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Research report

Reduced activation to implicit affect induction in euthymic bipolar patients: An fMRI study

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Abstract

Objective: To examine whether euthymic bipolar patients engage similar or contrasting brain regions as healthy subjects when responding to implicit affect induction.
Methods: The study examined 10 euthymic patients with bipolar I disorder, and 10 age- and gender-matched healthy subjects using event-related functional magnetic resonance imaging (fMRI) while subjects engaged in a modified word-based memory task designed to implicitly evoke negative, positive or no affective change. The activation paradigm involved nominating whether a target word was contained within a previously presented word list using specified response keys.
Results: The fMRI task produced significantly greater activation in healthy subjects as compared to patients in response to both negative and positive affect in the anterior and posterior cingulate, medial prefrontal cortex, middle frontal and right parahippocampal gyri. Only negative affect produced significantly greater activation in the postcentral gyrus, inferior parietal lobule, thalamus and putamen and only positive affect achieved the same in the precentral, superior temporal and lingual gyri, precuneus, cuneus, caudate, pons, midbrain and cerebellum. There were no brain regions in which responses were greater in patients as compared to healthy subjects. There were no statistically significant differences between the groups with respect to speed or accuracy.
Conclusions: Diminished prefrontal, cingulate, limbic and subcortical neural activity in euthymic bipolar patients as compared to healthy subjects is suggestive of emotional compromise that is independent of cognitive and executive functioning. This finding is of clinical importance and has implications both for the diagnosis and treatment of bipolar disorder. Future studies should aim to replicate these findings and examine the development of bipolar disorder, investigating in particular the effects of medication.

Keywords: fMRI; Affect; Bipolar disorder; Euthymia; Mood induction

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1. Introduction

In that sweet mood when pleasant thoughts bring sad thoughts to the mind

William Wordsworth *(1770–1850)*

The vicissitudes of mood, ranging from despair to delight, are common experiences that can be prompted by circumstance or chance, and as so eloquently described by Wordsworth can comprise varied and sometimes seemingly contrasting elements. However, even opposing emotions are sometimes miscible, as in bipolar disorder where patients have coterminous symptoms of dysphoria and hypomania described as 'mixed states' (Akiskal et al., 2005; Berk et al., 2005). Clinically, such admixtures are difficult to detect, often only manifesting as a subtle functional compromise. Indeed it has become increasingly apparent that 'euthymia' does not equate to recovery and that akin to its bedfellows, hypomania and depression, it too is associated with neurocognitive deficits (Ferrier et al., 1999; Olley et al., 2005). Recent studies have identified executive impairments and memory dysfunction (Malhi et al., in press; Malhi et al., 2004a; Martinez-Aran et al., 2004a,b) that perhaps underpin patient reports of 'diminished emotional reactivity' and 'an inability to negotiate real-world problems'. Functional neuroimaging studies in bipolar disorder have attempted to localise these deficits and have identified a number of key brain regions (Adler et al., 2004; Blumberg et al., 2003a; Malhi et al., 2004b,c; Monks et al., 2004).

1.1. Functional neuroimaging studies in bipolar disorder

Early research yielded somewhat disparate findings (see Ketter et al., 2001; Malhi et al., 2004d; Phillips et al., 2003) however, the results from more recent studies have been more consistent (Strakowski et al., 2005). A series of studies (Blumberg et al., 2003a,b) that partitioned trait and state effects by examining bipolar patients in all three phases of the disorder using the colour-naming Stroop task found activations in the prefrontal and dorsal anterior cingulate cortices across all groups. However, in comparison to controls, patients had blunted activation in a rostral region of the left ventral prefrontal cortex that was spatially distinct and independent of mood state, a finding that has been corroborated by a recent functional magnetic resonance imaging (fMRI) study that also employed an emotional Stroop paradigm (Malhi et al., 2005). Furthermore, in comparison to euthymic patients, the ventral prefrontal cortex increase in signal was blunted in patients with elevated mood on the right side but exaggerated in depressed patients on the left side. The authors thus opined that bipolar disorder may be associated with a trait abnormality in the left ventral prefrontal cortex and that additional lateralized abnormalities may relate to the valence of the mood episode. Extrapolating to a younger age group the same researchers also identified increased activation in the left thalamus and putamen of bipolar adolescents as compared to healthy subjects suggesting once again a subcortical dysfunction in bipolar disorder (Blumberg et al., 2003b). Interestingly, the lack of prefrontal cortical dysfunction in this age group prompted speculation that this may be a developmental abnormality that stems from subcortical dysfunction involving disruption of inhibitory regulation in the basal ganglia.

State-related differences in emotional processing have also been reported in two recent studies (Malhi et al., 2004b,c) that adopted an fMRI picture-caption cognition-based mood induction paradigm previously validated in healthy subjects (Teasdale et al., 1999) as well as patients with major depression (Kumari et al., 2003). Examining patients with bipolar depression and hypomania a pattern of subcortical activation emerged that prompted the suggestion that prefrontal cortex engagement is impaired in patients when unwell resulting in recruitment of additional subcortical brain regions.

1.2. Aim of the study

In this study we employed fMRI to contrast the brain regions engaged by euthymic bipolar patients and healthy subjects when responding to implicit affect induction. We examined euthymic patients to avoid a mood-state confound and employed an implicit design to ensure task engagement.

On the basis of extant literature and our previous studies we hypothesised that patients would have diminished activation as compared to healthy subjects, specifically in prefrontal and cingulate cortices and, that subcortical structures would be less responsive.

2. Methods

2.1. Subjects

Ten right-handed female patients with bipolar I disorder were recruited from our Sydney Bipolar Disorder Clinic at the Prince of Wales Hospital. A research psychiatrist made the diagnoses using the Structured Clinical Interview for DSM-IV (SCID-P) (First et al., 1995) supplemented by case note review. At

the time of participation, all patients had been in remission (no significant symptoms or alteration in medication status) for a period of at least three months (verified by self-report, clinical assessment and case note review). Subjects were excluded if they had a history of substance abuse, neurological disease or closed head injury, an additional Axis-I or any Axis-II psychiatric diagnosis or a medical disorder currently necessitating treatment.

Patients were aged 19–54 years (mean±SD 32.4±10.8 years) and gainfully employed. Symptoms were assessed using the 17-item Hamilton Depression Rating Scale (Hamilton, 1960), the Young Mania Rating Scale (Young et al., 1978), the Montgomery–Asberg Depression Rating Scale (Montgomery and Asberg, 1979), the Global Assessment of Functioning scale (American Psychiatric Association, 1994) and the CORE measure for psychomotor disturbance (Parker and Hadzi-Pavlovic, 1996). Patients were defined as euthymic if they scored 6 or less on the 17-item Hamilton Depression Rating Scale and 6 or less on the Young Mania Rating Scale. Patients also completed the following questionnaires: the Beck Depression Inventory (Beck et al., 1961) and the Spielberger State-Trait Anxiety Inventory (Spielberger, 1983).

The mean duration of illness from diagnosis was 8.8±5.8 years, and the mean number of previous depressive episodes was 4.9±4.1 and manic episodes 3.2±2.6. None of the patients met DSM-IV criteria for rapid cycling. At the time of fMRI scanning, seven patients were on mood-stabilising psychotropic medications and three were on no medication. Five patients were taking lithium (mean daily dose 1340±230.2 mg) with a mean plasma level of 0.76±0.09 mmol/L. One of these patients and one other were each taking lamotrigine 100 mg daily with the final patient on mood-stabilising medication taking carbamazepine alone (700 mg daily, plasma level of 40.0 μg/mL). Two patients had received electroconvulsive therapy (more than 12 months prior) and seven patients had at least one first-degree relative with an affective disorder.

Patients were compared with ten female volunteers matched for age (20–54 years; mean 31.7±11.9 years), handedness (all right-handed), level of education and premorbid IQ (see Table 1). 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 scanning.

2.2. fMRI task

To ensure that subjects satisfactorily engaged the implicit affect-inducing stimuli, the task was constructed to necessitate a response based on the material presented. Patients were not alerted to the affective components of the task.

2.2.1. Visual word stimuli

Two hundred and forty words were extracted from the Lang Affective Norms for English Words (ANEW) database (Bradley and Lang, 1999) such that with respect to affect a quarter (sixty) were unambiguously negative

Table 1
Demographic data and clinical assessment scores for patients and healthy comparison subjects

	Healthy subjects	Euthymic bipolar patients
	Mean (SD)	Mean (SD)
Age (years)	31.7 (11.9)	32.4 (10.8)
Years educated	15.9 (2.0)	16.1 (2.9)
IQ	111.4 (5.2)	110.2 (5.1)
BDI	4.8 (0.8)	7.6 (1.0)
Ham-D	3.1 (1.0)	4.2 (1.0)
MADRS	3.2 (0.9)	3.6 (0.8)
STAI-I	29.4 (4.4)	29.6 (5.1)
STAI-II	30.8 (4.0)	31.5 (4.7)
CORE [a]	0.0 (0.0)	0.4 (0.5)
YMRS	0.8 (0.9)	0.9 (0.8)
GAF [a]	91.5 (4.1)	86.5 (8.2)

[a] Patients and healthy subjects only differed significantly on CORE and GAF scores with *t*-test statistic *p*-values of 0.00 and 0.05 respectively. Abbreviations: HAM-D (17-item Hamilton Depression Rating Scale); YMRS (Young Mania Rating Scale); MADRS (Montgomery–Asberg Depression Rating Scale); GAF (Global Assessment of Functioning scale) CORE (measure for psychomotor disturbance); BDI (Beck Depression Inventory); STAI (Spielberger State-Trait Anxiety Inventory).

and another quarter were positive. The remaining words were neutral in terms of their affect and all three groups of words were matched with respect to arousal (means and standard deviations for positive, negative and neutral words respectively — 5.6 (3.0); 5.4 (2.7); 5.1 (2.0). Negative, positive and neutral lists of 3, 5 or 7 words were constructed and this produced 12 positive and 12 negative word lists with four of each length (3, 5 and 7), and 24 matching neutral word lists. Half of the 3, 5 and 7 word lists were then matched to a target word such that 50% of the responses would be affirmative (that the word is contained within the list). Target words and lists were matched with respect to affect and lists were balanced for order of presentation and target word position.

2.2.2. Task design

A delayed-response working memory paradigm (see Fig. 1) based on the Sternberg memory task (Sternberg, 1969) was constructed using emotionally valent words contained within word lists that had been generated as described above. Subjects were instructed to memorise vertical lists of 3, 5 or 7 words presented for 8 s after which the screen was blank (except for a fixation cross-hair) for 4 s. A target word then appeared and was presented for 2 s during which time the subject had to decide whether or not the target word was part of the previously presented word list and respond by pressing specified reaction time buttons using index (for Yes) and middle fingers (for No) of both hands. The target was then erased and a 1 second delay preceded the appearance of the next word list. Prior to scanning, subjects were instructed and the task was demonstrated using a practice set of neutral word stimuli. After scanning, all subjects rated the affect of a subset of the word stimuli.

An event-related task was designed with 15 s between successive word-list stimuli and a total run time of 720 s. Overall, 48 unique computer generated word lists (16 × 3 words, 16 × 5 words and 16 × 7 words) were presented in an order counterbalanced for valence, using a 50 point Arial font and back-projected in black ink onto a frosted white screen using an LCD video projector. Subjects viewed the screen through a mirror fixed to the head coil and words subtended a visual angle of approximately 8°–15° horizontally depending on their length. Mean reaction time as well as individual reaction times was acquired using a fibre optic device (response window 50–2000 ms) specifically designed for use in the MR scanner. Subjects were debriefed following completion of the experiments with respect to the mood induction effects of the imaging.

2.3. Statistical analyses of affective word-list ratings and behavioural data

Independent and one-sample *t*-test comparisons of mean valence ratings of positive, neutral and negative words for bipolar patients, healthy controls and a normative reference group were conducted. As the variance of the normative reference group data could not be calculated ANOVA analysis utilising valence as a within-subjects variable could not be conducted. In order to identify between group differences in performance, reaction time data were analysed using a 2 way ANOVA.

2.3.1. Functional imaging

Imaging was performed using a 1.5 T Philips Intera MRI scanner. Sixteen axial slices (7 mm thickness, no gap) parallel to the anterior and posterior commissure

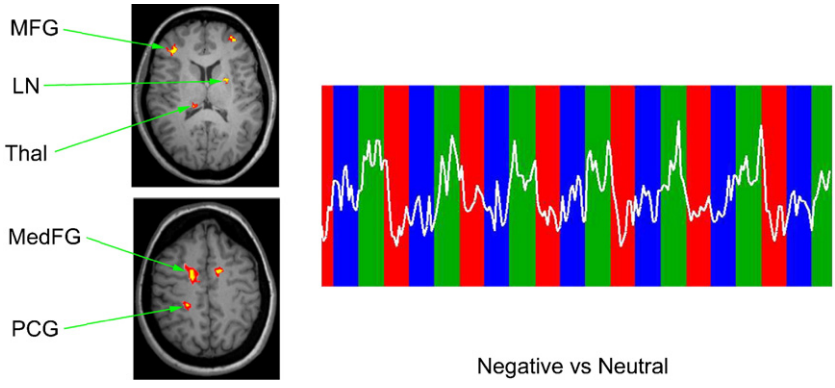

Fig. 1. Negative versus neutral: Group analysis activation foci and signal temporal display of the thalamic BOLD response. Note: Negative versus neutral group analysis images are radiologically orientated with the top image taken at $z=14$ and the bottom image taken at $z=49$. Regions labelled and depicted in yellow/red denote activations that were greater in healthy subjects than in euthymic bipolar patients. [MFG — middle frontal gyrus, LN — lentiform nuclei, Thal — thalamus, MedFG — medial frontal gyrus, PCG — posterior cingulate gyrus.]

Table 2
Ratings of positive and negative words

Valence of words	ANEW	Healthy subjects	Euthymic bipolar patients
	Mean (SD)	Mean (SD)	Mean (SD)
Positive	8.14 (2.51)	8.01 (0.15)	7.89 (0.15)
Negative	2.46 (2.12)	2.31 (0.17)	2.10 (0.21)[a]
Neutral	5.20 (1.99)	5.12 (0.16)	5.01 (0.17)

[a] Patients rated negative words significantly more negatively.

covering the whole brain were imaged with a temporal resolution of 3 s using a T2 weighted gradient echo EPI sequence (TE=45 ms; TR=3000 ms; matrix=64×64; flip angle=90°). The field of view was 400 mm and the effective in-plane functional spatial resolution was 3.59 mm. For each functional run a total of 240 whole brain scans were collected. As an aid to localisation of the activated voxels T_1-weighted high-resolution whole brain images (with the following parameters: TR=28, TE=5 ms, matrix 256×256, FOV 300 mm, acquired resolution=1.17×1.17×1.0 mm) were acquired. Additionally, high-resolution anatomical images in the plane of the functional slices were also acquired to facilitate the co-registration of the functional volumes to a Talairach (Talairach and Tournoux, 1988) calibrated whole brain image. All subjects had their heads firmly immobilized in the head coil using forehead straps and foam inserts.

2.4. Statistical analysis of fMRI data

All functional data was pre-processed using SPM99. Images were interrogated and carefully scrutinized for movement and susceptibility artefacts. Data was corrected for movement using least square minimisation and was smoothed using an 8×8×10 (FWHM) Gaussian kernel to compensate for residual spatial variability and to reduce the effect of variation of MR signal between runs.

Two separate statistical analyses were performed on individual and group data with respect to affect induction by negative and positive words.

Table 3
Tailarach and Tournoux coordinates of regions in patients and healthy subjects showing significant *within-group* differences in activation in response to *negative versus neutral* affect

Brain region	Brodmann's area	Healthy subjects				Bipolar patients			
		Talairach coordinates[a]				Talairach coordinates[a]			
		x	*y*	*z*	*z* score	*x*	*y*	*z*	*z* score
Superior frontal gyrus	9/10								
Right		14	58	20	5.32				
		16	42	34	5.44				
Left		−12	48	34	5.13				
Inferior frontal gyrus	45/47								
Right						50	26	4	4.60
Left		−34	22	−6	5.48	−38	22	−4	4.55
		−38	24	4	4.24	−46	30	4	4.21
		−44	20	12	5.72				
Posterior cingulate, left	30/31	−8	−54	20	6.03	−6	−60	14	6.78
Superior temporal gyrus	38								
Right		40	10	−22	5.71	52	4	−8	4.06
		40	6	−12	4.63				
Left		−42	10	−22	5.05				
		−48	−2	−6	5.24				
		−44	6	−12	5.15				
Middle temporal gyrus	21								
Left		−42	−46	6	4.21	−54	−4	−20	5.19
		−38	−62	20	4.56	−56	−14	−4	4.55
						−54	0	−10	4.08
Insula, left		−40	−22	−4	4.82				
Medial globus pallidus, right		12	2	−4	6.53				
Caudate (head), left		−8	4	4	4.12				
Precuneus, right	7	14	−40	44	5.91				
Lingual gyrus, right	18					26	−76	−10	5.09
Declive (cerebellum), right						30	−78	−18	4.92
Cerebellar tonsil, right						22	−60	−38	4.05

[a] Based on peak *z* value.

2.4.1. Within-group analysis

A within-group analysis on individual data was performed using MED × 3.4.1 (Sensor Systems, Sterling VA) with all functional data globally normalised to an empirically determined value of 1000. This involved proportional scaling of each voxel by the global mean at that time point and removal of low frequency noise by using a high-pass filter (3 cycles/min) applied across the fMRI time series for each voxel. A temporal smoothing function was then applied to the fMRI time series in order to enhance the temporal signal to noise ratio.

The resultant *Z*-score maps were thresholded to a Bonferroni-corrected probability of $p<0.05$, 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. The procedure of co-registering the *Z*-score maps (generated from the functional images) to the T_1-weighted whole brain anatomical images for the purpose of localisation of activation foci can be problematic, especially when the two sets of images are of different resolutions. In order to achieve a high degree of registration accuracy, the T_1-weighted anatomical image collected in the same plane as the functional images was first co-registered to the whole brain anatomical image. A transformation matrix describing this "successful" registration was then saved and later applied to the lower resolution *Z*-score map, effectively positioning it in the 3-D space in which the functional images were originally acquired. The whole brain anatomical image was then normalised into Talairach

Table 4
Tailarach and Tournoux coordinates of regions in patients and healthy subjects showing significant *within-group* differences in activation in response to *positive versus neutral* affect

Brain region	Brodmann's area	Healthy subjects				Bipolar patients			
		Talairach coordinates[a]				Talairach coordinates[a]			
		x	*y*	*z*	*z* score	*x*	*y*	*z*	*z* score
Inferior frontal gyrus									
Right	47	46	26	2	5.29	42	24	−6	5.07
						48	20	2	5.31
Left		−36	24	6	4.79	−44	20	2	5.28
		−32	18	−8	4.72				
Medial frontal gyrus									
Right	9/10					10	50	2	6.06
						8	48	−6	5.39
Left		−4	48	38	4.04				
		−2	56	20	4.75				
Precentral gyrus, right	4	60	−6	20	4.08				
Anterior cingulate, left	32					−6	42	−6	5.46
Posterior cingulate, left	31	−2	−44	20	4.56				
Superior temporal gyrus									
Right	38/39/42	64	−30	6	4.51	42	6	−24	4.81
						46	12	−12	4.96
Left		−36	2	−20	4.48				
		−36	2	−30	4.86				
		−46	−60	20	4.26				
Middle temporal gyrus									
Right	20/21	46	−2	−30	4.83				
Left		−56	−20	−8	4.86				
		−52	−48	2	5.29				
Insula, left		−40	20	2	4.97	−38	−16	−6	4.84
Fusiform gyrus, left	19	−34	−72	−12	4.76				
Lingual gyrus									
Right	18					18	−70	2	5.27
Left						−22	−90	−6	5.57
Cerebellar tonsil									
Right						22	−62	−38	5.08
Left		−14	−54	−42	4.61				
Tuber, right		32	−66	−30	5.38				

[a] Based on peak *z* value.

space using a piecewise-linear scaling method, and the resultant transformation matrix was saved. The latter was then applied to the transformed *Z*-score map and the resultant *Z*-score image was co-registered to the Talairach normalised whole brain anatomical image using AIR (Woods et al., 1993).

2.4.2. Between-group analysis

Individual pre-processed data that had been globally normalised and linearly detrended was analysed using the General Linear Model (GLM) and the theory of Gaussian random fields as implemented in the BrainVoyager software package (Brain Innovations, Netherlands). A between-group analysis was performed using a random-effects model to provide an estimate of the error variance for each condition of interest across subjects, rather than across scans thus providing a stronger generalisation to the population (Holmes and Friston, 1998).

Affective word-related differences between the controls and patients for Positive and Negative affective words were compared. Individual contrast images reflecting activations arising from Positive and Negative valenced words were created separately and contrast analysis of the predictors was used to find regions in which average activity was higher during the positive or negative word phases between groups.

3. Results

3.1. Affective word-list ratings

There were no statistically significant differences in mean rating scores for positive words between the patient, healthy control and normative reference groups. Similarly, comparisons of mean rating scores of neutral words failed to demonstrate significant differences between the three groups. However, when compared to the control group ($t8=2.52$, $p<0.05$) and the normative reference group ($t9=-4.99$. $p<0.01$), bipolar patients rated negative words significantly more negatively. Mean valence rating scores for the negative words did not differ significantly between the healthy control and normative reference groups (see Table 2).

3.2. Behavioural results

The performance of healthy subjects and patients was predictably better on the 3 word lists (96% and 93% accuracy, respectively) than on the more difficult 7 word lists (84% and 78%, respectively) however, there was no significant group difference in response accuracy [ANOVA: $F(2,56)=4.23$, $p=.11$]. Patients had slower

Table 5
Coordinates of brain regions showing between-group differences for *negative affect*

Brain region	Brodmann's area	Talairach coordinates			
		x	*y*	*z*	*p*-value
Middle frontal gyrus					
Right	9/10	28	28	36	4.08×10^{-11}
Left		−31	44	12	3.5×10^{-13}
Medial frontal gyrus					
Right	6	18	6	49	4.82×10^{-18}
Left		−10	5	49	4.76×10^{-14}
Postcentral gyrus					
Right	3	34	−18	36	9.63×10^{-13}
		20	−24	49	1.79×10^{-11}
Anterior cingulate gyrus					
Right	32	3	21	36	8.31×10^{-11}
Left		−12	18	36	2.83×10^{-13}
Posterior cingulate gyrus, right	31	17	−22	36	1.26×10^{-12}
Inferior parietal lobule					
Left	40	−43	−33	33	2.48×10^{-11}
		−43	−30	36	1.53×10^{-11}
Parahippocampal gyrus, right	30	17	−37	7	2.1×10^{-11}
Thalamus					
Right		18	−15	4	4.1×10^{-12}
		21	−15	7	1.68×10^{-10}
		16	−36	14	9.5×10^{-10}
		21	−23	14	3.75×10^{-11}
Putamen, left		−20	7	15	1.9×10^{-11}

All activations favoured healthy subjects.

reaction times but the difference was not statistically significant [$F(2,56)=3.19$, $p=.079$].

3.3. fMRI results

The results of within-group and between-group analyses of the responses to affect induction are presented in Tables 3–6 and described below.

3.3.1. Within-group analyses

3.3.1.1. Negative versus neutral words (Table 3). Healthy subjects showed significant activation in the superior and inferior frontal and superior and middle temporal gyri bilaterally. They also showed left-sided activation in the posterior cingulate, insula and head of caudate and right-sided activation in the medial globus pallidus and precuneus.

In common with healthy subjects, euthymic bipolar patients also showed bilateral activation in the inferior frontal and superior and middle temporal gyri and had left-sided activation in the posterior cingulate. Additionally, patients had right-sided activation in the lingual gyrus and cerebellum but lacked any significant lentiform nuclei activation.

3.3.1.2. Positive versus neutral words (Table 4). Healthy subjects again showed significant activation in the inferior frontal and superior and middle temporal gyri bilaterally. They also showed only left-sided activation in the medial frontal and fusiform gyri, posterior cingulate, insula and cerebellum. Purely right-sided activation occurred only in the precentral gyrus.

In contrast patients showed left-sided activation only in the anterior cingulate and insula. They also showed bilateral activation in the inferior frontal and lingual gyri and right-sided activation in the cerebellum, medial frontal and superior temporal gyri.

3.3.1.3. Summary. In response to negative affect both healthy subjects and patients showed activations in the inferior frontal, superior and middle temporal and posterior cingulate gyri. Only healthy subjects showed responses in the medial prefrontal cortex, insula, precuneus and subcortical nuclei and only patients showed responses in the lingual gyrus and cerebellum.

In response to positive affect both healthy subjects and patients showed activations in the insula, cerebellum, and superior temporal and inferior and medial frontal gyri. Only healthy subjects showed responses in the precentral, middle temporal, posterior cingulate and fusiform gyri and only patients showed responses in the anterior cingulate and lingual gyri.

Of note, inferior frontal and superior temporal activation occurred in both groups in response to both negative and positive affect and both anterior and posterior cingulate responses were all left-sided.

3.3.2. Between-group analyses

All activations in response to both negative and positive words were greater in healthy subjects as compared to patients.

3.3.2.1. Negative words (Table 5 and Fig. 1). Activations in response to negative words showed significant bilateral differences between patients and healthy subjects in the postcentral, middle and medial frontal gyri; right-sided differences in the posterior cingulate, parahippocampal gyrus and thalamus and

Table 6
Coordinates of brain regions showing between-group differences for *positive affect*

Brain region	Brodmann's area	Talairach coordinates			
		x	*y*	*z*	*p*-value
Superior frontal gyrus					
Right	10	11	43	19	3.3×10^{-4}
Left		−18	56	16	2.1×10^{-5}
		−19	59	27	2.3×10^{-4}
Middle frontal gyrus					
Right	9/10	27	47	16	5.0×10^{-8}
		27	54	13	3.0×10^{-6}
Left		−31	53	4	8.0×10^{-5}
Precentral gyrus					
Right	4	35	−16	61	1.7×10^{-4}
		48	−11	35	1.3×10^{-5}
Left		−46	−11	35	3.5×10^{-4}
Anterior cingulate gyrus, right	32	6	34	16	2.3×10^{-4}
Posterior cingulate gyrus, left	31	−7	−6	43	3.6×10^{-4}
Superior temporal gyrus, left	22	−61	−29	4	1.6×10^{-5}
Parahippocampal gyrus, right	30	17	−54	−6	3.8×10^{-5}
Lingual gyrus, right	18	16	−84	−6	2.6×10^{-5}
Precuneus and cuneus					
Right	7/18	12	−73	16	4.9×10^{-4}
Left		−13	−70	35	8.8×10^{-5}
Caudate					
Right	*Body*	11	11	16	3.3×10^{-4}
Left	*Head*	−13	17	−1	3.4×10^{-4}
Pons, right		13	−26	−19	4.9×10^{-4}
Midbrain, right		5	−39	−11	5.7×10^{-4}
Cerebellum, right		13	−33	−11	7.6×10^{-4}

All activations favoured healthy subjects.

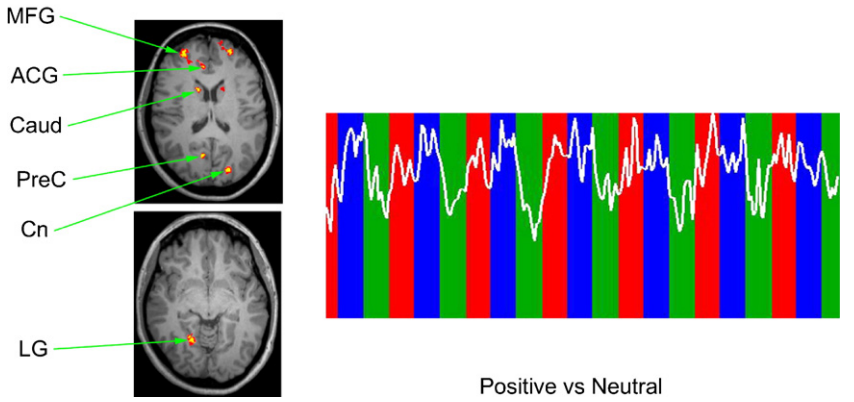

Fig. 2. Positive versus neutral: Group analysis activation foci and signal temporal display of the caudate BOLD response. Note: Positive versus neutral group analysis images are radiologically orientated with the top image taken at $z=14$ and the bottom image taken at $z=49$. Regions labelled and depicted in yellow/red denote activations that were greater in healthy subjects than in euthymic bipolar patients. [MFG — middle frontal gyrus, ACG — anterior cingulate gyrus, Caud — caudate, PreC — precuneus, Cn — cuneus, LG — lingual gyrus.]

left-sided differences in the anterior cingulate, inferior parietal lobule and putamen.

3.3.2.2. Positive words (Table 6 and Fig. 2). Activations in response to positive words showed significant bilateral differences between patients and healthy subjects in the precentral, superior and middle frontal gyri; right-sided differences in the anterior cingulate, parahippocampal and lingual gyri, cuneus, body of caudate, pons, midbrain and cerebellum and left-sided differences in the posterior cingulate and superior temporal gyri, precuneus and head of caudate (Fig. 2).

3.3.2.3. Summary. Significantly greater activation occurred in healthy subjects as compared to patients in response to both negative and positive affect in the anterior and posterior cingulate, medial prefrontal cortex, middle frontal and right parahippocampal gyri. Only negative affect produced significantly greater activation in the postcentral gyrus, inferior parietal lobule, thalamus and putamen and only positive affect achieved the same in the precentral, superior temporal and lingual gyri, precuneus, cuneus, caudate, pons, midbrain and cerebellum. There were no brain regions in which responses were greater in patients as compared to healthy subjects.

4. Discussion

The principal finding in this study is that euthymic bipolar patients are less responsive than healthy subjects with respect to both negative and positive affect and that the pattern of differences in activation between the two groups is dependent on affective valence. However, prior to a detailed discussion of the findings it is important to acknowledge a number of putative limitations.

4.1. Limitations

The most important potential confound is that of medication, with seven patients taking mood stabilisers at the time of scanning — the most common one being lithium. Lithium can alter vascular smooth muscle contractility and in the brain this may affect neurovascular coupling upon which the BOLD response is predicated (Dehpour et al., 1995). However, this is more likely to produce global effects than the specific regional changes, although it is important to note that global blood flow changes can affect local BOLD responses and the coupling between local neuronal activity and hemodynamics. As only three patients were unmedicated, a sub-analysis of the effect of medication was not possible.

It is likely that the relatively small sample size also diminished the power of the study with respect to identifying between-group differences in behavioural responses such as in reaction times. Performance and BOLD responses can also be affected by anxiety within the scanner (Lagopoulos et al., 2005) and it is possible that during the experiment patients were more or less anxious than controls.

Another limitation concerns the use of implicit affect induction and a specific memory task so as to ensure measurable engagement within the scanner. Effortful generation of affect as opposed to passive viewing may involve different brain regions and permit compensatory recruitment of additional resources that complicates

interpretation. However, such confounds may be associated with the introduction of a cognitive task *per se* (Phan et al., 2002), and although in this study, the behavioural responses suggest that patients performed as well as healthy subjects, it is possible that some of the differences in activation reflect cognitive variance as opposed to changes in affect.

Finally, wider application of our findings is somewhat limited as patients were confined to those suitable for scanning. Therefore extrapolating to patients with rapid cycling or bipolar II may not be appropriate, especially as co-morbid illnesses such as substance misuse and anxiety disorders were excluded, and only females were scanned.

4.2. Responses to both positive and negative words

Differences in activation in the medial prefrontal cortex, anterior and posterior cingulate and parahippocampal gyrus were present irrespective of whether the affect induced was negative or positive, suggesting that these regions are involved in the processing of emotional stimuli regardless of valence.

Reduced activity in the medial prefrontal cortex has been reported in euthymic and depressed bipolar patients, and remitted and depressed unipolar patients (Kruger et al., 2003; Liotti et al., 2002). In healthy subjects, medial prefrontal cortex activation has been associated with the appraisal of emotions (; Teasdale et al., 1999) and with self-referential evaluation (Craik et al., 1999; Kelley et al., 2002; Kircher et al., 2000, 2002). The allocation of additional resources to the recovery of emotional information (Schacter et al., 1996) or the need for heightened monitoring and evaluation of retrieved information within an emotional context involves prefrontal cortex activity (Fletcher and Henson, 2001; Henson et al., 1999a,b; Shallice et al., 1994). Therefore, reduced activity in euthymic bipolar patients can be interpreted as an inability to recruit additional resources or engage post-retrieval processing because of prefrontal dysfunction. This is in keeping with findings from recent studies that have detected state and trait-related prefrontal abnormalities (Blumberg et al., 2003a, b; Malhi et al., 2004b,c). However, within-group analyses show that affective words as compared to neutral words produced inferior prefrontal cortex activation in both patients and healthy subjects indicating that language-mediated processing of words with emotional salience (Beauregard et al., 1997; Elliott et al., 2000; Maddock et al., 2001; Strange et al., 2000), and the evaluation of emotional meaning remain intact (Maddock et al., 2003). Therefore the groups may differ simply because of a negativity bias in patients that is either inherent or stems from sub-syndromal symptomatology (Cacioppo and Gardner, 1999).

Emotional meaning and motivational information are also thought to be subserved by the affective division of the anterior cingulate cortex (ACC) (Devinsky et al., 1995), which is partitioned functionally into rostral–ventral affective (BA24/32 and BA 25) and dorsal cognitive (BA24/32) components (Bush et al., 2002). The ACC is involved in attention regulation during cognitive (Devinsky et al., 1995) and emotional processing (Bush et al., 2000; Whalen et al., 1998) and has close links with the medial prefrontal cortex (BA9/10) that computes and maintains online information necessary for the choice of an appropriate response, whilst the ACC facilitates implementation of the selected action (Paus, 2001). Previous studies have shown ventral ACC activation in response to emotionally salient words (Beauregard et al., 1997; Elliott et al., 2000; Tabert et al., 2001) however, in the present study patients were unable to activate the cognitive division (BA32) in response to negative words and the affective division (BA24) in response to positive words to the same extent as healthy subjects. This suggests that patients were unable to process the emotional valence of positive words — ultimately a function of the affective division of the ACC, and that the processing of negative words within its cognitive division was limited (Bush et al., 1998; Drevets and Raichle, 1998). One possible explanation is that patients, seemingly 'recovered', remain attuned to negative cues such that at a 'limbic level' they relate more to negative than positive affect but are impaired with respect to associated cognitive elaboration. However, the ACC has a variety of sophisticated functions including for instance, error detection and conflict monitoring, and so interpretation of our findings is guarded.

Like the ACC, the posterior cingulate cortex (PCC) has a number of putative roles. Its caudal region is robustly activated during the evaluation of emotional words (Maddock et al., 2003) in particular those associated with threat (Maddock, 1999; Maddock and Buonocore, 1997), and is also implicated in the modulation of memory by emotionally arousing stimuli (Andreasen et al., 1995; Grasby et al., 1993). However, a number of studies of episodic retrieval of emotionally neutral information have also reported posterior cingulate activation, suggesting that activity may reflect a more general function (Maratos et al., 2001). In the present study, both negative and positive affect produced less PCC activation in patients than in healthy subjects. However, within-group analyses showed that the left posterior cingulate (BA30/31), specifically its caudal region, is activated in patients in response to negative

affect whereas positive words failed to elicit any significant responses suggesting a valence-dependent differential in affective processing. One explanation is that negative words evoke more complex mental representations than positive words and are cognitively more demanding and that this type of cognitive processing that requires theory of mind (TOM), may be impaired in bipolar patients (Kerr et al., 2003). The caudal posterior cingulate cortex is also strongly interconnected with the subgenual cingulate (BA 25) (Van Hoesen and Solodkin, 1993), and has been repeatedly implicated in the pathophysiology of mood disorders (Drevets et al., 1997; Mayberg et al., 1999). However, in keeping with the findings of others (Kruger et al., 2003), diminished activity in this region in euthymic bipolar patients, suggests that this region is of greater pertinence to active depressive states (Liotti et al., 2002).

4.3. Responses to either negative or positive words

Negative affect produced uniquely greater activation in healthy subjects as compared to patients in the right postcentral gyrus, left inferior parietal lobule, right thalamus and left putamen.

Changes in basal ganglia activity are commonly observed in imaging studies involving the successful recognition of negative emotional stimuli (Fossati et al., 2004) and memory (Cabeza and Nyberg, 2000). Thalamic activation in response to both negative and positive affect has been noted in healthy subjects and depressed and hypomanic bipolar patients (Malhi et al., 2004b,c). Left putamen activation in response to negative words (Fossati et al., 2004) is thought to be associated with the integration of internal states and the maintenance of negative mood (Critchley et al., 2000). In the present study, diminished basal ganglia activation in euthymic bipolar patients in response to negative words suggests that subcortical thalamic processing of negative affect does not occur to the same extent as in healthy subjects. One explanation for this is that subcortical processing of negative affect is less critical in patients where a negative bias facilitates the generation of a negative emotional state, and in keeping with this left putamen activation was greater in healthy subjects.

Positive words produced greater activation in healthy subjects in the precentral gyrus, caudate, superior temporal and lingual gyrus, the cuneus and precuneus, pons, midbrain and cerebellum. Anterior left temporal cortex activation has been shown to occur when processing pictures with positive emotional content and when processing emotional words (Crosson et al., 1999; Phan et al., 2002). Specifically, left temporal activation has been implicated in monitoring the emotional connotation of words (Crosson et al., 2002) and in keeping with this, findings in the present study suggest that in comparison to healthy subjects, patients had less left superior temporal activation when processing words with positive affect.

Caudate activity modulates a neural system loop connecting it to the thalamus and anterior cingulate (Alexander et al., 1990) such that decreased caudate metabolism has been linked to bipolar depression (Baxter et al., 1989), and increased blood flow that diminishes upon the withdrawal of lithium, has been associated with mania (Goodwin et al., 1997). Greater left-sided activity in the head of the caudate has been reported in bipolar patients when hypomanic as compared to when euthymic (Blumberg et al., 2000) however, diminished activity in euthymic patients as compared to healthy subjects suggests that even when euthymic, bipolar patients are unable to engage the caudate to the same extent as in health. One reason for this may be that basal ganglia activation reflects dopaminergic innervation and the involvement of striatal structures in reward, motivation and happiness (Damasio et al., 2000; Davidson and Irwin, 1999; George et al., 1996; Rauch et al., 1999; Redoute et al., 2000) and that these processes are less accessible to patients. However, like the thalamus, the caudate relays many circuits and fMRI activation may simply reflect motor function. Alternatively, emotion and motor function may be coupled whereby the basal ganglia coordinate actions in response to emotions and produce response preparedness with respect to approach or withdrawal from a stimulus, depending on whether it elicits a positive or negative affect (Panksepp, 1998; Sprengelmeyer et al., 1998). Similarly, responses in the pons, midbrain and cerebellum (Konarski et al., 2005) may reflect motor activity and emotion-related processing (Fletcher and Henson, 2001; Schmahmann and Sherman, 1998).

4.4. Conclusion

The key finding in the present study is that of diminished neural activity in euthymic bipolar patients as compared to matched healthy subjects. Loss of prefrontal control in bipolar depressed patients perhaps produces increased subcortical thalamic and ventral striatal metabolism that results in limbic disinhibition and the manifestation of affective symptoms irrespective of affect, with only subcortical responses partitioning positive and negative emotional processing. Therefore, despite equivalent executive functioning and cognitive appraisal of emotions, euthymic bipolar patients appear

to engage emotional circuitry less robustly than do healthy subjects.

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