Psychiatry Research: Neuroimaging 174 (2009) 195–201

Contents lists available at ScienceDirect

Psychiatry Research: Neuroimaging

journal homepage: www.elsevier.com/locate/psychresns

Abnormally increased effective connectivity between parahippocampal gyrus and ventromedial prefrontal regions during emotion labeling in bipolar disorder

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ARTICLE INFO

Article history:
Received 26 November 2008
Received in revised form 24 April 2009
Accepted 24 April 2009

Keywords:
Bipolar disorder
Emotion regulation
Neuroimaging
fMRI
Dynamic causal modeling
Effective connectivity

ABSTRACT

Emotional liability and mood dysregulation characterize bipolar disorder (BD), yet no study has examined effective connectivity between parahippocampal gyrus and prefrontal cortical regions in ventromedial and dorsal/lateral neural systems subserving mood regulation in BD. Participants comprised 46 individuals (age range: 18–56 years): 21 with a DSM-IV diagnosis of BD, type I currently remitted; and 25 age- and gender-matched healthy controls (HC). Participants performed an event-related functional magnetic resonance imaging paradigm, viewing mild and intense happy and neutral faces. We employed dynamic causal modeling (DCM) to identify significant alterations in effective connectivity between BD and HC. Bayes model selection was used to determine the best model. The right parahippocampal gyrus (PHG) and right subgenual cingulate gyrus (sgCG) were included as representative regions of the ventromedial neural system. The right dorsolateral prefrontal cortex (DLPFC) region was included as representative of the dorsal/lateral neural system. Right PHG–sgCG effective connectivity was significantly greater in BD than HC, reflecting more rapid, forward PHG–sgCG signaling in BD than HC. There was no between-group difference in sgCG–DLPFC effective connectivity. In BD, abnormally increased right PHG–sgCG effective connectivity and reduced right PHG activity to emotional stimuli suggest a dysfunctional ventromedial neural system implicated in early stimulus appraisal, encoding and automatic regulation of emotion that may represent a pathophysiological functional neural mechanism for mood dysregulation in BD.

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1. Introduction

Bipolar disorder (BD), particularly the type 1 subtype, is a debilitating psychiatric disorder. The core feature is mood dysregulation, characterized by swings between depressed and manic episodes, and emotion instability that may persist during remission (Goodwin and Jamison, 2007). There has therefore been increasing interest in elucidating underlying neurobiological abnormalities that may be associated with mood dysregulation in BD (Drevets, 2000; Strakowski et al., 2000; Phillips et al., 2003).

Our recently revised neural model of emotion regulation (Phillips et al., 2008a), which builds on our earlier model (Phillips et al., 2003), comprises two neural systems: a ventromedial system and a dorsal/lateral system. The ventromedial neural system (comprising the parahippocampal gyrus, hippocampus, subgenual anterior cingulate gyrus, ventromedial and dorsomedial prefrontal cortices) is implicated in the early appraisal and encoding of emotional significance during regulation of behavioral responses to an emotional stimulus, which is automatic rather than under voluntary control. The dorsal/lateral neural system (comprising dorsal and lateral prefrontal cortical regions) is implicated in voluntary control of behavioral responses to emotional stimuli. These two neural systems may be activated concurrently during regulation of emotional behavior generated in subcortical limbic regions, including the amygdala, ventral striatum and thalamus. In this model, we proposed that abnormally elevated activity within subcortical limbic regions implicated in the initial response to emotional stimuli, together with a dysfunctional ventromedial emotion-regulatory neural system, may be implicated in the pathophysiology of BD (Phillips et al., 2008a). Abnormally elevated activity within subcortical limbic regions to emotional stimuli has, for example, been demonstrated in BD patients during remission (Yurgelun-Todd et al., 2000; Lawrence et al., 2004; Blumberg et al., 2005; Hassel et al., 2008), mania (Malhi et al., 2004a; Altshuler et al., 2005; Chen et al., 2006) and depression (Malhi et al., 2004b). Other studies indicate abnormal activity in the ventromedial emotion regulatory neural system, specifically, abnormally increased and

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doi:10.1016/j.pscychresns.2009.04.015

reduced activity, respectively, to emotional faces (Malhi et al., 2007b) and words (Malhi et al., 2007a) in paralimbic regions in remitted BD patients versus healthy individuals. There are further reports of reduced activity in remitted and manic BD patients versus healthy individuals in ventromedial prefrontal cortical regions during emotional Stroop and risk-taking tasks that depend on the ability to automatically focus attention away from emotionally salient stimuli (Rubinsztein et al., 2001; Malhi et al., 2005; Lagopoulos and Malhi, 2007). However, a limitation of these studies is the inability to determine if one region regulates the other, i.e.: they used a functional specialization approach.

Functional specialization assumes that different aspects of information processing engage distinct regions but cannot reveal how these regions may be functionally integrated during task performance. In neuroimaging, functional integration within a distributed network can be characterized in terms of "functional connectivity" and "effective connectivity" (Friston et al., 2007). Functional connectivity is model-free and refers to a correlation over time between activities in different neural regions. In contrast, effective connectivity is model-based and refers to the impact that activity in one region exerts over that in another. To date, one study has examined functional connectivity in BD. This study revealed reduced functional connectivity between ventrolateral prefrontal cortex (VLPFC) and amygdala in manic BD patients relative to healthy individuals during an emotion-labeling task (Foland et al., 2008). There are no previous studies investigating effective connectivity in BD.

Effective connectivity can be examined using dynamic causal modeling (DCM), a technique for estimating, and making inferences about, the negative or positive influence that one region exerts over another and how this is affected by the experimental context (Friston et al., 2003).

In the present study, we used DCM to examine in BD patients abnormalities persisting during remission in effective connectivity in ventromedial and dorsal/lateral neural systems implicated in mood regulation to emotionally salient stimuli: facial expressions of emotion. We applied DCM in a two-stage approach that involved (i) identifying the best model from a series of candidate models using Bayesian model selection (see Section 2.5); and (ii) testing the hypothesis that effective connectivity within the best model differed significantly between BD patients and healthy control individuals (HC; see Section 2.6). As no studies to date have employed DCM in BD, we were unable to specify the direction and nature of abnormal effective connectivity between regions in these two neural systems in BD. We first wished to examine the effective connectivity within the ventromedial neural system, i.e., parahippocampal gyrus versus ventromedial prefrontal cortex regions. We then wished to examine effective connectivity between ventromedial and dorsal/lateral neural systems in BD patients versus HC.

2. Methods

2.1. Participants

The University of Pittsburgh Institutional Review Board approved the study protocol. Twenty-one adults with BD, type I (mean age = 31.9, S.D. = 8.5, M/F = 10/11), diagnosed according to the criteria of DSM-IV and the Structured Clinical Interview for DSM-IV, Research Version (SCID-P) participated in the study. All BD patients were in remission at the time of scanning with Hamilton Depression Rating Scale(HDRS-17) score < 7 and Young Mania Rating Scale(YMRS) score < 10; however, two BD patients had subclinical symptoms of depression at the time of scan (HDRS-17 between 7 and 14) but did not meet criteria for depressive episode. All had experienced at least two episodes of illness in the last 4 years. Some BD patients had comorbid disorders, and most were medicated (two were medication-free; see Table 1).

Table 1
Demographic information and BD patient clinical characteristics.

	BD patients ($n=21$)	HC ($n=25$)
Gender[a]		
Male	10	10
Female	11	15
Mean age[b] (S.D.)	31.95 (8.47)	28.84 (9.63)
Mean age of illness onset (S.D.)	20.62 (6.73)	n/a
Mean illness duration (S.D.)	11.33 (6.25)	n/a
Mean HDRS (S.D.)	2.63 (3.64)	n/a
Mean YMRS (S.D.)	1.6 (2.6)	n/a
Medication load	2.5 (1.8)	n/a
Current comorbid diagnosis		
Social phobia	2	n/a
Specific phobia	1	
Anxiety disorder	1	
NOS		
GAD	1	
Medication: 19 BD were taking medication and 2 were drug free		
Mood-stabilizers ($n=15$)	Lithium ($n=6$)	n/a
	Lamotrigine ($n=3$)	
	Valproate sodium ($n=2$)	
	Gabapentin ($n=1$)	
	Carbamazepine/oxcarbazepine ($n=3$)	
Antidepressants ($n=9$)	Bupropion ($n=1$)	n/a
	Sertraline ($n=2$)	
	Trazodone ($n=1$)	
	Venlafaxine ($n=2$)	
	Mirtazapine ($n=1$)	
	Citalopram ($n=1$)	
	Fluoxetine ($n=1$)	
Antipsychotics ($n=13$)	Aripiprazole ($n=7$)	n/a
	Risperidone ($n=3$)	
	Quetiapine ($n=2$)	
	Olanzapine ($n=1$)	
Benzodiazepines ($n=5$)	Lorazepam ($n=4$)	n/a
	Clonazepam ($n=1$)	

Numbers are means; standard deviations in parentheses; BD: bipolar I disorder patient remitted, HC: healthy controls, HDRS: Hamilton Depression Rating Scale, YMRS: Young Mania Rating Scale, PTSD: posttraumatic stress disorder.
[a] BD patients and HC did not differ significantly in gender ratio ($X^2=0.27$, $P=0.6$).
[b] BD patients and HC did not differ significantly in age ($t(44)=1.1$, $P=0.26$).

Twenty-five HC (mean age = 29 (S.D. = 9.6), M/F = 10/15) with no previous personal or family history of psychiatric illness in first and second degree relatives participated in the study. HC were gender-ratio-matched with BD patients (chi-square = 0.27; $df=1$; $P=0.6$), and age matched ($t(44)=1.1$, $P=0.3$). All participants were right-handed and native English speaking. All participants were aware of the purpose of the study and gave written informed consent prior to participation in the study.

Exclusion criteria included history of head injury (from medical records and participant report) systemic medical illness, cognitive impairment (score < 24 Mini-Mental State Examination, premorbid IQ estimate < 85 — National Adult Reading Test), Axis-II borderline personality disorder, and general exclusion criteria for magnetic resonance imaging (MRI — presence or questionable history of metallic objects in the body, positive pregnancy test/self-reporting of pregnancy, and proness to panicking in enclosed spaces). For HC, current or previous alcohol and illicit substance abuse (determined by SCID-I, saliva and urine screen) were further exclusion criteria.

The participant population reflected the demographics of Pittsburgh and the surrounding area and/or the patient population of the University of Pittsburgh Medical Center (UPMC), through local advertising.

2.2. Paradigm

All individuals participated in a 6-minute event-related paradigm. The paradigm involved viewing mild and prototypically intense happy

and neutral faces from a standardized series (Surguladze et al., 2003). In the experiment, individuals viewed sixty facial expressions in which facial expressions of prototypical (100%) happy intensity were morphed using computer software with neutral expressions from the same poser to depict expressions of 50%, or mild, emotion (Young et al., 2002). Individuals therefore viewed 20 prototypically happy expressions; 20 mild happy expressions, and 20 neutral expressions. Each facial expression was presented for 2 s, with an inter-stimulus interval (ISI) of variable duration, according to a Poisson distribution (mean ISI = 4.9 s) (Surguladze et al., 2003). We chose happy facial expressions as an example of emotional stimuli, as previous functional neuroimaging studies have consistently demonstrated abnormally elevated activity in ventral prefrontal cortical regions to these stimuli in BD (Lawrence et al., 2004; Blumberg et al., 2005; Hassel et al., 2008). Participants labeled the emotion of each face by moving either the index or middle finger of the right hand to ensure that attention was directed to the emotional content of the face, and because emotion labeling has been associated with neural activity in both, ventromedial and dorsal/lateral, regulatory systems (Chen et al., 2006; Fairhall and Ishai, 2007). During scanning, there were no between-group differences in emotion labeling accuracy (see Table S1 in the Supplementary data).

2.3. Data acquisition

Functional magnetic resonance imaging (fMRI) data were collected using a 3.0 Tesla Siemens Allegra MRI scanner at the University of Pittsburgh/CMU Brain Imaging Research Center (BIRC). All scanning parameters were selected to optimize the quality of the BOLD signal while maintaining a sufficient number of slices to acquire whole-brain data (for parameters details, see Supplementary data).

2.4. Functional integration: dynamic causal modelling analyses

We first used standard SPM5 analyses to determine the main effect of group, condition (emotion intensity) and the group by condition interaction upon neural responses to the different facial expressions (see details in Supplementary data). We used DCM, an effective connectivity approach (Friston et al., 2003; Mechelli et al., 2003) in SPM5 software, in a two-step procedure that involved selection of the best model from a series of candidate models using Bayesian model selection (see Section 2.5) and testing the hypothesis that the effective connectivity within the best model differed significantly between BD patients and HC (see Section 2.6). The aim of DCM is to estimate, and make inferences about, the influence that one neural system exerts over another and how the experimental context affects the neural system. In DCM, a reasonably realistic but simple neural model of interacting neural regions is constructed. DCM uses a previously validated biophysical model of functional MRI measurements to estimate underling neural responses from observed hemodynamic responses (Buxton et al., 1998; Friston et al., 2000); the estimated underlying neural responses is then used to derive connectivity parameters, as described elsewhere (Friston et al., 2003). These two steps are repeated iteratively and correspond to the expectation and maximization step of an expectation-maximization algorithm (Friston et al., 2003). Two sets of parameters are of particular interest in DCM: (a) the endogenous connections that characterize the functional coupling between neural regions in a given model and (b) bilinear terms which mediate condition-specific changes in this coupling. In this study we were interested in the endogenous coupling under our emotional judgment task.

In DCM, the units of connections are per unit time and therefore correspond to rates: a strong connection means an influence that is expressed quickly or with a small time constant. A positive (i.e., greater than zero) endogenous connection indicates that an increase in activity in the "source" region is associated with an increase in activity in the "target" region. Conversely, a negative (i.e., smaller than zero) endogenous connection indicates that an increase in activity in the "source" region is associated with a decrease in activity in the "target" region.

2.4.1. Identifying representative regions of the ventromedial and dorsal/lateral neural system derived from neural activity differences between BD and HC

For each participant, a series of dynamic causal models was constructed that included three empirically-defined right-sided regions that emerged from the whole-brain ANOVA as representative regions of our ventromedial and dorsal/lateral neural systems for emotion regulation. The three regions included two from the ventromedial system (the parahippocampal gyrus and the ventromedial prefrontal cortex) and one from the dorsal/lateral neural system (the dorsolateral prefrontal cortex). We chose to include two regions of the ventromedial neural system because of its "two-site" location: temporal and prefrontal cortices. To account for individual differences, we extracted principal eigenvariates to summarize regional responses in 6 mm spheres centered on the regions above. The location of these regions was based upon the local maxima of the subject-specific statistical parametric maps within 6 mm of the group-maxima for the comparison between BD and HC.

2.4.2. Empirically based model proposal

Four alternative models that differed in terms of their endogenous connections were constructed. (models A, B, C and D in Fig. 1). The stimulus function, that encoded face presentation per se, entered each dynamic causal model through the temporal region and propagated to the rest of the network via interconnections between this region and the remaining ventromedial and dorsal/lateral prefrontal cortical nodes; none of the models included bilinear terms given the focus of the present investigation on endogenous coupling.

We chose to focus on a set of DCMs (i.e., a model space) that only modeled face-selective responses under emotional judgment. This simplification allowed us to specify a set of models with different endogenous connections in the forward and backward directions between our three regions. This reduced model space allowed us to select the best model using Bayesian model selection. It could be argued that better models exist, which allow for condition-specific differences through bilinear or modulatory changes in coupling. However, our main focus was on group-specific differences in connectivity and we deliberately opted for simple DCMs, whose parameters could be estimated efficiently.

2.5. Model comparisons

Our analysis was based on Bayesian model comparison using Bayes factors to select among the four competing models varying for their complexity (Section 2.4.2). Models were contrasted based on their ability to explain the observed data at the individual participant level. We used two criteria to assess the evidence in favor of one model versus another, namely Bayesian and Akaike's Information Criteria (Penny et al., 2004). The former biases towards simple models, whereas the latter biases towards complex models. One model was considered superior to a second when both criteria were met and the corresponding Bayes factors were above 3 for each individual (Raftery, 1995; Penny et al., 2004). The most prevalent best model across all subjects was considered to be the winning model.

2.6. Effect of group upon endogenous connections in the best model

Individual-specific estimates of effective connectivity for the best model were next entered into SPSS edition 15 (SPSS Inc.) for examination of the main effect of group in this model (thresholded at $P = 0.05$; Section 2.5). Resulting significant parameter estimates

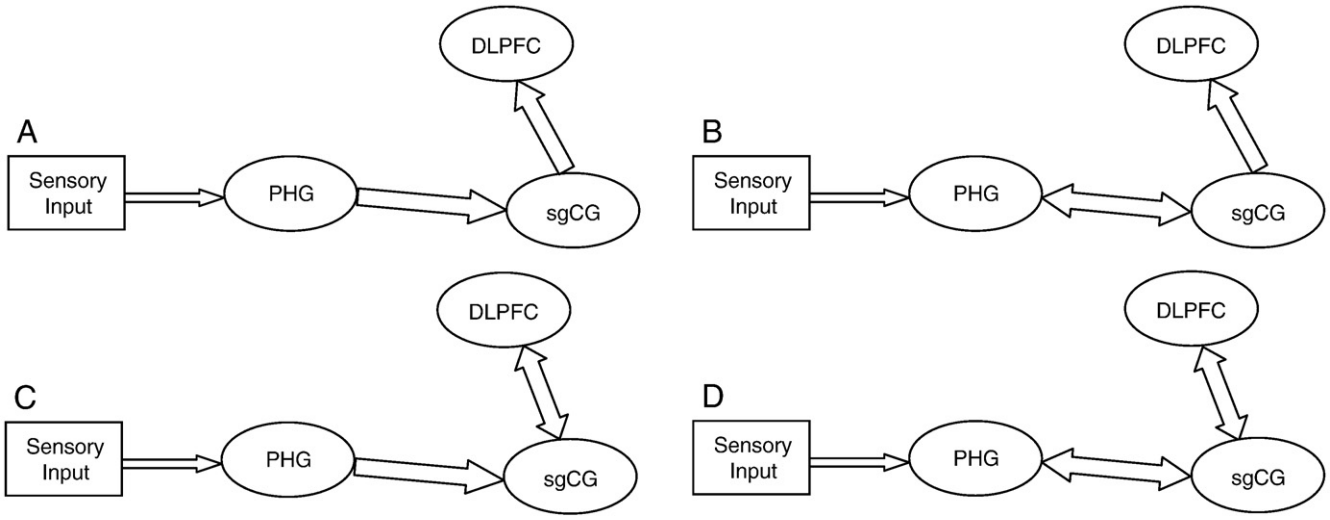

Fig. 1. Proposed models for Bayes comparison in healthy controls and bipolar disorder patients. A) Model with simple forward connections between regions. B) Model with bilateral connection between PHG and sgCG; and simple forward connection between sgCG and DLPFC. C) Model with a forward connection between PHG and sgCG and a bilateral connection between sgCG and DLPFC. D) Model with bilateral connections between PHG and sgCG; and between sgCG and DLPFC. The most consistent model after the model comparison was a simple forward model (model A). PHG: right parahippocampal gyrus; sgCG: right subgenual cingulate gyrus; DLPFC: right dorsolateral prefrontal cortex.

were then explored for possible relationships with the following demographic and clinical variables in BD patients: age, age of illness onset, illness duration, depression severity measured using the HRSD17, mania severity measured using the YMRS and medication load (thresholded at $P=0.008$, to correct for multiple comparisons). The impact of current comorbid disorders upon endogenous connections in BD patients was measured by comparing endogenous connections in those with, versus those without, such comorbid disorders.

2.7. Medication load

A problem for all neuroimaging studies of BD is the potential confounding effect of psychotropic medication, as it is difficult to recruit medication-free BD individuals into such studies (Phillips et al., 2008b). We wished to examine the potential impact of psychotropic medication upon effective connectivity in BD individuals using an index of "medication load". This index reflects the number and dose of different medications for each individual: the greater the number and dose of the medication, the greater the medication load. This strategy has been employed in our previous neuroimaging studies in BD (Hassel et al., 2008; Versace et al., 2008; Almeida et al., 2009).

3. Results

The article's main focus is on the findings from the DCM analyses. See Supplementary data for findings from the standard (functional specialization) SPM5 analyses regarding all regions showing main effects of group, condition and a group by condition interaction upon neuronal responses (Table S2).

3.1. Functional integration — dynamic causal modeling

3.1.1. Region selection within the emotion-processing model

The largest clusters in neural regions representative of the ventromedial neural system, (i.e. parahippocampal and ventromedial prefrontal cortical regions) and dorsal/lateral neural system (i.e. dorsal and lateral prefrontal cortical regions), were empirically chosen from our standard SPM5 analyses. These included two regions from the ventromedial system: right parahippocampal gyrus (PHG) [coordinates (x, y, z): 6, −45, −3; 5 voxels; group × condition interaction] and right subgenual anterior cingulate gyrus (sgCG, BA25) [coordinates (x, y, z): 0, 21, −9; 20 voxels; effect of condition]; and one from the dorsal/lateral system: right dorsolateral prefrontal cortex (DLPFC, BA 9) [coordinates (x, y, z): 51, 15, 36; 3 voxels; effect of group]. BD patients relative to HC showed significantly decreased right PHG activity to intense ($t(44)=3.97$; $P<0.001$) and mild happy faces ($t(44)=2.59$; $P=0.013$; Fig. S1a); significantly reduced right DLPFC activity to all emotional expressions (intense: $t(44)=2.66$; $P=0.011$; mild: $t(44)=2.94$; $P=0.005$; neutral: $t(44)=2.76$; $P=0.008$; Fig. S1c). In sgCG, all individuals showed deactivation to all three expression intensities, but significantly less so to intense happy versus other expressions: intense versus mild happy ($t(45)=3.12$; $P<0.003$); intense happy vs. neutral ($t(46)=4.26$; $P<0.001$; Fig. S1b).

Right-sided regions were chosen to allow construction of a simple, three-node unilateral model; and because the right hemisphere was the location of the majority of observed clusters. Previous DCM studies

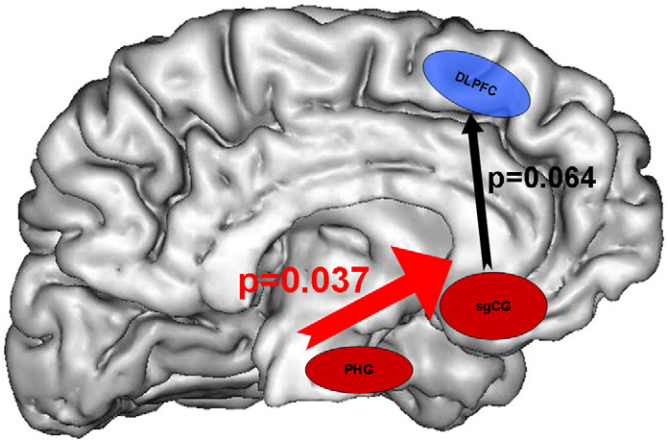

Fig. 2. Increased effective connectivity between parahippocampal gyrus and ventromedial prefrontal regions during happy emotion labeling in bipolar disorder. PHG: right parahippocampal gyrus; sgCG: right subgenual cingulate gyrus; DLPFC: right dorsolateral prefrontal cortex. Red arrow: significantly greater positive effective connectivity in BD patients versus HC between right PHG and right sgCG ($t(44)=2.15$, $P=0.037$). Here, an increase in activity in the PHG "source" region was associated with an increase in activity in the sgCG "target" region. Black arrow: non-significant effective connectivity between subgenual cingulate gyrus and dorsolateral prefrontal cortex ($t(44)=1.9$, $P=0.064$). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 2
Relationship between clinical variables and PHG to sgCG effective connectivity.

	BD patients ($n=21$) PHG to sgCG	
	r	P
Correlation analyses		
Age	0.11	0.76
Age of illness onset	0.33	0.14
Illness duration	−0.46	0.035
HDRS-17	0.19	0.44
YMRS	−0.05	0.84
Medication load	−0.05	0.82
BD patients with and without current comorbid diagnoses		
Comorbid diagnoses ($n=5$)	$t(19)=0.75$	0.46

PHG: right parahippocampal gyrus; sgCG: right subgenual cingulate gyrus; BD: bipolar I disorder patient remitted, HDRS-17: Hamilton Depression Rating Scale; YMRS: Young Mania Rating Scale.

have similarly employed a unilateral model for analyses (Sonty et al., 2007).

3.1.2. Bayes model comparison

Four different endogenous connection (effective connectivity) models (Fig. 1) were compared using the Bayes selection approach (see Fig. S2 for a typical comparison in one BD and in one HC). Our best model across all subjects was a simple forward model from the PHG to sgCG and from sgCG to DLPFC (Fig. 1, model A; Table S3a and b and Table S4 for estimated parameters in the "loser" models).

3.1.3. Between-group differences in endogenous connections in the best model (model A)

There was a significant group effect upon the endogenous connection between right PHG and right sgCG (BA25). The endogenous connection between these regions was significantly greater in BD patients than HC, reflecting a more rapid, forward signaling from PHG to sgCG in BD patients to all facial expressions [mean HC = −0.0032 (S.D. = 0.069), mean BD = 0.0407 (S.D. = 0.069); $t(44)=2.15$, $P=0.037$]. Here, increased activity in the PHG "source" region was associated with increased activity in the sgCG "target" region. There was no significant group effect upon the endogenous connection from sgCG to DLPFC [mean HC = −0.0027 (S.D. = 0.0096), mean BD = 0.005 (S.D. = 0.017); $t(44)=1.9$, $P=0.064$; Fig. 2].

3.1.4. Relationship between age, illness history variables, and medication load

Correlation analyses, using Pearson correlations, were performed to examine the relationship between these variables and the abnormal right PHG–sgCG endogenous connection in BD patients. These analyses revealed a negative trend only with illness duration ($r=-0.46$; $P=0.035$, using $P=0.008$ to control for multiple tests; Table 2).

4. Discussion

We employed DCM to examine effective connectivity in ventromedial and dorsal/lateral neural systems implicated in emotion regulation in BD patients. Our best model in all participants was a simple forward model. There was a greater positive endogenous connection (i.e., greater effective connectivity) in BD patients relative to HC between right PHG and right sgCG during emotion labeling of happy and neutral facial expressions. This indicated a more rapid, forward PHG–sgCG signaling in BD patients to all facial expressions, such that an increase in activity in PHG was associated with a rapid increase in activity in sgCG.

The PHG has multiple and direct connections with the hippocampus and amygdala (Altshuler et al., 2005). A dynamic functional relationship between amygdala and PHG may protect against potentially harmful experiences in response to emotional stimuli (Surguladze et al., 2006). The sgCG is implicated in the generation of sad mood (Mayberg et al., 1999), depression (Mayberg et al., 2005), and internal state monitoring in individuals with attachment-avoidant personality. Depression improvement after pharmacotherapy (Kennedy et al., 2007) and deep brain stimulation (Mayberg et al., 2005) are associated with decreased right and left sgCG activity, respectively. PHG–sgCG connections through the subiculum and entorhinal cortex (Ongur and Price, 2000; Price, 2007) make it plausible that these regions function together within the ventromedial neural system during early appraisal, encoding and automatic regulation of behavior to emotionally-salient stimuli. Our finding of abnormally increased right PHG–sgCG effective connectivity to all faces in a simple and forward model in BD patients supports our hypothesis in BD of a dysfunctional ventromedial forward neural system for encoding, early appraisal, and automatic regulation of emotion. Our finding further suggests that the major dysfunction in this neural system is faster signaling from PHG to sgCG rather than slower signaling back from sgCG to PHG in BD patients, and that this occurs to both emotional (happy) and more ambiguous, although potentially salient (Davis and Whalen, 2001; Surguladze et al., 2006), neutral facial expressions.

While healthy controls showed a small activation (BOLD signal amplitude) in the PHG, part of the ventromedial system, related to automatic (rather then voluntary) emotion regulation, BD showed reduced activity in the PHG relative to healthy controls. Decreased PHG activity to emotional words was previously reported in euthymic BD (Malhi et al., 2007b), and reduced PHG gray matter volume in BD (Almeida et al., 2009), patients versus HC. Some other studies found increased activation in the amygdala and striatum, subcortical regions involved in the emotion identification and behavior generation. In this study, we employed an emotional labeling task (explicit process). Consequently, participants were supposed to "think" about the emotion, rather then "feel" the emotion. Therefore, engagement of an emotion regulatory area (rather then an identification area) would be expected. We can speculate that reduced right PHG, together with abnormally increased effective right PHG–sgCG connectivity, may be associated with reduced early appraisal, increased encoding and greater attribution of salience to emotional stimuli that, in turn, may represent a potential pathophysiological mechanism for mood dysregulation in BD. Further studies, are needed to determine the relationship between effective connectivity and BOLD signal amplitude measures in neural systems implicated in emotion regulation in BD.

We found no significant group difference in right sgCG–DLPFC effective connectivity, although BD patients relative to HC showed reduced right DLPFC activity to all facial expressions, consistent with previous neuroimaging studies in BD (Yurgelun-Todd et al., 2000; Lawrence et al., 2004; Hassel et al., 2008). These findings indicate abnormal effective connectivity in the ventromedial rather than the dorsal/lateral emotion regulation system, although do suggest decreased involvement of components of the dorsal/lateral system to emotional stimuli in BD patients. All individuals showed right sgCG deactivation to all expressions, consistent with a role for the sgCG in encoding of negative emotional stimuli and negative rather than positive mood generation. There were no significant effects of age, illness variables, medication load or comorbid disorders upon effective connectivity between right PHG and right sgCG in BD patients. There was a negative trend only between illness duration and effective connectivity between these regions in BD patients, suggestive of a longer-term effect of BD of reducing the rate of the forward PHG–sgCG signaling.

In our functional specialization analyses, we also found activation in other regions related to emotional and visual processing, such as thalamus, insula, other parts of the anterior cingulate gyrus (BA24 and 32), lingual gyrus and cuneus. As a general pattern, we found

decreased activation in the BD patients in the between group contrast and an increased activation for neutral faces in the within contrast. It is beyond the scope of this work to discuss in detail the activation of these regions.

Nearly all studies to date examining functional connectivity in mood-disordered individuals using functional neuroimaging and electrophysiological techniques have focused on unipolar depressed rather than BD individuals (Pizzagalli et al., 2003; Anand et al., 2007; Holmes and Pizzagalli, 2008). These studies indicate disrupted functional connectivity between prefrontal cortical regions during attention tasks (Pizzagalli et al., 2003; Holmes and Pizzagalli, 2008) and increased prefrontal cortical-limbic functional connectivity at rest (Anand et al., 2007) or in response to sad facial stimuli after anti-depressant treatment (Chen et al., 2008) in unipolar depressed individuals. The only study examining functional connectivity in BD employed psychophysiological interaction, and demonstrated reduced VLPFC-amygdala functional connectivity in BD manic patients versus HC during an emotion-labeling task (Foland et al., 2008) that parallels findings indicating structural abnormalities in white matter tracts connecting subcortical limbic regions with ventral prefrontal cortex in BD (Versace et al., 2008). Our present findings using DCM make a significant contribution to this literature by demonstrating a specific abnormality in forward, temporal-ventral prefrontal cortical effective connectivity to emotionally salient stimuli in BD that may represent a pathophysiological functional neural mechanism for mood dysregulation in BD.

One limitation was that we recruited BD patients only during remission. Future studies should employ DCM to compare neural systems implicated in emotion regulation in BD patients in different mood states in cross-sectional and longitudinal designs. We focused on right-sided regions to allow construction of a simple unilateral model, and because the right hemisphere was the location of the majority of observed clusters of activation in BD patients and HC. Studies using different types of emotion processing paradigms that recruit bilateral ventromedial prefrontal neural systems could examine effective connectivity in these systems in each hemisphere in BD. We did not observe any significant relationships between medication load and effective connectivity in BD patients, but future studies employing DCM in BD populations should aim to include both unmedicated and medicated individuals to examine potential effects of different psychotropic medications upon effective connectivity in BD.

Our study is the first to employ DCM to examine effective connectivity in neural systems implicated in emotion regulation in BD. Our main finding of increased effective connectivity to emotional stimuli between temporal and ventromedial prefrontal cortical regions (part of the ventromedial neural system) implicated in early appraisal, encoding and automatic regulation of emotion contributes significantly to understanding of the nature of functional abnormalities in neural circuitry underlying mood dysregulation in BD. It is a step forward from the majority of previous neuroimaging studies in BD that focused on examination of functional abnormalities in neural regions rather than neural systems implicated in mood regulation. The employment of effective connectivity analyses in future neuroimaging studies of BD and unipolar depression will be key to identifying pathophysiological mechanisms that distinguish the two mood disorders.

Acknowledgments

All work was carried out within the Department of Psychiatry, University of Pittsburgh, neuroimaging data was collected at the Brain Imaging Research Center, University of Pittsburgh & Carnegie Mellon University. We thank Dr. K.J. Jung, S. Kurdilla and D. Vizslay for their help acquiring neuroimaging data. The research in this study was supported in part by a NARSAD Independent Investigator Award to MLP and 5R01 MH076971-01. MLP is the NARSAD Nellie Blumenthal Investigator. JRCA is supported by CAPES (Brazilian foundation, #190105-2).

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.pscychresns.2009.04.015.

References

Almeida, J.R., Akkal, D., Hassel, S., Travis, M.J., Banihashemi, L., Kerr, N., Kupfer, D.J., Phillips, M.L., 2009. Reduced gray matter volume in ventral prefrontal cortex but not amygdala in bipolar disorder: significant effects of gender and trait anxiety. Psychiatry Research 171, 54–68.

Altshuler, L., Bookheimer, S., Proenza, M.A., Townsend, J., Sabb, F., Firestine, A., Bartzokis, G., Mintz, J., Mazziotta, J., Cohen, M.S., 2005. Increased amygdala activation during mania: a functional magnetic resonance imaging study. American Journal of Psychiatry 162, 1211–1213.

Anand, A., Li, Y., Wang, Y., Gardner, K., Lowe, M.J., 2007. Reciprocal effects of antidepressant treatment on activity and connectivity of the mood regulating circuit: an FMRI study. Journal of Neuropsychiatry and Clinical Neurosciences 19, 274–282.

Blumberg, H.P., Donegan, N.H., Sanislow, C.A., Collins, S., Lacadie, C., Skudlarski, P., Gueorguieva, R., Fulbright, R.K., McGlashan, T.H., Gore, J.C., Krystal, J.H., 2005. Preliminary evidence for medication effects on functional abnormalities in the amygdala and anterior cingulate in bipolar disorder. Psychopharmacology 183, 308–313.

Buxton, R.B., Wong, E.C., Frank, L.R., 1998. Dynamics of blood flow and oxygenation changes during brain activation: the balloon model. Magnetic Resonance in Medicine 39, 855–864.

Chen, C.H., Lennox, B., Jacob, R., Calder, A., Lupson, V., Bisbrown-Chippendale, R., Suckling, J., Bullmore, E., 2006. Explicit and implicit facial affect recognition in manic and depressed states of bipolar disorder: a functional magnetic resonance imaging study. Biological Psychiatry 59, 31–39.

Chen, C.H., Suckling, J., Ooi, C., Fu, C.H., Williams, S.C., Walsh, N.D., Mitterschiffthaler, M.T., Pich, E.M., Bullmore, E., 2008. Functional coupling of the amygdala in depressed patients treated with antidepressant medication. Neuropsychopharmacology 33, 1909–1918.

Davis, M., Whalen, P.J., 2001. The amygdala: vigilance and emotion. Molecular Psychiatry 6, 13–34.

Drevets, W.C., 2000. Neuroimaging studies of mood disorders. Biological Psychiatry 48, 813–829.

Fairhall, S.L., Ishai, A., 2007. Effective connectivity within the distributed cortical network for face perception. Cerebral Cortex 17, 2400–2406.

Foland, L.C., Altshuler, L.L., Bookheimer, S.Y., Eisenberger, N., Townsend, J., Thompson, P.M., 2008. Evidence for deficient modulation of amygdala response by prefrontal cortex in bipolar mania. Psychiatry Research: Neuroimaging 162, 27–37.

Friston, K.J., Ashburner, J.T., Kiebel, S., Nichols, T.E., Penny, W., 2007. Statistical Parametric Mapping: the Analysis of Functional Brain Images. Academic Press, London.

Friston, K.J., Harrison, L., Penny, W., 2003. Dynamic causal modelling. Neuroimage 19, 1273–1302.

Friston, K.J., Mechelli, A., Turner, R., Price, C.J., 2000. Nonlinear responses in fMRI: the balloon model, Volterra kernels, and other hemodynamics. Neuroimage 12, 466–477.

Goodwin, F.K., Jamison, K.R., 2007. Manic-depressive Illness: Bipolar Disorders and Recurrent Depression. Oxford University Press, New York.

Hassel, S., Almeida, J.R.C., Kerr, N., Nau, S., Ladouceur, C.D., Fissell, K., Kupfer, D.J., Phillips, M.L., 2008. Elevated striatal and decreased dorsolateral prefrontal cortical activity in response to emotional stimuli in euthymic bipolar disorder: no associations with psychotropic medication load. Bipolar Disorders 10, 916–927.

Holmes, A.J., Pizzagalli, D.A., 2008. Spatiotemporal dynamics of error processing dysfunctions in major depressive disorder. Archives of General Psychiatry 65, 179–188.

Kennedy, S.H., Konarski, J.Z., Segal, Z.V., Lau, M.A., Bieling, P.J., McIntyre, R.S., Mayberg, H.S., 2007. Differences in brain glucose metabolism between responders to CBT and venlafaxine in a 16-week randomized controlled trial. American Journal of Psychiatry 164, 778–788.

Lagopoulos, J., Malhi, G.S., 2007. A functional magnetic resonance imaging study of emotional Stroop in euthymic bipolar disorder. Neuroreport 18, 1583–1587.

Lawrence, N.S., Williams, A.M., Surguladze, S., Giampietro, V., Brammer, M.J., Andrew, C., Frangou, S., Ecker, C., Phillips, M.L., 2004. Subcortical and ventral prefrontal cortical neural responses to facial expressions distinguish patients with bipolar disorder and major depression. Biological Psychiatry 55, 578–587.

Malhi, G.S., Lagopoulos, J., Owen, A.M., Ivanovski, B., Shnier, R., Sachdev, P., 2007a. Reduced activation to implicit affect induction in euthymic bipolar patients: an fMRI study. Journal of Affective Disorders 97, 109–122.

Malhi, G.S., Lagopoulos, J., Sachdev, P.S., Ivanovski, B., Shnier, R., 2005. An emotional Stroop functional MRI study of euthymic bipolar disorder. Bipolar Disorders 7 Suppl 5, 58–69.

Malhi, G.S., Lagopoulos, J., Sachdev, P.S., Ivanovski, B., Shnier, R., Ketter, T., 2007b. Is a lack of disgust something to fear? A functional magnetic resonance imaging facial emotion recognition study in euthymic bipolar disorder patients. Bipolar Disorders 9, 345–357.

Malhi, G.S., Lagopoulos, J., Sachdev, P., Mitchell, P.B., Ivanovski, B., Parker, G.B., 2004a. Cognitive generation of affect in hypomania: an fMRI study. Bipolar Disorders 6, 271–285.

Malhi, G.S., Lagopoulos, J., Ward, P.B., Kumari, V., Mitchell, P.B., Parker, G.B., Ivanovski, B., Sachdev, P., 2004b. Cognitive generation of affect in bipolar depression: an fMRI study. European Journal of Neuroscience 19, 741–754.

Mayberg, H.S., Liotti, M., Brannan, S.K., McGinnis, S., Mahurin, R.K., Jerabek, P.A., Silva, J.A., Tekell, J.L., Martin, C.C., Lancaster, J.L., Fox, P.T., 1999. Reciprocal limbic-cortical function and negative mood: converging PET findings in depression and normal sadness. American Journal of Psychiatry 156, 675–682.

Mayberg, H.S., Lozano, A.M., Voon, V., McNeely, H.E., Seminowicz, D., Hamani, C., Schwalb, J.M., Kennedy, S.H., 2005. Deep brain stimulation for treatment-resistant depression. Neuron 45, 651–660.

Mechelli, A., Price, C.J., Noppeney, U., Friston, K.J., 2003. A dynamic causal modeling study on category effects: bottom-up or top-down mediation? Journal of Cognitive Neuroscience 15, 925–934.

Ongur, D., Price, J.L., 2000. The organization of networks within the orbital and medial prefrontal cortex of rats, monkeys and humans. Cerebral Cortex 10, 206–219.

Penny, W.D., Stephan, K.E., Mechelli, A., Friston, K.J., 2004. Comparing dynamic causal models. Neuroimage 22, 1157–1172.

Phillips, M.L., Drevets, W.C., Rauch, S.L., Lane, R., 2003. Neurobiology of emotion perception II: implications for major psychiatric disorders. Biological Psychiatry 54, 515–528.

Phillips, M.L., Ladouceur, C.D., Drevets, W.C., 2008a. A neural model of voluntary and automatic emotion regulation: implications for understanding the pathophysiology and neurodevelopment of bipolar disorder. Molecular Psychiatry 13, 829, 833–857.

Phillips, M.L., Travis, M.J., Fagiolini, A., Kupfer, D.J., 2008b. Medication effects in neuroimaging studies of bipolar disorder. American Journal of Psychiatry 165, 313–320.

Pizzagalli, D.A., Oakes, T.R., Fox, A.S., Chung, M.K., Larson, C.L., Abercrombie, H.C., Schaefer, S.M., Benca, R.M., Davidson, R.J., 2003. Functional but not structural subgenual prefrontal cortex abnormalities in melancholia. Molecular Psychiatry 9 325, 393–405.

Price, J.L., 2007. Definition of the orbital cortex in relation to specific connections with limbic and visceral structures and other cortical regions. Annals of the New York Academy of Sciences 1121, 54–71.

Raftery, A.E., 1995. Bayesian model selection in social research. Sociological Methodology 25, 111–163.

Rubinsztein, J.S., Fletcher, P.C., Rogers, R.D., Ho, L.W., Aigbirhio, F.I., Paykel, E.S., Robbins, T.W., Sahakian, B.J., 2001. Decision-making in mania: a PET study. Brain 124, 2550–2563.

Sonty, S.P., Mesulam, M.M., Weintraub, S., Johnson, N.A., Parrish, T.B., Gitelman, D.R., 2007. Altered effective connectivity within the language network in primary progressive aphasia. Journal of Neuroscience 27, 1334–1345.

Strakowski, S.M., DelBello, M.P., Adler, C., Cecil, D.M., Sax, K.W., 2000. Neuroimaging in bipolar disorder. Bipolar Disorders 2, 148–164.

Surguladze, S.A., Brammer, M.J., Young, A.W., Andrew, C., Travis, M.J., Williams, S.C., Phillips, M.L., 2003. A preferential increase in the extrastriate response to signals of danger. Neuroimage 19, 1317–1328.

Surguladze, S., Russell, T., Kucharska-Pietura, K., Travis, M.J., Giampietro, V., David, A.S., Phillips, M.L., 2006. A reversal of the normal pattern of parahippocampal response to neutral and fearful faces is associated with reality distortion in schizophrenia. Biological Psychiatry 60, 423–431.

Versace, A., Almeida, J.R., Hassel, S., Walsh, N.D., Novelli, M., Klein, C.R., Kupfer, D.J., Phillips, M.L., 2008. Elevated left and reduced right orbitomedial prefrontal fractional anisotropy in adults with bipolar disorder revealed by tract-based spatial statistics. Archives of General Psychiatry 65, 1041–1052.

Young, A.W., Perrett, D.I., Calder, A.J., Sprengelmeyer, R., Ekman, P., 2002. Facial Expressions of Emotion: Stimuli and Tests (FEEST). Thames Valley Test Company, Bury St. Edmunds.

Yurgelun-Todd, D.A., Gruber, S.A., Kanayama, G., Killgore, W.D., Baird, A.A., Young, A.D., 2000. fMRI during affect discrimination in bipolar affective disorder. Bipolar Disorders 2, 237–248.