ventromedial prefrontal cortex (vmPFC) and subcortical areas like the amygdala and ventral striatum (VS) allow support interactions between goal states and attended information (Baxter et al., 2000; Janak and Tye, 2015).

1.2. Current investigation

Both the clinical neuroimaging and basic neuroscience work raise the important and intriguing possibility that mood spectrum disorders are better characterized along key process-based dimensions, such as how the brain represents positive and negative information between mood symptomatology (mania and depression), rather than along traditional diagnostic boundaries. Therefore, our early investigation into the neural systems that drive interactions between internal states and affective processes, using a specialized sample of individuals during acute mood phases (actively manic or depressed), allows us to parse the relevance of internal context versus diagnostic category and motivate further studies. We focused on neural circuits (connectivity) centered around the amygdala, given the aforementioned importance of interactions in state-stimulus processing, and given the task we used to probe affective processing. Critically, we tested two groups of BD individuals either in a currently manic or depressed mood phase and a third group of currently depressed MDD individuals.

We hypothesized that connectivity differences in affective processing would be divided along mood symptom profiles rather than diagnostic boundaries. That is, we predicted similar connectivity patterns within depressive mood symptoms, regardless of BD or MDD diagnostic classification, and different patterns between depression and mania within the same BD diagnosis. We expected to see differences in amygdala-vmPFC and –VS connectivity in the processing of negative or positive information, compared to neutral information. Given work showing modulation of this response profile by goals, it was reasonable to expect relative biases in connectivity strength towards negative stimuli in the depressed phases, and biases towards positive stimuli in the manic phase.

2. Materials and methods

2.1. Participants

We initialed screened 59 adults with a Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition (Text Revision; DSM IV-TR) Axis I diagnosis. 36 adults passed the drug screening, resulting in a group of 20 adults diagnosed with Bipolar I Disorder and 16 currently depressed adults with Major Depression Disorder. Participants were recruited using online advertisements and flyers posted in Hartford, CT and surrounding communities. Exclusion criteria were history of severe head trauma, stroke, neurological disease, severe medical illness (e.g., autoimmune disorder, HIV/AIDS), left-handedness, medications affecting cerebral blood flow (e.g., blood pressure medications), magnetic resonance imaging (MRI) safety incompatibility, pregnancy, suicidal ideation, and alcohol or substance abuse in the past six months. Consensus diagnoses were determined using a best estimate process. Participants provided informed consent approved by the institutional review board at Hartford Hospital and Yale University. One BD and one MDD participant were excluded immediately due to poor data acquisition (consistently high levels of motion) during functional MRI (fMRI) scanning. One BD and two MDD participants were further excluded from the final data analysis for failure to meet the mood status classification criteria, presented below in Section 2.1.1: Diagnostic Assessment. The final sample thus comprised 18 BD participants of which 11 were currently depressed (BD-D) and 7 were currently manic (BD-M), and 13 depressed MDD participants (Table 1).

2.1.1. Diagnostic assessment

Participants' diagnoses were confirmed following interview using the Structured Clinical Interview for Diagnosis (SCID; Nurnberger et al., 1994) based upon the data obtained from the interview and available medical records. Criteria from the DSM IV-TR were used to define diagnostic groups. Mood status was classified according to raters trained with videos and face to face assessments. Raters were required to have an inter-class correlation of greater than 0.90 with our gold standard before assessing subjects. Participants within each mood status group were further evaluated using self-report measures. Current symptoms of mania were measured using the Young Mania Rating Scale (YMRS; Young et al., 1978) and current symptoms of depression were measured using the 17-item Hamilton Rating Scale for Depression (HRS-D; Hamilton 1960). Participants were considered as being currently depressed if they scored 14 or greater on the HRS-D for the past two consecutive weeks. Participants were considered as being manic if they scored 12 or greater in the YMRS in the past week.

Table 1
Participant characteristics. BD-D = Bipolar depression group; BD-M = Bipolar mania group; YMRS = Young Mania Rating Scale; HRS-D = Hamilton Rating Scale for Depression; Mean values are displayed with standard deviations in parentheses where applicable. Medication characteristics display percentage of participants in each diagnostic group. Clinical information collected at initial laboratory visit. ** $p < 0.001$ in omnibus ANOVA. * $p < 0.05$ in χ^2 test.

	BD-D (n = 11)	BD-M (n = 7)	MDD (n = 13)	Statistic	Effect Size	P value
Demographic						
Age (Yr)	43.27 (10.07)	35.57 (16.18)	50.15 (13.62)	$F = 2.88$	$\eta_p^2 = 0.17$	0.073
Female (%)	72.73	57.15	76.92	$\chi^2 = 0.89$	$V = 0.17$	0.641
Caucasian (%)	63.63	100.00	76.92	$\chi^2 = 8.26$	$V = 0.37$	0.083
Education (Yr)	14.91 (2.21)	13.29 (1.60)	14.62 (2.26)	$F = 1.35$	$\eta_p^2 = 0.09$	0.275
Mother's Education (Yr)	11.73 (3.41)	13.29 (2.98)	12.46 (1.85)	$F = 0.70$	$\eta_p^2 = 0.05$	0.506
Father's Education (Yr)	13.10 (4.33)	13.57 (3.15)	12.64 (2.29)	$F = 0.17$	$\eta_p^2 = 0.01$	0.845
WAIS-FSIQ	106.64 (11.32)	100.17 (15.46)	104.15 (14.85)	$F = 0.43$	$\eta_p^2 = 0.03$	0.656
Clinical						
YMRS **	6.27 (2.83)	20.57 (3.21)	3.85 (2.30)	$F = 92.35$	$\eta_p^2 = 0.87$	4.69×10^{-13}
HRS-D **	20.91 (5.49)	6.57 (3.15)	20.00 (3.63)	$F = 28.18$	$\eta_p^2 = 0.67$	1.97×10^{-07}
Medication						
Antidepressant (%)	54.54	33.33	84.62	$\chi^2 = 5.23$	$V = 0.42$	0.073
Anxiolytic (%)	27.27	0.00	38.46	$\chi^2 = 3.11$	$V = 0.32$	0.211
Atyp. Antipsychotic (%)	36.36	33.33	15.38	$\chi^2 = 1.51$	$V = 0.224$	0.470
Typ. Antipsychotic (%)	0.00	0.00	0.00	–	–	–
Lithium (%)	9.09	16.67	0.00	$\chi^2 = 1.99$	$V = 0.26$	0.368
Mood Stabilizer (%) *	72.72	50.00	15.38	$\chi^2 = 8.11$	$V = 0.52$	0.017
Side-effect control (%)	0.00	0.00	7.69	$\chi^2 = 1.35$	$V = 0.21$	0.508
Stimulant (%)	0.00	0.00	7.69	$\chi^2 = 1.35$	$V = 0.21$	0.508

2.1.2. Medication

During the diagnostic assessment period, participants reported any use and current dosage of psychiatric medications. Medication classes included antidepressants, anxiolytics, typical and atypical antipsychotics, lithium, mood stabilizers, those to control side effects, and stimulants (see Table 1). The presence of current substance use was assessed during the SCID, and participants who tested positive for substance abuse or dependence diagnoses in the last 6 months were excluded.

2.1.3. Neurocognitive battery

We applied the Java Neurocognitive Test (JANET) version of the South Texas Assessment of Neurocognition (Glahn et al., 2007, 2010), a primarily computerized battery of standard and experimental neuropsychological tests used in our prior studies of bipolar disorder. The JANET measures attention, concentration, working and long-term memory, problem solving and speed of processing (See Supplementary Table S2). The JANET has parallel English and Spanish versions. In addition to JANET tests, all participants were administered a battery of cognitive tasks, which were not analyzed in the current study (see Supplementary Table S2).

2.2. Procedures

2.2.1. fMRI session

Participants completed a single session that comprised both the clinical assessment and the fMRI scanning. During the *pre-scan task training*, participants were trained on the affective picture-viewing task. Task training began with the experimenter explaining the task as step-by-step instructions were presented on a laptop. Participants also completed a simple emotion recognition task (not analyzed in the present paper). For the *fMRI task,* participants were then escorted to the scanner, where they completed one run of the affective picture-viewing task for approximately 8.75 minutes. The task run was composed of 18 blocks of 20 trials each. During the *post-scan phase*, participants were debriefed and received compensation.

2.2.2. Affective picture-viewing task

In order to probe valence processes across manic and depressive phases, participants were instructed to complete the Affective Viewing task while in the scanner. It consisted of 18 blocks of trials, each of which included 20 images of the same valence (neutral, positive, or negative) from the International Affective Picture System (IAPS; Lang et al., 2008). The run commenced with an initial 2 second fixation screen before the presentation of the first block of trials. Within each block, images were presented for 1 second each. At the end of a block of trials, participants were asked to indicate the valence of the block they had just viewed. The questions were presented for a variable duration (5–19 seconds) and were not entered into any subsequent analyses but allowed us to ensure participants' attention to the task. Finally, a fixation screen was presented for 1 second before the subsequent block. There were an equal number of blocks for each of the three valence categories: positive (6 blocks, 33%), negative (6 blocks, 33%) and neutral (6 blocks, 33%; Fig. 1).

2.3. Data acquisition

2.3.1. Behavioral data

E-Prime 2.0 software (Psychology Software Tools, Inc.) was used for stimulus presentation and collection of data. During the fMRI scan, stimuli were projected onto a screen behind the scanner, and participants viewed the stimuli via an angled mirror affixed to the head coil. Responses were made with the right hand using the response box.

2.3.2. fMRI data

Data were collected on a Siemens 3T Allegra scanner (Siemens Medical Solutions, Erlangen, Germany). Functional images were acquired with a T_2-weighted echo planar image (EPI) blood-oxygen-level dependent (BOLD) sequence (TR = 2000 ms; TE = 27 ms; Flip Angel 70; FOV 220 mm; voxel dimensions = 3.4 × 3.4 × 4 mm; 36 slices; 8 m 44 s scan time). Structural images were obtained using a T_1-weighted MPRAGE acquisition (TR = 2200 ms; TE = 4.13 ms; Flip Angel 13; FOV = 220 mm; 0.8 mm isotropic voxels; 208 slices). Preprocessing was carried out using the fMRI Expert Analysis Tool (FEAT) Version 6.00 part of FSL (FMRIB's Software Library, http://www.fmrib.ox.ac.uk/fsl), For the EPI images, we performed robust brain extraction using BET, motion estimation using MCFLIRT (Jenkinson et al., 2002) and spatial smoothing with a Gaussian kernel (FWHM = 5 mm). The data were high pass filtered at 0.01 Hz and grand-mean intensity normalized. Extreme motion outliers in the time series were estimated with FSL's *fsl_motion_outliers* function. The root mean square (RMS) intensity difference between each volume to a reference was calculated, and

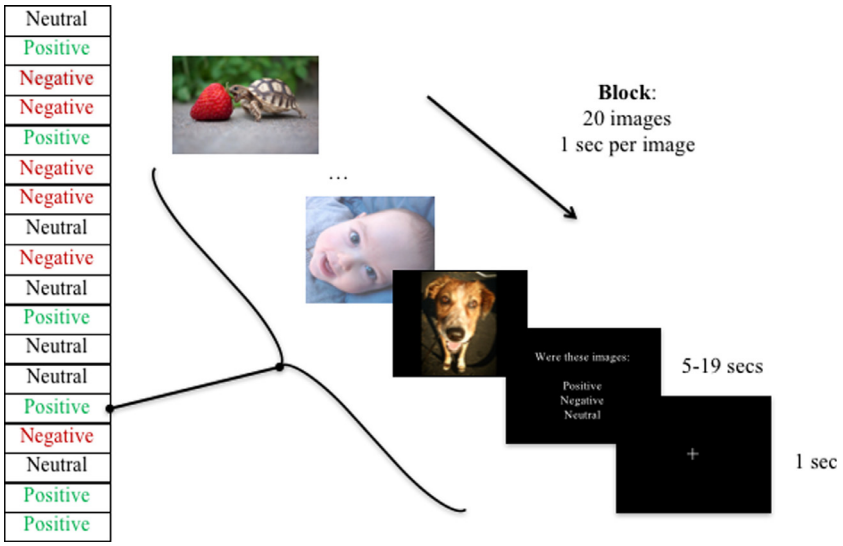

Fig. 1. Overview of the experimental paradigm. Participants were shown randomized, alternating blocks of neutral, positive, and negative images from the IAPS stimuli bank (Lang et al., 2008). Each block comprised 20 images, shown at a rate of 1 image per second. At the end of each block, participants were asked to indicate the valence of the block. A fixation screen of 1 second duration was presented between blocks. The stimuli in the figure were not in the study, but used to illustrate the task.

volumes with a RMS difference higher than the 75th percentile plus 1.5 times the inter-quartile range were marked and regressed out of the data. After pre-processing, EPI images were linearly co-registered to each participant's anatomical T1-weighted image using FLIRT (Jenkinson and Smith, 2001) with boundary based registration (Greve and Fischl, 2009), and then non-linearly normalized to MNI152 (2 mm) template space using FNIRT (Andersson et al., 2007), with a 10 mm warp resolution. We extracted motion parameters along six dimensions (3 rotations and 3 translations). T1-weighted anatomical images were individually segmented into gray matter, white matter and ventricular maps for each participant using FSL's FAST algorithm (Zhang et al., 2001); the segmented maps were subsequently transformed to template space using individualized transformation parameters from FLIRT. This allowed us to estimate individualized mean white matter and ventricular beta series to enter as covariates in subsequent analyses.

2.4. Statistical analysis

2.4.1. Group differences in motion confounds

Due to the known impact of motion confounds on connectivity methods (Power et al., 2012; Van Dijk et al., 2012), we tested for group differences along the six estimated motion parameters. Separate multilevel models were run that regressed diagnostic group onto each of the six motion parameters, nesting each motion parameter estimates within run, and nesting runs within participants.

2.4.2. Single-block beta analysis

Given our interest in estimating commonalities in task-related activity across brain regions, we first tested the fit of the fMRI time series with the task data by computing separate beta values for each block onset. To so do, we regressed the time series data for each participant against a gamma function convolved with a boxcar function of 20 seconds duration, matched to the block duration in the experimental design. The peak amplitude of the gamma function was set to one, and beta coefficients were estimated using the individual modulation option in AFNI (*3dDeconvolve –stim_times_IM*; see Mumford et al., 2012; Rissman et al., 2004 for similar approaches). At this stage, the six motion parameters were entered as nuisance covariates in the general linear model. The block-wise beta estimates were then despiked using AFNI's *3dDespike* function.

2.4.3. Beta-series correlation

After estimating the degree to which our design regressors predicted BOLD activity, we conducted a task-related beta-series correlation analysis. To do so, we delineated anatomically-based masks of the left and right amygdala from the Harvard-Oxford (H–O) probabilistic atlas included in FSL (Desikan et al., 2006) by setting probability thresholds to 0.25 (See Supplementary Figure S1). The left and right amygdala were separately examined to account for potential differences in beta-series variance across hemispheres, though we expected similar whole-brain correlation patterns given their high similarity. The mean beta values for each seed mask were computed across voxels, and entered in separate whole-brain voxel-wise mixed-effects models. For each seed, the model predicted whole-brain voxel-wise beta series from the mean seed beta series, the task condition (i.e., positive, negative, neutral), and clinical phase (i.e., BD-D, BD-M, MDD), as well as their three-way interaction. Fixed effects were nested within each participant by estimating a random intercept for each participant, using an unstructured covariance matrix and the between-within method of estimating degrees of freedom (the *lme* function from *nlme* package in R, Pinheiro et al., 2015, implemented in Python via *rpy2*). Mean beta-values corresponding to white matter and CSF were extracted from the individualized white matter and cerebrospinal fluid masks, and entered as nuisance regressors in the model. This beta-series correlation approach is similar to traditional psychophysiological interaction analyses (PPI; Friston et al., 1997) but allows the modeling of connectivity between brain regions during distinct task demands explicitly, and has been validated as an approach to study task-modulated functional connectivity (Rissman et al., 2004).

2.4.4. Multiple comparisons correction

F-maps of the three-way interaction term were submitted to cluster-wise multiple comparisons correction to keep family wise error < 0.05. For each model (i.e. seed), the residual standard deviation map from the mixed-effects model was used to estimate the spatial autocorrelation function in AFNI (*3dFWHMx –acf*; Cox et al., 2017); these parameters were then used to estimate minimum cluster sizes (See Supplementary Table S1). The F-maps were thresholded with a cluster-defining threshold of $p < 0.001$ (see Eklund et al., 2016), and resulting clusters smaller than the minimum cluster sizes were removed. Unthresholded statistical maps are available at https://neurovault.org/collections/3323/. The code for all stage of are available at https://github.com/manvincent/bipolarFC/.

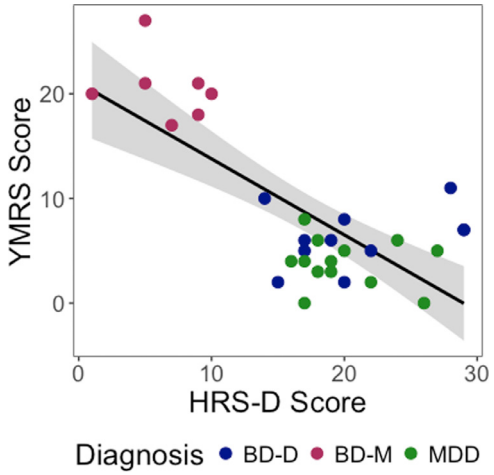

Fig. 2. YMRS (Young et al., 1978) in grey and the HRS-D (Hamilton, 1960) shown for each participant in the study. Individual data points as colored by assigned clinical group (BD-D, BD-M, or MDD). Shaded area around best fit correlation line show 95% confidence interval.

3. Results

3.1. Participant characteristics

Given our central focus on differences in neural processes across mood state rather than diagnostic boundaries, it was critical to significantly distinguish manic and depressive mood phase subgroups. We found a significant omnibus difference across all three clinical groups in both YMRS and HRS-D ratings (Table 1). Planned contrasts demonstrated significant differences in YMRS ($F(1,28) = 179.92$, $p < 0.001$) and HRS-D ($F(1,28) = 56.09$, $p < 0.001$) ratings between the BD-M group and the two depression groups (MDD and BD-D). Between MDD and BD-D, there was a significant difference in YMRS ratings ($F(1,28) = 4.77$, $p = 0.037$), but no significant difference in HRS-D ratings ($F(1,28) = 0.27$, $p = 0.610$). Across all participants, ratings on the YMRS and HRS-D were significantly negatively correlated ($r = -0.73$, $t(29) = -5.71$, $p < 0.001$; Fig. 2). As shown in Table 1, the three groups did not significantly differ along other demographic variables including age, gender ratio, race, and years of education. This confirmed meaningful differences in current mood phase between the mania group (BD-M) and the two depression groups (BD-D and MDD).

The three groups did not differ along any of the six motion parameters, which included the x-rotation, $F(2,28) = 0.20$, $p = 0.817$, y-rotation, $F(2,28) = 3.09$, $p = 0.061$, z-rotation, $F(2,28) = 0.77$, $p = 0.474$, x-translation, $F(2,28) = 0.96$, $p = 0.395$, y-translation, $F(2,28) = 2.20$, $p = 0.129$, and z-translation, $F(2,28) = 0.28$, $p = 0.888$ (See Supplementary Figure S2).

3.2. Affective circuits across clinical groups

Two distinct clusters reflected the three-way interaction between amygdala beta value, clinical group status, and task condition, for both the left and right amygdala models: one predominantly covering the bilateral ventral striatum and some areas of the subcallosal cortex (left amygdala seed; Fig. 3a), and another in the right ventrolateral prefrontal cortex (vlPFC; right amygdala seed; Fig. 4a). See Table 2 for all surviving clusters reflecting a three-way interaction across both amygdala seed models. To report the statistics of this effect and conduct simple effects tests, we extracted the mean beta series across voxels in each cluster and ran the same mixed-effects model specified above on this aggregate (mean beta) dependent measure.

The left amygdala beta series interacted with clinical group and task condition, modeled as two sets of differences values: positive minus neutral and negative minus neutral, to significantly predict mean beta values in the ventral striatum ($F(2,27) = 6.16$, $p = 0.006$; Fig. 3b). Planned contrasts confirmed that the interaction was driven by differences across mood phase (BD-M versus the two depression groups; $F(1,27) = 12.12$, $p = 0.002$) rather than across diagnostic categories (MDD versus the two bipolar groups; $F(1,28) = 2.88$, $p = 0.10$). Simple effects tests revealed no significant differences in left amygdala – ventral striatum correlation across negative and positive conditions, compared to the baseline neutral condition, in the two depression groups (BD-D: $F(1,26) = 0.0001$, $p = 0.994$; MDD: $F(1,32) = 0.04$, $p = 0.844$), though this interaction was significant for the BD-M group ($F(1,30) = 19.20$, $p = 0.0001$). Further decomposition of the simple effects showed that left amygdala betas were significantly negatively correlated with ventral striatal betas for the negative versus neutral condition ($t(44) = -3.05$, $p = 0.004$), but not the positive versus neutral condition ($t(41) = 1.13$, $p = 0.26$). When we probed the left amygdala – vlPFC correlation, we found a similar three-way interaction pattern though it was not significant ($F(2,29) = 1.97$, $p = 0.158$; Fig. 3c), so no further simple effect tests were conducted.

For the right amygdala, we similarly found a significant three-way interaction at the ventral striatum ($F(2,20) = 9.802$, $p = 0.006$; Fig. 4b) so proceeded with simple effect tests. Again, planned contrasts confirmed that the interaction was driven by differences across mood phase (BD-M versus the two depression groups; $F(1,31) = 16.48$, $p = 0.0003$) rather than across diagnostic categories (MDD versus the two bipolar groups; $F(1,28) = 0.48$, $p = 0.494$). Simple effects tests again revealed no significant differences in right amygdala – ventral striatum correlation across negative and positive conditions, compared to the baseline neutral condition, in the two depression groups (BD-D: $F(1,27) = 1.09$, $p = 0.305$; MDD: $F(1,35) = 0.51$, $p = 0.481$). Again, this interaction was significant for the BD-M group ($F(1,36) = 20.36$, $p < 0.001$). The right amygdala betas were significantly negatively correlated with ventral striatal betas for the negative versus neutral condition ($t(51) = -3.05$, $p = 0.004$), but not the positive versus neutral condition ($t(50) = 0.62$, $p = 0.536$). Again, we did not find a significant three-way interaction between right amygdala, clinical group, and task condition in the vlPFC ($F(2,29) = 2.85$, $p = 0.074$; Fig. 4c) clusters.

To gain statistical power, we ran similar mixed-effects models regressing whole-brain voxel-wise beta series onto the respective seed beta series, task condition, and individual differences in YMRS and HRS-D symptom severity scores (See Supplementary Materials), rather than clinical group. We found consistent patterns of correlation with mean ventral striatum beta values when we moderated amygdala beta values with task condition and both continuous measures of depression and mania severity, across both left (Figure S3 and Figure S4) and right amygdala (Figure S5 and Figure S6) seeds.

4. Discussion

We sought to examine the neural substrates of affective processing in order to characterize the organization of mood symptomatology. To do so, we imposed affective processing demands with a passive viewing task and tested for neural differences in whole-brain functional connectivity patterns with the amygdala. Broadly, we predicted connectivity differences between mood symptom subgroups, rather than between diagnostic divisions. That is, we expected differential connectivity profiles between the BD-M group and the two depression groups but no difference between the depression mood-disordered groups. This prediction was driven by a framework which posits that psychiatric illnesses are in part characterized by transdiagnostic psychological constructs (in our case, depressive and manic symptoms) and neural processes that cut across traditional diagnostic boundaries (Insel et al., 2010).

Across all three clinical groups we found a similar pattern of positive amygdala—ventral striatum correlation for positive stimuli (relative to neutral). Surprisingly, while we hypothesized biases in

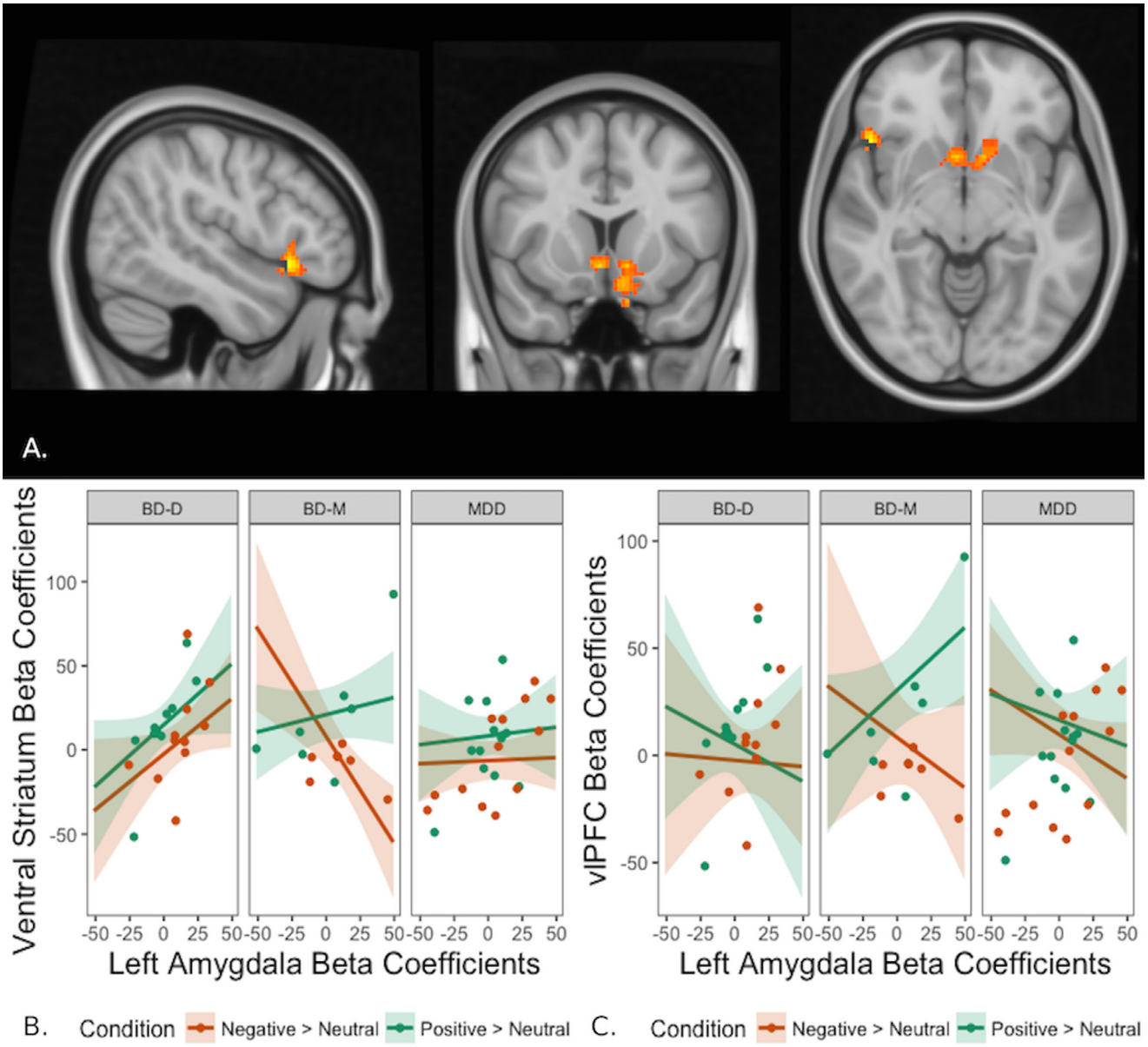

Fig. 3. Results from the mixed-effects model of the left amygdala seed, interacting with clinical group and task condition. (A) Clusters from the whole brain analysis, showing a cluster in the ventral striatum and at the right vlPFC. Coordinates: $x = 48$, $y = 12$, $z = -y$. Effect plots of three-way interactions predicting the mean beta value extracted from the (B) ventral striatum and (C) right vlPFC clusters. Shaded area around lines represent 95% confidence intervals, and points represent estimated beta values, for negative versus neutral and positive versus neutral task conditions.

connectivity strength for valenced information to fall in a manner consistent with the mood phase (i.e., a bias in processing positive information in mania, and a bias in processing negative information in depression), this hypothesis was not confirmed by the data. We found a consistent positive correlation between the amygdala and ventral striatum for positive stimuli, regardless of mood phase (and regardless of manic or depressive symptom severity). Instead, it was this neural pathway's correlation profile to negative information that tracked mood phase (and symptom severity) distinctions. This finding adds an important nuance to existing work that largely details increased activation among subcortical structures in bipolar disorder (Bermpohl et al., 2009; Rich et al., 2006); here we demonstrate that interactions within this limbic system are dependent on both the internal mood state of the individual as well as the relative balance between positivity and negativity in incoming information.

On the other hand, delineation of neural processing for affective stimuli along mood phase, rather than diagnostic lines, was consistent with our hypothesis and provides another piece to the growing body of evidence that certain psychiatric illnesses are well characterized by core mechanisms, which may be shared across traditional diagnostic categories. Indeed, we found that for both the left and right amygdala seeds (and for the ventrolateral prefrontal cortex, albeit non-significantly), differences in connectivity profiles were driven by the current mood phase of the participant, where BD-M was differentiated from BD-D and MDD, and there was a lack of connectivity differentiation across task demands in both BD-D and MDD. Importantly, we found significant differences across mood symptomatology within diagnostic category (BD-M versus BD-D), but no significant differences across diagnostic category with similar mood symptomatology (BD-D versus MDD). Interestingly, these findings differ from previous work using similar sample characteristics that describes differences in connectivity between the amygdala and orbitofrontal cortex between unipolar and bipolar depression (Almeida et al., 2009). One key difference from our current experiment, however, is that their participants were tasked to

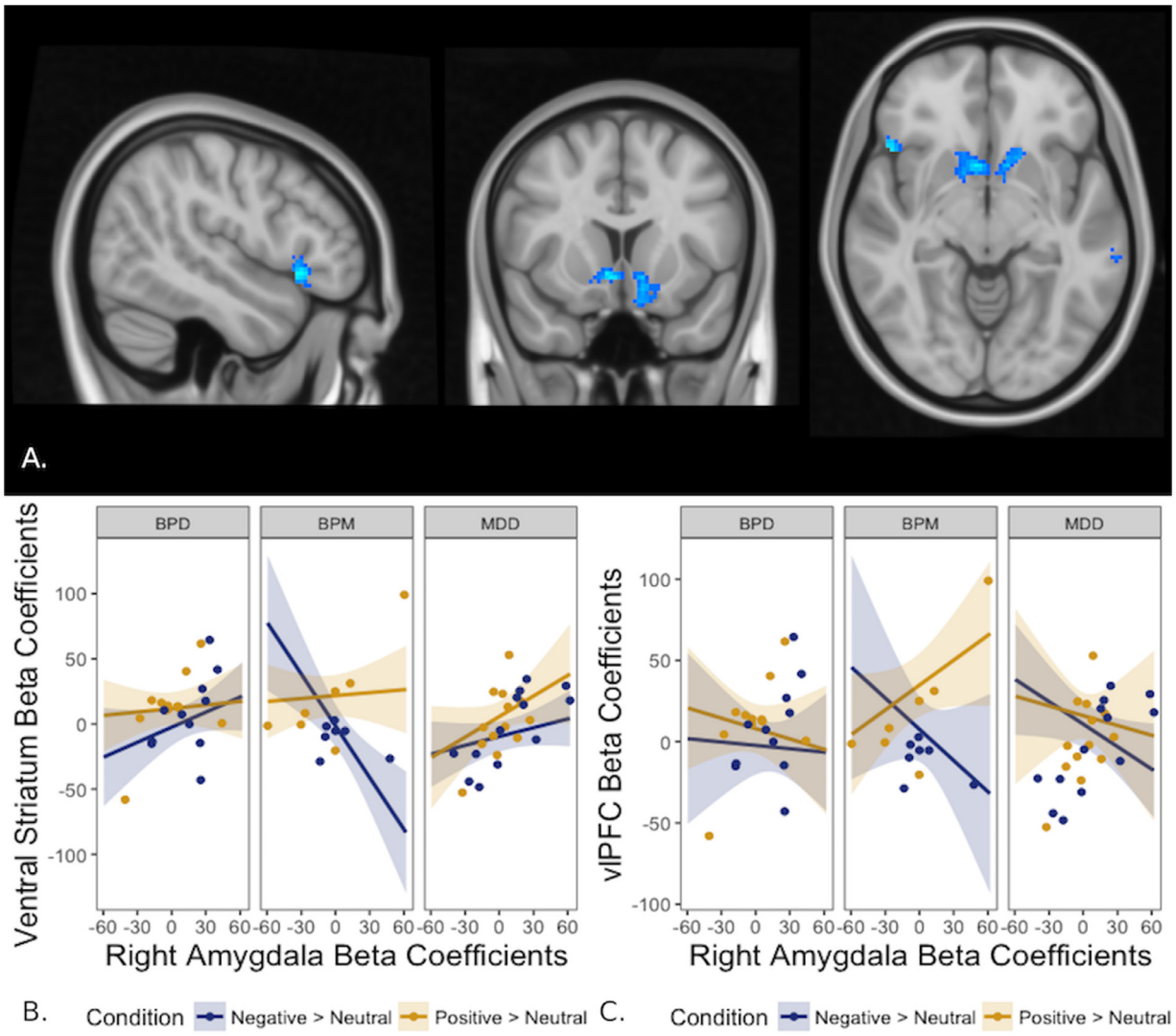

Fig. 4. Results from the mixed-effects model of the right amygdala seed, interacting with clinical group and task condition. (A). Clusters from the whole brain analysis, showing a cluster in the ventral striatum and at the right ventrolateral PFC. Coordinates: x = 48, y = 12, z = -y. Effect plots of three-way interactions predicting the mean beta value extracted from the (B) ventral striatum and (C) right vlPFC clusters. Shaded area around lines represent 95% confidence intervals, and points represent estimated beta values, for negative versus neutral and positive versus neutral task conditions.

Table 2
Significant 3-way interaction clusters. Peak coordinates for significant clusters are reported in Montreal Neurological Institute (MNI) space (x, y, z). Results are cluster corrected to keep FWE < 0.05 with a CDT of $p < 0.001$.

Seed	x	y	z	Cluster size	Regions in cluster
					Bilateral VS
L amygdala	4	12	−8	291	Ventromedial PFC
	38	20	−6	120	Ventrolateral PFC
	−24	−16	−12	101	Ventromedial PFC
	26	−46	16	84	R cerebral white matter
	−32	−86	8	84	L lateral occipital cortex
	−50	−20	10	84	L superior temporal sulcus
					Bilateral VS
R amygdala	−6	12	−8	419	Ventromedial PFC
	48	22	−6	98	Ventrolateral PFC
	−50	−20	10	80	L superior temporal sulcus
	−64	−34	−16	78	L middle temporal gyrus

label the emotional intensity of valenced faces. This demand likely elicits different (e.g. top-down) cognitive processes than the passive viewing paradigm we employ, and might explain the stronger effects we found for correlations with the ventral striatum across the bilateral amygdala, compared to the vlPFC.

It is also important to note that while we tested individuals with bipolar disorder during acute mood phases, these same individuals at other times experience opposing mood profiles. That individuals with bipolar mania were so distinct in their response profile compared to bipolar depression provides evidence that the role of particular neural pathways in affective processes, such as that between the amygdala and ventral striatum, as markers of disease are highlighted mainly at the process (i.e. internal state), rather than diagnostic, level. Together, this suggests that for the processing of incoming affective information, this neural circuit reflects the internal affective context through which this information is encountered, rather than the diagnostic categorization of the individual.

5. Limitations

These findings reinforce the importance of emphasizing that neural circuits underlying certain affective processes can be delineated along process dimensions, such as internal mood state, rather than strict diagnostic boundaries. As a useful starting point, the current work aims to shed light on specific processes that organize mood-based psychiatric

illnesses, and motivate further work that deeply dives into the nuance of how and when these mechanisms differ between disease symptomatology. Concurrently, we aim with this work to highlight the importance of considering internal states as significant modulators of neural and psychological processes. It is, however, is not without some limitations which need to be addressed in future studies. Our small sample sizes and the lack of a healthy control condition bear constraints on our interpretations; this work therefore needs to be replicated in a larger sample. While it is not in the primary goals of this current work to speak to the neural pathophysiology in BD and MDD, which would require comparison to similar affective circuits in healthy individuals, having a healthy control condition or a euthymic BD group would also allow insight for our aims by providing another type of internal state, one relatively not affected by mood symptoms. Furthermore, given heterogeneity in treatment approaches between our participants, there is the possibility that certain pharmacological interventions have influence on cerebral blood flow, thereby potentially influencing BOLD response. We did not assess cerebral blood flow nor conduct a blood test to rule out the impact of hormones or cortisol levels, and these potential physiological confounds need to be addressed in future investigations. Finally, the defined grouping in the current study was based on measures of symptom severity in mania and depression. Examining the role of interactions between internal states and more stable traits measures will be useful in carving out undiscovered disease mechanisms. Future work that describes the interplay between transdiagnostic core processes and diagnostic definitions to better describe heterogeneity in psychiatric illness will be very exciting.

Conflict of interest

The authors declare no competing conflicts of interest.

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Contributors

W.A.C, J.G. and D.C.G. designed the study. J.G. and D.C.G. collected the data. V.M. conducted the analyses. V.M., J.G., D.C.G., and W.A.C. wrote the manuscript. All authors have approved the final article.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2018.11.008.

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