Psychiatry Research: Neuroimaging 201 (2012) 196–205

Contents lists available at SciVerse ScienceDirect

Psychiatry Research: Neuroimaging

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

An fMRI study of attentional control in the context of emotional distracters in euthymic adults with bipolar disorder

Benjamin C. Mullin [a,b,*], Susan B. Perlman [a], Amelia Versace [a], Jorge R.C. de Almeida [a], Edmund J. LaBarbara [a], Crystal Klein [a], Cecile D. Ladouceur [a], Mary L. Phillips [a,c]

[a] Department of Psychiatry, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA
[b] Department of Child Psychiatry and Behavioral Sciences, Children's Hospital Colorado, Aurora, CO, USA
[c] Department of Psychological Medicine, Cardiff University, Cardiff, UK

ARTICLE INFO

Article history:
Received 12 March 2011
Received in revised form 8 August 2011
Accepted 2 September 2011

Keywords:
Magnetic resonance imaging
Attention
Working memory
Emotion regulation
Effective connectivity

ABSTRACT

Inability to modulate attention away from emotional stimuli may be a key component of dysregulated emotion in bipolar disorder (BD). Previous studies of BD indicate abnormalities in neural circuitry underlying attentional control, yet few studies examined attentional control in the context of emotional distracters. We compared activity and connectivity in neural circuitry supporting attentional control and emotion processing among 22 individuals with BD type 1, currently remitted and euthymic, and 19 healthy controls. Participants performed an emotional n-back paradigm, comprising high and low attentional demand conditions, each with either emotional (happy, fearful), neutral or no face flanker distracters. During the high attentional control demand conditions without emotional distracters, BD individuals showed reduced activity relative to controls in dorsolateral prefrontal cortex, dorsal anterior cingulate cortex (dACC), and inferior parietal cortex. During the high attentional control demand conditions with fearful-face distracters, BD individuals showed greater activity than controls in these regions and amygdala and striatum. Relative to controls, BD individuals also showed abnormal patterns of effective connectivity between dACC and amygdala during high attentional control demand with emotional face distracters. Inter-episode bipolar disorder is characterized by abnormal recruitment of attentional control neural circuitry, especially in the context of emotionally distracting information.

1. Introduction

Bipolar disorder (BD), one of the 10 most debilitating illnesses worldwide (World Health Organization, 2004), is characterized by a central deficit in the ability to regulate emotion (Goodwin and Jamison, 2007). Importantly, this deficit may persist even during remission (Phillips et al., 2003); thus, examining the neural basis of emotion dysregulation in BD may advance understanding of key pathophysiologic processes of the illness. The ability to flexibly redirect attention (i.e., attentional control) away from emotionally distracting stimuli represents an important component of emotion regulation that may be deficient in BD (Phillips et al., 2008a).

Attentional control entails 1. selective attention toward goal-relevant stimuli, and 2. redirection of attention away from distracting, goal-irrelevant stimuli (Phillips et al., 2008a). Attentional control is fundamental to a range of cognitive tasks, including working memory (Gazzaley, 2010), sustained attention (Braver et al., 2003), and attentional set shifting (Nagahama et al., 2001). Maintaining attention to pertinent information is particularly challenging in the presence of distracting emotional stimuli, which compete for cognitive resources (Luo et al., 2007). Distributed prefrontal and parietal–cortical, anterior cingulate-cortical, and striatal-thalamo circuitry mediates attentional control (Alexander and Crutcher, 1990; Bush and Shin, 2006). Furthermore, maintaining attention in the presence of emotional distracters is dependent on this circuitry (Bishop et al., 2004; Dolcos and McCarthy, 2006; Erk et al., 2007; Goldstein et al., 2007) and intact functional coupling between prefrontal and anterior cingulate cortices and amygdala (Etkin et al., 2006; Urry et al., 2006).

Attentional control deficits have been documented among BD individuals using tests of sustained attention (Clark et al., 2002, 2005; Maalouf et al., 2010) and working memory (Martínez-Arán et al., 2005; Thompson et al., 2007). Neuroimaging studies

* Corresponding author at: Department of Child Psychiatry and Behavioral Sciences, Children's Hospital Colorado, 13123 E 16th Avenue, Box 130, Aurora, CO 80045, USA. Tel.: +1 720 777 4931; fax: +1 720 777 7309.
E-mail address: benjamin.mullin@childrenscolorado.org (B.C. Mullin).

0925-4927/$ – see front matter © 2011 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.pscychresns.2011.09.002

employing working memory paradigms reported reduced (Lagopoulos et al., 2007; Monks et al., 2004; Townsend et al., 2010), but also increased (Adler et al., 2004), activity in prefrontal attentional control circuitry in BD individuals relative to controls. Studies using the Stroop color-word selective attention task reported reduced activity in BD individuals vs. controls in ventral prefrontal regions (Blumberg et al., 2003; Kronhaus et al., 2006; Strakowski et al., 2005) and anterior cingulate cortex (ACC) (Gruber et al., 2004), although greater activity in dorsolateral prefrontal cortex (dlPFC) (Gruber et al., 2004). Although some inconsistencies remain, these findings suggest that attentional control deficits among BD individuals may reflect diminished recruitment of underlying attentional control neural circuitry.

Paradigms with intersecting cognitive and emotional demands may be particularly relevant to BD, given the aforementioned attentional control deficiencies and consistent findings of abnormally increased activity in subcortical regions supporting emotion processing among BD individuals (Altshuler et al., 2005; Almeida et al., 2010; Hassel et al., 2008, 2009; Lawrence et al., 2004). The few studies in this area have provided conflicting results, with some studies indicating that BD individuals show abnormally *elevated* activity in attentional control prefrontal cortical (Deckersbach et al., 2008; Elliott et al., 2004; Wessa et al., 2007) and in emotion processing subcortical (Wessa et al., 2007) circuitry during cognitive task performance with emotional distraction, while others have found abnormally *reduced* activity in attentional control circuitry relative to healthy controls (Malhi et al., 2005; Strakowski et al., 2005; Lagopoulos and Malhi, 2007). Several factors likely contributed to these discrepancies, including the use of different paradigms, unequal between-group task performance (Malhi et al., 2005), and recruitment of BD individuals in different mood states. Furthermore, while all of the tasks used in these studies required attentional control, they addressed slightly different domains of executive functioning, from response inhibition (e.g., affective Go/No-Go; Elliott et al., 2004; Wessa et al., 2007), set shifting (e.g., emotional Stroop; Lagopoulos and Malhi, 2007; Malhi et al., 2005), to working memory (Deckersbach et al., 2008), each engaging partially distinct patterns of cortical activation. Another factor is the use of different types of emotionally distracting stimuli, from emotional words (Elliott et al., 2004; Wessa et al., 2007), to pictures (Strakowski et al., 2011), to induced negative mood (Deckersbach et al., 2008). Also noteworthy is that some studies employed only negative emotionally distracting information (Deckersbach et al., 2008), while other used negative emotional and neutral distracters (Lagopoulos and Malhi, 2007; Strakowski et al., 2011), or negative and positive emotional distracters (Elliott et al., 2004; Malhi et al., 2005; Wessa et al., 2007). Further research is clearly required to elucidate possible neural system abnormalities among BD individuals during cognitive tasks requiring redirection of attention away from emotional distracters.

Given that attentional control is mediated by distributed neural circuitry, connectivity analyses are a natural extension of this literature. Functional connectivity (FC) measures correlations over time between activity in different neural regions, while effective connectivity (EC) measures the impact of activity in one region over another (Roebroeck et al., 2005). Thus far, studies employing these techniques in BD have used emotion processing paradigms, and reported decreased amygdala-vlPFC FC (Foland et al., 2008), decreased amygdala-ACC FC (Wang et al., 2009), increased parahippocampal-subgenual cingulate cortical EC (Almeida et al., 2009a), and reduced vmPFC-amygdala EC in BD individuals vs. controls (Almeida et al., 2009b). One study also described decreased resting state amygdala-VPFC FC among BD individuals relative to controls (Chepenik et al., 2010). In the current study, we employed the *Emotional Face N-Back* (EFNBACK) task, a paradigm requiring direction of attention away from emotional (fearful and happy) and neutral-face distracters to perform an n-back working memory task (Ladouceur et al., 2009). The paradigm also includes a no-distracter, attentional control condition. We previously showed slower task performance on the attentional demand condition with fearful-face distracters in high trait anxiety individuals at risk of mood disorders (Ladouceur et al., 2009), and significantly greater dlPFC activity to this condition in remitted individuals with a history of major depressive disorder (Kerestes et al., 2012). We used a region of interest (ROI) approach to examine differences in activity and EC between BD individuals and controls within: 1. attentional control neural circuitry: prefrontal and parietal cortices, ACC and striatum during attentional control; and 2. this neutral circuitry and the amygdala, a key emotion processing region, during attentional control in the context of emotional distracters. The EFNBACK has two important features, the combination of which distinguishes it from previous paradigms examining attentional control in the context of emotional distracters in BD. First, the distracters in this task are distinct from the stimuli comprising the attentional control component (unlike, for example, affective Go/No-Go tasks). Second, the paradigm includes neutral, positive, and negative emotional distracters, enabling us to comprehensively examine neural circuitry supporting attentional control vs. attentional control in the context of different types of emotional and neutral distracting stimuli. Furthermore, we examined neural circuitry when task performance was equivalent across groups, to avoid the potential confound of poor task performance upon neural activity of some studies in BD (Adler et al., 2004; Gruber et al., 2004; Malhi et al., 2005; Strakowski et al., 2005; Thermenos et al., 2010). We examined remitted, euthymic BD individuals to identify functional neural abnormalities that were mood state independent.

We formulated the following hypotheses based on the collection of previous attentional control studies in BD, as well as the neural model of emotion regulation deficits in BD previously described by our group (Phillips et al., 2008a). This model highlights the role of abnormal dorsolateral, ventrolateral and dorsomedial (including dACC) prefrontal cortices activity during voluntary regulation of attention away from emotional distracters among BD individuals. In light of previous studies of attentional control neural circuitry in BD (Blumberg et al., 2003; Kronhaus et al., 2006; Lagopoulos et al., 2007; Monks et al., 2004; Strakowski et al., 2004), we hypothesized that BD individuals would show *reduced* activity in attentional control neural circuitry vs. controls, particularly in dlPFC and dACC, during the no-distracter, attentional control condition. We hypothesized that during attentional control in the context of emotional distracters, BD individuals would show abnormally *elevated* activity in this circuitry and amygdala vs. controls, given that the only previous study of euthymic BD individuals using a paradigm employing both positive and negative emotional distracters documented *greater* activity in BD vs. healthy individuals (Wessa et al., 2007). Exploratory analyses compared EC between neural regions in attentional control circuitry and the amygdala during attentional control in the context of emotional distracters in BD individuals vs. controls.

2. Materials and methods

2.1. Participants

The study was approved by the Institutional Review Board at the University of Pittsburgh. All individuals provided written informed consent before participation. 41 participants (aged 19–46 years): 22 individuals with bipolar I disorder (Structured Clinical Interview for DSM-IV, Research Version (SCID-P) (First et al., 1995) criteria), and 19 healthy controls without previous personal or family history of

Table 1
Demographic and clinical variables.

	BD individuals ($n=22$)		Controls ($n=19$)			
	Mean	S.D.	Mean	S.D.	Statistic	*P* value
Age at scan	31.68	8.96	32.54	6.56	$t(39)=0.35$	0.73
Gender (M/F)	8/14		8/11		$\chi^2=0.14$	0.71
NART full scale IQ	112.55	7.92	112.20	7.15	$t(39)=-0.15$	0.88
Level of completed education [a]	5.91	1.23	6.32	1.29	$U=171.0$	0.30
HRSD-25	6.27	4.17	2.36	2.40	$U=53.50$	<0.001
YMRS	2.36	2.40	0.37	1.01	$U=100.00$	0.001
Age at illness onset	18.27	6.42	—	—	—	—
Illness duration	13.41	7.97	—	—	—	—
Medication load	2.91	1.66	—	—	—	—
Use of antidepressants (proportion)	9/22	—	—	—	—	—
Use of antipsychotics (proportion)	12/22	—	—	—	—	—
Use of mood stabilizers (proportion)	16/22	—	—	—	—	—
Use of benzodiazepines (proportion)	3/22	—	—	—	—	—
Lifetime presence of anxiety disorders (proportion)	9/22	—	—	—	—	—
Lifetime presence of psychosis (proportion)	9/22	—	—	—	—	—
Lifetime presence of alcohol/drug abuse or dependence disorder (proportion)	14/22	—	—	—	—	—
Current average number of days consuming alcohol per week	0.48	1.03	1.18	1.82	$t(39)=1.56$	0.13
Average number of alcoholic drinks consumed when drinking	0.73	1.24	0.97	1.06	$t(39)=0.67$	0.50

Abbreviations: S.D. = standard deviation; NART = National Adult Reading Test; HRSD-25 = 25-item Hamilton Rating Scale for Depression; YMRS = Young Mania Rating Scale. Medication load was derived for each individual using an algorithm that takes into account the number and type of medications used, as well as the dosage relative to typical prescribing practices.

[a] 1 = less than 7th grade, 2 = 7 − 9th grade, 3 = partial high school, 4 = high school diploma or GED, 5 = some college, 6 = technical school or associate's degree, 7 = college diploma, 8 = graduate or professional degree.

psychiatric illness in first- or second-degree relatives, were recruited (Table 1). All BD individuals had experienced ≥2 mood episodes in the last 4 years, were euthymic (Hamilton Depression Rating Scale (HDRS-25) (Hamilton, 1960) score ≤7 and a Young Mania Rating Scale (YMRS) (Young et al., 1978) score ≤10), and in remission (euthymic for ≥2 months at the time of scanning). All BD individuals were medicated; 64% endorsed a previous history of DSM-IV alcohol or substance abuse disorder, but the minimum reported period of abstinence was 7 months (mean:100 months); 41% a history of anxiety disorder, and 41% a history of psychotic symptoms. Groups were age- and gender-ratio-matched. All participants were right-handed, native English speakers. Handedness was assessed using the Behavioral Handedness Index (Annett, 1967).

Exclusion criteria for all participants included: history of head injury; systemic medical illness; cognitive impairment (score <24 on the Mini-mental State Examination (Folstein et al., 1975)); premorbid IQ estimate <85 using the National Adult Reading Test (Nelson, 1982); borderline personality disorder; MRI exclusion criteria (presence/questionable history of metallic objects in the body, positive pregnancy test/self-reporting of pregnancy, panicking in enclosed spaces); alcohol or substance abuse disorder during the previous 2 months (determined by SCID-P, saliva and urine screen); and task performance accuracy <70% (no BD individuals, and one control participant, were excluded for this reason). Previous lifetime history of substance abuse was an exclusion criterion for controls. Presence of rapid-cycling (≥4 illness episodes per year) or required emergency psychiatric management were additional exclusion criteria for BD individuals.

Participants were recruited using local advertisements, and were demographically representative of Pittsburgh and the surrounding area. BD individuals were recruited from the University of Pittsburgh Medical Center.

2.2. Paradigm

Participants performed the EFNBACK task during neuroimaging (Fig. 1). This task is a modified version of the *n-back* working memory task (Cohen et al., 1994). The original task includes two memory conditions with varied attentional control demands: a low-attentional control (0-back: "Press the button to a 'G'") and a high-attentional control (2-back: "Press the button whenever the current letter is identical to the letter presented two trials previously (G-X-G)") condition. The EFNBACK task comprises the original *n*-back task with additional blocks in which each trial letter is flanked by two identical face pictures (actors posing neutral, fearful, or happy expressions). Facial stimuli are grayscale male and female pictures from the NimStim facial expression series (Tottenham et al., 2009). Facial images comprise a cropped oval of 400×600 pixels, normalized for size and luminance, and aligned by eye positioning, such that all face stimuli appear at the same location. In each of three quickly-successive runs, 8 blocks are presented: two attentional load conditions (0-back, 2-back), each combined with one of the 4 face distracter conditions (no-distracter, neutral-face, fearful-face, happy-face). Each block comprises 12 500-ms trials, with intertrial interval (ITI) jittered (mean duration = 3500 ms). Task duration is 21 min, 12 s. Participants respond to target letters by pressing a button with their index finger, ignoring face distracters. Each run begins with the most simple, 0-back no-distracter block to ease participants into the task, followed by the remaining 0-back and 2-back blocks in different pseudorandomized orders for each run. At the beginning of each block, instructions are briefly presented on the screen stating whether the block will be 0-back or 2-back.

2.3. Data acquisition

Neuroimaging data were collected using a 3.0 Tesla Siemens Trio MRI scanner at the Magnetic Resonance Imaging Center in the University of Pittsburgh Medical Center. (see Supplementary Methods for data acquisition parameters).

2.4. Behavioral data analyses

Behavioral data were analyzed using SPSS 16.0 software (SPSS Inc.). We performed a mixed multivariate analysis of variance (MANOVA), with diagnostic group as the between-subjects factor, and attentional load and emotional distracter as within-subjects factors. Number of correct trials, and reaction time on correct trials were the dependent variables. The multivariate test statistic reported is Wilks' lambda. Univariate and post hoc multiple comparisons were conducted with Bonferroni corrections.

2.5. Demographic and clinical data analyses

Between-group differences among demographic and clinical variables were analyzed using independent-samples *t*-tests and non-parametric tests as appropriate (Table 1).

2.6. Neuroimaging analyses

Data were preprocessed and analyzed using Statistical Parametric Mapping software (SPM5; http://www.fil.ion.ucl.ac.uk/spm). Data were corrected for differences in acquisition time between slices, spatially normalized into a standard stereotactic space (Montreal Neurologic Institute, MNI; http://www.bic.mni.mcgill.ca), realigned and unwarped, resampled to $2\times2\times2$ mm^3 voxels, and smoothed using a 6 mm FWHM Gaussian kernel. Trials with incorrect behavioral responses were excluded from fMRI analysis. Incorrect trials were omitted because our focus was the examination of group differences in neural activity during *successful* attentional control, so as to avoid the confound of including unsuccessful trials that

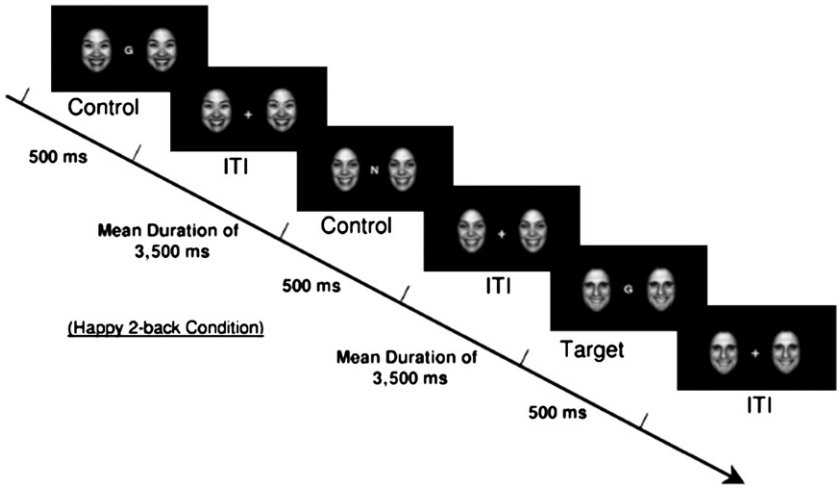

Fig. 1. The Emotional Face *N-back* (EFNBACK) task. This is an example of the 2-back (high attentional demand) happy-face distracter condition. During the 0-back (low attentional demand) condition, participants must respond to the letter M.Abbreviations: ITI = intertrial stimulus interval, ms = milliseconds Figure was reproduced with permission from (2009).

may have reflected a variety of different, non-attentional control processes (e.g., fatigue, boredom). As discussed in the Results section, task performance was strong in both groups, resulting in less than 3% of trials being excluded for controls, and less than 5% for bipolar individuals.

We used a two-level random-effects procedure to analyze fMRI data. This task had many components, but in order to test our specific hypotheses we focused on attentional control and emotion processing circuitry during: 1. attentional control; and 2. attentional control in the context of emotional distracters in euthymic BD individuals vs. controls. For 1. we examined between-group differences in neural activity during the high attentional demand (2-back) no-distracter vs. low attentional demand (0-back) no-distracter condition. For 2. we examined between-group differences in neural activity to the high attentional demand (2-back) condition with emotional face (either happy or fearful) distracters vs. non-emotional, neutral-face distracters. We also examined between-group differences in activity in attentional control neural circuitry during the high attentional demand (2-back) condition with neutral face distracters vs. no-face distracters to determine whether between-group findings for contrasts in 2. above were specific to the distracting effect of emotion (fearful vs. neutral/happy vs. neutral), or to faces in general (neutral vs. no-face). We used the WFU PickAtlas (Wake Forest University, Winston-Salem, NC) to construct anatomical masks corresponding to Talairach regions: bilateral dlPFC (BA9, BA46), parietal cortex (BA40) and dACC (BA24, BA32), as key ROIs in attentional control (Alexander and Crutcher, 1990; Bush and Shin, 2006), and attentional control in the context of emotional distracters (Dolcos et al., 2008; Erk et al., 2007). We also included as ROIs bilateral striatum (caudate nucleus, putamen and ventral striatum) and bilateral amygdalae, as representative subcortical regions in attentional control (striatum) and emotion processing (ventral striatum and amygdala) (Alexander and Crutcher, 1990).

At the first level, individual wholebrain statistical maps were constructed to evaluate each of the four main condition contrasts: 2-back no-distracter vs. 0-back no-distracter; 2-back fearful-face vs. 2-back neutral-face; 2-back happy-face vs. 2-back neutral-face; 2-back neutral-face vs. 2-back no-distracter. Movement parameters derived from realignment were included as covariates of no-interest. The effects of emotional and neutral-face distracters on activity to the 0-back condition, which is much less cognitively demanding and not expected to engage attentional control neural circuitry, were analyzed in parallel fashion to the above 2-back condition contrasts and included as supplementary data.

In a second level, random-effects group analysis in each of the ROIs described above, *t*-tests compared BD individuals and controls on each of the condition contrasts. For second level analyses, we included age as a covariate of no-interest, given evidence of age-related changes in attentional control neural circuitry (Milham et al., 2002).

We controlled for multiple comparisons in our regions of interest using the AlphaSim program (http://afni.nimh.nih.gov/afni/doc/manual/AlphaSim) with 1000 Monte Carlo simulations to compute extent thresholds corrected for family-wise error at $P<0.05$. The derived thresholds were as follows: dlPFC = 70 voxels; parietal cortex = 79 voxels; dACC = 105 voxels; amygdala = 24 voxels; striatum = 88 voxels. AlphaSim is a validated method for correction for multiple voxelwise comparisons that has previously been employed in neuroimaging studies adopting an ROI approach in studying clinical samples (e.g., Hamilton and Gotlib, 2008; Almeida et al., 2010; Hamilton et al., 2011; Matthews et al., 2011).

2.7. EC analyses

Granger Causality Mapping (GCM) was employed to examine group differences in EC between a key emotion processing region, the amygdala, and prefrontal and parietal regions during attentional control and attentional control in the context of emotional distracters. Granger Causality theory states that a discrete time series X "Granger-causes" a discrete time series Y if the past values of X improve the prediction of the current value of Y, given that all other sources of influence have been taken into account (Roebroeck et al., 2005). Owing to interregional variation in timing of the hemodynamic response, GCM may determine temporal precedence between regions in which neuronal firing is instantaneously coupled (David et al., 2008). This limitation is not relevant in analyses, such as those in the present study, examining *different* within and between-group GCM maps for multiple experimental conditions: if within- and between-group differences in connectivity patterns were due solely to hemodynamic response timing, or physiologic noise, the same pattern of within-group, and between-group differences in connectivity would be observed between neural regions across all stimulus conditions. This did not occur in the present study (see Results).

DICOM images were preprocessed using the Brain Voyager QX2.1 software package (Brain Innovation, Maastricht, The Netherlands) with the same parameters as those listed above. We chose bilateral amygdala as the seed region for EC analyses to examine functional coupling between this key emotion processing region and prefrontal and parietal regions during attentional control and attentional control in the context of emotional distracters. We used the WFU Pickatlas to create the anatomically-defined bilateral amygdala ROI.

GCM was conducted at the individual level to generate an individual *t*-statistic image of the GCM map for all controls and all BD individuals. For each Granger map, *p*-values were subjected to a multiple-comparison correction (FDR(q)<0.01) (Genovese et al., 2002) over the wholebrain, a significance threshold that ensures that, on average, the proportion of false positives among activated voxels<q. Next, GCM maps were computed at the group level, and ANOVAs were employed to compare controls and BD individuals for each 2-back distracter condition. As we were primarily interested in EC between amygdala and attentional control neural circuitry during attentional control in the context of emotional distracters, we focused on between-group differences in EC between amygdala and prefrontal and parietal cortices.

2.8. Medication

To quantify medication, commonly taken by the majority of individuals with BD (Phillips et al., 2008b), we computed a medication load for each participant, as in previous studies (Almeida et al., 2009a, 2009b; Hassel et al., 2008, 2009; Versace et al., 2008) (Supplementary Table 1). We conducted exploratory analyses of associations between medication load and activity in ROIs, and between-group differences in activity in these ROIs for BD individuals taking, vs. not taking, each of the four main psychotropic medication classes: antidepressants, antipsychotics, mood stabilizers, and benzodiazepines.

2.9. Relationships between task performance, clinical variables, and neural activity and EC

For each participant group, we extracted mean BOLD signal from ROIs showing significant between-group differences in activity for each of the main 2-back stimulus condition contrasts. We computed corresponding reaction time contrasts. Correlations were computed for each group between activity in each cluster and reaction times for corresponding stimulus conditions contrasts.

In BD individuals, we explored associations between activity in ROIs and several demographic and clinical variables: HDRS-25 total score, YMRS total score, age of illness onset, illness duration, medication load, taking vs. not-taking each of the four main classes of psychotropic medication, gender, comorbid anxiety disorder, and comorbid substance use. Analyses for each ROI were controlled for the total of thirteen multiple tests between activity and task performance, demographic and clinical variables, using Bonferroni (corrected threshold, $P<0.004$).

We performed similar exploratory analyses between demographic and clinical variables and amygdala EC, using extracted Granger connectivity values from prefrontal and parietal regions showing significant between-group differences in amygdala EC.

3. Results

3.1. Task performance

MANOVA revealed significant main effects of attentional load, $F(2,38)=20.28$, $P<0.001$, and emotional distracter condition, $F(6,34)=4.43$, $P=.0.002$. The effect of diagnostic group was non-significant, and there were no significant diagnostic group*attentional load or group*emotional distracter condition interactions, or a significant group*attentional load*emotional distracter interaction. Overall accuracy on the task was good; both groups had mean accuracies over 90% even on the more difficult 2-back conditions (Supplementary Table 2). Accuracy was lower, $F(1,39)=17.07$, $P<0.001$, partial $\eta^2=0.30$ (2-back mean = 34.04 vs. 0-back mean = 35.48), and reaction times were slower, $F(1,39)=39.41$, $P<0.001$, partial $\eta^2=0.50$ (2-back mean = 766.76 ms vs. 0-back mean = 578.15 ms), in the high vs. low attentional load condition. Reaction times were also slower, $F(3,96)=6.26$, $P<0.001$, partial $\eta^2=0.15$ (mean for emotional-face distracter conditions = 685.99 vs. no-distracter condition = 631.86 ms), but accuracy was equivalent, in the emotional face distracter vs. no-face condition. Post hoc tests indicated that reaction time in all participants was significantly slower during neutral-face ($P=0.001$, mean = 690.13 ms), fearful-face ($P=0.004$, mean = 689.41 ms) and happy-face ($P=0.001$, mean = 678.42 ms) distracters than the no-distracter condition. Accuracy did not differ significantly among the emotion face distracter conditions.

3.2. Neuroimaging findings

3.2.1. Attentional control

For the 2-back no-distracter vs. 0-back no-distracter contrast, BD individuals showed significantly *reduced* activity vs. controls in right dlPFC, right dACC, bilateral inferior parietal cortex, and right putamen ($P<0.05$, corrected; Fig. 2; Table 2).

3.2.2. Attentional control with emotional distracters

For the 2-back fearful-face vs. neutral-face distracter contrast, BD individuals showed significantly *greater* activity relative to controls in left dlPFC, bilateral inferior parietal cortex, right amygdala, and right putamen ($P<0.05$, corrected; Fig. 3; Table 3).

There were no significant between-group findings for the 2-back happy-face vs. neutral-face distracter, or neutral-face vs. no-distracter contrasts.

3.2.3. EC

To the 2-back fearful-face distracter condition, controls showed significantly greater preceding EC from rostral/dACC to amygdala than BD individuals ($t(39)=-3.40$, $P=0.002$; Fig. 4).

To the 2-back happy-face distracter condition, BD individuals showed significantly greater preceding EC from rostral/dACC to amygdala than controls ($t(39)=2.83$, $P=0.007$; Fig. 4). There were no significant between-group differences in amygdala EC to the 2-back neutral-face or no-distracter conditions.

3.2.4. Task performance, clinical variables, and neural activity and EC

For BD individuals, activity in left parietal cortex to the 2-back fearful-face vs. neutral-face condition was negatively associated with age of illness onset ($r=-0.614$, $P=0.002$). No other relationships between clinical, demographic, medication or reaction time variables and activity or EC in any of the clusters showing between-group differences in activity survived Bonferroni correction (see Supplementary Analyses for the small number of exploratory findings at $P<0.05$ not meeting Bonferroni thresholds).

4. Discussion

We aimed to identify functional abnormalities in neural circuitry supporting attentional control and attentional control in the context of emotional distracters in euthymic BD individuals using an emotional n-back task. During the no-distracter attentional control condition, BD individuals showed reduced activity vs. controls in fronto-cingulo-parietal regions, consistent with previous studies using different attentional control paradigms (Blumberg et al., 2003; Gruber et al., 2004; Kronhaus et al., 2006; Lagopoulos et al., 2007; Monks et al., 2004; Strakowski et al., 2005). Furthermore, BD individuals vs. controls had the opposite pattern of *elevated* activity in this circuitry, and in amygdala and striatum, for modulation of attention in the presence of distracting negative emotional stimuli (fearful vs. neutral faces), but not positive (happy vs. neutral faces), or neutral-face distracters per se. These findings are consistent with some of the few studies in BD individuals of attentional control in the context of emotional distracters, that show greater activity in dlPFC, dACC, and vmPFC in BD individuals vs. controls (Deckersbach et al., 2008; Elliott et al., 2004; Wessa et al., 2007). While BD individuals showed significantly *reduced* preceding "top–down" EC from rostral/dACC to amygdala vs. controls during the 2-back fearful-face condition, during attentional control in the presence of happy distracters, BD individuals showed *greater* preceding rostral/dACC-amygdala EC than controls.

In the current study, the addition of negative, but not positive, emotional distracters resulted in abnormal recruitment of attentional control circuitry in BD individuals, yet both distracter types elicited abnormal patterns of rostral/dACC-amygdala EC. Our findings may thus indicate a two-stage response to maintain attentional control and diminish emotional response in the amygdala in the presence of emotionally salient distracters in BD individuals. The first strategy involves strengthening top–down connectivity between the ACC and amygdala. This strategy appears to have been implemented successfully by our BD participants in the context of happy-face distracters, given the lack of abnormal activity or impaired task performance. When there is a failure of top–down connectivity between the ACC and amygdala, BD individuals appear to implement a second strategy, however, which involves increasing recruitment of attentional control circuitry. This seemingly less-efficient strategy, which our BD participants exhibited in response to fearful-face distracters, did not prevent significant amygdala activation in these individuals. These findings thus suggest that for BD individuals, negatively valenced social stimuli may be more distracting, and therefore require greater recruitment of attentional control neural circuitry than positively-valenced social stimuli, to equate task performance with that shown by healthy individuals.

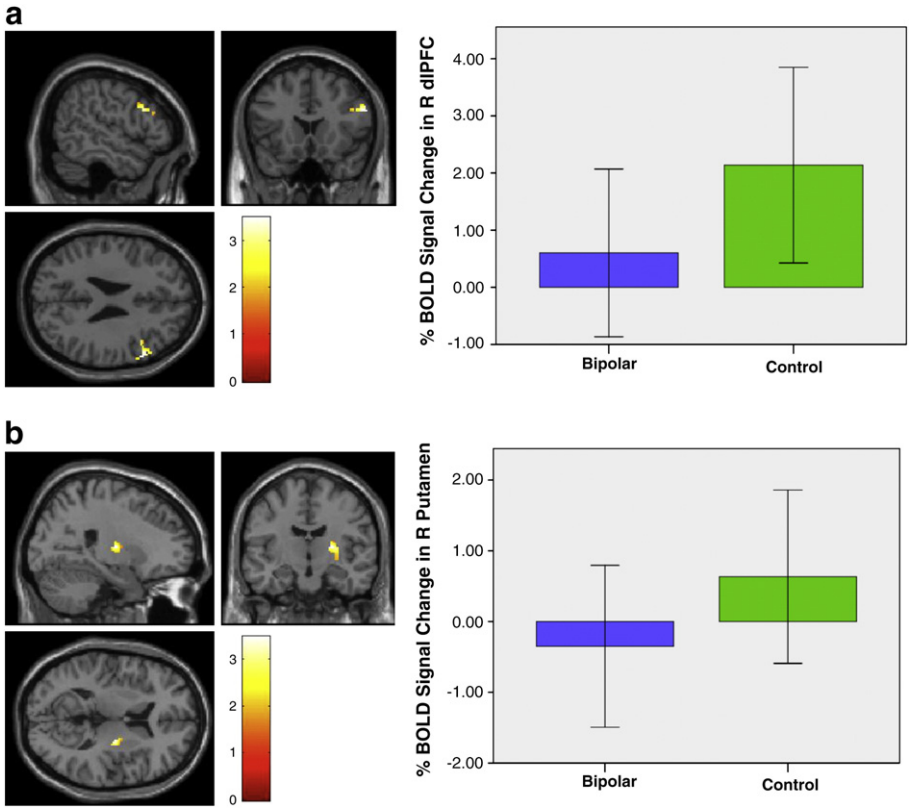

Fig. 2. Significantly reduced activity in BD individuals relative to controls during the high vs. low attentional control condition without face distracters in (a) right dorsolateral prefrontal cortex (175 voxels, [peak voxel = 56, 18, 27], and (b) right putamen (125 voxels, [peak voxel = 23, −13, 12]. Graphs represent activity in each region during the 2-back high attentional demand no-distracters condition relative to the 0-back low attentional demand no-distracters condition. Individual bars represent mean group BOLD signal change, and error bars represent standard deviations. Between group differences were significant using corrected regional thresholds (clusterwise) at $P<0.05$. Abbreviations: BD = individuals with bipolar disorder, HC = healthy control individuals, R = Right, L = Left, dlPFC = dorsolateral prefrontal cortex.

Greater activity in attentional control neural circuitry among BD individuals has been conceptualized as a compensatory response to overcome otherwise impaired attentional control (Elliott et al., 2004; Wessa et al., 2007). In the current study, BD individuals exhibited equivalent task performance, despite aberrant patterns of activity and connectivity. It is possible that a ceiling effect may exist, such that with a greater attentional load, e.g., a more taxing 3-back or 4-back memory task, or more potent emotional distracters, no further recruitment of attentional control neural circuitry would be possible, resulting in BD individuals being unable to orient away from distracters to maintain performance. In real-world situations, in which cognitive and emotional demands far surpass those in our experimental paradigm, the ability to efficiently modulate attention is critical to avoid engaging with emotional contexts that may interfere with goal-directed behavior. Thus, the patterns of abnormal activity and EC to emotional distracters we detected may signal risk for significant emotion dysregulation in the real world, when BD individuals are confronted with distracting stimuli of a positive (e.g., perceived praise) or negative (e.g., perceived criticism) valence. Furthermore, it is important to consider that our participants with BD were in remission; in the context of a manic or depressed mood episode, deficiencies in the ability to flexibly modulate attention may be exacerbated, and may perpetuate abnormal mood by restricting attention to mood-congruent stimuli in the environment.

Table 2
Between group differences during high vs. low attentional control conditions without emotional face distracters. Region of interest analyses, with a voxelwise threshold of $P<0.05$, corrected for multiple comparisons using AlphaSim Monte Carlo simulations. Each line in the table represents the voxel of peak activity difference within the specified region. None of the regions of interest showed greater activity in BD individuals than HC in the attentional control condition.

			Talairach coordinates				
Region	BA	*k*	*x*	*y*	*z*	*t*	*P* value
Attentional control: 2-back no-distracter vs. 0-back no-distracter							
BD individuals<Controls							
Right dorsolateral prefrontal cortex	9	175	56	18	27	3.49	0.001
Right anterior cingulate cortex	31	55	8	−7	46	2.93	0.002
Right inferior parietal cortex	40	354	53	−38	46	3.85	<0.001
Left inferior parietal cortex	40	306	−46	−47	41	3.30	0.001
Right putamen		125	23	−13	12	3.49	0.001

Abbreviations: BA = Brodmann area; *k* = cluster size in voxels.

Our findings provide an interesting parallel to structural and structural connectivity studies in BD. Investigations of structural abnormalities among BD individuals have generally provided inconsistent results, yet three recent meta-analyses reported decreased gray matter in attentional control circuitry among BD individuals, specifically within dlPFC (Houenou et al., 2011) and ACC (Bora et al., 2010; Ellison-Wright and Bullmore, 2010; Houenou et al., 2011). Meanwhile, diffusion tensor imaging studies have reported abnormalities in white matter tracts linking emotion processing and prefrontal cortical regions among BD individuals (Benedetti et al., 2011; Lin et al., 2011; Versace et al., 2008) relative to controls. Thus, our findings of abnormal activity and EC in attentional control neural circuitry may in part reflect abnormal underlying morphology and white matter connectivity in

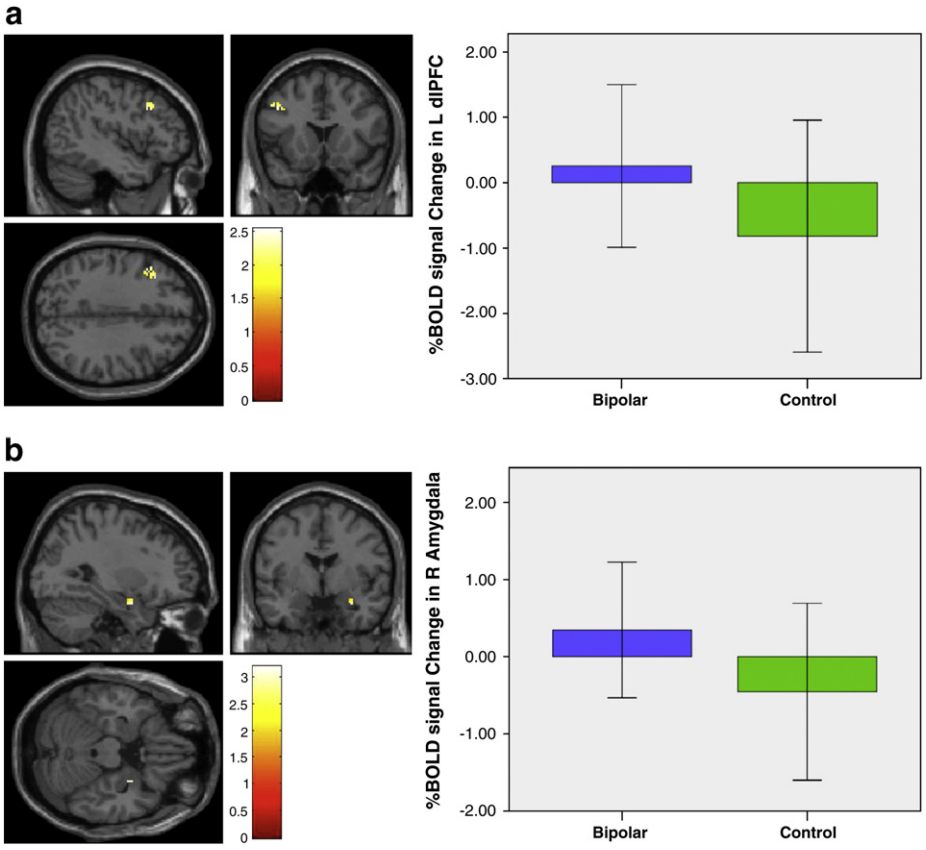

Fig. 3. Significantly greater activity in BD individuals relative to controls during the 2-back high attentional demand condition with fearful-face vs. neutral-face distracters in (a) left dorsolateral prefrontal cortex (74 voxels, [peak voxel = −45, 18, 36], and (b) right amygdala (11 voxels, [peak voxel = 29, −7, −15]. Graphs represent activity in each region during the 2-back high attentional demand with fearful-face distracters relative to the neutral-face distracter condition. Individual bars represent mean group BOLD signal change, and error bars represent standard deviations. Between group differences were significant using corrected regional thresholds (clusterwise) at $P<0.05$. Abbreviations: BD = individuals with bipolar disorder, HC = healthy control individuals, R = Right, L = Left, dlPFC = dorsolateral prefrontal cortex.

this circuitry in individuals with BD. The relationship between structure and functional activation is not yet well established, however.

All BD individuals were between mood episodes, yet many were still experiencing subthreshold mood symptoms. Persistence of low-level mood disturbance during inter-episode periods is a well-documented feature of bipolar I disorder (Judd et al., 2002). While there were no significant relationships between depression and mania severity and activity or EC measures, it is still possible that residual mood symptoms may have influenced patterns of abnormal activity and EC to happy and fearful face distracters.

In our exploratory analyses, we found a negative association between activity in left parietal cortex to the 2-back fearful-face vs. neutral-face condition and age of illness onset, suggesting that earlier onset of bipolar disorder was associated with more abnormally elevated activity in this region during the high attentional demand condition with fearful-face distracters. This is consistent with reports that earlier illness onset confers a more severe and chronic course in bipolar disorder (Wilcutt and McQueen, 2010).

There are limitations of this study. First, nearly all BD individuals were taking psychotropic medications. Maintenance treatment with mood stabilizing medication between episodes is necessary for most BD individuals (Goodwin and Jamison, 2007). Recruiting an unmedicated remitted sample is therefore difficult and potentially unrepresentative of the BD population. In this study, psychotropic medication use was initially associated with abnormalities in activity and EC in bipolar individuals using a lenient threshold of $P<0.05$, but not after applying a Bonferroni correction for multiple comparisons. Thus it is difficult to consider this finding given the large number of tests performed. Nonetheless, further examination of the effects of psychotropic medications on neural activity in BD during performance of cognitive and affective tasks is needed. Many BD individuals had comorbid Axis-I disorders but exploratory

Table 3
Between group differences during attentional control in the context of emotional distracters. Region of interest analyses, with a voxelwise threshold of $P<0.05$, corrected for multiple comparisons using AlphaSim Monte Carlo simulations. Each line in the table represents the voxel of peak activity difference within the specified region. No regions exceeded AlphaSim thresholds for the happy vs. neutral-face or neutral vs. no-distracter contrasts.

Region	BA	*k*	Talairach coordinates			*t*	*P* value
			x	*y*	*z*		
Attentional control with emotional distracters: 2-back fearful-face vs. 2-back neutral-face							
BD individuals > Controls							
Left dorsolateral prefrontal cortex	9	74	−45	18	36	2.92	0.003
Left inferior parietal cortex	40	132	−50	−59	43	2.70	0.003
Right inferior parietal cortex	40	95	47	−44	53	2.59	0.007
Right amygdala		11	29	−7	−15	2.78	0.003
Right putamen		305	23	8	11	3.70	<0.001

Abbreviations: BA = Brodmann area; *k* = cluster size in voxels.

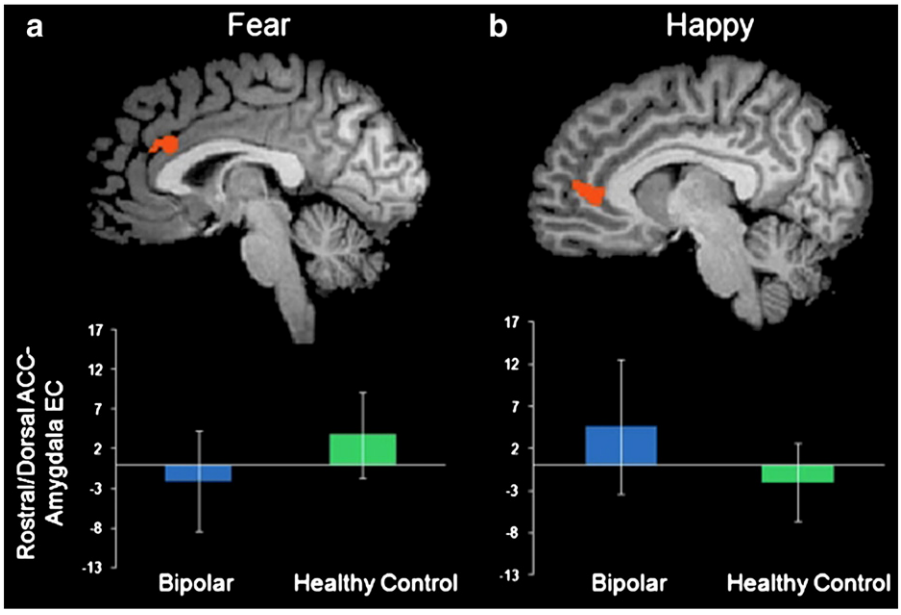

Fig. 4. Group differences in effective connectivity during attentional control in the context of emotional distracters. Using Granger Causality Mapping (GCM), BD individuals exhibited (a) significantly reduced preceding "top–down" effective connectivity from rostral/dorsal anterior cingulate cortex (ACC; peak voxel = −1, 25, 27; 48 voxels) to the amygdala vs. controls during the 2-back fearful-face distracter condition; and (b) significantly greater preceding "top–down" effective connectivity from rostral/dorsal ACC to the amygdala (peak voxel = 5, 40, 12; 55 voxels) vs. controls during the 2-back happy-face distracter condition (shown as the red clusters). The Granger map was corrected (FDR(q)<0.01) at the whole brain level.

analyses did not reveal any significant differences in neural activity or EC between BD individuals with, vs. those without, comorbid substance use or anxiety.

Our present findings provide insights into potential pathophysiologic processes underlying emotion dysregulation in BD, highlighting the role of functional abnormalities in attentional control neural circuitry, and connectivity between this circuitry and the amygdala. Future studies should examine neural circuitry supporting attentional control in the context of emotional distracters in BD individuals during different mood states, to determine whether abnormal activity and EC in this circuitry represents persistent trait, rather than mood-state dependent, features of the illness, and if these abnormalities are associated with future illness course.

Acknowledgments

This study was supported by grant R01 MH076971 from the National Institutes of Health (Dr. Phillips), T32 grants HL082610 (Dr. Mullin) and MH18951 (Dr. Perlman), a NARSAD (National Alliance for Research on Schizophrenia and Depression) Young Investigator Award (Dr. Versace), a KO1 MH083001 from the National Institute of Mental Health, and a NARSAD Young Investigator Award (Dr. Ladouceur).

Appendix A. Supplementary data

Supplementary data to this article can be found online at doi:10.1016/j.pscychresns.2011.09.002.

References

Adler, C.M., Holland, S.K., Schmithorst, V., Tuchfarber, M.J., Strakowski, S.M., 2004. Changes in neuronal activation in patients with bipolar disorder during performance of a working memory task. Bipolar Disorders 6 (6), 540–549.

Alexander, G.E., Crutcher, M.D., 1990. Functional architecture of basal ganglia circuits: neural substrates of parallel processing. Trends in Neurosciences 13 (7), 266–271.

Almeida, J.R.C., Mechelli, A., Hassel, S., Versace, A., Kupfer, D.J., Phillips, M.L., 2009a. Abnormally increased effective connectivity between parahippocampal gyrus and ventromedial prefrontal regions during emotion labeling in bipolar disorder. Psychiatry Research: Neuroimaging 174 (3), 195–201.

Almeida, J.R.C., Versace, A., Mechelli, A., Hassel, S., Quevedo, K., Kupfer, D.J., Phillips, M.L., 2009b. Abnormal amygdala-prefrontal effective connectivity to happy faces differentiates bipolar from major depression. Biological Psychiatry 66 (5), 451–459.

Almeida, J.R.C., Versace, A., Hassel, S., Kupfer, D.J., Phillips, M.L., 2010. Elevated amygdala activity to sad facial expressions: a state marker of bipolar but not unipolar depression. Biological Psychiatry 67 (5), 414–421.

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. The American Journal of Psychiatry 162 (6), 1211–1213.

Annett, M., 1967. The binomial distribution of right, mixed and left handedness. Quarterly Journal of Experimental Psychology 19, 327–333.

Benedetti, F., Yeh, P.-H., Bellani, M., Radaelli, D., Nicoletti, M.A., Poletti, S., Falini, A., Dallaspezia, S., Colombo, C., Scotti, G., Smeraldi, E., Soares, J.C., Brambilla, P., 2011. Disruption of white matter integrity in bipolar depression as a possible structural marker of illness. Biological Psychiatry 69 (4), 309–317.

Bishop, S., Duncan, J., Brett, M., Lawrence, A.D., 2004. Prefrontal cortical function and anxiety: controlling attention to threat-related stimuli. Nature Neuroscience 7 (2), 184–188.

Blumberg, H.P., Leung, H.-C., Skudlarski, P., Lacadie, C.M., Fredericks, C.A., Harris, B.C., Charney, D.S., Gore, J.C., Krystal, J.H., Peterson, B.S., 2003. A functional magnetic resonance imaging study of bipolar disorder: state- and trait-related dysfunction in ventral prefrontal cortices. Archives of General Psychiatry 60 (6), 601–609.

Bora, E., Fornito, A., Yücel, M., Pantelis, C., 2010. Voxelwise meta-analysis of gray matter abnormalities in bipolar disorder. Biological Psychiatry 67 (11), 1097–1105.

Braver, T.S., Reynolds, J.R., Donaldson, D.I., 2003. Neural mechanisms of transient and sustained cognitive control during task switching. Neuron 39 (4), 713–726.

Bush, G., Shin, L.M., 2006. The Multi-Source Interference Task: an fMRI task that reliably activates the cingulo-frontal–parietal cognitive/attention network. Nature Protocols 1 (1), 308–313.

Chepenik, L.G., Raffo, M., Hampson, M., Lacadie, C., Wang, F., Jones, M.M., Pittman, B., Skudlarski, P., Blumberg, H.P., 2010. Functional connectivity between ventral prefrontal cortex and amygdala at low frequency in the resting state in bipolar disorder. Psychiatry Research: Neuroimaging 182 (3), 207–210.

Clark, L., Iversen, S.D., Goodwin, G.M., 2002. Sustained attention deficit in bipolar disorder. The British Journal of Psychiatry 180 (4), 313–319.

Clark, L., Kempton, M.J., Scarnà, A., Grasby, P.M., Goodwin, G.M., 2005. Sustained attention-deficit confirmed in euthymic bipolar disorder but not in first-degree relatives of bipolar patients or euthymic unipolar depression. Biological Psychiatry 57 (2), 183–187.

Cohen, J.D., Forman, S.D., Braver, T.S., Casey, B.J., Servan-Schreiber, D., Noll, D.C., 1994. Activation of the prefrontal cortex in a nonspatial working memory task with functional MRI. Human Brain Mapping 1 (4), 293–304.

David, O., Guillemain, I., Saillet, S., Reyt, S., Deransart, C., Segebarth, C., Depaulis, A., 2008. Identifying neural drivers with functional MRI: an electrophysiological validation. PLoS Biology 6 (12), e315.

Deckersbach, T., Rauch, S.L., Buhlmann, U., Ostacher, M.J., Beucke, J.-C., Nierenberg, A.A., Sachs, G., Dougherty, D.D., 2008. An fMRI investigation of working memory and

sadness in females with bipolar disorder: a brief report. Bipolar Disorders 10 (8), 928–942.
Dolcos, F., McCarthy, G., 2006. Brain systems mediating cognitive interference by emotional distraction. Journal of Neuroscience 26 (7), 2072–2079.
Dolcos, F., Diaz-Granados, P., Wang, L., McCarthy, G., 2008. Opposing influences of emotional and non-emotional distracters upon sustained prefrontal cortex activity during a delayed-response working memory task. Neuropsychologia 46 (1), 326–335.
Elliott, R., Ogilvie, A., Rubinsztein, J.S., Calderon, G., Dolan, R.J., Sahakian, B.J., 2004. Abnormal ventral frontal response during performance of an affective go/no go task in patients with mania. Biological Psychiatry 55 (12), 1163–1170.
Ellison-Wright, I., Bullmore, E., 2010. Anatomy of bipolar disorder and schizophrenia: a meta-analysis. Schizophrenia Research 117 (1), 1–12.
Erk, S., Kleczar, A., Walter, H., 2007. Valence-specific regulation effects in a working memory task with emotional context. NeuroImage 37 (2), 623–632.
Etkin, A., Egner, T., Peraza, D.M., Kandel, E.R., Hirsch, J., 2006. Resolving emotional conflict: a role for the rostral anterior cingulate cortex in modulating activity in the amygdala. Neuron 51 (6), 871–882.
First, M., Spitzer, R., Gibbon, M., Williams, J., 1995. Structured Clinical Interview for DSM-IV Axis I Disorders, Version 2.0. Biometric Research Department, New York State Psychiatric Institute, New York.
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 (1), 27–37.
Folstein, M.F., Folstein, S.E., McHugh, P.R., 1975. "Mini-Mental State": a practical method for grading the cognitive state of patients for the clinician. Journal of Psychiatric Research 12, 189–198.
Gazzaley, A., 2010. Influence of early attentional modulation on working memory. Neuropsychologia 49 (6), 1410–1424.
Genovese, C.R., Lazar, N.A., Nichols, T., 2002. Thresholding of statistical maps in functional neuroimaging using the false discovery rate. NeuroImage 15 (4), 870–878.
Goldstein, M., Brendel, G., Tuescher, O., Pan, H., Epstein, J., Beutel, M., Yang, Y., Thomas, K., Levy, K., Silverman, M., Clarkin, J., Posner, M., Kernberg, O., Stern, E., Silbersweig, D., 2007. Neural substrates of the interaction of emotional stimulus processing and motor inhibitory control: an emotional linguistic go/no-go fMRI study. NeuroImage 36 (3), 1026–1040.
Goodwin, F., Jamison, K.R., 2007. Manic-Depressive Illness: Bipolar Disorders and Recurrent Depression, 2nd ed. Oxford University Press, USA.
Gruber, S.A., Rogowska, J., Yurgelun-Todd, D.A., 2004. Decreased activation of the anterior cingulate in bipolar patients: an fMRI study. Journal of Affective Disorders 82 (2), 191–201.
Hamilton, M., 1960. A rating scale for depression. Journal of Neurology, Neurosurgery, and Psychiatry 23, 56–62.
Hamilton, J.P., Gotlib, I.H., 2008. Neural substrates of increased memory sensitivity for negative stimuli in major depression. Biological Psychiatry 63 (12), 1155–1162.
Hamilton, J.P., Chen, G., Thomason, M.E., Schwartz, M.E., Gotlib, I.H., 2011. Investigating neural primacy in Major Depressive Disorder: multivariate Granger causality analysis of resting-state fMRI time-series data. Molecular Psychiatry 16 (7), 763–772.
Hassel, S., Almeida, J.R., 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 (8), 916–927.
Hassel, S., Almeida, J.R., Frank, E., Versace, A., Nau, S.A., Klein, C.R., Kupfer, D.J., Phillips, M.L., 2009. Prefrontal cortical and striatal activity to happy and fear faces in bipolar disorder is associated with comorbid substance abuse and eating disorder. Journal of Affective Disorders 118 (1), 19–27.
Houenou, J., Frommberger, J., Carde, S., Glasbrenner, M., Diener, C., Leboyer, M., Wessa, M., 2011. Neuroimaging-based markers of bipolar disorder: evidence from two meta-analyses. Journal of Affective Disorders 132 (3), 344–355.
Judd, L.L., Akiskal, H.S., Schetteler, P.J., Endicott, J., Maser, J., Solomon, D.A., Leon, A.C., Rice, J.A., Keller, M.B., 2002. The long-term natural history of the weekly symptomatic status of bipolar I disorder. Archives of General Psychiatry 59 (6), 530–537.
Kerestes, R., Ladouceur, C.D., Meda, S., Nathan, P.J., Blumberg, H.P., Maloney, K., Ruf, B., Saricicek, A., Pearlson, G.D., Bhagwagar, Z., Phillips, M.L., 2012. Abnormal prefrontal activity subserving attentional control of emotion in remitted depressed patients during a working memory task with emotional distracters. Psychological Medicine 42 (1), 29–40. doi:10.1017/S0033291711001097.
Kronhaus, D.M., Lawrence, N.S., Williams, A.M., Frangou, S., Brammer, M.J., Williams, S.C., Andrew, C.M., Phillips, M.L., 2006. Stroop performance in bipolar disorder: further evidence for abnormalities in the ventral prefrontal cortex. Bipolar Disorders 8, 28–39.
Ladouceur, C.D., Silk, J.S., Dahl, R.E., Ostapenko, L., Kronhaus, D.M., Phillips, M.L., 2009. Fearful faces influence attentional control processes in anxious youth and adults. Emotion 9 (6), 855–864.
Lagopoulos, J., Malhi, G.S., 2007. A functional magnetic resonance imaging study of emotional Stroop in euthymic bipolar disorder. NeuroReport 18 (15), 1583–1587.
Lagopoulos, J., Ivanovski, B., Malhi, G.S., 2007. An event-related functional MRI study of working memory in euthymic bipolar disorder. Journal of Psychiatry & Neuroscience 32 (3), 174–184.
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 (6), 578–587.
Lin, F., Weng, S., Xie, B., Wu, G., Lei, H., 2011. Abnormal frontal cortex white matter connections in bipolar disorder: a DTI tractography study. Journal of Affective Disorders 131 (1), 299–306.
Luo, Q., Mitchell, D., Jones, M., Mondillo, K., Vythilingam, M., Blair, R.J.R., 2007. Common regions of dorsal anterior cingulate and prefrontal–parietal cortices provide attentional control of distracters varying in emotionality and visibility. NeuroImage 38 (3), 631–639.
Maalouf, F.T., Klein, C., Clark, L., Sahakian, B.J., Labarbara, E.J., Versace, A., Hassel, S., Almeida, J.R.C., Phillips, M.L., 2010. Impaired sustained attention and executive dysfunction: bipolar disorder versus depression-specific markers of affective disorders. Neuropsychologia 48 (6), 1862–1868.
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.
Martínez-Arán, A., Vieta, E., Colom, F., Torrent, C., Reinares, M., Goikolea, J.M., Benabarre, A., Comes, M., Sánchez-Moreno, J., 2005. Do cognitive complaints in euthymic bipolar patients reflect objective cognitive impairment? Psychotherapy and Psychosomatics 74 (5), 295–302.
Matthews, S.C., Strigo, I.A., Simmons, A.N., O'Connell, R.M., Reinhardt, L.E., Moseley, S.A., 2011. A multimodal imaging study in U.S. veterans of Operations Iraqi and Enduring Freedom with and without major depression after blast-related concussion. NeuroImage 54 (Suppl 1), S69–S75.
Milham, M.P., Erickson, K.I., Banich, M.T., Kramer, A.F., Webb, A., Wszalek, T., Cohen, N.J., 2002. Attentional control in the aging brain: insights from an fMRI study of the Stroop task. Brain and Cognition 49 (3), 277–296.
Monks, P.J., Thompson, J.M., Bullmore, E.T., Suckling, J., Brammer, M.J., Williams, S.C., Simmons, A., Giles, N., Lloyd, A.J., Harrison, C.L., Seal, M., Murray, R.M., Ferrier, I.N., Young, A.H., Curtis, V.A., 2004. A functional MRI study of working memory task in euthymic bipolar disorder: evidence for task-specific dysfunction. Bipolar Disorders 6 (6), 550–564.
Nagahama, Y., Okada, T., Katsumi, Y., Hayashi, T., Yamauchi, H., Oyanagi, C., Konishi, J., Fukuyama, H., Shibasaki, H., 2001. Dissociable mechanisms of attentional control within the human prefrontal cortex. Cerebral Cortex 11 (1), 85–92.
Nelson, H., 1982. National Adult Reading Test (NART): Test Manual. NFER-Nelson, Windsor, UK.
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 (5), 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, 833–857.
Phillips, M.L., Travis, M.J., Fagiolini, A., Kupfer, D.J., 2008b. Medication effects in neuroimaging studies of bipolar disorder. The American Journal of Psychiatry 165 (3), 313–320.
Roebroeck, A., Formisano, E., Goebel, R., 2005. Mapping directed influence over the brain using Granger causality and fMRI. NeuroImage 25 (1), 230–242.
Strakowski, S.M., Adler, C.M., Holland, S.K., Mills, N., DelBello, M.P., 2004. A preliminary fMRI study of sustained attention in euthymic, unmedicated bipolar disorder. Neuropsychopharmacology 29 (9), 1734–1740.
Strakowski, S.M., Adler, C.M., Holland, S.K., Mills, N.P., DelBello, M.P., Eliassen, J.C., 2005. Abnormal fMRI brain activation in euthymic bipolar disorder patients during a counting stroop interference task. The American Journal of Psychiatry 162 (9), 1697–1705.
Strakowski, S.M., Eliassen, J.C., Lamy, M., Cerullo, M.A., Allendorfer, J.B., Madore, M., Lee, J.-H., Welge, J.A., DelBello, M.P., Fleck, D.E., 2011. Functional magnetic resonance imaging brain activation in bipolar mania: evidence for disruption of the ventrolateral prefrontal-amygdala emotional pathway. Biological Psychiatry 69 (4), 381–388.
Thermenos, H.W., Goldstein, J.M., Milanovic, S.M., Whitfield-Gabrieli, S., Makris, N., LaViolette, P., Koch, J.K., Faraone, S.V., Tsuang, M.T., Buka, S.L., Seidman, L.J., 2010. An fMRI study of working memory in persons with bipolar disorder or at genetic risk for bipolar disorder. American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics 153B (1), 120–131.
Thompson, J.M., Gray, J.M., Hughes, J.H., Watson, S., Young, A.H., Ferrier, I.N., 2007. Impaired working memory monitoring in euthymic bipolar patients. Bipolar Disorders 9 (5), 478–489.
Tottenham, N., Tanaka, J.W., Leon, A.C., McCarry, T., Nurse, M., Hare, T.A., Marcus, D.J., Westerlund, A., Casey, B., Nelson, C., 2009. The NimStim set of facial expressions: judgments from untrained research participants. Psychiatry Research 168 (3), 242–249.
Townsend, J., Bookheimer, S.Y., Foland-Ross, L.C., Sugar, C.A., Altshuler, L.L., 2010. fMRI abnormalities in dorsolateral prefrontal cortex during a working memory task in manic, euthymic and depressed bipolar subjects. Psychiatry Research: Neuroimaging 182 (1), 22–29.
Urry, H.L., van Reekum, C.M., Johnstone, T., Kalin, N.H., Thurow, M.E., Schaefer, H.S., Jackson, C.A., Frye, C.J., Greischar, L.L., Alexander, A.L., Davidson, R.J., 2006. Amygdala and ventromedial prefrontal cortex are inversely coupled during regulation of negative affect and predict the diurnal pattern of cortisol secretion among older adults. Journal of Neuroscience 26 (16), 4415–4425.
Versace, A., Almeida, J.R.C., 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 (9), 1041–1052.
Wang, F., Kalmar, J.H., He, Y., Jackowski, M., Chepenik, L.G., Edmiston, E.E., Tie, K., Gong, G., Shah, M.P., Jones, M., 2009. Functional and structural connectivity between the perigenual anterior cingulate and amygdala in bipolar disorder. Biological Psychiatry 66 (5), 516–521.

Wessa, M., Houenou, J., Paillere-Martinot, M.L., Berthoz, S., Artiges, E., Leboyer, M., Martinot, J.-L., 2007. Fronto-striatal overactivation in euthymic bipolar patients during an emotional go/nogo task. The American Journal of Psychiatry 164 (4), 638–646.
Wilcutt, E., McQueen, M., 2010. Genetic and environmental vulnerability to bipolar spectrum disorders. In: Miklowitz, D.J., Cicchetti, D. (Eds.), Understanding Bipolar Disorder: A Developmental Psychopathology Perspective. The Guilford Press, New York, pp. 225–258.
World Health Organization, 2004. The Global Burden of Disease: 2004 Update. Geneva, Switzerland.
Young, R.C., Biggs, J.T., Ziegler, V.E., Meyer, D.A., 1978. A rating scale for mania: reliability, validity, and sensitivity. The British Journal of Psychiatry 133, 429–435.