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Decision-making cognition in mania and depression

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ABSTRACT

Background. Despite markedly different clinical presentations, few studies have reported differences in neuropsychological functioning between mania and depression. Recent work has suggested that differences may emerge on cognitive tasks requiring affective processing, such as decision-making. The present study sought to compare decision-making cognition in mania and depression in order to clarify the current profiles of impairment for these disorders and to contribute to our more general understanding of the relationship between mood and cognition.

Methods. Medicated manic patients, depressed patients, and normal healthy controls completed a computerized decision-making task. All subjects were asked to win as many points as possible by choosing outcomes based on variably-weighted probabilities and by placing 'bets' on each decision.

Results. Both patient groups were impaired on this task, as evidenced by slower deliberation times, a failure to accumulate as many points as controls and suboptimal betting strategies. Manic, but not depressed, patients made suboptimal decisions – an impairment that correlated with the severity of their illness.

Conclusions. These findings are consistent with a growing consensus that manic and depressed patients are characterized by significant impairments in cognitive and particularly executive, functioning. Furthermore, the distinct patterns of observed impairment in manic and depressed patients suggests that the nature and extent of cognitive impairment differ between these two groups. Viewed in the context of other recent studies, these findings are consistent with a role for the ventromedial prefrontal cortex in mediating mood–cognition relationships.

INTRODUCTION

While depressed patients exhibit extensive neuropsychological deficits on tests of attention, memory and executive functioning (Miller, 1975; Weingartner *et al*. 1981; Austin *et al*. 1992; Brown *et al*. 1994; Beats *et al*. 1996; Elliott *et al*. 1996), the study of cognitive performance in mania has been less extensively investigated (Henry *et al*. 1971; Taylor & Abrams, 1986; Morice, 1990; Murphy *et al*. 1999). A few studies have sought to compare the cognitive impairments associated with mania and depression, but have found it difficult to distinguish the two groups (Bulbena & Berrios, 1993; Goldberg *et al*. 1993). However, these studies employed neuropsychological tasks based on emotionally 'neutral' stimuli – materials not seemingly positive or negative in affective tone. An alternative approach is to target the clinically-observed difference between these two disorders, their markedly different emotional presentations. It seems logical that if differences in the cognitive functioning of manic and depressed patients do exist, these differences will emerge most clearly on tasks that tap both cognitive and affective processes (Murphy *et al*. 1999; Murphy & Sahakian, 2001).

Damasio, Bechara and colleagues (Bechara *et al*. 1994, 1996, 1997; Damasio, 1994; Adolphs *et al*. 1996) have introduced a novel approach to the study of decision-making cognition which suggests that in normal, healthy individuals with

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intact orbitofrontal cortical function, emotion-guided reasoning facilitates the decision-making process. This research is relevant to clinical descriptions of mania and depression, as the DSM-IV (American Psychiatric Association, 1994) states that individuals currently experiencing major depressive episodes often have difficulty making decisions; likewise, individuals experiencing manic episodes tend to display excessive involvement in pleasurable activities carrying a high potential for painful consequences, suggesting a possible aberration in the decision-making process.

This study aimed to explore decision-making cognition in mania and depression and, more specifically, to determine whether this ability is differentially impaired in these two forms of affective disorder. The computerized decision-making task administered to medicated manic and depressed patients in the present study, developed by our group (Rogers *et al.* 1999*a*) based on the 'gambling' paradigm used by Bechara and colleagues (Bechara *et al.* 1994; 1996; 1997; Adolphs *et al.* 1996), requires subjects to make a probability-based choice and to further qualify this choice with an associated 'bet'. This betting component allows an assessment of the subject's level of confidence in the decision, via the affective evaluation of its possible consequences in terms of points won or lost.

Another important goal of the present study was to investigate possible neural substrates implicated in the decision-making cognition of manic and depressed patients. The particular task employed here was especially suitable for this purpose, as it has already been administered in previous studies to a variety of other subject groups, including patients with focal lesions of orbital or dorsolateral/medial prefrontal cortex (PFC) (Rogers *et al.* 1999*a*), patients with fronto-temporal dementia (Rahman *et al.* 1999), and patients with Huntington's disease (Watkins *et al.* 2000), in which there is probably a disruption of functioning of frontostriatal 'loops' (Alexander *et al.* 1986). In addition, the neural systems associated with completion of a related task have been examined in a recent activation study (Rogers *et al.* 1999*b*). The association between PFC lesion patients and patients with mood disorders was of particular interest to us, as PFC is known to be implicated in the neuroanatomy of mood disorders (Drevets *et al.* 1997; Goodwin, 1997; Soares & Mann, 1997; Elliott & Dolan, 1998). By considering the findings of the current study in the context of these earlier investigations, we hope to shed some light on the neural pathways implicated in these neuropsychiatric affective disorders.

METHOD

Participants

This study was approved by the local research ethics committees involved, and all participants gave informed written consent prior to participation. All subjects were given the National Adult Reading Test (NART) (Nelson, 1982) to estimate pre-morbid verbal IQ and the Mini-Mental State Examination (MMSE) (Folstein *et al.* 1975) to screen for possible dementia. Demographic and clinical details for all subject groups are presented in Table 1 and patient medications are detailed in Table 2.

Manic patients

Ward staff were consulted prior to selection of manic patients and only those patients considered suitable were approached concerning participation in this study (e.g. patients were seen only if considered 'testable' by their consultant psychiatrist but not if aggressive or heavily sedated). The exclusion criteria included history of neurological illness or head injury, untreated thyroid disease or other major medical disorder likely to affect cognition (e.g. diabetes mellitus), use of steroids, or ECT in the previous 3 months. The 17 in-patients determined to be suitable, who were initially referred to in-patient wards based on the severity of their symptoms, were assessed 2 weeks post admission on average. One day-patient was also studied. All manic patients met DSM-IV (American Psychiatric Association, 1994) and Research Diagnostic Criteria (RDC) (Spitzer *et al.* 1978) for bipolar I disorder, manic episode. Three patients also received a current RDC diagnosis of alcohol or drug abuse, but to our knowledge none had taken alcohol or drugs in the week prior to testing. The Schedule for Affective Disorders and Schizophrenia-Lifetime Version (SADS-L) (Endicott & Spitzer, 1978) and Young Mania Rating Scale (YMRS) (Young *et al.* 1978) were administered to all patients.

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Table 1. *Demographic and clinical characteristics of the manic and depressed patient groups and matched control subjects. Data in parentheses are standard errors of the means*

	Manic patients	Depressed patients	Control subjects
N	18	22	26
Female:male	10:8	13:9	14:12
Mean age*	36·3 (2·4)	39·4 (1·9)	36·4 (2·0)
In-patients:day-patients	17:1	11:11	—
Hospitalized manic episodes, *N*	4·7 (0·9)	—	—
NART-IQ*	109·1 (2·2)	112·5 (1·4)	111·8 (1·4)
MMSE*	28·8 (0·3)	28·8 (0·2)	29·6 (0·1)
YMRS	22·6 (1·9)	—	—
Ham-D	—	24·3 (0·9)	—
MADRS	—	37·1 (0·8)	—
CID	—	59·7 (2·1)	—
BDI	—	—	3·5 (0·6)

NART National Adult Reading Test; MMSE, Mini-Mental State Examination; YMRS, Young Mania Rating Scale; Ham-D, Hamilton Depression Scale; MADRS, Montgomery–Åsberg Depression Rating Scale; CID, Clinical Interview for Depression; BDI, Beck Depression Inventory.

*One-way ANOVAs revealed that manic patients, depressed patients and matched controls did not differ significantly in terms of age ($F(2,63) = 0·7$, $P = 0·5$), NART-IQ ($F(2,63) = 1·1$, $P = 0·35$), or MMSE scores ($F(2,63) = 0·6$, $P > 0·5$).

Table 2. *Medication status of manic and depressed patients*

	Manic patients *N*	Depressed patients *N*
No medication	2	0
Antidepressants		
SSRI	0	12
Tricyclic	0	7
Noradrenaline reuptake inhibitor	0	1
SSRI + tricyclic or MAOI	0	2
Mood stabilizers*	15	9
Neuroleptics†	16	0
Benzodiazepines	7	0

*In manic patients, mood stabilizers included lithium carbonate, carbamazepine or sodium valproate alone or in combination. Of these, depressed patients received only lithium.

†Mean dose was 500 mg chlorpromazine equivalents.

Depressed patients

Eleven in-patients and 11 day-patients meeting DSM-IV criteria for major depressive disorder participated in this study. Exclusion criteria were the same as those for manic patients. None had a current and/or past diagnosis of psychoactive substance abuse. Severity of depression was assessed using the Hamilton Depression Scale (Ham-D) (Hamilton, 1960), the Montgomery–Åsberg Depression Rating Scale (MADRS) (Montgomery & Åsberg, 1979), and the Clinical Interview for Depression (CID) (Paykel, 1985).

Control subjects

Twenty-six control subjects were recruited by advertisement in the community and were selected to match the patient groups as closely as possible for age, sex, and NART-IQ (see Table 1). The exclusion criteria included any psychiatric or neurological illness, psychoactive substance abuse, use of medication which might potentially influence cognition, and a score of 10 or above on screening with the Beck Depression Inventory (BDI) (Beck *et al.* 1961).

Decision-making task

The computerized decision-making task was administered to participants as soon as possible after clinical assessment and was presented on a portable 486 microcomputer fitted with a Datalux touch-sensitive screen. A typical display from this task, described in detail by Rogers *et al.* (1999*a*), is shown in Fig. 1. On each trial, subjects were initially presented with a configuration of ten red and blue boxes at the top of the screen and were told that the computer had

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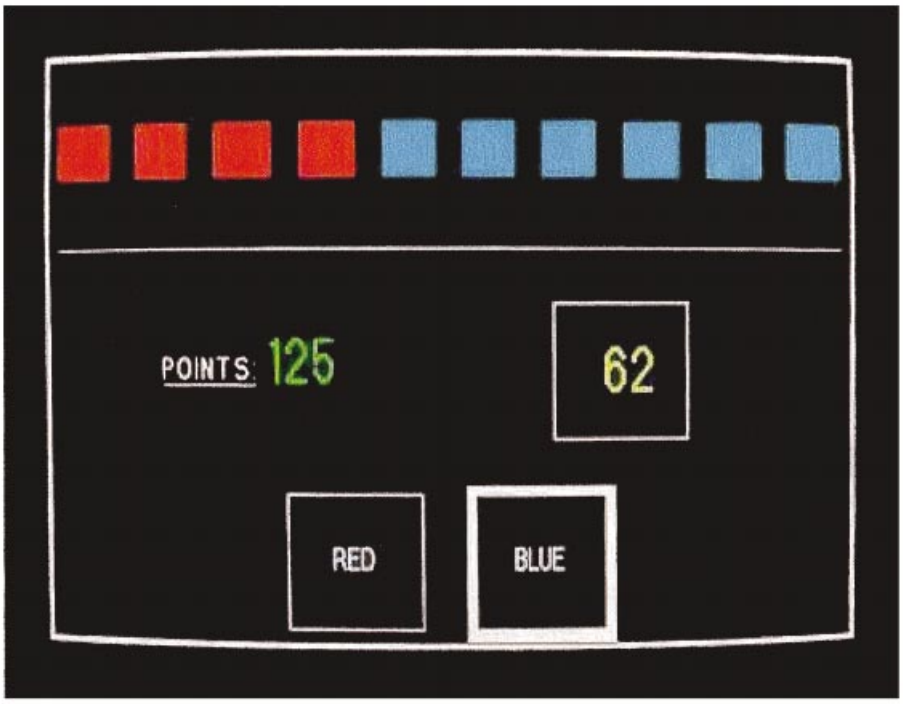

FIG. 1. A typical display from the computerized decision-making task. The total points score and available bets are displayed in boxes at the left and right of the screen, respectively. Note that the red:blue box ratio changed from trial to trial.

hidden a yellow token at random inside one of these boxes. Their task was to decide whether the token had been hidden inside a red or blue box and to indicate their decision by touching the appropriate 'RED' or 'BLUE' response panel. Immediately following, subjects attempted to increase a total points score by placing a 'bet' on whether or not they believed their initial colour decision to be correct. For this purpose, possible bets appeared in a sequence one after the other, in a box positioned toward the right of the display, and subjects could select any bet by touching it. One of the boxes at the top of the display then opened to reveal the actual location of the yellow token, and the chosen bet was added to or subtracted from the total points score according to whether or not the initial prediction was correct.

The task comprised eight blocks of nine trials each (four 'ascend' blocks and four 'descend' blocks: see below). Subjects were given 100 points at the beginning of each block of trials, and although no real monetary significance was attached to the points accumulated by the end of the task, subjects were encouraged to treat the points as valuable and to accumulate as many as possible. If a subject's score fell to just one point, the current block terminated and the next began.

Three important features of this task allowed for a detailed analysis of decision-making performance. First, the opportunity to bet a variable proportion of the total points score allowed for assessment of willingness to risk already-accumulated reinforcement in order to acquire further reward, and provided a rating of the subject's confidence in the associated decision. For this purpose, five bets, each representing a fixed percentage of the current total points score (5, 25, 50, 75, and 95%) were offered on each trial.

Secondly, subjects performed the task in two separate conditions, ascend and descend, with the order of condition counterbalanced across subjects. In the ascend condition, the available bets were initially small and were replaced by increasingly larger bets until the subject made a selection. In the descend condition, the available bets were initially large and were replaced by

increasingly smaller bets. The inclusion of both ascend and descend conditions allowed us to distinguish between impulsive and risk-taking betting strategies. For example, an impulsive subject would be expected to have difficulty withholding manual responses to the bets as they were presented, resulting in early bets in both the ascend and descend conditions (i.e. consistently low bets in ascend, and high bets in descend). A subject actively seeking risks, however, would be expected to choose early bets in the descend condition but late bets in the ascend condition. Thus, a large difference between the mean percentage bet in these two conditions indicated impulsivity, and a small difference indicated risk-seeking.

Finally, the ratio of red to blue boxes varied from trial to trial, with some contingencies more closely balanced in terms of the probabilities associated with their respective outcomes (e.g. 4 red : 6 blue box) than others (e.g. 9 red : 1 blue box). As some ratios provided a better indication than others about the response likely to be reinforced, this aspect of the task allowed for assessment of participant sensitivity to changing information. Thus, a subject's colour decisions, associated bets, and deliberation times were expected to vary as a function of the ratio of red to blue boxes. In terms of associated bets, for example, one would expect subjects to bet heavily on red for a 9 red : 1 blue box trial, as opposed to a 4 red : 6 blue box trial, where more conservative behaviour might be appropriate.

Data analyses centred around five dependent measures: (1) total points earned per block of trials; (2) number of blocks lost (e.g. points score fell to one point); (3) speed of decision-making: time to decide whether the token had been hidden in a red or blue box; (4) quality of decision-making: percentage of trials on which subjects chose the more likely outcome (e.g. red is the more likely outcome on a 9 red : 1 blue box trial); (5) percentage bets, i.e. percentage of accumulated points risked on each trial.

Statistical analysis

Data were analysed using SPSS for Macintosh. The total points earned and number of blocks lost were analysed by means of one-way analysis of variance (ANOVA), with subject group (manic patients, depressed patients, control subjects) as the sole factor. Deliberation times, percentage trials favourable outcome chosen, and percentage bets were subjected to repeated measures ANOVAs with subject group (manic, depressed, controls) and order of condition (ascend/descend, descend/ascend) as between-subjects factors, and condition (ascend, descend), and ratio of red to blue boxes (6 : 4, 7 : 3, 8 : 2, 9 : 1) as within-subjects factors. Prior to analysis, proportion data were arcsine-transformed as has been recommended for instances where the variance is proportional to the mean (see Howell, 1997). However, data presented in text and figures are untransformed means. In those instances in which the assumption of homogeneity of covariance in repeated-measures ANOVA was violated, as assessed using the Mauchly sphericity test, the degrees of freedom against which the F term was tested were reduced by the value of the Greenhouse–Geisser epsilon (Howell, 1997). *Post-hoc* comparisons were conducted using Tukey's HSD. Pearson's product moment correlation coefficients were computed in correlational analyses.

RESULTS

General performance indicators: points earned and blocks lost

Mean decision-making scores of manic patients, depressed patients, and control subjects are presented in Table 3. For total points earned, a one-way ANOVA revealed a significant main effect of subject group: averaged over condition, manic and depressed patients earned fewer points than controls ($F(2,63) = 3{\cdot}5$, $P < 0{\cdot}05$). A significant main group effect also emerged in the analysis of total number of blocks lost, which was due to manic patients losing more blocks than depressed patients or controls ($F(2,63) = 3{\cdot}9$, $P < 0{\cdot}05$).

Speed of decision-making

Fig. 2 shows the mean deliberation times associated with deciding whether the yellow token had been hidden in a red or blue box, as a function of the ratio of red to blue boxes. Analysis of deliberation times revealed a significant main effect of ratio ($F(3,180) = 4{\cdot}6$, $P < 0{\cdot}01$); deliberation times were significantly longer at the less favourable ratios than at the more favourable ones, suggesting that decisions were more difficult when the display provided

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Table 3. *Performance of manic patients, depressed patients, and matched control subjects, averaged over condition and ratio, on the computerized decision-making task. Data shown are means with standard errors of the means in parentheses*

	Manic patients	Depressed patients	Control subjects
Total points earned	269·0 (46·0)	317·1 (35·6)	440·8 (55·5)
Blocks lost (maximum = 8), *N*	1·4 (0·9)	0·8 (0·7)	0·5 (0·6)
Deliberation times (ms)	3993·5 (427·3)	3698·0 (231·2)	2484·5 (165·4)
Trials likely outcome chosen %	87·6 (4·5)	94·0 (2·9)	96·0 (1·7)
Bets %	61·8 (5·2)	58·7 (5·9)	64·3 (4·2)

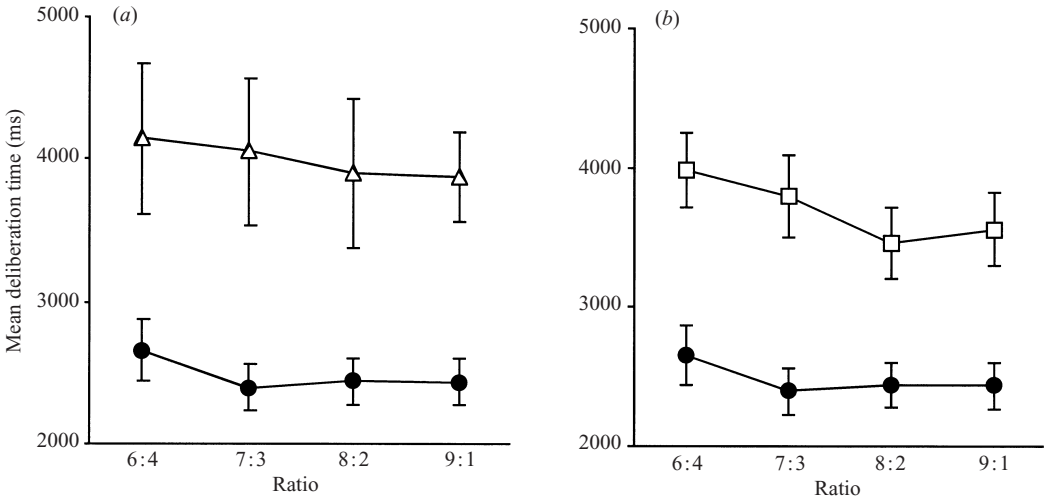

FIG. 2. Speed of decision-making. Mean deliberation times (ms) associated with deciding which colour box was hiding the yellow token, as a function of the red:blue box ratio, for (*a*) manic patients (△) and control subjects (●) and (*b*) depressed patients (□) and controls (●). Bars represent 1 standard error of the mean (S.E.M).

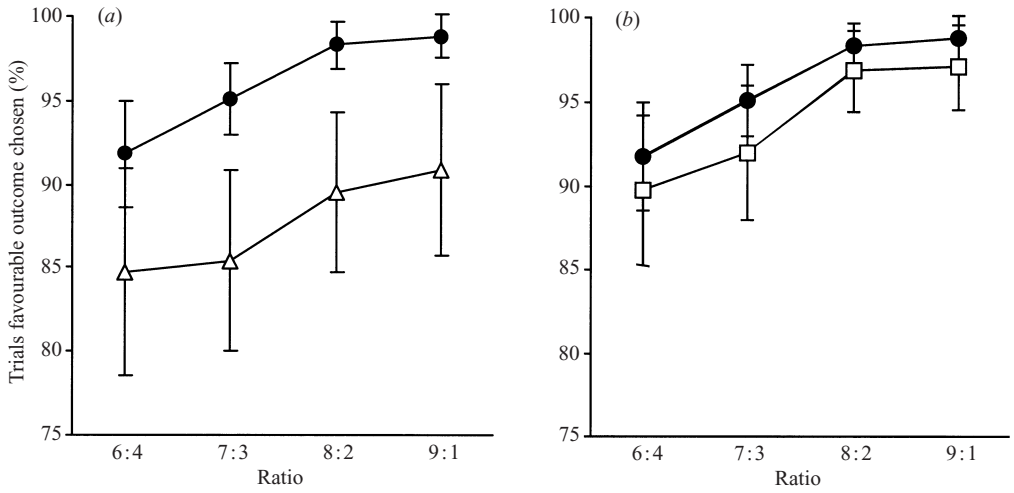

FIG. 3. Quality of decision-making. Percentage of trials on which more likely outcome was chosen, as a function of the red:blue box ratio, by: (*a*) manic patients (△) and control subjects (●); and (*b*) depressed patients (□) and controls (●). Bars represent 1 S.E.M.

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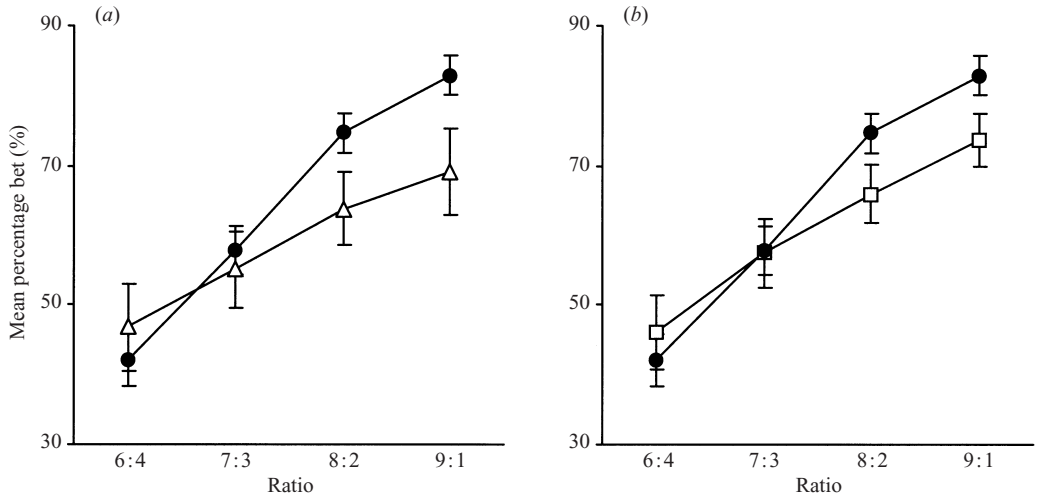

FIG. 4. Betting strategies. Percentage of points risked in order to earn reward, as a function of the red : blue box ratio, by: (*a*) manic patients (△) and control subjects (●); and (*b*) depressed patients (□) and controls (●). Bars represent 1 S.E.M.

poor information about the rewarded response. A significant main effect of subject group also emerged, with both patient groups taking longer than controls to make decisions ($F(2,60) = 12{\cdot}8$, $P < 0{\cdot}001$; see Table 3). This deficit was independent of information provided about the rewarded response, as the two-way interaction between subject group and ratio was not significant ($F < 1$; see Fig. 2).

Quality of decision-making

Fig. 3 shows the percentage of trials on which subjects chose the more likely of the two possible outcomes, as a function of the ratio of red to blue boxes. Averaging over subject group, the percentage of trials on which subjects chose the more likely outcome increased as the ratio became progressively more favourable ($F(2{\cdot}4,155) = 12{\cdot}3$, $P < 0{\cdot}001$). Manic patients made such optimal choices less often than both depressed patients and control subjects ($F(2,60) = 4{\cdot}6$, $P = 0{\cdot}01$; see Table 3). However, this tendency was independent of the relative probabilities of the two outcomes, as the two-way interaction between group and ratio was not significant ($F(4{\cdot}8,155) < 1$; see Fig. 3).

Percentage bets

Fig. 4 shows the percentage of total points that subjects were prepared to risk in order to increase their total points scores, as a function of the ratio of red to blue boxes. This analysis was restricted to those trials where subjects chose the more likely outcome (i.e. 'good' decisions) so that valid comparisons could be made between the performance of patients and control subjects. Averaging over subject group, percentage bets increased at a relatively constant rate as the ratio of red to blue boxes increased ($F(3,180) = 103{\cdot}5$, $P < 0{\cdot}001$). The interaction between subject group and ratio was also significant, with both patient groups increasing their bets at a slower rate than controls in response to increasingly favourable ratios ($F(6,180) = 3{\cdot}0$, $P < 0{\cdot}01$).

All subjects placed larger bets in the descend than in the ascend condition (72% *v.* 52%; $F(1,60) = 86{\cdot}7$, $P < 0{\cdot}001$), and this effect was exaggerated in both patient groups (group by condition interaction, $F(2,60) = 3{\cdot}3$, $P < 0{\cdot}05$). As shown in Fig. 5, this interaction was due to depressed and manic patients making smaller bets than controls in the ascend but not descend condition. Finally, there were no significant differences in the mean percentage bets (averaged over condition) placed by manic or depressed patients and controls ($F(2,60) = 1{\cdot}3$, $P = 0{\cdot}27$).

Correlational analyses

Correlational analyses were performed in order to assess whether there was any statistical association between neuropsychological performance and demographic or clinical variables for depressed and manic patients. The demo-

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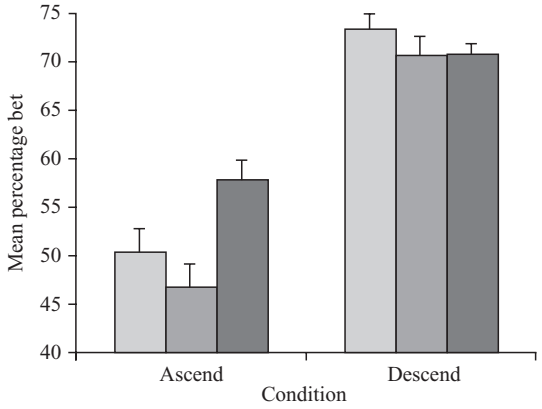

FIG. 5. Mean percentage bets of patients (□, depressed; ■, manic) and control subjects (■) in ascend and descend betting conditions. Bars represent 1 S.E.M.

graphic and clinical variables considered were age and NART-IQ; YMRS scores and number of hospitalized episodes (manic patients); and HAM-D, MADRS, and CID scores (depressed patients). Correlations between these clinical measures and the main performance measures for the decision-making task (see above) were computed.

In manic patients, YMRS scores were negatively correlated with percentage trials on which the more likely outcome was chosen ($r = -0{\cdot}54$, $P = 0{\cdot}02$; see Fig. 6), suggesting that increasing severity of manic symptomatology is associated with poorer quality decisions. In depressed patients, mean deliberation times were negatively correlated with percentage trials on which the favourable outcome was chosen ($r = -0{\cdot}49$, $P = 0{\cdot}02$), indicating that those subjects who took the longest to make decisions tended to be the same subjects who made suboptimal decisions. Data for control subjects revealed a similar association between deliberation times and quality of decisions ($r = -0{\cdot}53$, $P = 0{\cdot}005$) and a significant correlation between deliberation times and age ($r = 0{\cdot}69$, $P = 0{\cdot}001$), with older subjects taking longer to make decisions.

DISCUSSION

This is possibly the first study to have directly compared decision-making performance in manic and depressed patients. The results showed manic and depressed patients to be impaired on a computerized decision-making task. While the most general indicators of performance showed similarities between these two groups, close examination of the individual components of the task revealed distinct patterns of impairment: although both manic and depressed patients demonstrated similarly delayed deliberation times and altered betting strategies, impairments in the quality of decisions were confined to manic patients. This aspect of the performance of manic patients was strikingly

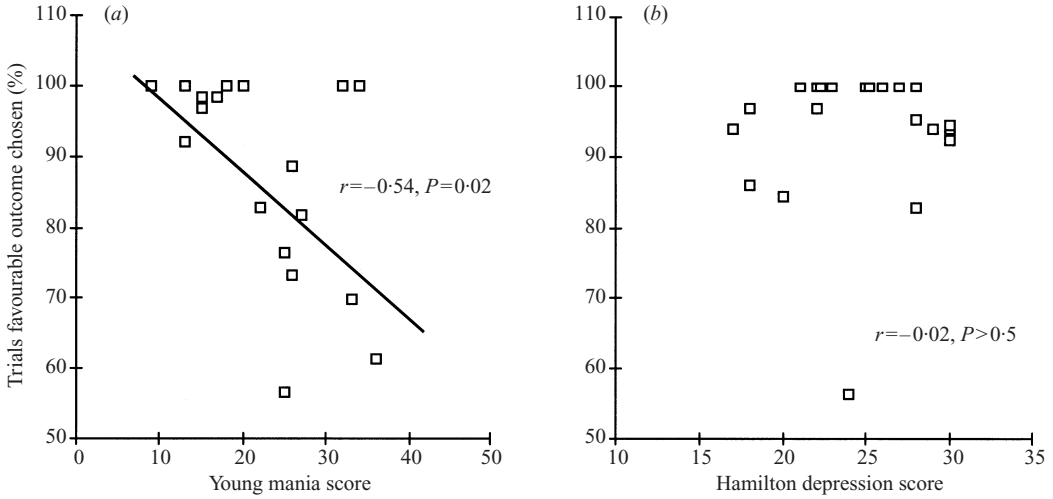

FIG. 6. Relationship between severity of illness and quality of decision-making for: (*a*) manic patients; and (*b*) depressed patients. A significant negative correlation was found for mania but not depression.

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similar to that previously found, using the same test (Rogers *et al*. 1999*a*), for patients with lesions of the orbitofrontal cortex, and was related to severity of illness. Below, we explore the similarities and differences exhibited by manic and depressed patients in this study in the context of recent research into the affective disorders. We then consider in detail the possible relationship of orbitofrontal systems to decision-making and the cognitive deficits observed in mania and depression, attempting to clarify our developing map of the neural substrates of these disorders. Finally, we address the possible contributions of patient medications and general illness severity to the decision-making impairments observed in manic and depressed patients.

General indicators of performance

Manic and depressed patients were markedly and similarly impaired on two of the most general indicators of decision-making performance: compared with control subjects matched for age and IQ, both patient groups earned significantly fewer points per block of trials and took considerably longer to decide which of two competing outcomes would be more likely to occur. This finding is consistent with a growing corpus of studies reporting cognitive deficits in these neuropsychiatric disorders (Miller, 1975; Taylor & Abrams, 1986; Austin *et al*. 1992; Brown *et al*. 1994; Elliott, 1998; Veiel, 1997; Murphy *et al*. 1999) and with recent experiments demonstrating pronounced impairments in both these patient groups on other tests of executive function, such as the Tower of London test of planning ability and tests of cognitive set-shifting (Morice, 1990; Martin *et al*. 1991; Franke *et al*. 1993; Goldberg *et al*. 1993; McKay *et al*. 1995; Beats *et al*. 1996; Elliott *et al*. 1996; Degl'Innocenti *et al*. 1998; Murphy *et al*. 1999).

This view of generalised impairment was refined by another general performance measure, the number of blocks 'lost' by participants. We considered this measure an especially meaningful indicator of poor decision-making ability, as all subjects were specifically told that if their accumulated points score fell to just one point, they would 'lose the game', and the current block would be terminated. Manic, but not depressed, patients lost on average more blocks than did controls – a finding that suggested underlying differences in the strategies used by different subject groups in completing this decision-making task. Indeed, an important feature of this decision-making task is that it separates two constituent elements of the decision-making process, the decision itself and the subject's willingness to risk accumulated points in order to obtain further reward (i.e. bets). Thus, analysing subjects' performance on the individual components of the task allowed us to explore whether the impaired performance observed in manic and depressed patients resulted from poor quality decisions, poor betting strategies, or a combination of the two.

Quality of decision-making

Although this study is not the first to have adopted a neuropsychological approach to the study of decision-making, its design adds important modifications to earlier investigations. A salient feature of the card 'gambling' task developed by Bechara and colleagues was an absence of explicit information that could be useful in guiding the selection of an appropriate response (Bechara *et al*. 1994, 1996, 1997; Adolphs *et al*. 1996). The computerized task used here, in contrast, provides explicit and changing information about the relative favourability of two mutually exclusive response options: by changing the ratio of red to blue boxes, subjects are given more information about the response likely to be reinforced on some trials than on others (e.g. compare 9 red:1 blue box with 6 red:4 blue box). It was thus possible to analyse the decision-making process of subjects very closely, noting how different groups responded to contextual information of a given quality, and how they responded to a change in the quality of contextual information.

Impairment in the quality of decisions was confined to manic patients. Relative to control subjects and depressed patients, manic patients, as a group, displayed a heightened tendency to choose the less likely of two possible outcomes, attempting to earn reward on the basis of the less favourable response option. This impairment correlated with Young mania scores, suggesting that increasing severity of manic symptomatology is associated with poorer decisions. While this deficit is consistent with clinical descriptions of manic illness, not all manic patients were impaired on this measure

(see Fig. 6*a*). Determination of the specific patient factors that correlate with this deficit should be an important goal for future research.

As regards changes in information, both manic and depressed patients responded to increasingly informative red : blue box ratios by choosing the more likely outcome on a larger percentage of trials. Although manic patients chose the more likely outcome less often than depressives and controls, this impairment was unrelated to the quality of contextual information provided on individual trials. Given that manic patients adjusted their 'good' responses in line with more heavily weighted red : blue box ratios at the same rate as depressed and control subjects, their tendency to make more decisions based on less favourable outcomes might be linked to a tendency to take risks in some patients (see below). This interpretation would be consistent with clinical characterizations of manic patients as being prone to risk-seeking behaviour (American Psychiatric Association, 1994). Finally, it is worth noting that this impairment was evident in the context of near-ceiling performance in healthy controls, suggesting that this deficit might be even more pronounced in future studies employing a more difficult version of the task.

Betting strategies

The 'betting' component of this decision-making paradigm allowed the subject to risk a variable percentage of resources on a given decision in order to obtain reward, thereby demonstrating numerically his or her confidence in the forecasted outcome. While neither patient group made smaller bets than controls overall – that is, the average bet for the three groups was not significantly different – the rate at which patients increased their percentage bets in response to more heavily weighted outcomes was lower than that of controls. Thus, both patient groups tended to adopt less responsive betting strategies.

The pronounced tendency of depressed patients to bet less than controls on favourable outcomes suggests behaviour compatible with reports of a conservative response style associated with depression on tests of recognition memory (Miller & Lewis, 1977; Dunbar & Lishman, 1984; Corwin *et al.* 1990). Consistent with this view, depression has been associated with distorted perception and recall of environmental feedback (see Murphy *et al.* 1998, for review) and more recently, with an abnormal response to negative performance feedback that may contribute to the performance deficits often observed in these patients (Beats *et al.* 1996; Elliott *et al.* 1996, 1997, but see also Purcell *et al.* 1997; Shah *et al.* 1999). The findings of the present study would seem to corroborate such claims that depression is closely linked to dysregulation of reinforcement systems.

In manic patients, the 'conservative' tendency to bet less than controls on favourable outcomes appears superficially at odds with their poor quality or 'risky' decisions. It is unlikely that their suboptimal betting strategies reflect some fundamental impairment of cognition, such as a general failure to understand the changing task contingencies, as their deliberation times and quality of decisions varied in line with changing red : blue box ratios at the same rate as controls'. Alternatively, this 'conservative' behaviour could reflect a lack of confidence in their 'risky' decisions, perhaps suggesting that reward-reinforcement systems may also be compromised in mania.

Impulsivity and risk-seeking

An important feature of the betting component of this decision-making task is its ability to distinguish between impulsive and genuine risk-seeking behaviour. In particular, early bets in both the ascend and descend task conditions (i.e. small bets in the ascend condition and large bets in the descend condition) would suggest consistent impulsive, or disinhibited, responding, but large bets in both conditions would indicate risk-seeking. While the responses of manic and depressed patients did not entirely conform to either of these patterns, the earlier bets chosen by both patient groups relative to controls in the ascend betting condition appear more consistent with impulsive than with risk-seeking behaviour. This interpretation would be consistent with previous research in manic patients demonstrating difficulty with inhibition of behavioural responses to emotionally-charged stimuli on a go/no-go task (Murphy *et al.* 1999). Impulsivity, as measured using clinician- and self-administered rating scales, has also been shown to be an important dimension of clinical depression, especially in relation to suicide

attempts (Corruble *et al*. 1999). The tendency of both patient groups to respond quickly in the ascend betting condition may thus reflect a possible dysfunction of inhibitory systems in the cognition of mood disorders.

Importantly, the apparent impulsive responding of manic and depressed patients and the risk-taking observed in manics' heightened tendency to choose less favourable outcomes contrast starkly with the apparently conservative betting strategies of both patient groups. Relevant to this observation is research suggesting that impulsiveness, venturesomeness/sensation-seeking, time to make decisions, persistence, and boredom are important facets of the ill-defined concept of impulsivity (Buss & Plomin, 1975; Eysenck, 1993) and that impulsivity, as commonly understood and defined, probably consists of several independent factors reflecting different aspects of behaviour and having separate biological bases (Evenden, 1999). Indeed, recent evidence indicates that inhibitory control is selective for particular cognitive functions, with different prefrontal regions providing inhibitory control over different forms of cognitive processing (Dias *et al*. 1996). We should therefore not be surprised that in some elements of this task, manic and depressed patients demonstrated impulsive and venturesome behaviour, while in other elements tapping different cognitive functions, more conservative behaviour seemed prevalent in both groups.

Implications for neural pathways involved in mania and depression

The pattern of performance demonstrated here by manic patients is strikingly similar to that previously found for patients with damage to orbitofrontal sectors of PFC (Rogers *et al*. 1999*a*). Specifically, manic and orbitofrontal patients, but not patients with lesions of dorsolateral or dorsomedial PFC, took significantly longer than matched controls to decide which of two mutually exclusive outcomes would be more likely to occur and made suboptimal decisions, as evidenced by heightened tendencies to choose the less favourable of two possible response options.

The impaired quality of decisions of manic patients in the present study, in the context of similar findings in patients with orbital but not more superior prefrontal lesions (Rogers *et al*. 1999*a*), suggests that dysfunction of neural circuitry involving orbitofrontal cortex may underlie the decision-making deficits associated with mania. The present data do not rule out the possibility that orbitofrontal dysfunction also features in depressive pathology; indeed, recent neuroimaging studies suggest that dysfunction of medial prefrontal cortex, including anterior cingulate and medial orbitofrontal cortex and related limbic regions, is central to clinical depression (Elliott & Dolan, 1998; Mayberg *et al*. 1999). Rather, our data suggest that the functioning of this neural region may be differentially activated in depression and mania. This view finds support in a recent neuroimaging study by Drevets and colleagues, who identified a region of ventromedial PFC that is overactive during periods of mania and underactive in unipolar and bipolar forms of depression (Drevets *et al*. 1997). Increased activity of the anterior cingulate and orbitofrontal cortex have also been reported following the development of manic symptoms in stable bipolar patients taken off lithium (Goodwin *et al*. 1997).

Recent behavioural studies suggest a key role for orbitofrontal or medial orbitofrontal regions in decision-making and reward-punishment paradigms (Bechara *et al*. 1994, 1996, 1997, 1998). Recent functional imaging work, too, confirms the importance of orbital PFC in guessing or decision-making tasks. In healthy volunteers, choosing between alternative responses in a simple card-playing task was associated with activation in a network of structures that included the medial orbitofrontal cortex (Elliott *et al*. 1999). More recently, a PET study by our group highlighted the contribution of the orbitomedial regions in processing changes in reward-related information (Rogers *et al*. 1999*b*). Specifically, in a risk-taking task similar to the one used here, choosing between 'conflicting' response options was related to increases in activity of the right inferior and orbital PFC. Finally, a recent cognitive activation study suggests that in depressed patients, the behavioural response to performance feedback is associated with an abnormal neural response in regions implicated in reward mechanisms – the medial caudate and ventromedial orbitofrontal cortex (Elliott *et al*. 1998). The present findings are also consistent with evidence that orbital or ventromedial regions of

Table 4. *A comparison of the decision-making performance of medicated and unmedicated manic patients to that of depressed patients and control subjects*

	Deliberation times (ms)	Trials likely outcome chosen %	Bets %*
Manic patients			
Medicated ($N = 16$)	4038	88·0	65·9
Unmedicated ($N = 2$)	3642	84·4	71·6
Depressed patients ($N = 22$)	3698	94·0	70·0
Control subjects ($N = 26$)	2485	96·0	78·7

*Bet data are restricted to the 8 red : 2 blue box and 9 red : 1 blue box conditions, as it was only in these conditions that manic and depressed patients were impaired.

PFC are thought to subserve other processes that require affective information, such as processing emotion-related meanings (Beauregard *et al.* 1997; Teasdale *et al.* 1999) and reversing associations between stimulus and reward (Dias *et al.* 1996; Rolls *et al.* 1994). Indeed, these regions are extensively connected with limbic and other neural structures involved in processes of incentive motivation and reinforcement (Damasio, 1994; Pandya & Yeterian, 1996).

Possible constraints on interpretation: effects of medication and severity of illness

Recent reviews of the effects of medication on cognitive performance in the neuropsychiatric disorders have raised some cautions for researchers, though presence and severity of confounds appear to vary substantially across medications. For example, some investigations have highlighted the possibility for adverse effects of benzodiazepines on psychomotor ability and memory (Stein, 1998) and of antipsychotics and mood stabilizers on general cognitive functioning (King, 1990; Mortimer, 1997). On the other hand, it has been suggested that the major anti-convulsant drugs, taken by some of the manic patients in the present study for their mood stabilizing properties, are unlikely to have adverse cognitive effects (Devinsky, 1995). Similarly, there is evidence to suggest that tolerance to lithium administration may develop over the long term (e.g. Engelsmann *et al.* 1988), and anti-depressants are generally a concern only when they have strong anticholinergic or sedative effects (e.g. tricyclic antidepressants; Stein & Strickland, 1998).

The possible influence of medication on manic performance was a primary concern in the present study, as all but two of the patients in this group were receiving some combination of mood stabilizing, antipsychotic, and benzodiazepine medications. We therefore compared the performance of medicated ($N = 16$) and unmedicated ($N = 2$) manic patients; a close look at Table 4 shows that those manic patients receiving medication took slightly longer to deliberate, chose the likely outcome slightly more often, and made smaller bets relative to medication-free manic patients. While these differences may not be statistically significant, finding that medicated manic patients chose the likely outcome more often than unmedicated patients suggests that the suboptimal decision-making demonstrated by manic but not depressed patients (discussed above) cannot be explained by medication factors alone. The data presented in Table 4 further suggest that unmedicated manic patients, like depressed patients, show heightened deliberation times and smaller percentage bets relative to controls (in the 8 red : 2 blue box and 9 red : 1 blue box conditions). It is also worth noting that a recent companion study assessed decision-making cognition in euthymic bipolar patients who were receiving mood stabilizing drugs (lithium and anti-epileptic drugs) similar to those taken by manic patients in the present study (Rubinsztein *et al.* 2000); the results of that study showed residual deficits on tests of visuo–spatial recognition memory, but intact quality of decision-making and risk adjustments on the decision-making task used here.

Additional analyses were conducted to explore the effects of specific classes of medication on neuropsychological performance in manic and depressed patients. Comparing manic subgroups receiving ($N = 7$) and not receiving ($N = 11$) benzodiazepines failed to show marked differences in the speed or quality of decision-making and associated betting strategies. Simi-

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larly, no marked difference emerged between those depressed patients receiving ($N = 9$) and not receiving ($N = 13$) lithium or between depressed patients receiving ($N = 7$) and not receiving ($N = 15$) tricyclic antidepressants. While a recent study using the same decision-making task observed performance deficits in chronic amphetamine and opiate abusers (Rogers *et al.* 1999*a*), the low incidence of substance abuse in our manic patients was not expected to have significant effects on group performance; indeed, removal of the three patients with past diagnoses of alcohol or drug abuse did not change the profile of impairment associated with mania.

A final potential confounding factor in the present study was overall severity of illness in manic *versus* depressed patients. For example, it could be argued that the quality of depressed patients' decision-making (i.e. percentage trials likely outcome chosen) might be unimpaired relative to that of manic patients, within a context of lower overall psychiatric distress in depressed patients. It is unfortunate that the different symptom rating scales used for these two patient groups (YMRS for manic patients; Ham-D, MADRS, and CID for depressed patients) preclude direct comparison of disease severity. To address this potential confound, we used patient status (in-patient *v.* out-patient) as a common indicator of disease severity. A comparison of the quality of decision-making in subgroups of in-patient ($N = 11$) and out-patient ($N = 11$) depressed subjects failed to reveal significant group differences (in-patient = 93%; out-patient = 95%). In addition, a comparison of depressed and manic in-patients confirmed a group difference on this measure (depressed in-patients = 93%; manic in-patients = 86%).

In this context, it may be helpful to note that Huntington's disease patients have demonstrated more pronounced recognition memory and planning deficits (Lawrence *et al.* 1996; Watkins *et al.* 2000) than a group of manic patients almost identical to the present manic sample in terms of age and IQ (Murphy *et al.* 1999). However, Huntington's disease patients are unimpaired in the quality of their decision-making, as assessed with the same decision-making task as that used here (Watkins *et al.* 2000). These findings point to some diagnostic specificity in the profile of decision-making deficits observed in manic patients, and suggest that the different profiles associated with depression and mania in the present study are unlikely to be due to differences in overall severity of illness.

In sum, although we cannot entirely exclude the possibility that varying patient medication regimes, substance abuse, and severity of illness have influenced our findings, reasonable reconsideration of the data suggests that these factors are unlikely to account for the full range of neuropsychological deficits observed in this study.

Conclusion

On the most general measures of performance, medicated manic and depressed patients acted quite consistently on this decision-making task: both groups showed increased deliberation times but not lengthened 'betting' times, indicating some specific cognitive difficulty in decision-making, and both groups failed to score as highly as controls. A more careful analysis of the individual components of this task revealed important differences in the performance of manic and depressed patients. Although both patient groups adopted less responsive betting strategies than controls, only manic patients made more 'bad' decisions based on red:blue box ratios, and these 'poor' decisions were associated with increasing severity of manic symptomatology. Such differences between patient groups show how manic subjects were more likely to 'ground out', ending more blocks with a score of just one point. These distinct impairments observed for manic and depressed patients may be related to dysregulation of reward-reinforcement systems, a hypothesis supported by recent behavioural and imaging studies that employed decision-making and reward-punishment paradigms. The convergence of findings from these studies suggests that the decision-making impairments observed here in mania and depression might be related to differences in the functioning of neural circuits involving the ventromedial prefrontal cortex.

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