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Decision-making in mania: a PET study

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Summary

Poor decision-making is often observed clinically in the manic syndrome. In normal volunteers, decision-making has been associated with activation in the ventral prefrontal cortex and the anterior cingulate gyrus. The aim of this study was to evaluate task-related activation in bipolar manic patients in these regions of the prefrontal cortex using PET. Six subjects with mania, 10 controls and six subjects with unipolar depression (an affective patient control group) were scanned using the bolus $H_2{}^{15}O$ method while they were performing a decision-making task. Activations associated with the decision-making task were observed at two levels of difficulty. Task-related activation was increased in the manic patients compared with the control patients in the left dorsal anterior cingulate [Brodmann area (BA) 32] but decreased in the right frontal polar region (BA 10). In addition, controls showed greater task-related activation in the inferior frontal gyrus (BA 47) than manic patients. A positive correlation (r_s = 0.88) between task-related activation in the anterior cingulate and increasing severity of manic symptoms was found. Depressed patients did not show significant task-related differences in activation compared with control subjects in the regions of interest. In conclusion, these patterns of activation point to abnormal task-related responses in specific frontal regions in manic patients. Moreover, they are consistent with neuropsychological observations in patients with lesions in the ventromedial prefrontal cortex, who show similar difficulties with decision-making and provide early evidence for context-specific neural correlates of mania.

Keywords: mania; positron emission tomography; decision-making; anterior cingulate; ventral prefrontal cortex

Abbreviations: BA = Brodmann area; MMSE = Mini-Mental State Examination; NART = National Adult Reading Test; rCBF = regional cerebral blood flow; SPM = statistical parametric mapping; VMPFC = ventromedial prefrontal cortex

Introduction

Mania is characterized by elated, expansive or irritable mood and is usually accompanied by abnormalities of cognition and speech, overactivity and decreased need for sleep. Manic patients often become involved in risky or indiscreet behaviour that may have painful consequences [Diagnostic and Statistical Manual of Mental Disorders (DSM IV); American Psychiatric Association, 1994). PET may provide useful information about which regions of the brain are dysfunctional in the manic syndrome. Many PET studies of patients with major depression point to the importance of the ventral and medial prefrontal cortex, particularly the orbitofrontal and the anterior cingulate regions (for reviews, see Ebert and Ebmeier, 1996; Goodwin, 1996; Drevets, 1998*a*; Elliott and Dolan, 1998; Videbech, 2000). A key question therefore concerns the importance of these regions in mania. There have, however, been very few PET studies of manic patients (Baxter *et al*., 1985; Al Mousawi *et al*., 1996; Drevets *et al*., 1997; Blumberg *et al*., 1999, 2000) probably because of the difficulties involved in imaging this clinically unstable patient group.

Evidence from lesion studies links the ventromedial prefrontal cortex (VMPFC) to symptoms that characterize mania. Fuster describes euphoria together with distractibility, impulsivity and overactivity in patients with orbitofrontal lesions (Fuster, 1989). Bechara and colleagues have described profound disruption of social behaviour in patients with ventromedial lesions who are unable to observe social conventions and decide advantageously on matters pertaining to their own lives (Bechara *et al*., 1994, 1996, 1997). Despite normal performance on many cognitive tasks (including tasks of learning and memory, language and attention and executive function tests, such as the Wisconsin Card-Sorting Test), patients with VMPFC lesions have specific deficits on a gambling task, which may relate to their social difficulties

(Eslinger and Damasio, 1985; Bechara *et al*., 1994, 1996, 1997, 1998, 2000). Furthermore, in a case series of patients with secondary mania (i.e. mania with a possible underlying toxic, metabolic or neurological cause), the site of the lesions often involved the orbitofrontal cortex or closely related circuits (Starkstein *et al*., 1988, 1990).

Despite very different clinical presentations, manic and depressed patients perform similarly on many cognitive tasks (Murphy *et al*., 1999). Poor decision-making is evident behaviourally in mania when, for example, patients overspend or take risky or impulsive business decisions. We have recently identified specific qualitative impairments in decision-making cognition in mania (Murphy *et al*., 2001). Manic patients, but not controls and unipolar depressed patients, chose the 'less likely' outcome on the probability-based decision-making task significantly more frequently (Murphy *et al*., 2001). Depressed and manic patients deliberated significantly longer than controls on their choice and bet suboptimally on their correct decisions. The manic patients performed in a very similar manner to patients with lesions in the VMPFC (Rogers *et al*., 1999*b*) on this task. Rogers and colleagues (Rogers *et al*., 1999*a*) found that normal volunteers performing a new decision-making task [which combines the measures looking at quality of decision making with a specific points score rather than a 'bet' chosen by the subject as in our previous study (Murphy *et al*., 2001)] showed activation of the right orbital prefrontal cortex and of the inferior prefrontal convexity [Brodmann area (BA) 47]. In addition, the rostral anterior cingulate was activated by this task in association with increasing difficulty of decision-making. We anticipated that we would demonstrate task-related abnormal activations in these prefrontal regions if we compared the performance of manic with control subjects, but not depressed with control subjects.

There are thus strong *a priori* reasons for linking the disrupted behaviour and impaired cognition that characterize mania to dysfunction in a number of prefrontal regions: specifically the anterior cingulate cortex and the ventral (both lateral and medial) prefrontal cortex. The purpose of the present experiment was to evaluate task-related activations in these regions using PET with the decision-making task of Rogers and colleagues (Rogers *et al*., 1999*a*).

Material and methods

This study was approved by the Cambridge Local Research Ethics Committee and by the Administration of Radioactive Substances Advisory Committee of the United Kingdom. The subjects' consent was obtained according to the Declaration of Helsinki. Six manic, six depressed and 10 control subjects with an age range of 21–50 years were scanned. All subjects were given the National Adult Reading Test (NART) (Nelson, 1982) to estimate premorbid IQ. There were no significant differences between the ages [$F(2,21) = 0.34$, $P = 0.70$] or NART IQ [$F(2,21) = 2.76$, $P = 0.09$] scores of the manic, depressed and control subjects (for means and standard deviations, see Table 1). All subjects were male and right-handed. Subjects underwent a T_1-weighted MRI scan and 12 PET scans, with the exception of two manic subjects who underwent six and seven PET scans, respectively. These two subjects requested to terminate the PET scans early because of discomfort from the headgear and from lying in the supine position for an extended period of time.

Table 1 *Mean age, NART IQ and mean scores on the YMS, HAM-D, MADRS and BDI*

	Group		
	Manic	Depressed	Controls
Age (years)	34 (4)	32 (4)	31 (2)
NART	109 (2)	118 (2)	117 (3)
MMSE	28 (0.4)	29.7 (0.3)	
HAM-D		17.5 (3)	
MADRS		24 (4)	
BDI		28.5 (5)	
YMS	25 (3)		

The standard errors are shown in parentheses. YMS = Young Mania Scale; MMSE = Mini-Mental State Examination; HAM-D = Hamilton Depression Scale; MADRS = Montgomery–Åsberg Depression Rating Scale; BDI = Beck Depression Inventory.

Subjects

Patient selection

Manic patients were recruited by a psychiatrist (J.S.R. or L.W.H.) from acute psychiatric inpatient wards. Patients were considered for inclusion if they were not overly aggressive, overactive or heavily sedated. Patients with unipolar major depressive disorder were recruited from psychiatric out-patients after discussion with their clinician and review of the case notes. Patients had to fulfil Research Diagnostic Criteria (Endicott and Spitzer, 1978) for mania or for major depressive disorder for inclusion in the study, and details about their history of psychiatric illness were obtained using the Schedule for Affective Disorders and Schizophrenia—lifetime version (Endicott and Spitzer, 1978). All patients were euthyroid. Patients were excluded if they had a current comorbid diagnosis of anxiety disorder or substance dependence [based on DSM IV criteria (American Psychiatric Association, 1994)], if they had an unstable medical condition or if they had received electroconvulsive therapy in the last year. Rating of symptoms for the manic subjects was performed using the Young Mania Scale (Young *et al*., 1978) within a day of the scan. The severities of symptoms of depression were rated using the Hamilton Depression Scale (17 items) (Hamilton, 1960), the MADRS (Montgomery-Åsberg Depression Rating Scale) (Montgomery and Åsberg, 1979) and the BDI (Beck Depression Inventory) (Beck *et al*., 1961) within a week of the scan (Table 1). Scores on the Mini-Mental State Examination (MMSE) (Folstein *et al*.,

Table 2 *Summary of prescribed medication in patients*

Prescribed medication	Mean dose	No. of manic subjects	No of depressed subjects
Paroxetine	25 mg		2
Cipramil	20 mg		1
Venlafaxine	387.5 mg		2
Dutonin	500 mg		1
No medication		1	
Lithium	867 mg	3	
Sodium valproate	600 mg	1	
Carbamazepine	300 mg	2	
Antipsychotic	550 mg	5	
Benzodiazepines	8 mg		1
Zopiclone	7.5 g	1	1

The antipsychotic dose is shown in chlorpromazine equivalents (British National Formulary, 2000).

1975) are also shown (Table 1). All patients except one manic patient (on no medication for 1 week) were taking their usual medication (psychotropic medication is summarized in Table 2).

Control subjects

Control subjects were recruited by advertisement in the community. The results for eight of these 10 subjects have been reported elsewhere (Rogers *et al*., 1999*a*). An additional two subjects were scanned for this study to ensure that the controls matched the patient groups in terms of age and NART IQ. Control subjects were excluded if they had a history of psychiatric or neurological illness or if they were taking medication that might affect cognition.

Task design

The probability-based decision-making task has been described fully by Rogers and colleagues (Rogers *et al*., 1999*a*). Two typical displays from the task are shown in Fig. 1A and B. The subjects were told that the computer had hidden at random a yellow token inside one of the red or blue boxes at the top of the screen and that this array of blue and red boxes would change from trial to trial. The subjects had to decide if the token was hidden under a red or blue box. The subjects were also given 100 points (their points score was shown on the screen) and told that each time they made their choice of a red/blue box they would have to risk some of their points on their choice being correct. So, in the example shown in Fig. 1A, if the subject chose red, then he gained 30 points if the yellow token was hidden under a red box but would lose 30 points if the token was under a blue box. On the other hand, if the subject chose blue then he would gain 70 points if he was correct but lose 70 points if he was incorrect. The subjects were required to indicate their decision by touching one of the two square response panels located at the bottom of the display, which contained the associated 'stake'. Immediately after selection, one of the boxes opened to reveal the location of the yellow token and the subject was given a message: 'You win!' or 'You lose!'. If the subject chose the correct colour the stake was added to his points score, and if he chose the wrong colour the points were subtracted. It was emphasized that these choices may be conservative or risky but that the subject should do whatever he felt was necessary to increase his score by as much as possible. During the scanning period, subjects were presented with red and blue boxes in a ratio of 4 : 2 or 5 : 1, the greater reward always favouring the least likely outcome, thus capturing the conflict inherent in risk-taking situations. The subjects always began working through a randomized sequences of decisions 1 min before the scan commenced. At the start of the scanning window, i.e. when the 'head count' began to rise, the experimenter advanced the sequence to one of two conditions (4 : 2 or 5 : 1 ratio) for ~1 min. The subjects were given rewards of 30 : 70, 20 : 80 or 10 : 90 for these decisions. All three ratios of reward appeared within one scan.

In the control condition, alternative displays showed only red or blue boxes, the yellow token already being revealed at onset. The box, which had shown the total points score, and the panel, which had shown the size of the reward, were now replaced with Xs. The subjects were required to monitor the displays until one of the response panels lit up with a white border before they touched the panel.

The 12 scans were divided into four runs of three scans. The first scan of each run was always a 4 : 2 choice, whereas the second and third scans were always either a 5 : 1 or a control condition scan. This was to control for possible differences in the visual and motor processing associated with the 4 : 2 and 5 : 1 choice conditions; the presentation rate of trials in each of the 5 : 1 and choice condition was always yoked to the latencies of choices in an earlier 4 : 2 choice condition (Rogers *et al*., 1999*a*). In addition, the frequency of reward in the 5 : 1 condition was always yoked to earlier 4 : 2 choice conditions, as regional cerebral blood flow (rCBF) changes have been observed in the orbital prefrontal cortex and associated limbic circuitry with changes in reinforcement rate (Elliott *et al*., 1999). The order of the 5 : 1 and control conditions was counterbalanced across scans within and between subjects. To remove linear time effects associated with earlier versus later scans, scan order was entered as a covariate (of no interest) in all analyses of the rCBF data. The nature of the task was explained to the subject and the subject was allowed to practise on one example before the start of the first scan after he had been positioned in the scanner.

Task analysis

Analyses of the behavioural data centred around two main measures: (i) the mean deliberation time (in ms) and the choice of the most likely outcome (associated with the smaller

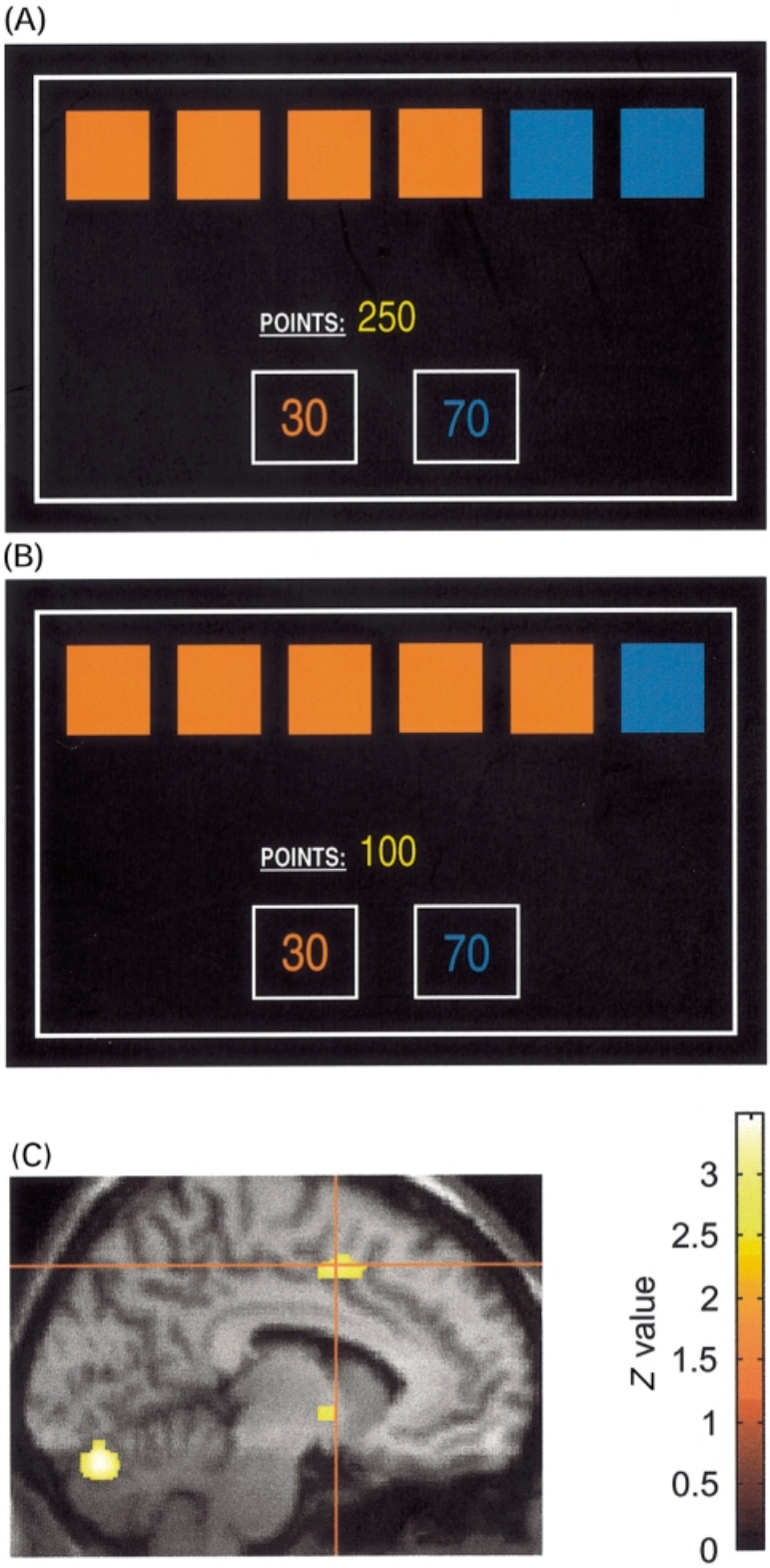

Fig. 1 (**A**) Typical display from the decision-making task in the 4 : 2 condition. (**B**) Typical display from the decision-making task in the 5 : 1 condition. (**C**) Interaction analysis between the controls and the manic patients for the 4 : 2 condition compared with the 5 : 1 condition.

reward). These data were analysed using repeated measures ANOVA (analysis of variance) with the subject group (controls, manic, depressed) as the between-subject factor and ratio (4 : 2 or 5 : 1) and balance of reward (30 : 70, 20 : 80 or 10 : 90) as the within-subject factors. Although the data presented are untransformed, before analysis the proportion data were arcsine-transformed (as is appropriate when the variance is proportional to the mean) and deliberation times were log-transformed [as is appropriate when the data are positively skewed (Howell, 1987)]. When the additional assumption of homogeneity of covariance in repeated-measures ANOVA was violated, as assessed using the Mauchly sphericity test, the number of degrees of freedom against which the F term was tested was reduced by the value of the Greenhouse–Geisser epsilon (Howell, 1987).

Scanning procedure

Each subject was scanned in the presence of a low level of background noise and the lighting was dimmed. The task displays were presented on a MicroTouch 20C touch-sensitive screen (3M Touch Systems, Methuen, Mass., USA) controlled by a Pentium microcomputer. The screen was mounted at a viewing distance of ~50 cm and the subject rested his dominant hand on his chest between responses.

PET scans were obtained with a General Electrics Advance scanner, which produces 35 image slices at an intrinsic resolution of ~5 × 5 × 5 mm. Using the bolus $H_2{}^{15}O$ method (Raichle *et al*., 1983) without arterial sampling (Fox and Raichle, 1984), rCBF was measured during four separate scans for each of the three experimental and control conditions (12 scans). For each scan, the subject received 300 MBq/ml $H_2{}^{15}O$ administered intravenously over 20 s through a forearm cannula. Each scan provided an image of rCBF integrated over a period of 90 s from when the tracer first entered the cerebral circulation. The 12 PET scans were initially realigned using the first scan as a reference and again using the mean of the scans as a reference, normalized to the standard brain template that forms part of the Statistical Parametric Mapping 98 (SPM98) software (Wellcome Department of Cognitive Neurology, London, UK). The images were then smoothed using an isotropic Gaussian kernel at 16 mm full width half maximum. For each subject, a three-dimensional MRI volume was acquired and resliced to be co-registered with the PET data. Composite stereotaxic MRI and PET volumes were co-registered to allow direct anatomical localization of regions with a statistically significant rCBF change between conditions.

The data from the manic, depressed and control subjects were all included in one analysis. Proportional scaling was applied to normalize the data globally. Multiple linear regression analyses were performed between and within groups (within and across conditions) at every voxel with SPM96 according to the general linear model (Friston *et al.*, 1995) and probabilities were estimated according to the theory of random fields. The resulting set of voxel t statistics constituted a statistical parametric map (SPM{t}). SPM{t} maps were transformed to the unit normal distribution SPM{Z} for display and thresholded at 3.09. Our *a priori* interest lay in the ventral and medial prefrontal cortex and the anterior cingulate cortex on theoretical grounds and the regions activated by this task in normal volunteers. For this reason, an acceptable level of type 1 error control for these regions only was $P < 0.001$, uncorrected for multiple comparisons. For all other regions, a corrected level of significance ($P < 0.05$) was set. We will focus our discussion on the regions that were hypothesized to be of interest.

Table 3 *Behavioural data acquired during scanning*

Choice of the most likely outcome (%)	Balance of reward		
	30 versus 70	20 versus 80	10 versus 90
Controls	0.92 (0.03)	0.85 (0.04)	0.77 (0.1)
Depressed	0.96 (0.02)	0.91 (0.06)	0.78 (0.09)
Manics	0.8 (0.06)	0.86 (0.07)	0.77 (0.08)
Deliberation time	5 : 1 trial ratio	4 : 2 trial ratio	
Controls	2208 (162)	2627 (197)	
Depressed	2465 (488)	3209 (554)	
Manic	2623 (438)	2573 (433)	

Data are mean (standard error).

Results

Task performance

For the percentage choice of the most likely outcome, there was no main effect of group ($F < 1$). An anticipated main effect of balance of reward was evident [$F(2,38) = 10.3$, $P < 0.001$] (Table 3). The subject's choice of the most likely outcome was reduced significantly as the size of the reward declined in comparison with that of the least likely outcome. There was no main effect of ratio ($F < 1$) or significant interaction between group and ratio ($F < 1$) or between group and balance of reward ($F = 1$), and no significant interaction between group, ratio and balance of reward ($F < 1$).

For the deliberation time, there was no main effect of group ($F < 1$). A main effect of ratio was seen [$F(1,19) = 20$, $P < 0.001$], subjects being slower to respond to the 4 : 2 ratio than to the 5 : 1 ratio in general. However, there was also a subject group × ratio interaction [$F(2,19) = 6.1$, $P < 0.009$]. Simple effects analysis demonstrated that this interaction arose because the control and depressed patients had slower deliberation times when the choice of boxes was presented in the 4 : 2 ratio compared with the 5 : 1 ratio [control subjects $F(1,9) = 11.5$, $P < 0.008$; depressed subjects $F(1,5) = 33.0$, $P < 0.002$]. Manic patients, however, did not show a significant difference in their deliberation times for the 4 : 2 compared with the 5 : 1 ratio (Table 3). Simple effects analysis showed no significant between-group differences at the 4 : 2 or the 5 : 1 ratio. There was an

Table 4 *Task-related within-group effects*

	Z score	Coordinates			Region	BA
		x	*y*	*z*		
Controls						
(4 : 2 plus 5 : 1) minus baseline	4.49	34	60	–4	Right middle frontal gyrus	10
	6.63	–34	–54	52	Superior parietal	7
	5.42	28	–64	44	Superior parietal	7
	5.55	–40	–72	–24	Cerebellum	
	5.26	–8	–32	–48	Cerebellum	
Baseline minus (4 : 2 plus 5 : 1)	3.65	–4	2	40	Anterior cingulate	32
	5.52	62	–44	16	Superior temporal gyrus	22
	5.24	–50	–72	16	Middle temporal gyrus	39
	4.55	52	–72	12	Middle temporal gyrus	39
Manic patients						
(4 : 2 plus 5 : 1) minus baseline	3.45	48	48	–8	Right middle frontal gyrus	10
	3.41	–2	18	28	Anterior cingulate	32
	4.88	–6	–78	–32	Cerebellum	
Baseline minus (4 : 2 plus 5 : 1)	4.53	–8	54	–8	Left superior frontal gyrus	10
	4.54	–62	–24	–16	Inferior temporal gyrus	20
	4.33	36	12	–36	Superior temporal gyrus	38
Depressed						
(4 : 2 plus 5 : 1) minus baseline	3.37	30	48	–8	Middle frontal gyrus	10
Baseline minus (4 : 2 plus 5 : 1)	4.63	–46	–16	–36	Inferior temporal gyrus	20
	4.34	–60	–46	–4	Middle temporal gyrus	37
Manic patients						
5 : 1 minus 4 : 2	2.92	–4	–4	44	Anterior cingulate	32

Significance level was set at $P < 0.001$ uncorrected for multiple comparisons in hypothesized regions and $P < 0.05$ corrected in all other regions.

expected overall main effect of reward ratio [$F(2,38) = 5.99$, $P = 0.006$]: subjects were slower when the reward was largest for the least likely probability ratio.

In summary, no significant impairment in the choice of the most likely outcome was shown between groups. Deliberation times differed only in that manic patients, unlike depressed and control subjects, did not slow down their responses in trials in which conflict was greatest.

PET results

Significance levels were set at $P < 0.001$ uncorrected for multiple comparisons for the ventral prefrontal cortex and anterior cingulate, and $P < 0.05$ corrected for multiple comparisons for all other regions on the basis of the *a priori* hypotheses stated above.

Task-related effects within each subject group

Task-related effects within each group are shown in Table 4 and Fig. 2. These are provided to clarify the direction of the task-related interactions between groups, i.e. whether these were relative increases or decreases in task-related activation (Table 5 and Fig. 3). For controls, there was significant activation of the right middle frontal gyrus, the superior parietal lobe and the cerebellum. Deactivation of the rostral anterior cingulate, superior temporal gyrus and midtemporal gyrus was noted. In the manic group, there was activation of the right middle frontal gyrus, the dorsal anterior cingulate and the cerebellum and deactivation of the left superior frontal gyrus (frontal pole) (this deactivation survived correction for multiple comparisons), the inferior temporal gyrus and the superior temporal gyrus. In common with the other subject groups, the depressed patients showed activation of the midfrontal gyrus and deactivation in the inferior and midtemporal gyri. In further analyses, we made explicit comparison between the groups by determining task × group interactions where appropriate.

Task-related effects between subject groups

Controls (task versus baseline) versus manic patients (task versus baseline) (Fig. 3A and Table 5). This interaction between the control and manic subjects

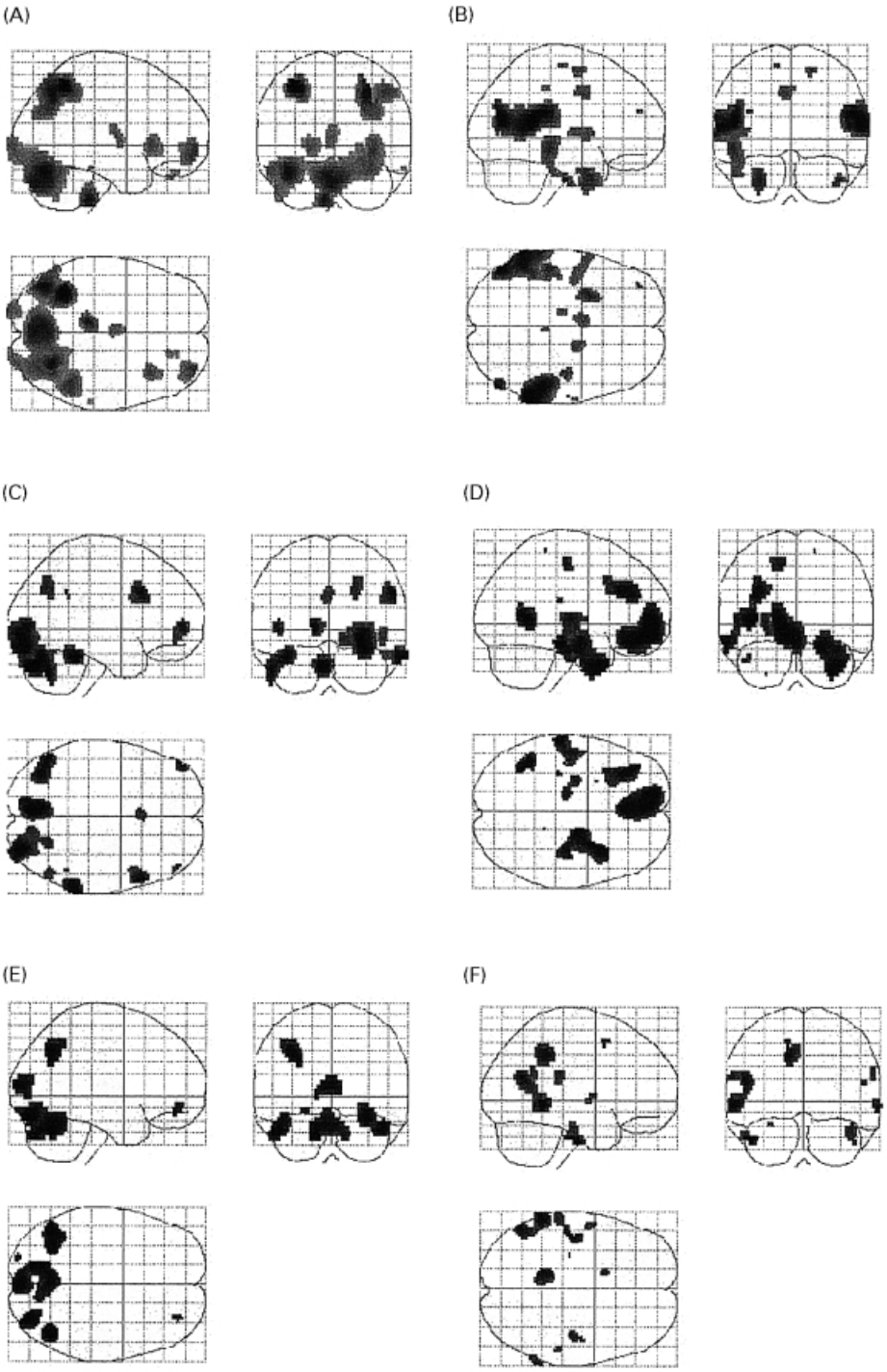

Fig. 2 The task-related within-subject effects are shown in the sagittal, coronal and horizontal planes with the threshold for the voxel height set at $P = 0.001$. Subtraction of the rCBF associated with the visuomotor baseline conditions from the 4 : 2 and 5 : 1 conditions combined are termed 'activations'. The effects of the combined tasks subtracted from the baseline condition are termed 'deactivations'. (**A**) Controls: activations. (**B**) Controls: deactivations. (**C**) Manic patients: activations. (**D**) Manic patients: deactivations. (**E**) Depressed patients: activations. (**F**) Depressed patients: deactivations.

revealed a significant difference in the anterior VMPFC, i.e. the superior frontal gyrus (frontal pole, BA 10), which reflects a task-related decrease in activity in manic patients that is not seen in control subjects (Fig. 2D). Also highlighted by this between-group comparison was the task-related increase in activity of the inferior frontal gyrus (BA 47), which was seen in control subjects in the inferior frontal gyrus (BA 47) (Fig. 2A) but not in manic patients.

Manic patients (task versus baseline) versus controls (task versus baseline) (Fig. 3B and Table 5). This interaction analysis (the reverse of that described above) showed a difference in the anterior cingulate gyrus (BA 32). The within-group effect analysis (Fig. 2C) revealed a task-related increase in activity in this region in the manic patients that was not measurably present in control subjects.

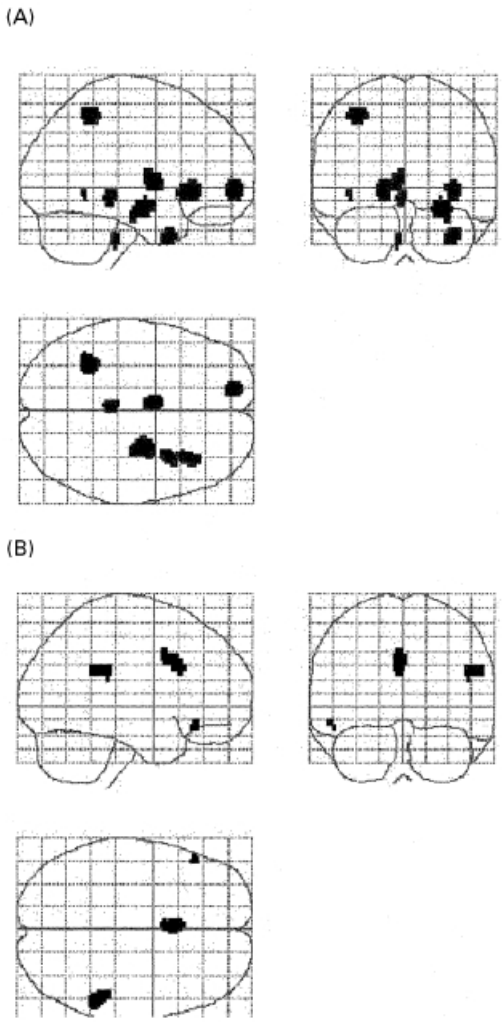

Fig. 3 Task-related effects between the controls and the manic subjects. Voxel height threshold is set at $P = 0.001$. (**A**) Controls (task versus baseline) minus manic patients (task versus baseline). (**B**) Manic patients (task versus baseline) minus controls (task versus baseline).

Controls (task versus baseline) versus depressed patients (task versus baseline). No differences in task-related activity were observed in the hypothesized regions of the prefrontal cortex and no comparisons in other regions survived correction for multiple comparisons.

Comparison of the 4 : 2 condition and the 5 : 1 condition

Controls (4 : 2 condition versus 5 : 1 condition) versus manic patients (4 : 2 condition versus 5:1 condition). Manic patients showed an activation in the caudal anterior cingulate (Z score = 3.09, $x = -8$, $y = 2$, $z = 48$) (Fig. 1C) that was not present in the control subjects. The easier (5 : 1) condition contributed more than the hard condition to this activation, as seen from the within-group analysis (Table 4).

In summary, the manic patients showed a task-related decrease in activation in the frontal pole and a task-related increase in the caudal anterior cingulate relative to the controls. In addition, a task-related increase in activity in the controls was seen in the inferior prefrontal cortex that was not observed in the manic patients.

Correlations

Correlations between the task-related activation (derived from the task minus baseline subtraction) in the regions of interest in the prefrontal cortex (the anterior cingulate, frontal pole and inferior prefrontal cortex) and mean scores on the decision-making task, chlopromazine equivalent dose [BNF 2000 (British National Formulary, 2000)] and scores on the Young Mania Scale (Young *et al*., 1978) were calculated. None of these correlations was significant except for a positive correlation (Spearman's $r_s = 0.88$, $P = 0.02$) between the task-related activation in the anterior cingulate and scores on the Young Mania Scale and a positive correlation between

Table 5 *Differences between task-related effects in the control and manic subject groups*

	Z score	Coordinates			Region	BA
		x	y	z		
Control (T versus B) minus manic patients (T versus B)	3.85	–16	58	0	Superior frontal gyrus	10
	3.67	36	26	–4	Inferior frontal gyrus	47
Manic patients (T versus B) minus controls (T vs B)	3.73	–4	14	32	Anterior cingulate	32

T = task; B = baseline. Significance level was set at $P < 0.001$ uncorrected for multiple comparisons in hypothesized regions and $P < 0.05$ corrected in all other regions.

the levels of chlorpromazine and task-related activation in the rostral prefrontal cortex (Pearson's $r = 0.86$, $P = 0.03$).

Discussion

The PET data demonstrate that manic patients compared with control subjects showed increased task-related activation in the dorsal anterior cingulate region and decreased task-related activation in the left frontal polar region (i.e. close to the orbitomedial prefrontal cortex). In contrast, the controls showed greater task-related activation in the right inferior frontal cortex than the manic patients. Moderately depressed patients did not show significant task-related activation differences compared with the controls. These data support our hypothesis that abnormalities in task-related activation are observed in the ventral and medial prefrontal cortex as well as the anterior cingulate in mania.

The behavioural data from this PET study indicated no significant impairments in patients and control subjects for the choice of the most likely outcome. In the more difficult trials, depressed and control subjects increased their deliberation time significantly, but manic patients did not show this difference in response time. This lack of change in response latency in manic patients may reflect impulsive responding (as they did not slow their speed with increasing level of conflict). These behavioural results differ from those shown in our previous study of mania (Murphy *et al*., 2001), but critical changes in the task design probably account for these differences. In that study, the quality of decision-making could be assessed separately from the points score chosen by the subject. The task used in the present PET study combined quality of decision-making with a fixed points score (which was always lower for the more likely probability) so that separation of these two measures was not possible, as it was in the previous task design (Murphy *et al*., 2001).

However, the lack of a significant performance impairment in manic subjects on this new decision-making task reduces some of the problems of interpretation that commonly plague neuroimaging studies in patients (Weinberger and Berman, 1996). Since behavioural measures of task performance were similar across groups, we can be more confident that the activation differences did not arise from inability to carry out the tasks satisfactorily. Nevertheless, balancing performance across groups is associated with a number of ambiguities (Fletcher, 2000). Unlike control subjects, manic patients maintain performance levels without the necessity of activating the ventral frontal cortex. One possible reason for this is that this activation is not necessary for maintaining task performance. However, an alternative suggestion is that manic patients adopt different strategies in order to maintain performance.

Task-related activation in the anterior cingulate

Overactivation of the dorsal anterior cingulate cortex (BA 32) in the manic subjects is interesting and significant in the light of previous PET studies of the function of this region in normal individuals. A number of studies have shown that this region is activated during the performance of tasks that require attentional control and selection for action (for reviews, see Posner and Peterson, 1990; Drevets and Raichle, 1998). Carter and colleagues showed that this region contributes to performance monitoring, possibly in the detection of errors (Carter *et al*., 1998). The region has also been shown to have a role in response selection when a range of novel choices is required, but not during practised responses (Paus *et al*., 1993; Raichle *et al.*, 1994; Jueptner *et al*., 1997). This role in novel response selection may be particularly relevant in mania.

The anterior cingulate has also been implicated in a SPECT (single photon emission computed tomography) study of mania. Goodwin and colleagues showed that, following lithium withdrawal in remitted bipolar patients, patients who had developed manic symptoms showed relative increases in perfusion in the superior anterior cingulate (Goodwin *et al*., 1997). In our study, it should be noted that there was a positive correlation in manic patients between the increased task-related activation in the anterior cingulate and the severity of the manic symptoms. Blumberg and colleagues also demonstrated recently that manic patients showed increased activity in the left dorsal anterior cingulate and the head of the left caudate in the resting state compared with euthymic bipolar patients (Blumberg *et al*., 2000). Drevets and colleagues had shown earlier that there was increased metabolism in a more ventral subgenual cingulate region in manic patients in the resting state (Drevets *et al*., 1997).

The increased activation in the anterior cingulate in this study suggests that the manic subjects were trying novel approaches to the task, being unable to grasp the automatic or heuristic, probability-based reasoning that facilitated task performance in the normal controls and depressed patients. Rogers and colleagues demonstrated that the task-related activity in the anterior cingulate region was increased specifically when responses to the more difficult (4 : 2) ratios were compared with responses to the easier (5 : 1) ratios (Rogers *et al*., 1999*a*). Further analysis of our data in this study using this contrast (4 : 2 minus 5 : 1) revealed that manic patients had increased task-related activity in the caudal region of the anterior cingulate. Paradoxically, this activity was greatest during performance of the easier (5 : 1) ratio. Any explanation for this intriguing pattern of findings is necessarily *post hoc* and speculative. We are keen to embrace the idea suggested above, that, in the presence of attenuated ventral frontal activation, the relative overactivation of the anterior cingulate cortex in manic patients reflects the adoption of alternative strategies and an abnormality at the neural level. However, the strategies mediated by this region, while appropriate under easier task conditions, are insufficient when the task requires more thought. Such an explanation might lead to the prediction that task performance in manic patients would deteriorate more precipitously for the more difficult task (since

performance is no longer being maintained by the alternative, cingulate-mediated strategies), but this does not appear to have been the case [although it is worth noting (Table 3) that deliberation time under easy conditions, though variable, was not significantly greater than for control subjects]. A second possibility is that manic patients find something more demanding about the 'easier' task, possibly because their attention is more readily drawn to stimuli that are unrelated to the task. If, as is often the case, manic patients tend to be more distractible, this effect might be more pronounced when the demands of the task absorb fewer cognitive resources. Regardless of these alternative accounts, we have demonstrated an altered pattern of functional activation involving the anterior cingulate cortex region, which has been implicated previously in bipolar mania, using other methods.

The question arises of whether this increased activation in the anterior cingulate is due to the effects of medication, with antipsychotic drugs in particular. Studies examining the site of action of typical antipsychotic medication in schizophrenia suggest that these drugs reduce metabolism or rCBF in the anterior cingulate and that relative increases in this region follow their withdrawal (Holcomb *et al*., 1996; Miller *et al*., 1997). Thus, our finding of relatively increased task-related activity in the anterior cingulate of manic patients, despite antipsychotic medication, makes this effect even more remarkable. In addition, the correlation between task-related activation in the anterior cingulate region and the dose of chlorpromazine did not approach significance, although such a relationship was found in the rostral prefrontal cortex.

Bench and colleagues found that CBF was decreased in the resting state in severely depressed in-patients relative to non-depressed controls in the dorsal anterior cingulate (Bench *et al*., 1992). The depressed subjects in our study, however, were performing a task during the scan and so our failure to see any differences in this region may have been due to the functional response to task performance. Another contributory factor may have been the severity of depressive symptoms, the majority of patients in this study being out-patients, in contrast to the in-patient sample scanned by Bench and colleagues. Moreover, our patients were not as globally impaired in cognitive terms, according to their MMSE score, as those described by Bench and colleagues (only 10 of their 33 patients scored $\geqslant$29).

Task-related activation in the inferior frontal gyrus

We predicted involvement of the right inferior frontal gyrus because Rogers and colleagues demonstrated activation of this region during decision-making (Rogers *et al*., 1999*a*). The inferior prefrontal gyrus has been associated with inhibitory functions during performance of go/no-go tasks (Kawashima *et al*., 1996; Casey *et al*., 1997; Elliott *et al*., 2000*a*). Subjects in the present study may have needed to suppress or inhibit primed responses, e.g. towards the larger but less probable rewards. However, it should be noted that the peak in the inferior prefrontal cortex in this study was more inferior than that reported in a recent event-related functional MRI study on no-go trials (Konishi *et al*., 1999).

In the decision-making task, each trial is a separate entity and, for subjects to do well, decisions should be based on the assessment of the probabilities of each trial. Some comparisons (using working memory processes) over trials were probably necessary, particularly initially, to provide feedback to the subject indicating that their strategy was successful. Although patients with VMPFC lesions with deficits in decision-making may have intact working memory, decision-making has been noted to be worse in the presence of working memory deficits (Bechara *et al*., 1998). The region of the ventrolateral prefrontal cortex (BA 47) has been shown to be important in working memory for the retrieval and maintenance of information from posterior cortical areas (Owen *et al*., 1996). This model has been elaborated upon by D'Esposito and colleagues in an event-related functional MRI study showing that this region (inferior frontal gyrus, BA 45) exhibited significant activity during different phases of a verbal working memory task, including target presentation, delay period and probes for inducing proactive interference (D'Esposito *et al*., 1999). However, the functional MRI signal was significantly greater for recently presented probes than for probes that had not been presented recently. Whether this applies to the non-verbal working memory tasks that were more relevant in this study is unclear. Functional imaging studies have indicated that the ventral prefrontal cortex (including the inferior frontal gyrus) is important in associative learning between visual cues and responses (Passingham *et al*., 2000). In the present study, manic patients activated this region relatively less than the controls despite normal task performance. This may reflect their difficulties at a neural level in inhibiting responses, monitoring information in working memory or in associative learning, all of which may contribute to the decision-making process.

Task-related activation in the frontal polar region

Several considerations make it unsurprising that the anterior or polar ventromedial prefrontal region was deactivated in mania. First, there are interconnections within the ventral prefrontal cortex (Barbas and Pandya, 1989). This ventral prefrontal region includes the orbital prefrontal cortex, which has specific limbic connections (Carmichael and Price, 1995; Price, 1999). Secondly, a number of patients with ventromedial lesions who showed disadvantageous strategies on the gambling (Bechara *et al*., 1996) and decision-making tasks (Rogers *et al*., 1999*b*) had lesions that were not confined to the orbital gyrus but often included the frontal polar region. Thirdly, this frontal polar region was similarly deactivated in

a recent PET study of manic patients in which a verbal fluency task was used (Blumberg *et al*., 1999). Fourthly, functional imaging studies have recently highlighted associations between the frontal polar region and prospective memory tasks (Okuda *et al.*, 1998; Burgess *et al*., 2000) and during a task that involved keeping a goal in mind while exploring and processing secondary goals (Koechlin *et al*., 1999). The decision-making task may require just such a complex executive control process, involving the assessment of probabilities in the trials presented and at the same time having as the principal goal the achievement of a high points score. Elliott and colleagues argue that the orbitofrontal cortex is activated in functional imaging studies when the problem of what to do next is best solved by taking into account the likely reward value of stimuli and responses (Elliott *et al*., 2000*b*). In our previous behavioural study of mania (Murphy *et al*., 2001), manic patients adopted a conservative style of betting, consistent with the dysregulation of reinforcement processes. Manic patients may have difficulties with this type of complex executive task, in which goals and subgoals need to be evaluated, particularly when the assessment of these goals requires intact reinforcement systems.

We also detected a correlation between increased task-related activation with higher doses of antipsychotic medication in the frontal pole. This suggests that, in more severely manic patients (requiring more medication), task-related activation would be increased. However, despite such medication, decreased task-related activity was found in this study, making it unlikely that this is a false-positive result, and again suggesting that this difference may have been even greater off medication.

Depressed patients

We did not predict major differences in task-related activation in the depressed patients compared with controls on the basis of our previous behavioural work (Murphy *et al*., 2001). We employed the depressed subjects as an 'affective' patient control group. When compared with control subjects, the depressed subjects did not show any significant uncorrected task-related prefrontal or cingulate activation. However, we do need to be cautious in interpreting this result as the depressed patients were taking antidepressant medication, which may conceivably have influenced task-related activation.

Neural networks in decision-making cognition in mania

The three main regions implicated in this study—the anterior cingulate, the inferior prefrontal cortex and the frontal pole—are interconnected (Barbas and Pandya, 1989; Barbas, 1995) and also have prominent connections with limbic structures, such as the amygdala, midline thalamus, insula and temporal pole (Mesulam and Mufson, 1982; Yeterian and Pandya, 1988; Barbas and De Olmos, 1990; Barbas, 1995; Carmichael and Price, 1995; Devinsky *et al*., 1995; Price, 1999). Increased task-related cingulate gyrus activity and decreased activity in the ventral prefrontal cortex may reflect a neural circuitry that is altered in mania. As behavioural performance in this PET study was not compromised significantly in mania using the new decision-making task, this difference in activity at a neural level needs further investigation, possibly by looking at integrated brain function through the use of path analysis. Alternatively, it would be useful to demonstrate similar alterations in these regions in mania using another task. This altered mode of functioning of a neural network in decision-making cognition bears some resemblance to the changes in the different prefrontal circuitry that have been implicated in the performance of the Wisconsin Card-Sorting Test in schizophrenia (Weinberger and Berman, 1996).

Conclusions

We observed abnormal task-related blood flow in three prefrontal regions. There was increased activation of the dorsal anterior cingulate region and reduced task-related blood flow in the superior frontal gyrus in the manic patients. In addition, there was increased activation in the controls in the inferior frontal gyrus. One interpretation of the 'overactivation' in the dorsal anterior cingulate activation in the manic patients is that these patients were exercising additional task-related effort (e.g. trying new strategies) rather than invoking automatic processes to solve this probabilistic decision-making task. We showed increased task-related activation in the controls compared with the manic patients in the ventrolateral prefrontal cortex, possibly suggesting that manic patients were not activating this paralimbic region effectively because of associated deficits in the cognitive processes engaged by the task. The reduced task-related activation in the frontal pole may reflect the difficulties that manic patients experience in performing a task in which a primary goal has to be kept in mind whilst they are concurrently attaining subgoals. Thus, despite relatively normal task performance, reduced task-related activation in the ventral prefrontal cortex and increased task-related activation in the anterior cingulate were found in manic patients performing a probabilistic decision-making task. This suggests a fundamental alteration in the neural networks involved in decision-making in the manic state.

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