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Cognitive generation of affect in bipolar depression: an fMRI study

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Abstract

Individuals with bipolar disorder manifest the full spectrum of emotions ranging from depression to mania. In attempting to understand the functional substrates of mood we attempted to identify brain regions associated with the cognitive generation of affect in bipolar depressed patients. We therefore examined ten depressed female subjects with bipolar affective disorder, and ten age-matched and sex-matched healthy comparison subjects using functional magnetic resonance imaging (fMRI) while viewing alternating blocks of captioned pictures designed to evoke negative, positive or no affective change. The activation paradigm involved the presentation of the same visual materials over three experiments alternating (experiment 1) negative and reference; (experiment 2) positive and reference and (experiment 3) positive and negative captioned pictures. The stimuli produced activation in both patients and comparison subjects in brain regions previously implicated in the generation and modulation of affect, in particular the prefrontal and anterior cingulate cortices. The activation in patients, when compared with healthy subjects, involved additional subcortical regions, in particular the amygdala, thalamus, hypothalamus and medial globus pallidus. Patients and comparison subjects displayed differential sensitivity to affective change with negative (experiment 1) and positive (experiment 2) affect induction producing converse patterns of activation. We conclude that bipolar depressed patients perhaps recruit additional subcortical limbic systems for emotional evaluation and this may reflect state-related or trait-related dysfunction. The differential patterns of activation inform us about bipolar depression and have potential diagnostic and therapeutic significance.

Introduction

Bipolar depression

Bipolar disorder, also referred to as manic-depressive illness, is a common psychiatric condition, characterized by periods of mania and or hypomania interspersed amongst episodes of depression (Mitchell & Malhi, 2002). Traditionally, diagnostic distinction and treatment have focused on the manic phase of the disorder, even though bipolar depression (BD) is its predominant mood state (Malhi *et al*., 2003). Like major depression, BD is characterized by poor affective and cognitive control, and may be driven by stressful life events (Goodwin & Jamison, 1990). There are however, phenomenological differences between these two depressive disorders (Mitchell & Malhi, 2004), suggesting pathophysiological separation that can perhaps be elucidated using neuroimaging technology. Patients with BD are more likely to manifest signs of psychomotor retardation; melancholic symptoms such as worthlessness, unvarying mood and marked anhedonia; 'atypical' depressive symptoms such as hypersomnia and leaden paralysis; a past history of psychotic depression and the absence of tearfulness, anxiety, initial insomnia and tendency to blame others (Mitchell *et al*., 2001). Therefore, in this study we have attempted to identify the key brain regions in bipolar depressed patients associated with the generation of both positive and negative affect. However, the investigation of the pathophysiology of mood disorders requires some appreciation of the neurobiology of emotion.

Emotion circuits

The perception of emotion initially involves identification of the emotional significance of a stimulus to which the individual then responds by producing of an affective state and emotional behaviour. This process is carefully monitored and closely regulated allowing for the generation of complex emotions (Damasio, 1999; Critchley, 2003). It has been proposed that these various functions are subserved by two neural systems (Phillips *et al*., 2003a). A ventral system that comprises the insula, amygdala, ventral striatum and ventral regions of the anterior cingulate and prefrontal cortex, and a dorsal system that consists of the hippocampus and dorsal regions of the anterior cingulate gyrus and prefrontal cortex. The ventral system is thought to be responsible for the appraisal of emotional input, the production of an affective state and the regulation of autonomic responses whereas the dorsal system is involved in effortful regulation of affective states.

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Neural circuits, comprising projections connecting prefrontal regions to striatal structures with further projections to thalamic nuclei, underpin these emotion-generating functional systems that regulate cognitive, emotional and social behaviour (Cummings, 1993). Dysfunction in these limbic brain networks is thought to result in major depressive and bipolar disorders as shown by neuroimaging studies (Soares & Mann, 1997; Strakowski *et al*., 2000).

Structural neuroimaging findings

Volumetric studies of patients with major depression and bipolar disorder (reviewed in Soares & Mann, 1997; Strakowski *et al*., 2002; Sheline, 2003) suggest that in comparison to healthy controls, prefrontal and subgenual cingulate volumes are reduced in both (Drevets *et al*., 1997; Hirayasu *et al*., 1999; Lopez-Larson *et al*., 2002) and that in contrast, subcortical and medial temporal structures, such as the basal ganglia and amygdala, are smaller in unipolar depressed patients but enlarged in patients with bipolar disorder (Altshuler *et al*., 1998, 2000; Strakowski *et al*., 1999). The phenotypic separation of changes and the fact that in bipolar disorder these are independent of phase, suggests that prefrontal cortical deficits are shared but that divergent subcortical changes contribute to clinical distinction. Volume loss, hippocampal in particular, has been associated with recurrent depressive episodes (Bell-McGinty *et al*., 2002; MacQueen *et al*., 2003) and may be the consequence of glucocorticoid neurotoxicity (Sapolsky, 2000). The converse, volume increase is more difficult to explain, however, subgenual cingulate volume has been shown to increase with long-term lithium administration (Manji & Lenox, 2000; Harrison, 2002) suggesting that volume changes in either direction are possible and that structural findings need functional corroboration.

Functional neuroimaging findings

Early functional neuroimaging studies (reviewed in Ketter. *et al*., 1996) that measured regional cerebral blood flow (rCBF) and glucose metabolism (rCMRglu) in patients with major depression and bipolar disorder frequently reported 'hypofrontality', a finding recently replicated in treatment-resistant bipolar depressed patients (Ketter *et al*., 2001). This suggests that prefrontal hypometabolism may be a neural substrate for depression, independent of aetiology and subtype. A finding that is supported by decreased prefrontal cortex activity (rCBF and rCMRglu), with corresponding grey matter volume reduction, ventral to the genu of the corpus callosum in familial unipolar and bipolar depressed patients (Drevets *et al*., 1997). These studies strongly implicate the prefrontal cortex in the pathophysiology of depressive disorders. However, a decrease in blood flow to the medial prefrontal cortex is also seen in healthy subjects during the induction of sad mood (Mayberg *et al*., 1999) suggesting, along with other studies, a more fundamental role for this brain region in the regulation of autonomic responses and arousal associated with affective states and emotional behaviour (Simpson *et al*., 2001).

Another region with emotional salience is the anterior cingulate cortex (ACC), which is functionally divided into dorsal and rostral-ventral divisions (Devinsky *et al*., 1995; Bush *et al*., 2000). During studies examining attention to subjective emotional states and experiences there is an increase in blood flow to both the dorsal and rostral regions of the ACC (Gusnard *et al*., 2001; Lane *et al*., 1998) implicating them in the effortful regulation of arousal associated with affective states (Lane *et al*., 2000). However, this role is thought to be partitioned such that the dorsal ACC is associated principally with the direct experience of emotion whereas the rostral-ventral component is involved in reflection and the representation of an emotional state (Devinsky *et al*., 1995; Bush *et al*., 2000).

In addition to the prefrontal cortex and ACC, findings from a number of functional neuroimaging studies (Beauregard *et al*., 1998; Pardo *et al*., 1993; George *et al*., 1995; Partiot *et al*., 1995; Schneider *et al*., 1995; Lane *et al*., 1997a, 1997b; Paradiso *et al*., 1997; Canli *et al*., 1998; Mayberg *et al*., 1999; Teasdale *et al*., 1999; Berthoz *et al*., 2002) implicate other brain regions, such as the insula, amygdala and striatal structures, in the generation and modulation of mood in healthy volunteers and patients with major depression (reviewed in Critchley, 2003; Mayberg, 1997a; Mayberg, 2003). In comparison, relatively few studies have examined bipolar disorder – in particular bipolar depression, partly because of the inherent complexity of emotional processing in this illness but also because of difficulty in defining and capturing its clinical phases.

Studies of manic patients at rest and whilst performing executive tasks have shown increases in ventral striatal (O'Connell *et al*., 1995; Blumberg *et al*., 2000) and dorsal ACC (Blumberg *et al*., 2000; Goodwin *et al*., 1997; Rubinsztein *et al*., 2001) activity and decreases in prefrontal cortical (O'Connell *et al*., 1995; Blumberg *et al*., 1999) activity. Studies in patients with bipolar depression, at rest and whilst performing executive tasks, have identified reductions in dorsolateral and dorsomedial prefrontal cortical metabolism (Baxter *et al*., 1989; Ketter *et al*., 2001) but increases in metabolism within the thalamus and the amygdala (Ketter *et al*., 2001) in comparison to healthy controls. A recent fMRI study (Blumberg *et al*., 2003) that examined all three phases of bipolar disorder noted abnormalities in manic and depressed patients (state-related) in the caudal ventral prefrontal cortex (cVPFC) and additional abnormalities (trait-related) in both mood states and euthymia in the rostral ventral prefrontal cortex. Generally, fewer functional abnormalities have been noted in euthymic bipolar patients (Baxter *et al*., 1989; Blumberg *et al*., 1999; Blumberg *et al*., 2000; Berns *et al*., 2002); however, one study that examined affect discrimination in euthymic bipolar patients found increased amygdalar and reduced prefrontal cortical activation (Yurgelun-Todd *et al*., 2000) and suggested that affective and attentive processing deficits may occur because of diminished frontal cortical functioning. Building upon these various lines of investigation, examining the generation of affect in bipolar depression, in particular the cognitive processes that this entails, may help elucidate the pathophysiology of bipolar disorder.

Aims and hypotheses

The present study therefore, set out to investigate the neural correlates of positive and negative affect in patients with bipolar depression during passive viewing of cognitively generated emotional stimuli using an established activation paradigm (Teasdale *et al*., 1999). The latter exploits the fact that specific affective responses can be produced via two separate routes. The first, a subcortical route, generates affective responses to the simple and perceptual associative aspects of stimuli, whereas the second, a principally cortical route, generates affective responses on the basis of meaning or by interpretation of stimuli (Izard, 1993; Partiot *et al*., 1995).

We hypothesized that depressed bipolar patients and healthy comparison subjects would have distinct patterns of activation as seen on fMRI when responding to both positive and negative cognition-based emotional stimuli. More specifically, we hypothesized that both patients and controls would engage prefrontal cortical brain regions when processing affect-related meaning but that patients would demonstrate additional subcortical activation indicating the recruitment of subcortical-limbic processing. We also predicted that in keeping with their baseline mood, BD patients and comparison subjects would demonstrate differential patterns of fMRI activation in brain regions implicated in the pathophysiology of mood disorders such as the anterior cingulate cortex.

Materials and methods

Subjects

Ten right-handed female patients with bipolar depression were recruited from our Sydney bipolar disorder clinic providing a second opinion for patients currently receiving treatment. A research psychiatrist (GM), using the Structured Clinical Interview for DSM-IV (SCID-P) (First *et al*., 1995) supplemented by a case note review, made the diagnoses. Subjects were excluded if they had a history of substance abuse, neurological disease or closed head injury, or had an additional Axis-I or Axis-II psychiatric diagnosis based on DSM-IV or a medical disorder currently necessitating treatment.

Patients were aged 19–53 years (mean ± SD 34.3 ± 12.0 years). Severity of illness was assessed using the 17-item Hamilton Depression Scale (Hamilton, 1960), the Montgomery–Asberg Depression Rating Scale (Montgomery & Asberg, 1979), the Young Mania Rating Scale (Young *et al*., 1978) and the CORE measure for psychomotor disturbance (Parker & Hadzi-Pavlovic, 1996). Patients also completed the following questionnaires: the Beck Depression Inventory (Beck *et al*., 1961), the Fawcett–Clark Pleasure Scale (Fawcett *et al*., 1983) and the Spielberger State-Trait-Anxiety Inventory (Spielberger, 1983). The mean duration of illness from diagnosis was 12.4 ± 7.0 years, and the mean number of previous depressive episodes was 9.3 ± 8.0 and manic episodes 8.2 ± 6.8. Six of the ten patients fulfilled DSM-IV criteria for rapid cycling bipolar disorder.

At the time of fMRI scanning, all ten patients were on mood-stabilizing psychotropic medications only, with dosages unaltered over the preceding two weeks. Seven patients were taking lithium (mean daily dose 892.9 ± 214.9 mg) with a mean plasma level of 0.74 ± 0.1 mmol/L. Two of these patients and two others were taking valproate (mean daily dose 1450.0 ± 173.2 mg) with a mean plasma level of 398.3 ± 85.2 μmol/L. The tenth patient was taking carbamazepine (800 mg daily), with a plasma level of 30.0 μg/mL. Two patients had previously received electroconvulsive therapy (more than 3 months prior), and eight patients had at least one first-degree relative with an affective disorder (two bipolar disorder and six major depression).

Patients were compared with ten female volunteers matched for age (20–53 years; mean 34.0 ± 13.0 years) and handedness (all right-handed), recruited via local advertisement. Comparison subjects were screened for a history of neurological or psychiatric disorder (with SCID-NP version) or a family history of the same. They also underwent the same clinical assessments and self-report questionnaires as patients immediately prior to fMRI scanning.

The Prince of Wales Hospital and University of New South Wales ethics committees approved the study and all participants provided written informed consent.

Experimental design and procedure

The cognitive activation paradigm described by Teasdale and colleagues (Teasdale *et al*., 1999) involved video-playback of captioned pictures. The caption, in combination with the content of the picture, is designed to produce a positive or a negative affect (experimental captioned pictures) or is irrelevantly paired and, as such, produces little, if any, emotion (reference captioned pictures). The pictures themselves were not evocative of affect.

Subjects were scanned while undergoing three 5-min experiments counter-balanced across subjects, which either contrasted blocks of affect-inducing captioned pictures (positive vs. negative), or alternated these with reference captioned pictures (positive vs. reference and negative vs. reference). Each experiment involved five alternating 30-second blocks of images. Each captioned-picture was presented for 9 s, with a one-second interstimulus interval. For each captioned-picture the subjects were given explicit instructions to passively examine each picture and then mentally read the caption below. Furthermore, no verbal or motor response was necessary at any time during the experiment. In total, subjects viewed 30 captioned pictures (three per block ×10). In each group, the same number of individuals viewed any given picture or caption as part of an experimental captioned-picture and the remainder viewed it as part of a reference captioned-picture, so that the experimental and control captioned pictures had identical pictures and captions and only differed in terms of the relationship between them. To ensure compliance subjects were continuously monitored within the scanner using closed circuit television and to increase stimulus engagement all subjects were informed that after being scanned they would have to fill in a questionnaire concerning the stimuli presented. This involved rating each captioned-picture on a nine point scale (−4 to +4), according to the amount of negative or positive affect it generated. Immediately after scanning, all participants rated each captioned-picture on a nine-point-scale (−4 to +4), according to the amount of negative or positive affect experienced (none at all, 0; slightly, 1; moderate, 2; very much, 3; extreme, 4).

Image acquisition

Imaging was performed using a 1.5T GE LX Signa MRI scanner (Wisconsin, USA), using single shot echo planar imaging (EPI). Functional MRI volumes were acquired using a gradient EPI sequence (TE, 40 ms; TR, 3000 ms; FOV, 400; matrix, 64 × 64; flip angle, 90°) and each volume contained 16 interleaved 7-mm-thick slices. T_1-weighted high-resolution whole brain images (with the following parameters: matrix, 256 × 256, FOV, 300 mm, slice thickness, 1.3 mm) were acquired as an aid to localization of the activated voxels. Additionally, high-resolution anatomical images in the plane of the functional slices were acquired to facilitate in the coregistration of the functional volumes to a Talairach (Talairach & Tournoux, 1988) calibrated whole brain image. All anatomical and functional images were acquired in an axial plane parallel to the AC-PC line.

Data analysis

Affect ratings

Affect ratings for captioned pictures evoking positive and negative affect and for reference captioned pictures (averaged across all three experiments) in depressed patients and comparison subjects were analysed by 2 (Group: patients, controls) ×3 (Valence: positive, reference, negative captioned pictures) analyses of variance.

Functional MRI

Image analysis was performed using MEDx 3.4.1 (Sensor Systems, Inc.). Functional images were reconstructed offline using the Epirecon feature of MEDx. fMR images were grouped (according to condition) into positive (POS), negative (NEG), and reference (REF) stimuli. All subjects were mechanically immobilized by applying Velcro strapping across their foreheads and by placing foam inserts alongside their ears, between them and the head coil. Before analysis all data were interrogated and carefully scrutinized for movement and susceptibility artifacts. Data indicative of movement greater than 0.5 mm in any plane were motion corrected using the Automated Image Registration (AIR) algorithm (Woods *et al*., 1993), and functional data were smoothed using a 13 × 13 × 14 (FWHM) Gaussian kernel to compensate for residual variability in brain anatomy. To reduce the effect of variation of MR signal between runs, images were globally normalized to an empirically determined value of 1000. A voxel by voxel detrending algorithm was then applied to remove any linear drift in the MR signal. Unpaired *t*-tests were applied to the groups of images. Three comparisons using a boxcar function to model subject response

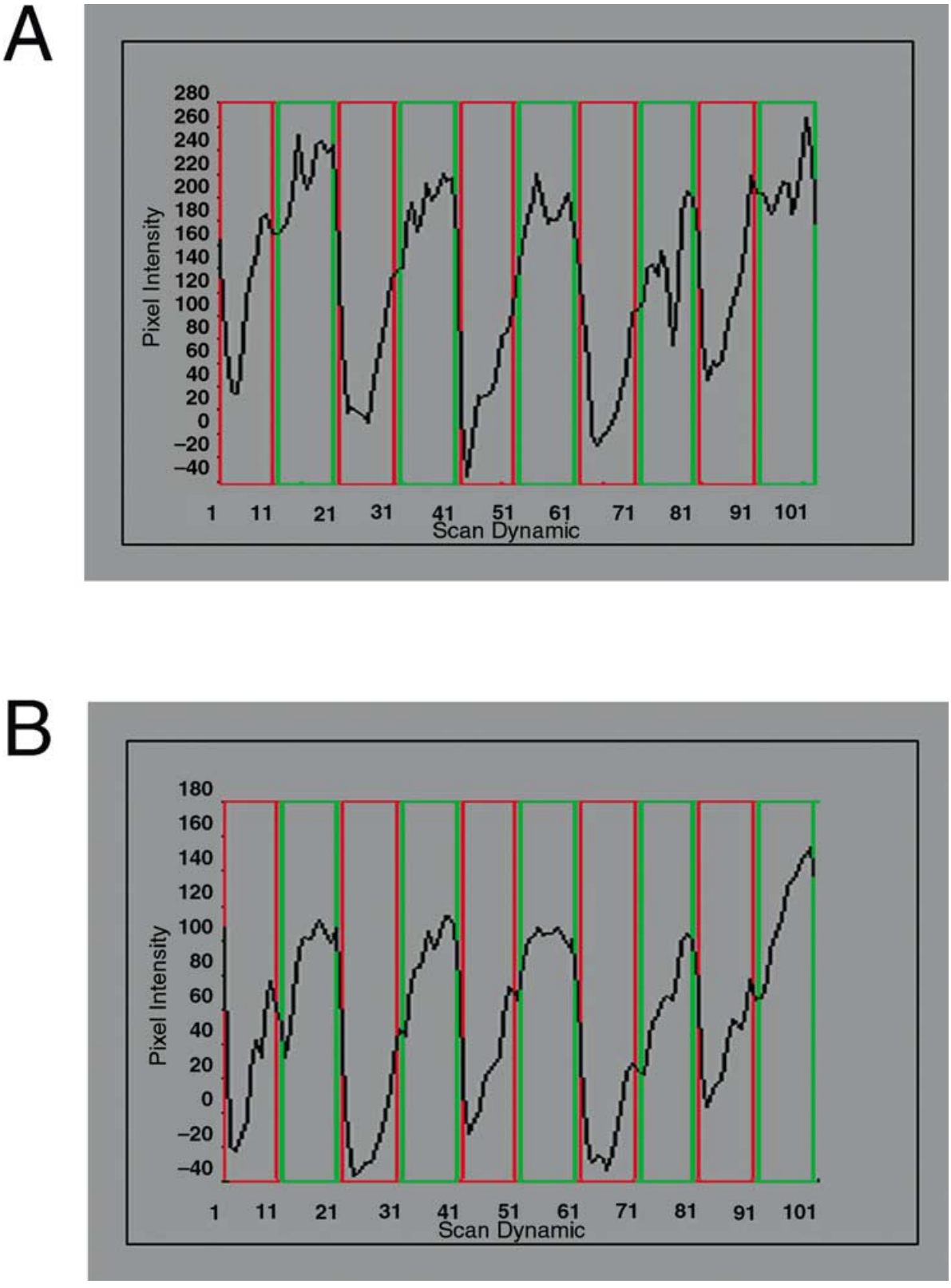

FIG. 1. The temporal display of pixel intensity relative to the time course (a total of 100 scan dynamics) for the 5-min experimental task taken from (A) a single bipolar subject from the positive vs. reference comparison in the parahippocampal gyrus and (B) a single control subject from the negative vs. reference comparison in the superior frontal gyrus.

TABLE 1. Age and clinical rating scale scores

	Bipolar depressed patients	Healthy comparison subjects	t_9-value*
Age (years)	34.3 ± 12.0	34.0 ± 13.0	0.06
FCPS	2.0 ± 0.7	4.2 ± 0.3	−8.32**
BDI	41.2 ± 10.2	2.9 ± 1.9	11.88**
HAM-D	24.0 ± 3.7	2.6 ± 1.7	15.20**
MADRS	25.9 ± 3.5	1.5 ± 1.2	18.63**
STAI-I	28.9 ± 6.5	30.1 ± 6.4	−0.33
STAI-II	33.2 ± 7.0	32.0 ± 7.1	0.29
CORE	4.7 ± 2.4	0.0 ± 0.0	6.12**
YMRS	2.4 ± 1.0	0.7 ± 0.8	4.64**

Data are presented as mean ± SD. FCPS, Fawcett-Clarke Pleasure Scale (24); BDI, Beck Depression Inventory (23); HAM-D, Hamilton depression rating scale (19); MADRS, Montgomery Asberg Depression Rating Scale (20); STAI, State Trait Anxiety Inventory (25); CORE, Psychomotor scale (22); YMRS, Young Mania Rating Scale (21). *Nine degrees of freedom; **$P < 0.003$.

were made: (i) POS vs. REF; (ii) NEG vs. REF; and (iii) POS vs. NEG. The *Z*-score maps were thresholded to a Bonferroni-corrected probability of 0.05, which corresponded to a statistically significant *Z*-score threshold of 4.00. Thresholded *Z*-score maps were used to determine the presence of significant activation foci. In-plane T_1-weighted images were used to derive a transformation matrix, which was subsequently applied to the lower resolution *Z*-score maps. Finally, individual clusters of activated voxels were interrogated to ensure that the temporal timeline of the signal matched that of the experimental paradigm (see Fig. 1). Unless otherwise specified, data are presented as means ± SD.

Results

Clinical and affect ratings

Patients and comparison subjects had the same levels of baseline anxiety (STAI-I/II). However, they differed significantly on measures of mood (HAM-D, MADRS, BDI, YMRS), psychomotor disturbance (CORE) and pleasure (Fawcett–Clarke Pleasure Scale) (see Table 1).

The affect ratings ranged from −3.3 to +3.4 for patients and from −3.5 to +3.7 for comparison subjects, indicating that the procedure induced moderate levels of affect in both groups with positive captioned pictures evoking positive affect and negative captioned pictures evoking negative affect. The means and standard deviations of affect ratings for patients and comparison subjects are presented in Table 2. The effect of valence was highly significant ($F_{2,36} = 293.4$, $P < 0.0001$). However, there was no significant difference between groups on affect ratings ($F_{1,18} = 0.256$, $P > 0.05$) and the Group × Valence effect was not statistically significant ($F_{1,18} = 0.002$, $P > 0.05$).

Functional MRI

The results of the three experiments comparing the responses of patients and controls are presented in Tables 3–5 and described below.

Experiment 1: negative vs. reference captioned pictures

(See Fig. 2 and Table 3.) Patients showed significant activation in the superior and middle frontal, superior temporal, lingual and subcallosal gyri, thalamus, hypothalamus and cerebellum. In contrast to comparison subjects, they showed only right-sided activation.

Comparison subjects showed predominantly right-sided superior, middle and inferior frontal and supramarginal and angular gyri activation. They also showed predominantly left-sided activation in the superior and middle temporal and parahippocampal gyri and cuneus. They showed bilateral activation in the superior and inferior parietal lobules, the precuneus and lateralized responses in the pre- and postcentral gyri.

Patients showed less widespread cortical activation in response to negative affect than comparison subjects and the only regions common to both groups were the frontal and temporal gyri. Whilst activation in comparison subjects was more widespread, only patients showed significant activation in subcortical brain regions.

Experiment 2: positive vs. reference captioned pictures

(See Fig. 3 and Table 4.) Patients showed significant activation in the left medial and middle frontal, parahippocampal and fusiform gyri as well as the amygdala. They also showed right-sided responses in the inferior frontal gyrus and thalamus, and bilateral responses in the superior frontal gyrus and uncus.

Comparison subjects showed significant left inferior parietal lobule, superior frontal and postcentral gyrus activation. They also showed significant right cuneus and midline precuneus and bilateral superior lobule activation.

Overall, none of the regions that showed significant activation in response to positive affect were common to both groups. Bipolar depressed patients showed more widespread activation than comparison subjects including subcortical activation.

Experiment 3: positive vs. negative captioned pictures

(See Fig. 4 and Table 5.) Patients showed bilateral activation in the middle and inferior frontal gyri and right-sided activation in the

TABLE 2. Affect ratings

	Affect ratings		Within-group effects, valence ($F_{1,9}$, *P*-value)		Between-group effects ($F_{1,9}$, *P*-value)	
	Patients	Controls	Patients	Controls	Valence	Group × Valence
Negative CPs	−2.19 ± 0.62	−2.56 ± 0.73				
Reference CPs	0.07 ± 0.27	0.16 ± 0.25				
Positive CPs	2.35 ± 0.71	2.45 ± 0.68				
Negative CPs vs. reference CPs			120.51, <0.001	201.33, <0.001		
Positive CPs vs. reference CPs			136.50, <0.001	99.78, <0.001		
Positive CPs vs. negative CPs			146.13, <0.001	161.34, <0.001		
Negative CPs vs. reference CPs					313.18, <0.0001	2.540, NS
Positive CPs vs. reference CPs					230.36, <0.0001	0.002, NS
Positive CPs vs. negative CPs					307.47, <0.0001	0.719, NS

Affect ratings – mean ± SD, averaged across all three experiments, for reference captioned pictures (CPs) and those evoking positive and negative affect in bipolar depressed patients and healthy comparison subjects and the results from ANOVAs for within-group effects. NS, not statistically significant.

TABLE 3. Talairach and Tournoux coordinates and *Z*-scores of regions in patients and control subjects showing significant differences in activation in response to negative vs. reference captioned pictures

Brain region	Brodmann's area	Bipolar depressed patients				Healthy control subjects			
		x	*y*	*z*	*Z*-score	*x*	*y*	*z*	Z_9-score
Superior frontal gyrus	6/10	34	66	18	4.75	24	32	54	5.24
		26	66	18	4.41	18	24	58	4.75
		34	60	26	4.04	2	32	56	4.68
						2	20	56	4.20
						12	32	54	4.33
						−4	18	56	4.23
						−2	6	56	4.13
Middle frontal gyrus	6/10	26	66	22	4.46	26	24	56	5.25
						44	6	54	4.68
						38	6	56	4.68
						38	12	54	4.60
Inferior frontal gyrus	9					60	8	32	4.47
Precentral gyrus	6					66	2	30	4.73
						42	−16	58	4.31
						68	−8	30	4.13
Postcentral gyrus	3					−52	−12	56	4.35
Superior parietal lobule	7					4	−68	56	4.43
						32	−60	56	4.31
						−36	−54	56	4.04
						−4	−68	56	4.29
Inferior parietal lobule	39/40					52	−60	40	4.26
						−60	−54	40	4.28
						−52	−60	42	4.26
						−46	−60	86	4.08
						−44	−42	58	4.45
Supramarginal gyrus						62	−52	34	4.09
Angular gyrus	39					50	−72	32	4.46
Superior temporal gyrus	38	42	16	−18	4.25	−42	12	−26	4.00
		48	12	−16	4.48				
Middle temporal gyrus						−42	6	−24	4.06
Parahippocampal gyrus	30					−4	−38	−6	4.27
						−8	−32	−6	4.23
Subcallosal gyrus	34	18	4	−14	5.09				
Lingual gyrus	18	12	−90	−16	4.17				
Cuneus	19					0	−88	36	5.79
						−26	−92	34	4.62
						−26	−86	36	4.43
Precuneus	7/19					38	−76	36	4.58
						38	−82	36	4.51
						−4	−60	56	4.14
						−24	−86	42	4.65
Thalamus (pulvinar)		6	−26	10	4.66				
Hypothalamus		2	0	−12	4.55				
Cerebellum		6	−40	−12	4.48				

superior frontal, pre- and postcentral and parahippocampal gyri and in the posterior cingulate and inferior parietal lobule. They also showed activation in the right thalamus, medial globus pallidus and left insular cortex.

Comparison subjects showed significant right-sided activation in the superior, middle and inferior frontal, superior and inferior parietal, supramarginal and precentral gyri. They also showed activation in the left uncus and bilateral activation in the anterior cingulate.

In contrast to the results of experiments 1 and 2, patients and comparison subjects shared several cortical regions that showed activation in response to alternating positive and negative captioned pictures. However, only patients showed significant activation in subcortical brain regions.

In summary, experiments 1 and 2 produced very different patterns of regional brain activation in patients and comparison subjects. In experiment 1, activated brain regions in patients were all right-sided and in experiment 2, there was no overlap between activated brain regions in patients and comparison subjects. Experiment 3 differed in that several activated brain regions were common to both groups although once again subcortical activation only occurred in patients.

Discussion

This fMRI study is the first to examine the cognitive generation of affect in BD using both positive and negative captioned pictures . The main findings were distinct patterns of regional activation in bipolar depressed patients when compared to healthy comparison subjects. Patients showed more widespread activation with positive affect whereas comparison subjects responded principally to negative affect induction. Patients also demonstrated subcortical activation during affect generation, something not seen in comparison subjects, and although both groups had anterior and posterior cingulate activation, the pattern of activation in the anterior cingulate distinguished them.

TABLE 4. Talairach and Tournoux coordinates and *Z*-scores of regions in patients and control subjects showing significant differences in activation in response to positive vs. reference captioned pictures

Brain region	Brodmann's area	Bipolar depressed patients				Healthy control subjects			
		x	*y*	*z*	*Z*-score	*x*	*y*	*z*	Z_9-score
Superior frontal gyrus	9/10	8	62	30	5.25	−2	48	32	4.70
		8	68	28	5.20				
		−10	−68	28	4.71				
		−20	66	26	4.07				
Middle frontal gyrus	10	−22	72	8	4.07				
Medial frontal gyrus	10/25	−2	60	−6	4.29				
		0	70	−2	4.04				
		−14	8	−18	4.61				
Inferior frontal gyrus	47	28	12	−18	4.39				
Precentral gyrus	6					66	2	30	4.73
						42	−16	58	4.31
						68	−8	30	4.13
Postcentral gyrus	3					−52	−12	56	4.35
Superior parietal lobule	7					4	−68	56	4.43
						32	−60	56	4.31
						−36	−54	56	4.04
						−4	−68	56	4.29
Inferior parietal lobule	39					−54	−62	42	4.47
Superior temporal gyrus	38	−38	22	−24	5.13				
		40	12	−22	4.23				
Uncus	28/34/36	−14	−2	−20	5.25				
		−20	2	−28	4.21				
		−26	2	−32	4.14				
		16	4	−22	4.12				
Amygdala		−20	−8	−20	4.83				
Fusiform gyrus	20	−34	−12	−22	4.69				
Parahippocampal gyrus	30	−26	−10	−22	4.70				
Cuneus	19					10	−94	36	4.86
Precuneus	7/19					0	−66	54	4.46
						6	−86	42	4.35
						14	−86	44	4.35
Thalamus (pulvinar)		2	−30	6	4.19				

TABLE 5. Talairach and Tournoux coordinates and *Z*-scores of regions in patients and control subjects showing significant differences in activation in response to positive vs. negative captioned pictures

Brain region	Brodmann's area	Bipolar depressed patients				Healthy control subjects			
		x	*y*	*z*	*Z*-score	*x*	*y*	*z*	Z_9-score
Superior frontal gyrus	6/10/11	34	56	−2	5.72	1	52	−22	4.08
		20	32	60	4.00				
Middle frontal gyrus	6/9/10	64	22	32	4.17	52	20	36	4.06
		−38	66	8	5.20				
		−40	58	6	5.01				
		38	8	64	4.47				
		34	62	0	5.98				
Inferior frontal gyrus	9	62	10	34	4.88	70	10	20	4.16
		−38	50	−2	4.90				
Cingulate gyrus	24					2	16	30	4.11
						−8	−2	32	4.96
Anterior cingulate	25	−2	4	−6	5.23				
Posterior cingulate	29/31	8	−46	4	5.34	−4	−68	14	4.29
		2	−40	6	4.84				
Precentral gyrus	4/6	26	−26	68	4.91	70	2	22	4.03
Postcentral gyrus	5	40	−44	60	4.31				
		26	−36	72	4.64				
Superior parietal lobule	7	−40	−56	56	4.39	26	−64	40	4.13
Inferior parietal lobule	40	40	−50	60	4.31	56	−30	38	4.26
Supramarginal gyrus	40					54	−36	36	4.29
Uncus	28					−20	−18	−32	4.25
Parahippocampal gyrus	30	8	−40	6	4.89				
		8	−40	2	4.94				
Insula	13	−44	12	0	4.46				
Medial globus pallidus		10	0	−8	5.90				
Thalamus (pulvinar)		6	−26	10	4.66				

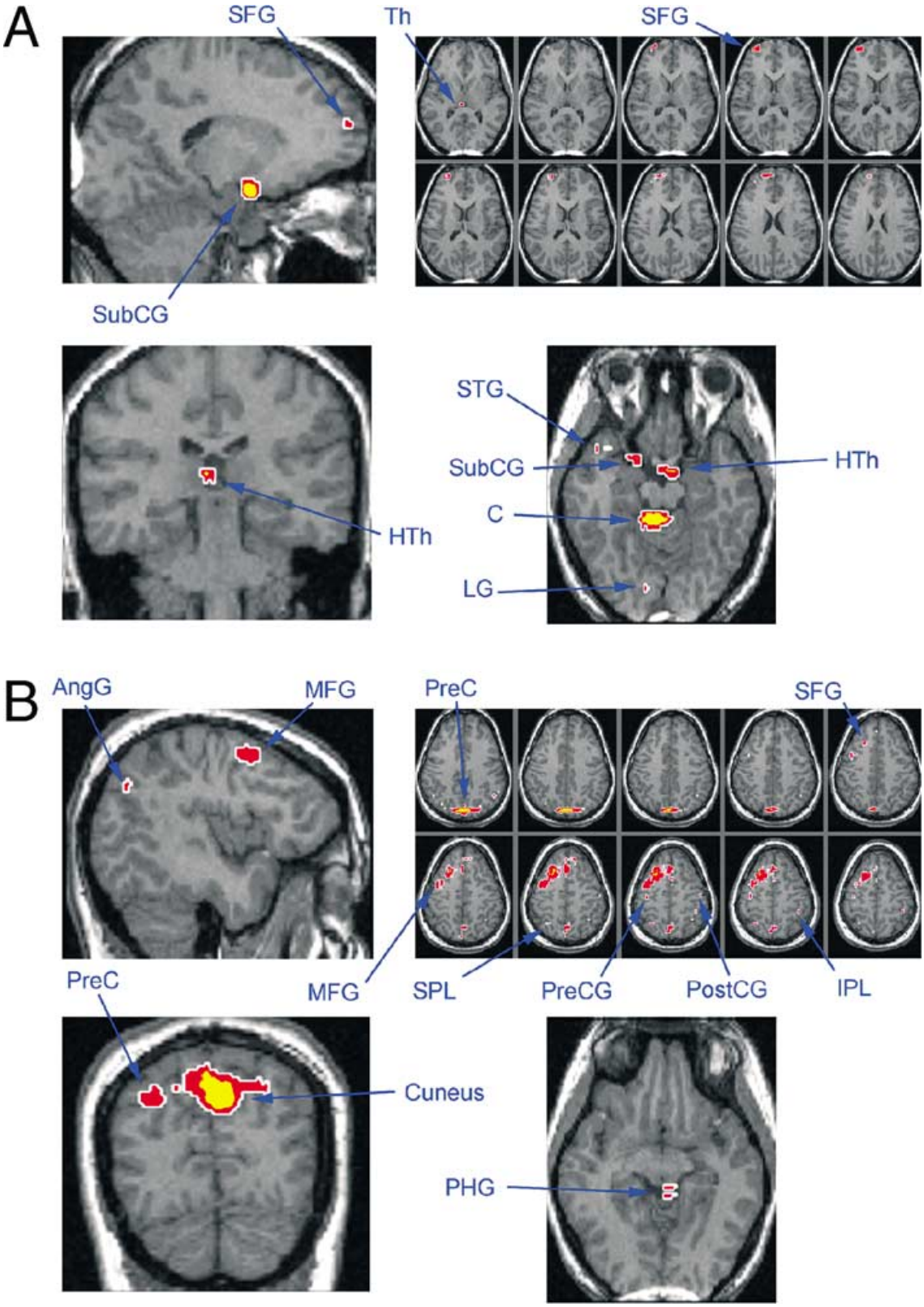

FIG. 2. Experiment 1, NEG vs. REF captioned pictures. Sagittal, coronal and axial slices depicting fMRI activation (see Table 3 for exact coordinates of activation foci). (A) Bipolar depressed patients. (B) Healthy comparison subjects. Abbreviations: SFG, superior frontal gyrus; SubCG, subcallosal gyrus; Th, thalamus; HTh, hypothalamus; STG, superior temporal gyrus; C, cerebellum; LG, lingual gyrus; AngG, angular gyrus; MFG, middle frontal gyrus; PreC, precuneus; SPL, superior parietal lobule; PreCG, precentral gyrus; PostCG, postcentral gyrus; IPL, inferior parietal lobule; PHG, parahipocampal gyrus.

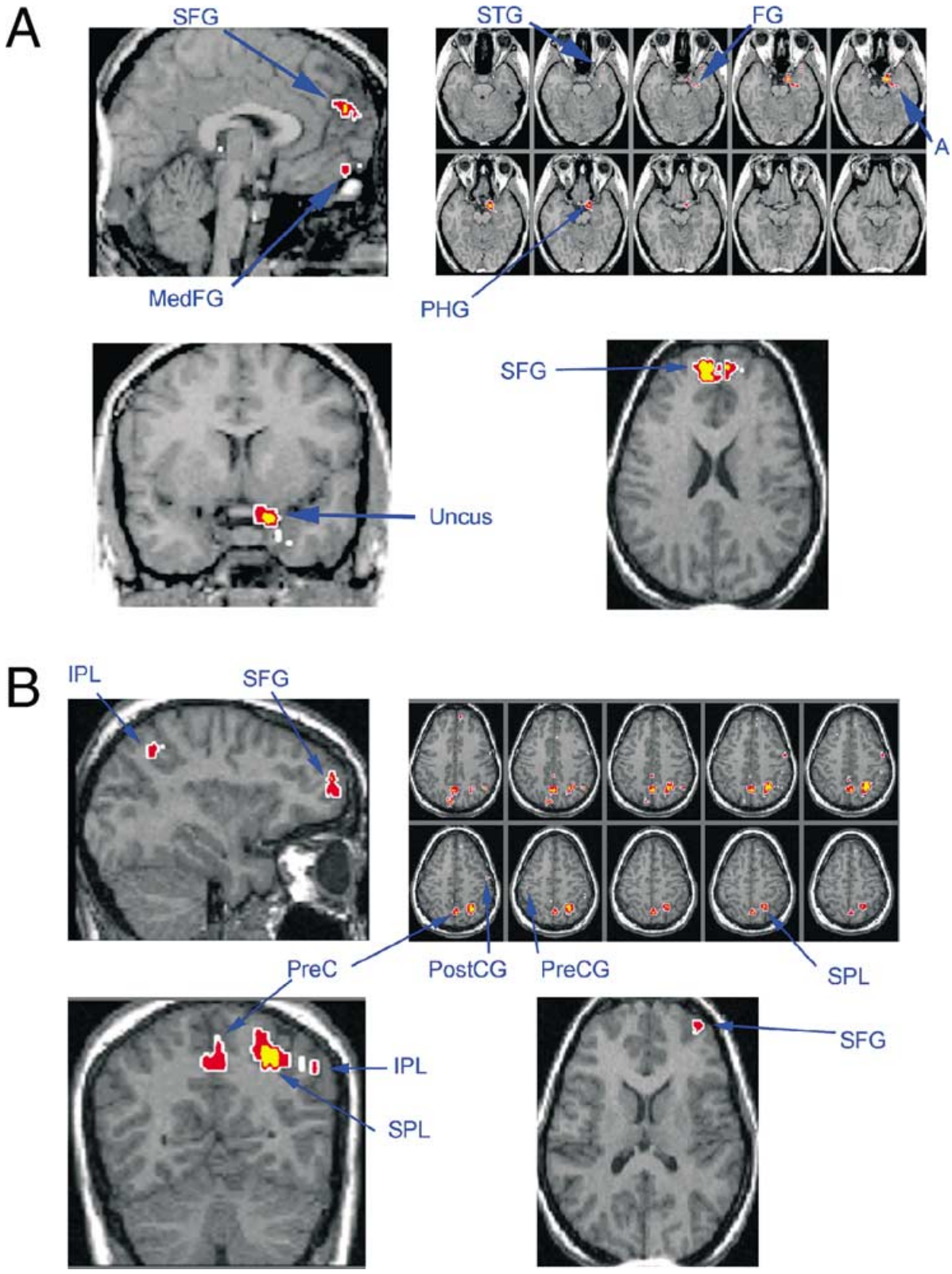

FIG. 3. Experiment 2, POS vs. REF captioned pictures. Sagittal, coronal and axial slices depicting fMRI activation (see Table 4 for exact coordinates of activation foci). (A) Bipolar depressed patients. (B) Healthy comparison subjects. Abbreviations as in Fig. 2 plus MedFG, medial frontal gyrus.

Regional activations

The pattern of activation in our comparison subjects also differed to some extent to that found by Teasdale and colleagues (Teasdale *et al*., 1999) and Kumari and colleagues (Kumari *et al*., 2003) in healthy volunteers. In all three groups there was robust prefrontal cortex activation involving overlapping middle frontal gyrus regions and anterior cingulate cortex and in general, negative affect produced

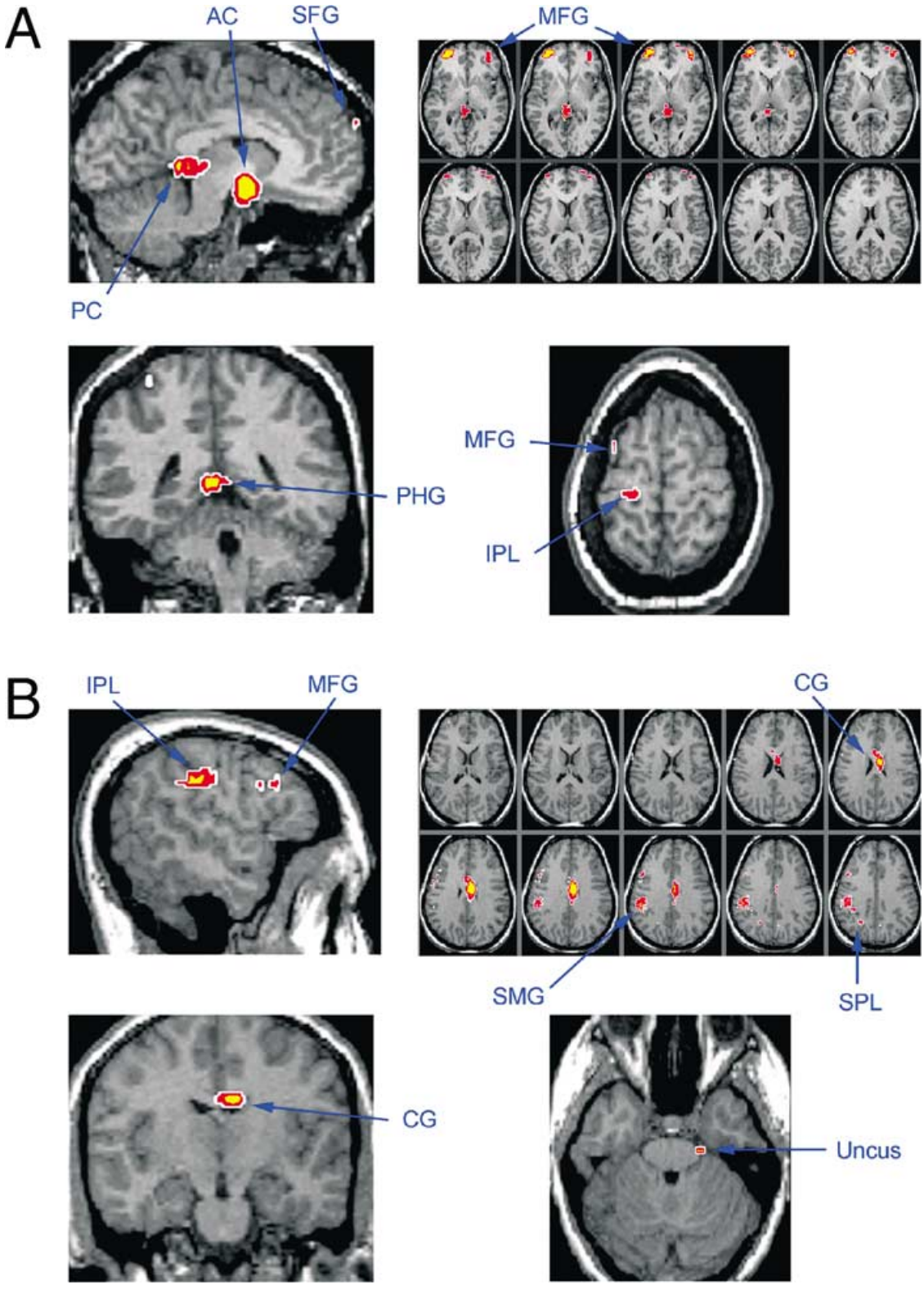

FIG. 4. Experiment 3, POS vs. NEG captioned pictures. Sagittal, coronal and axial slices depicting fMRI activation (see Table 5 for exact coordinates of activation foci). (A) Bipolar depressed patients. (B) Healthy comparison subjects. Abbreviations as in Fig. 3 plus AC, anterior cingulate; PC, posterior cingulate; CG, cingulate gyrus.

more widespread activation than positive affect. However, thalamic activation that occurred in both Kumari's and Teasdale's controls and caudate activation observed only in the latter did not occur in our control subjects. Instead, our comparison subjects had additional parietal and temporal cortex activation. However, these activation patterns cannot be compared directly because of sample size and gender differences between the various studies. Our patient and comparison groups each had ten subjects and all were female. Both

other studies (Teasdale *et al*., 1999; Kumari *et al*., 2003) had sample sizes of six, and half of Teasdale's controls were male. Furthermore, significant methodological differences with respect to analysis and the contrasts sought, also make direct comparison difficult.

Cortical

Patients showed widespread frontal activation with positive affect induction in contrast to comparison subjects who responded much more so to negative affect. Prefrontal cortex activation reflects cognitive emotional processing (George *et al*., 1995) that requires attention to internal emotional states and the ability to appraise interoceptive and exteroceptive cues (Lane *et al*., 1997a; Reiman *et al*., 1997; Ochsner *et al*., 2002). Hence, we speculate that patients and comparison subjects engage such cognitive processes more so when adopting an affect of contrasting valence to their current mood state. This may reflect abnormal cognitive emotional processing or compensatory activity although a recent report by Blumberg *et al*. (2003), in which they identify ventral prefrontal cortex (VPFC) dysfunction in patients with bipolar disorder, suggests that the former is more likely.

In experiment 3, patients and comparison subjects activated subgenual (BA25) and anterior (BA24) cingulate regions, respectively, and both groups had posterior cingulate (BA29/31) activation, consistent with its putative role in processing negative emotions (Mayberg *et al*., 1999; Maddock *et al*., 2003) and emotional episodic memory (Maddock *et al*., 2001). Functionally, the anterior cingulate cortex is divided into rostral-ventral affective (rostral BA24/32 and BA25) and dorsal cognitive (dorsal BA24/32) divisions (Bush *et al*., 2000). The affective division determines the salience of emotional and motivational information and regulates affective responses (Devinsky *et al*., 1995). The subgenual anterior cingulate (BA25), implicated in the pathogenesis of clinical depression, is activated during autobiographical script-induced sadness, thought to reflect the cognitive processing of internally generated emotion as opposed to sadness itself (George *et al*., 1995; Drevets *et al*., 1997; Lane *et al*., 1997a; Lane *et al*., 1997b; Reiman *et al*., 1997; Mayberg *et al*., 1999; Liotti *et al*., 2000; Botterton *et al*., 2002; Liotti *et al*., 2002). However, this remains speculative (Phuan *et al*., 2002) and, in our experiments subgenual activation only occurred in patients, indicating it may be a marker of depressed mood. Furthermore, in contrast to comparison subjects, patients lacked rostral anterior cingulate (BA24) activation, a region in which 'hypoactivity' has been associated with poor treatment responsiveness in both PET (Mayberg *et al*., 1997b) and fMRI (Davidson *et al*., 2003; Kumari *et al*., 2003) studies, suggesting that the pattern in our BD patients is similar to that shown to be associated with a lower response rate to treatment in depression. In keeping with this, only comparison subjects had activation in the occipital-visual cortex (OVC), which includes the cuneus and precuneus, and is responsible for appraising emotionally salient visual perceptions (Reiman *et al*., 1997; Beauregard *et al*., 1998) and preprocessing them (Lang *et al*., 1998). This suggests that patients may be limited in their ability to effectively engage sophisticated cortical processes. However, it is important to note that as performance was not directly monitored *per se*, it is possible that decreased attention during experiments contributed to the diminished dorsal anterior cingulate activation in our BD patients.

Subcortical

In contrast to the above, subcortical activation occurred solely in patients. Activations were all right-sided, except those in the amygdala, and involved the basal ganglia, thalamus and hypothalamus.

Pulvinar activation occurred with both positive and negative affect, and as this nucleus is central to many neural processes by virtue of its reciprocal connections with other thalamic nuclei and cortical brain regions, its activation suggests heightened subcortical processing in patients. This is borne out to some extent by medial globus pallidus activation during alternating positive and negative affect in experiment 3 and by the finding that globus pallidus fMRI activation also occurs in manic patients performing a simple reaction time task (Caligiuri *et al*., 2003). Basal ganglia activation has been associated with recall-induced happiness (Damasio *et al*., 2000) and viewing pleasant stimuli (Mitterschiffthaler *et al*., 2003) including happy faces (Morris *et al*., 1998); however, our pictures lacked emotional stimuli based on facial expression and studies using such paradigms report amygdala activation (Phuan *et al*., 2002; Wild *et al*., 2003). The amygdala is therefore thought to be less engaged by internally generated emotional recall (Reiman *et al*., 1997; Damasio *et al*., 2000) than by externally cued emotional stimuli (Teasdale *et al*., 1999; Reiman *et al*., 1997; Schaefer *et al*., 2002) as it signals salience and modulates visual emotional processing within the occipital cortex. It may therefore have determined the lack of OVC activation in our patients. However, aversive and fearful stimuli (Phillips *et al*., 1997; Simpson *et al*., 2000) can also produce amygdala activation and it is therefore possible that in bipolar depressed patients, incongruous positive affect is a stressor that triggers fear and apprehension.

A more chronic stress, found in both depression and bipolar disorder (Manji *et al*., 2000), is that of hypothalamic-pituitary-adrenal (HPA) axis dysfunction. It is therefore interesting to note that in our patients, fMRI activation occurred in the region of the hypothalamus in response to negative affect induction. However, the diverse functions of this densely innervated brain region make it difficult to determine with any meaningful specificity the exact processes involved.

Experimental factors and limitations

Anxiety

In addition to amygdala activation, neuroimaging studies that have used faces to induce emotions (Phillips *et al*., 1997; Harmer *et al*., 2002) have noted accompanying changes of facial expression that produce activation in the motor regions of the brain. In our study, motor cortex (BA4) activation only occurred in patients with positive affect whereas premotor area (BA6) activation occurred in comparison subjects with both negative and positive affect and when alternating between them. These findings are difficult to interpret as our experiments did not rely on facial expression, and this was not monitored. However, the inferior parietal lobe (BA39/40) is also implicated in facial expression processing (Adolphs, 1996) and is thought to regulate negative emotional arousal. Consistent with this, negative affect produced inferior parietal activation in comparison subjects, suggesting a role in processing the cognitive aspects of negative emotions. However, inferior parietal activation is also associated with perceptually driven anxiety (Kimbrell *et al*., 1999) and occurred in patients during alternating positive and negative affect suggesting that this paradigm may be anxiogenic.

Anxiety often coexists with depression (Malhi *et al*., 2002) and the two no doubt engage overlapping regions of the brain (Liotti *et al*., 2000). For instance, anxiety (Reiman *et al*., 1997; Kimbrell *et al*., 1999) and film/picture-generated emotion (Blair *et al*., 1999) both produce anterior temporal cortex activation. In our study, negative captioned pictures produced anterior temporal cortex (BA22/38) activation in both patients and comparison subjects, possibly because they also evoked anxiety. However, positive captioned pictures produced similar activation, but only in patients. This may reflect the induction of incongruous affect, or that patients with BD construed positive affect as denoting illness. ′Switching′ between alternating affects is perhaps particularly anxiogenic for bipolar patients because clinically

it mimics their affective instability. However, it is important to note that patients and comparison subjects did not differ in terms of their baseline levels of anxiety.

Baseline mood

By design, the groups differed in their baseline mood states and this is likely to have influenced our experiments. For instance, in comparison subjects, parahippocampal cortex activation only occurred with negative affect whereas, in patients, it also occurred with positive affect and when alternating between them. This is consonant with its putative role in processing negative emotions (Lane *et al*., 1997a; Lane *et al*., 1997b; Reiman *et al*., 1997) but also implies involvement in processing affect of incongruent valence. This can be explained in that depressed patients are more likely to rely on recall to develop a positive affect, and the converse applies to comparison subjects. The differing patterns of cerebral activation, with patients showing more extensive activation with positive affect and the converse occurring in comparison subjects, can perhaps also be partly explained on the basis of differing mood states. As patients were already depressed, they would have limited capacity for further negative change in affect, and would have to 'work harder' to generate positive affect.

Behaviourally, patients tended towards reduced responsiveness to both negative and positive captioned pictures . However, there was no difference in their ratings of affect, possibly because of demand characteristics (Polivy & Doyle, 1980). Furthermore, it is interesting to note that in BD patients, negative affect produced solely right-sided activation across all brain structures, supporting the concept of emotional hemispheric asymmetry (Davidson *et al*., 1995). However, this did not hold in the remaining experiments or in the pattern of activation in comparison subjects, although right-hemispheric lateralization in response to negative affect induction was observed in Teasdale's controls (Teasdale *et al*., 1999). This is in tune with the laterality literature in bipolar disorder (Soars & Mann, 1997; Strakowski *et al*., 2000), which lacks consensus. However, one possible explanation for this is that emotions only observe laterality at matching levels of arousal (Canli *et al*., 1998) and that this may not have occurred to the degree necessary in our experiments. Another is that the activations observed in BD patients may reflect a composite of trait and state-related dysfunctions that are difficult to separate by examining a single mood-state cross-sectionally.

Medication

Another important consideration is the effect of medication. It could be argued that because patients remained on mood-stabilizers and had received variable past treatment, interpretation is confounded (Phuan *et al*., 2002). Recent studies support this view reporting the possible effects of psychotropic medication, in particular antipsychotics and antidepressants, on neuroimaging parameters such as the BOLD response (Blumberg *et al*., 2003; Davidson *et al*., 2003) and cerebellar blood volume (Loeber *et al*., 2002). Furthermore, given that chronic treatment with valproate and lithium has been shown to slow neurodegenerative processes (Manji *et al*., 2000), it is quite possible that activation as seen on fMRI is altered by such medication. Indeed a recent study (Caligiuri *et al*., 2003) in patients with bipolar disorder, has shown that mood stabilizers may also suppress activation as seen on fMRI, although the extent to which this occurs and the mechanisms by which this may happen, remain unknown.

Conclusions

In keeping with our aims and hypotheses, this fMRI study has identified distinct patterns of activation in patients with BD and healthy comparison subjects using both positive and negative affect induction. In common with comparison subjects, patients showed cortical activation in regions implicated in the cognitive processing of affective stimuli (Teasdale *et al*., 1999). However, they also showed additional activation in several important subcortical nuclei, such as the thalamus and amygdala, suggesting that patients with BD perhaps by design or because of necessity engage a subcortical route for the processing of affective responses. This is in keeping with the findings from other lines of investigation that also implicate subcortical mechanisms in bipolar disorder (Vuillmeumier *et al*., 1998; Miyawaki *et al*., 2000).

The findings from this study therefore reinforce the critical role played by the prefrontal cortex, cingulate and subcortical structures in the processing of emotionally salient information in depressive disorders (Mayberg, 2003; Phillips *et al*., 2003b), in particular BD (Blumberg *et al*., 2003), and assist in the further dissection of function within these regions. However, it is important to remember the background complexity to many of our interpretations. For instance, baseline mood is in itself a determining influence and even simple stimuli such as positive affect may in fact have compound effects, such as producing anxiety. It is also necessary to be cognisant of the limitations of this study and note that these preliminary findings require replication.

Future studies should ideally seek to examine drug-free patients and conduct longitudinal comparisons across the different phases of bipolar disorder – contrasting these where possible against other affective disorders. Corroboration of a distinct differential pattern of activation in BD is likely to have significant diagnostic value and important implications for our understanding of the pathophysiological basis of bipolar disorder and its treatment.

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Abbreviations

ACC, anterior cingulate cortex; BD, bipolar depression; fMRI, functional magnetic resonance imaging.

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