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Emotional bias and inhibitory control processes 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. The disinhibited behaviour characteristic of mania and evidence that subgenual prefrontal cortex is differentially activated in mania and depression both suggest that dissociable deficits will emerge on tasks that require inhibitory control and are subserved by ventromedial prefrontal cortex.

Methods. Manic patients and controls undertook computerized neuropsychological tests of memory and planning ability. In addition, manic and depressed patients were directly compared with controls on a novel affective shifting task that requires inhibitory control over different components of cognitive and emotional processing.

Results. Manic patients were impaired on tests of memory and planning. Importantly, affective shifting performance of manic patients differed from that of depressed patients. Manic patients were impaired in their ability to inhibit behavioural responses and focus attention, but depressed patients were impaired in their ability to shift the focus of attention. Depressed patients exhibited an affective bias for negative stimuli, and we believe this to be the first demonstration of an affective bias for positive stimuli in manic patients.

Conclusions. Observed impairments on tests of memory and planning suggest a global pathology for mania consistent with previous profiles for this disorder and similar to established profiles for depression. The results on the affective shifting task demonstrate the presence of mood-congruent bias and dissociable components of inhibitory control in mania and depression. Against a background of memory and planning impairments in the two groups, these findings are consistent with a role for the ventromedial prefrontal cortex in mediating mood–cognition relationships.

INTRODUCTION

In recent years, many studies have demonstrated the presence of wide-ranging neuropsychological deficits in individuals suffering from depression, with impairments reported in attention, memory and executive functioning (Brown *et al.* 1994; Beats *et al.* 1996; Elliott *et al.* 1996). It has long been recognized that mania is also associated with cognitive change (Kraepelin, 1921; Bunney & Hartmann, 1965), but few studies have investigated the nature and extent of impairments in bipolar patients who are manic at the time of neuropsychological assessment (Henry *et al.* 1971; Taylor & Abrams, 1986; Johnson & Magaro, 1987; Bulbena & Berrios, 1993; Goldberg *et al.* 1993; Bruder *et al.* 1994). The cognitive and neural pathways underlying these disorders of emotion remain poorly understood, but demonstration of distinct neuropsychological profiles in mania and depression could have considerable implications for our understanding of these pathways.

In earlier studies, bipolar patients in the manic phase of their illness were found to be impaired on conventional neuropsychological tests of attention (Bulbena & Berrios, 1993),

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memory (Henry *et al*. 1971; Taylor & Abrams, 1986; Johnson & Magaro, 1987; Bulbena & Berrios, 1993), visuospatial function (Taylor & Abrams, 1986; Bulbena & Berrios, 1993), choice reaction time (Bulbena & Berrios, 1993) and dichotic listening (Bruder *et al*. 1994). The few studies that have directly compared performance of manic and depressed patients on a range of neuropsychological tasks failed to find group differences (Bulbena & Berrios, 1993; Goldberg *et al*. 1993). These findings have led some to argue that similar, rather than opposite, processes are involved in mania and depression despite markedly different clinical presentations (Johnson & Magaro, 1987).

In a recent PET study, Drevets and colleagues identified a region of prefrontal cortex (pfc) that is differentially activated during periods of mania and depression (Drevets *et al*. 1997). Specifically, the subgenual pfc, which lies in the ventromedial prefrontal cortex (vmpfc), was found to be overactive during periods of mania but underactive during periods of unipolar and bipolar depression. The disinhibited behaviour characteristic of mania provides converging evidence for involvement of vmpfc, as similar behaviour is observed in patients with damage to this frontal region (Damasio, 1994).

Indeed, prefrontal regions have been shown to play an important role in tasks requiring inhibitory control in animal and human neuropsychological and imaging studies (Iversen & Mishkin, 1970; Leimkuhler & Mesulam, 1985; Fuster, 1989; Kalaska & Crammond, 1995; Godefroy *et al*. 1996; Godefroy & Rousseaux, 1996; Kawashima *et al*. 1996; Casey *et al*. 1997). It should be noted, however, that it has recently been suggested 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, 1997). In marmoset monkeys, for example, damage to lateral pfc caused a loss of inhibitory control in attentional selection, but damage to vmpfc caused a loss of control in affective processing as shown by impaired ability to reverse an association between stimulus and reward (Dias *et al*. 1996).

Based on the above, it seems reasonable to propose that if neuropsychological differences between manic and depressed patients do exist, they should emerge on tasks requiring inhibitory control. We have recently developed a novel affective shifting task that requires subjects to respond to target words of either positive or negative affective tone while inhibiting responses to words of the competing affective category, and also to shift both attention and response set from one affective category to the other. Importantly, this task demands inhibitory control at three distinct levels – response or attentional selection, association of stimulus and reward, and attention to emotional stimuli – each of which can be separately quantified.

The goals of the present study were thus twofold. First, we aimed to understand more fully the profile of neuropsychological impairment associated with mania by administering conventional neuropsychological tests of visual memory and planning ability. Secondly, we aimed to examine distinct inhibitory control processes and the presence of mood-congruent attentional bias in both mania and depression by administering the novel affective shifting task described above. By exploring inhibitory control in these two disorders, we have sought to address one of the central problems facing studies of mania today, the difficulty in dissociating it experimentally from depression.

METHOD

Participants

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

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; all but four of those approached agreed to participate. Patients were excluded from participation on the basis of the following criteria: history of neurological illness or head injury; untreated thyroid disease or

Table 1. *Demographic and clinical data from manic patients, depressed patients, and control groups. Data shown are means with standard errors of the mean in parentheses*

	Manic patients ($N = 18$)	Controls A ($N = 18$)	Depressed patients ($N = 28$)	Controls B ($N = 22$)
Female:male ratio	9:9	9:9	17:11	13:9
Age	35·6 (2·4)	35·8 (2·6)	36·3 (1·6)	36·1 (2·3)
NART-IQ	109·0 (2·3)	113·4 (1·8)	113·7 (1·5)	113·9 (1·5)
MMSE	28·9 (0·3)	29·6 (0·2)	28·9 (0·3)	29·4 (0·5)
Young	23·6 (1·9)	—	—	—
Ham-D	—	—	23·5 (0·8)	—
MADRS	—	—	34·2 (1·0)	—
CID	—	—	57·4 (2·0)	—
BDI	—	3·2 (0·7)	—	3·7 (0·7)

other major medical disorders likely to effect cognition (e.g. diabetes mellitus); use of steroids; and ECT in the previous 3 months. The 18 patients determined to be suitable for participation were seen 2 weeks post admission on average and met DSM-IV (APA, 1994) and Research Diagnostic Criteria (Spitzer *et al*. 1978) for bipolar I disorder, manic episode. All patients received the Schedule for Affective Disorders and Schizophrenia-Lifetime Version (Endicott & Spitzer, 1978), and severity of mania was assessed by means of the Young Mania Rating Scale (Young *et al*. 1978).

The 17 in-patients and one day-patient ranged from 16 to 54 years of age and had experienced 4·7 hospitalized manic episodes on average. Only two patients were not taking any medication. Of the remainder, all were receiving antipsychotics (mean dose, 500 mg chlorpromazine equivalents), 15 were taking lithium carbonate, carbamazepine or sodium valproate alone or in combination, and seven were taking benzodiazepines. Although three patients received a current diagnosis of alcohol or drug abuse, to the best of our knowledge none had taken alcohol or drugs in the week prior to testing.

Depressed patients

Twenty-eight patients meeting DSM-IV (APA, 1994) criteria for major depressive disorder participated in this study. Exclusion criteria were the same as those for manic patients. Additionally, patients with a current and/or past diagnosis of psychoactive substance abuse were excluded from participation. 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).

The depressed sample comprised 19 in-patients and 9 out-patients between 26 and 57 years of age. Two patients were not taking any medication; of the remaining 26 patients taking antidepressant medication, nine were taking SSRIs, six tricyclics, two MAOIs, one noradrenaline reuptake inhibitor, one SSRI plus MAOI, and seven lithium plus SSRI, tricyclic, or MAOI. All patients were taking antidepressant doses equivalent to a minimum of 150 mg of amitriptyline. Three patients were also receiving neuroleptics or benzodiazepines.

Control subjects

Control subjects were recruited by advertisement in the community and were excluded if there was evidence on questioning of psychiatric history, neurological history, psychoactive substance abuse, or use of medication which might potentially influence cognition. The Beck Depression Inventory (BDI; Beck *et al*. 1961) was administered to screen subjects for depressive symptomatology, and those with a score greater than nine were excluded.

The selection of control subjects was adjusted to reflect the fact that manic patients completed three background tasks as well as the novel affective shifting task, whereas depressed patients were administered only the latter (see below). As a result, 18 control subjects (Controls A) were selected to match manic patients as closely as possible for age, sex, and NART-

estimated verbal IQ; these control subjects completed the three background neuropsychological tests. An additional four control subjects were added to these 18 controls to form a new control group (Controls B) that would more closely match both manic and depressed patient samples for age, sex, and NART-IQ. Control group B completed only the affective shifting task.

Controls A: Background neuropsychological tests

The 18 control subjects selected to match manic patients for age, sex, and NART-IQ ranged from 16 to 57 years of age. Unpaired t tests revealed that manic patients and controls did not differ in terms of age ($t = -0{\cdot}06$, $P = 0{\cdot}95$) or NART-IQ ($t = -1{\cdot}47$, $P = 0{\cdot}15$).

Controls B: Affective shifting task

The 22 control subjects selected to match manic and depressed patients for age, sex, and NART-IQ ranged between 16 and 59 years of age. One-way ANOVAs revealed that the three groups did not differ in terms of age ($F(2,65) = 0{\cdot}10$, $P > 0{\cdot}5$) or NART-IQ ($F(2,65) = 2{\cdot}01$, $P = 0{\cdot}14$).

Computerized neuropsychological assessment

Computerized neuropsychological assessment was carried out as soon as possible after clinical assessment, with tests presented on a portable 486 microcomputer fitted with a Datalux touch-sensitive screen. Subjects sat at a distance of approximately 0·5 m from the touchscreen and responded to stimuli by touching the screen or by pressing the space bar, as necessary, with the index finger of their dominant hand. Manic patients were tested over two to three sessions during the same week, beginning 2 weeks post-admission on average. As research suggests that diurnal variation in mood can have a significant effect on neuropsychological performance (Moffoot *et al*. 1994), attempts were made to test patients at approximately the same time of day when more than one test session was necessary. All patients were tested between 9 a.m. and 4 p.m.

Except for the affective shifting task, which is novel to the present study, the neuropsychological tasks employed were taken directly or adapted from the Cambridge Neuropsychological Test Automated Battery (CANTAB) visuospatial memory and working memory/planning batteries. These tests are reliable and valid (Robbins *et al*. 1994, 1998) and have been described in detail elsewhere (Sahakian *et al*. 1988; Owen *et al*. 1990). Manic patients completed the four tasks described below. Depressed patients completed only the affective shifting task as the background tasks had been administered to a different sample of depressed patients in a previous study (Elliott *et al*. 1996).

Background neuropsychological tests

Pattern and spatial recognition memory

This test assesses recognition memory for geometric patterns and spatial locations. To assess pattern recognition memory, 12 abstract coloured patterns are presented sequentially in the centre of the screen. Following a short delay, the same patterns (each now paired with a novel pattern), are presented in reverse order and subjects must touch the pattern they have already seen. This procedure is then repeated with new patterns. To assess spatial recognition memory, five squares are presented sequentially in different locations on the screen. Following a short delay each square is presented again, now paired with a novel location. Subjects must touch the correct locations. This procedure is repeated three more times.

Simultaneous (SMTS) and Delayed Matching to Sample (DMTS)

At the beginning of each trial, a sample complex abstract pattern appears at the top of the screen for 4·5 s. Subjects are required to remember the sample stimulus so they can identify it from four choice stimuli (the sample plus three distractor patterns) presented below the sample. In simultaneous matching (SMTS) trials, the sample pattern remains on the screen while the four choice stimuli are presented. In delayed matching (DMTS) trials, the sample pattern disappears and there is a delay of either 0, 4 or 12 s before choice stimuli are presented. The test begins with three practice trials followed by 40 test trials (10 of each condition: SMTS, 0 s, 4 s, 12 s) presented in a fixed, pseudo-random order.

One-touch Tower of London Task

This task was adapted from the Tower of London planning task in the CANTAB battery

(see Owen *et al*. 1995*a*, for details) in order to reduce motor demands and to encourage subjects to 'plan' responses. In this adaptation, two arrays of three coloured balls are presented on the screen, arranged in hanging pockets. Subjects are required to compute 'in mind' the minimum number of moves needed to rearrange the coloured balls in one array in order to match the goal arrangement, and to touch the appropriate response on the bottom of the screen. Trials vary in difficulty, with problems requiring a minimum of one, two, three, four, or five moves. The task begins with four practice trials (two 1-move and two 2-move problems) followed by 16 test trials (two 1-move, four 2-move, two 3-move, four 4-move, four 5-move) presented in a fixed, pseudo-random order.

Affective shifting task

In this go/no-go task, words are rapidly presented in the centre of the screen, one by one. Half of the words are targets and half are distractors. Subjects must respond to targets by pressing the space bar as quickly as possible but withhold responses to distractors. Words are presented for 300 ms, with an inter-stimulus interval of 900 ms. A 500 ms/450 Hz tone sounds for each error, but not omission (see below for explanation of errors and omissions).

The task comprises two practice blocks followed by eight test blocks of 18 stimuli each (nine 'happy' (H) words and nine 'sad' (S) words). In each block, either happy or sad words are specified as targets, with targets for the 10 blocks presented in a HHSSHHSSHH or SSHHSSHHSS order. Due to this arrangement, four test blocks are 'shift' blocks, where subjects must begin responding to stimuli which were distractors and cease responding to stimuli which were targets in the previous block, and four test blocks are 'non-shift' blocks, where subjects must continue responding to stimuli which were targets and withholding responses to stimuli which were distractors in the previous block. Target presentation order is randomly assigned to subjects.

The 45 happy and 45 sad words used were selected from an original list of 180 happy, sad, and neutral words because they were consistently rated, by five raters blind to the purpose of the study, as being 'very happy' or 'very sad' (on a 7-point Likert scale with endpoints (−3) 'very happy' and (+3) 'very sad'). The happy and sad words do not differ in terms of word length ($t = -0{\cdot}59$, $P > 0{\cdot}05$) or word frequency ($t = -0{\cdot}10$, $P > 0{\cdot}05$) as determined using the norms of Hofland & Johansson (1982). Representative examples from the happy and sad word-lists are 'joyful', 'success', 'confident' and 'gloomy', 'hopeless', 'failure', respectively.

Dependent measures of interest were response times (time taken to respond to each target), errors (responses to distractor stimuli), and omissions (failure to respond to target stimuli). These measures allowed for examination of different levels of inhibitory control: (*i*) by examining overall performance irrespective of target valence and shift condition, general ability to inhibit behavioural responses and focus attention could be assessed; (*ii*) by comparing overall performance on shift relative to non-shift blocks, subjects' ability to inhibit and reverse stimulus–reward associations could be determined; and (*iii*) by contrasting performance measures for happy and sad targets, the presence of mood-congruent attentional biases could be confirmed.

Statistical analysis

Data were analysed using SPSS for Macintosh (Nie *et al*. 1970) with *t* tests, univariate or repeated-measures analysis of variance (ANOVA) as appropriate. Although data presented are untransformed means, prior to analysis, proportion data were arcsine transformed, count data were square root transformed, and latency data were logarithmically transformed where necessary to stabilize variance or reduce skew in the distributions (see Howell, 1997). Pearson's product moment correlation coefficients were employed in correlational analyses. In tests where delay or difficulty level were variables, although main effects of delay or difficulty were significant in all cases, only main group effects and interactions are reported.

RESULTS

Background neuropsychological tests

Pattern and spatial recognition memory

Data for pattern and spatial recognition memory were analysed separately with proportion correct and latency to respond as dependent measures.

On the test of pattern recognition memory, manic patients were impaired in terms of mean proportion of correct responses (manic = 0·78, control = 0·90; $F(1,34) = 5{\cdot}37$, $P < 0{\cdot}05$) and response latency (manic = 2835 ms, control = 1999 ms; $F(1,34) = 16{\cdot}46$, $P < 0{\cdot}001$). Both mean proportion of correct responses (manic = 0·80, control = 0·91; $F(1,34) = 8{\cdot}77$, $P < 0{\cdot}01$) and response latency (manic = 2808 ms, control = 1871 ms; $F(1,34) = 13{\cdot}00$, $P < 0{\cdot}001$) were impaired for spatial recognition memory as well.

Simultaneous (SMTS) and Delayed Matching to Sample (DMTS)

Data for simultaneous and delayed matching conditions were analysed separately with proportion correct and response latency as dependent measures. Proportions of stimuli remembered correctly at each delay for the two groups are shown in Fig. 1*a*. On SMTS trials, patients were not impaired relative to controls ($F(1,34) = 0{\cdot}25$, $P > 0{\cdot}5$). On DMTS trials, however, repeated measures ANOVA showed a significant main effect of group ($F(1,34) = 8{\cdot}74$, $P < 0{\cdot}01$), with manic patients performing worse than controls, but no significant interaction between group and delay ($F < 1$). When DMTS scores were adjusted to account for SMTS performance using analysis of covariance (ANCOVA), impaired performance in the patient group remained significant ($F(1,33) = 8{\cdot}57$, $P < 0{\cdot}01$).

Mean response latencies for the two groups are shown in Fig. 1*b*. Manic patients were significantly slower than controls, both on SMTS ($F(1,34) = 8{\cdot}22$, $P < 0{\cdot}01$) and DMTS trials where there was a significant main effect of group ($F(1,34) = 4{\cdot}10$, $P = 0{\cdot}05$) but no significant group by delay interaction ($F < 1$). Covarying for SMTS, however, removed this latency impairment ($F < 1$).

One-touch Tower of London

Mean percentage of problems solved correctly and mean latency at each level of difficulty for manic patients and controls are shown in Figs 2*a* and 2*b*, respectively. These measures were based on participants' first response to each problem (although subjects continued to respond until the correct response had been made) as first responses provide a purer index of planning ability *per se*. One manic patient refused to complete this task and latency data from one control was lost due to a technical problem.

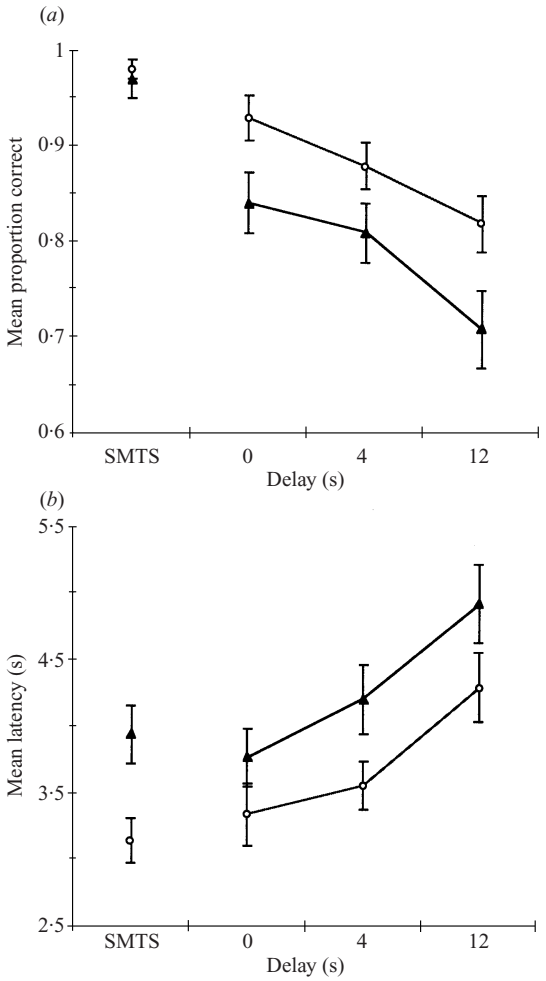

FIG. 1. Mean proportion of correct responses (*a*) and mean latency as a function of delay on the delayed matching-to-sample task (*b*) for both manic patients (▲) and controls (○). Bars represent one standard error of the mean (S.E.M.).

With respect to percentage correct, repeated measures ANOVA revealed a significant main effect of group with manic patients solving fewer problems correctly than controls ($F(1,33) = 7{\cdot}30$, $P = 0{\cdot}01$). The group by difficulty interaction also approached significance, with manic patients solving fewer of the more difficult (i.e. 4- and 5-move) problems correctly ($F(4,132) = 2{\cdot}26$, $P = 0{\cdot}06$). Similarly, repeated measures ANOVA for response latencies revealed a

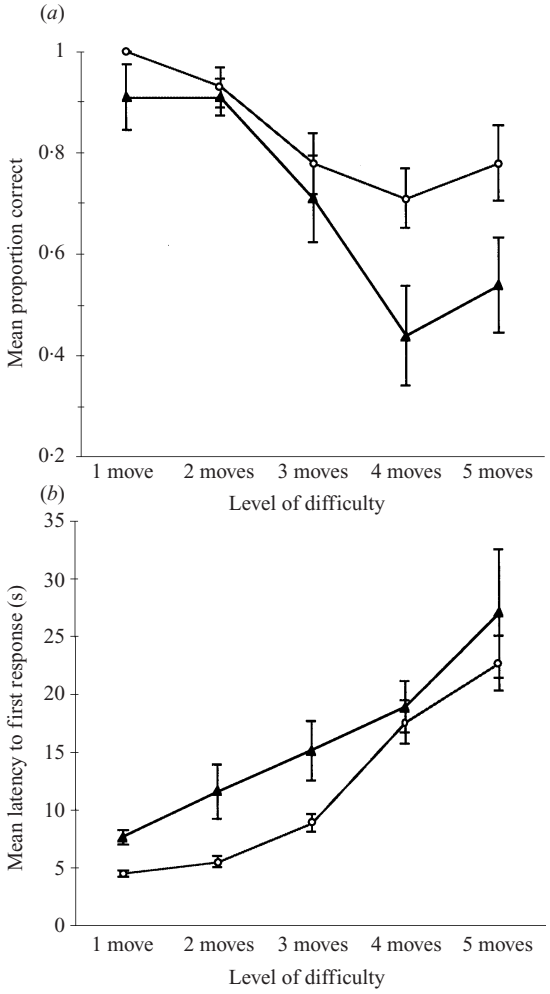

FIG. 2. Performance of manic patients (▲) and control subjects (○) as a function of difficulty level on the one-touch Tower of London task. The dependent measures shown are: (*a*) mean proportion of problems solved correctly by first response; and (*b*) mean latency to first response. Bars represent 1 S.E.M.

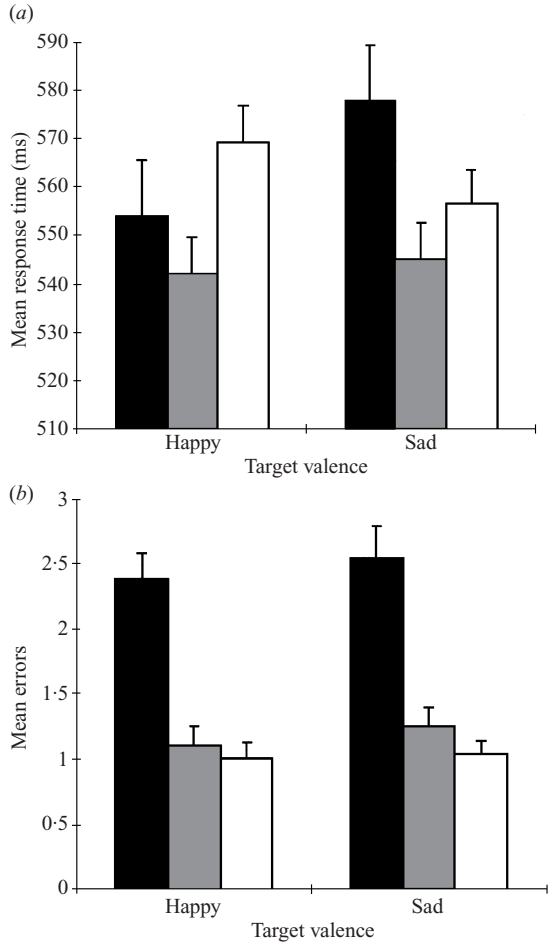

FIG. 3. Mean (*a*) RTs and (*b*) errors for happy and sad targets in the affective shifting task for manic patients (■), depressed patients (□), and control subjects (▩). Bars represent 1 S.E.M.

significant main effect of group ($F(1,32) = 6{\cdot}47$, $P < 0{\cdot}05$) that was primarily due to patients taking longer than controls on easy but not difficult problems as shown by the significant group by difficulty interaction ($F(4,128) = 5{\cdot}38$, $P < 0{\cdot}001$).

Affective shifting task

Mean response times, errors, and omissions for each block of 18 trials were initially analysed by way of repeated measures ANOVAs with patient group (manic, depressed, control) and target presentation order (happy targets first, sad targets first), as between-subject factors, and target valence (happy targets, sad targets) and shift condition (shift, non-shift) as within-subject factors. As no effects involving both subject group and target presentation order approached significance, and as no specific predictions involving target presentation order were made on an *a priori* basis, data were reanalysed for the purpose of clarity; specifically, three ANOVAs were performed (one each for the three dependent variables of interest: RTs, errors, omissions), with group, target valence, and shift condition as factors. Response times (RTs) less than 100 ms (anticipations) were excluded from analysis.

Table 2. *Mean RTs, errors, and omissions per block of trials for manic patients, depressed patients, and control subjects on the affective shifting task. Numbers in parentheses are standard errors of the mean*

	Shift condition	Manic patients ($N = 18$)	Depressed patients ($N = 28$)	Control subjects ($N = 22$)
RTs	Shift	555·08 (12·57)	570·12 (7·57)	545·09 (8·17)
	Non-shift	576·88 (10·51)	556·05 (6·49)	542·20 (6·99)
Errors	Shift	2·57 (0·22)	1·09 (0·10)	1·34 (0·15)
	Non-shift	2·36 (0·21)	0·96 (0·11)	1·02 (0·14)
Omissions	Shift	1·48 (0·20)	0·63 (0·10)	0·28 (0·07)
	Non-shift	1·58 (0·21)	0·58 (0·10)	0·24 (0·06)

RTs

Fig. 3*a* shows mean RTs as a function of target valence for manic patients, depressed patients, and control subjects. Analysis of RTs revealed a significant interaction between subject group and target valence ($F(2,65) = 8{\cdot}36$, $P < 0{\cdot}001$). Simple effects analysis demonstrated that compared with control subjects, manic patients were slower to respond to sad but not happy targets ($F(1,65) = 4{\cdot}87$, $P < 0{\cdot}05$), while depressed patients were slower to respond to happy but not sad targets ($F(1,65) = 4{\cdot}05$, $P < 0{\cdot}05$). Thus, manic and depressed patients demonstrated attention and/or response biases for happy and sad targets, respectively; control subjects, on the other hand, had similar RTs for happy and sad targets. When RT data were reanalysed in order to covary for the mean number of errors made by the different subject groups, the interaction between subject group and target valence remained significant.

Table 2 shows mean RTs, errors, and omissions as a function of shift condition for manic patients, depressed patients, and control subjects. A significant subject group by shift condition interaction emerged ($F(2,65) = 4{\cdot}59$, $P < 0{\cdot}05$); simple effects analysis (see Howell, 1997) showed that this interaction was due to significant time costs associated with shifting (i.e. subjects take longer on shift compared with non-shift blocks) in depressed patients ($F(1,65) = 6{\cdot}38$, $P < 0{\cdot}05$) but not controls ($F < 1$) or manic patients, where relative time benefits (i.e. subjects are faster on shift compared with non-shift blocks) were found ($F(1,65) = 8{\cdot}36$, $P < 0{\cdot}001$). Importantly, the apparent benefits observed in manic patients were due to increased RTs on non-shift blocks and not decreased RTs on shift blocks. Thus, it seems that relative to control subjects, ability to shift attention is impaired in depressed but not manic patients. Shift costs did not interact with target valence (i.e. happy *versus* sad targets), as the three-way subject group by shift condition by target valence interaction was not significant ($F < 1$). Furthermore, main effects of subject group ($F < 1$) and shift condition ($F < 1$) did not approach significance.

Errors

Fig. 3*b* shows mean errors as a function of target valence for manic patients, depressed patients, and control subjects. Analysis of errors revealed a main effect of subject group, with manic patients making more errors than either depressed patients or controls ($F(2,65) = 12{\cdot}48$, $P < 0{\cdot}001$). A main effect of shift condition also emerged, with subjects on average making significantly more errors on shift relative to non-shift blocks ($F(1,65) = 8{\cdot}32$, $P < 0{\cdot}01$; see Table 2). The interactions between subject group and target valence or subject group and shift condition did not approach significance (Fs < 1; see Fig. 3*b* and Table 2).

Omissions

Analysis of omissions revealed a significant main effect of subject group, with manic patients missing more targets than either depressed patients or control subjects ($F(2,65) = 12{\cdot}77$, $P < 0{\cdot}001$; see Table 2). A near-significant subject group by target valence interaction also emerged ($F(2,65) = 3{\cdot}01$, $P = 0{\cdot}06$). Specifically, manic patients missed more happy than sad targets; omissions for controls and depressed patients, however, were not influenced by target valence. No other effects approached significance.

Relationship between neuropsychological performance and clinical characteristics

Correlations between neuropsychological performance and clinical characteristics were calculated separately for manic and depressed patient groups. The clinical measures considered were Young mania scores and number of hospitalized manic episodes in manic patients, and Ham-D, MADRS, and CID scores in depressed patients. Correlations between these clinical measures and pattern and spatial recognition memory, matching to sample, one-touch Tower of London, and affective shifting performance were computed. No correlations approach significance ($P = 0{\cdot}05$) in either patient group.

DISCUSSION

The present findings indicate that manic patients exhibit impaired functioning on a range of neuropsychological tasks. Substantial impairments were found on tests of pattern and spatial recognition memory, matching to sample and planning ability. These novel findings for mania are consistent with a pattern of global cognitive deficits. Moreover, this profile is similar to that observed in depressed patients in a previously published study by our group (Elliott *et al.* 1996). Given the apparent similarities between profiles established separately in these two studies, the group differences between mania and depression contrasted directly here on the novel affective shifting task are particularly striking. While manic patients were impaired in their ability to focus attention and inhibit inappropriate responses, depressed patients were impaired in their ability to shift, or reverse, the focus of their attention. Additionally, both patient groups exhibited attentional biases for emotional stimuli congruent with their current mood. To our knowledge, this is one of the first demonstrations of a positive affective bias in manic patients and also of contrasting patterns of cognitive performance in mania and depression.

Memory and planning impairments in mania

Manic patients were significantly impaired on tests of pattern and spatial recognition memory in terms of both proportion of correct responses and response latency. On the task of delayed visual recognition, the accuracy deficits observed in manic patients were independent of delay, and remained when perceptual factors were accounted for by covariance – a pattern suggestive of mnemonic, rather than basic perceptual, impairment. On the Tower of London test of planning, manic patients solved fewer problems correctly, especially at the more challenging levels, and were slower to solve easy but not difficult problems.

These tests assess different cognitive functions and are believed to be subserved by different neural regions. The deficits seen on tests of spatial recognition memory and planning ability are comparable to those seen in patients with frontal dysfunction (Owen *et al.* 1995*a*, *b*) or basal ganglia disorders like Parkinson's disease (Owen *et al.* 1995*a*) in which there is probably a disruption of functioning of frontostriatal 'loops' (Alexander *et al.* 1986). In contrast, the deficits observed on tests of object recognition memory are comparable to those observed in patients with more posterior dysfunction, such as temporal lobe lesions or mild Alzheimer's dementia (Sahakian *et al.* 1988; Owen *et al.* 1995*b*; see Elliott & Dolan, 1999).

The finding that manic patients demonstrated marked deficits on all of the background neuropsychological tasks administered – including tasks largely dependent upon intact functioning of both temporal and frontal neural regions – suggests a global, rather than a specific, profile of impairment. Although the range of tasks administered in the present study is certainly limited, other investigators have also reported impaired functioning across task domains. For example, in a study conducted by Taylor & Abrams (1986), tests of attention, visuospatial function and memory were administered to manic patients, and approximately half the manic sample exhibited moderate or severe global cognitive impairment.

A similar picture has emerged from recent work on the cognitive performance of depressed patients. Elliott *et al.* (1996) administered the same background tasks used here (as part of a much more extensive test battery) to patients with major depression, finding neuropsychological deficits across the full spectrum. The authors of at least two reviews of cognitive functioning in depression (Miller, 1975; Veiel,

1997) have concluded that there is little evidence for a profile of deficits unique to depression (Miller, 1975); on the contrary, the extensive range of neuropsychological deficits frequently registered in patients with major depression is thought by one author to be consistent with a 'global-diffuse impairment of brain function' (Veiel, 1997).

The finding that both manic and depressed patients are impaired on a range of cognitive tasks subserved by different neural regions leaves open the possibility that some underlying process, perhaps even common to the two disorders, could account for the noted deficits. Several theories have been put forth to explain the pervasive deficits observed in depressed patients, including an abnormal response to performance feedback (Elliott *et al*. 1996), reduced motivation (Miller, 1975; Richards & Ruff, 1989), diminished cognitive capacity and processing resources (Hasher & Zacks, 1979), and a narrowing of attentional focus to depression-relevant thoughts (Ellis & Ashbrook, 1988). To date, however, few investigators have considered mania-related deficits within these and similar frameworks. If some global pathology common to depression and mania continues to appear plausible – and certainly more comprehensive studies employing a wider range of tasks are needed before firmer similarities can be hypothesized – it may become necessary to devise theories accounting for more generalized deficits in both of these forms of affective disorder.

Contrasting affective bias in mania and depression

As noted above, direct comparisons of manic and depressed patients suggest that these patient groups are similarly impaired on neuropsychological tests of attention, memory and visuospatial function (Taylor & Abrams, 1986; Bulbena & Berrios, 1993). The present study did not assess again depressed patients on the same background neuropsychological tasks administered to manic patients; however, when viewed in the context of findings for depressed patients in the companion study by Elliott *et al*. (1996), the present study suggests that manic and depressed patients exhibit somewhat similar deficits on tests of recognition memory, matching to sample, and planning ability. In contrast to these apparent similarities, manic and depressed patients in this study demonstrated different patterns of performance on the novel affective shifting task. This task requires subjects not only to attend and respond to relevant targets while inhibiting responses to stimuli of the competing affective category, but also to shift attention and response from happy to sad targets, and vice versa. In the introduction, we argued that this task requires inhibitory control over three different components of cognitive processing: selection of attention and/or response, association between stimulus and reward, and processing of emotional stimuli from long-term memory.

With respect to the latter, manic and depressed patients exhibited biases for processing happy and sad stimuli, respectively. We believe this to be the first demonstration of a positive attentional bias in manic patients – a finding consistent with Bower's network theory of mood and affect (Bower, 1981) and with evidence that healthy controls in an induced elated mood exhibit a positive bias for remembering past experiences (Teasdale & Fogarty, 1979). Demonstration of a negative bias in depressed patients is consistent not only with Bower's network theory (Bower, 1981) and Beck's cognitive theory of depression (Beck, 1967, 1976), but also with studies demonstrating biases of memory and attention associated with depression (Lloyd & Lishman, 1975; Clark & Teasdale, 1982; Blaney, 1986; Gotlib & Cane, 1987; Mogg *et al*. 1995; Bradley *et al*. 1996; Williams *et al*. 1997). According to Beck, such dysfunctional negative schemas are used to interpret incoming experience and play a role in the development and maintenance of the affective, physiological and behavioural components of depression (Beck, 1967, 1976).

It should be noted that the longer RTs observed for happy compared with sad targets in depressed patients could be due to interference from sad distractors; that is, compared with controls, depressives were slower to respond to happy, but not quicker to respond to sad, targets. Consistent with this hypothesis, Gotlib & Cane (1987) found interference for depression-related but not neutral- or manic-related words in depressed patients using an emotional analogue of the Stroop task, as have others (Klieger & Cordner, 1990; Segal *et al*. 1995). A parallel argument could also account for the longer RTs

observed for sad as compared with happy targets in manic patients. This 'mirror-view' construction of the data posits an opposite mechanism, but is still compatible with our hypothesis of attentional biases in mania and depression.

Disinhibited responding in manic patients

With respect to mechanisms of response selection, manic patients were impaired in their ability to inhibit behavioural responses to irrelevant stimuli. Such behaviour is reminiscent of that observed in patients with medial or ventromedial frontal damage on go/no-go tasks (Drewe, 1975; Leimkuhler & Mesulam, 1985; Malloy *et al*. 1985, 1994; Fuster, 1989; Mega & Cummings, 1994); as such, it might well be asked why disinhibition was not observed in manic patients on the other task known to implicate pfc, the Tower of London task. An hypothesis of impulsive or rapid responding could in fact potentially explain manics' impaired accuracy on the more difficult 4- and 5-move Tower of London planning problems. On the easier 1-, 2-, and 3-move problems, manic patients responded more slowly than controls and solved as many correctly; on the more difficult problems, however, manic patients did not increase latencies to the same degree as controls – possibly due to a tendency to respond impulsively – and perhaps solved fewer problems correctly as a result. It is possible that impulsive responding was not observed across all difficulty levels because the one-touch version of this task, which is based on the earlier CANTAB Tower of London, was specifically designed to discourage patients from making impulsive and disinhibited responses and to encourage them to 'plan' responses carefully instead.

As rapid responding was not observed across all difficulty levels on the Tower of London test of planning or on the other neuropsychological tasks administered, it is difficult to reconcile the specific finding of impulsive responding on the affective shifting task with a hypothesis of global disinhibition in manic patients. As mentioned in the introduction, inhibitory control is not necessarily a unitary concept, but can be specific to different cognitive functions. It is now known that performance on the Tower of London task is subserved by dorsolateral rather than ventromedial regions of pfc (Baker *et al*. 1996). Thus, the finding that manic patients demonstrate disinhibition on the affective shifting task but not on the other tasks administered may suggest that the disinhibition sometimes observed in manic patients reflects specific alterations of vmpfc functioning.

The possibility that this deficit is related to a more general inability to focus attention should be borne in mind, as omissions were also elevated in manics. This interpretation is consistent with research by Godefroy and colleagues suggesting that ability to focus attention on a go/no-go task is compromised in patients with prefrontal lesions (Godefroy *et al*. 1996; Godefroy & Rousseaux, 1996). Difficulty in focusing attention could also potentially explain the deficits in accuracy and latency observed in manic patients on the CANTAB tests of visual memory and planning. Although such attentional difficulty cannot explain the positive emotional bias obtained on the affective shifting task and thus account for the full range of neuropsychological performance observed, the reverse may be true – that is, a narrowing of attentional focus to mania-related thoughts may contribute to widespread problems with focusing attention on all of the tasks administered. The possibility that some underlying process determines the generalized profile of impairment on conventional tests of memory and planning ability was discussed above; perhaps a bias for processing mood-congruent stimuli, already proposed as a theoretical model for cognition in depression (Ellis & Ashbrook, 1988), might likewise serve as such a model for cognition in mania.

Shifting the focus of attention in depressed patients

Although depressed patients were unimpaired in their ability to focus attention and withhold responses to irrelevant stimuli, they had difficulty shifting attention and response from one affective category to the other as shown by elevated RTs on shift blocks. While manic patients appeared to show enhanced shifting ability, this effect was largely due to impaired performance on non-shift blocks (and not improved performance on shift blocks).

In marmoset monkeys, damage to vmpfc causes a loss of inhibitory control over affective processing, thereby impairing the ability to alter

behaviour in response to changes in the emotional significance of stimuli (Dias *et al.* 1996). Impaired reversal in simple visual discrimination tests has been found in humans with ventral frontal damage also (Rolls *et al.* 1994). It is perhaps not surprising that the shifting impairment in depressed patients was evident in RTs and not errors given the important observation of an abnormal response to negative feedback in depressed individuals (Nelson & Craighead, 1977; Carver & Scheier, 1981; Pyszczynski & Greenberg, 1985; Greenberg & Pyszczynski, 1986; Conway *et al.* 1991; Beats *et al.* 1996; Elliott *et al.* 1996, 1997). As errors made in the affective shifting task were accompanied by a salient low tone, it seems reasonable to speculate that depressed patients adopted a strategy of increased RTs in order to avoid making errors.

It is interesting to note that both manic and depressed patients are impaired in their ability to shift cognitive set as assessed by the Wisconsin Card Sort Test (WCST) (Morice, 1990; Martin *et al.* 1991; Franke *et al.* 1993; Trichard *et al.* 1995). Although shifting set on the WCST is believed to be subserved by dorsolateral regions of prefrontal cortex (Milner, 1963), we believe reversing stimulus-reward associations in the affective shifting task used here to be subserved by more ventromedial regions of pfc. Consistent with our finding that manic and depressed patients are differentially impaired on the affective shifting task but not the WCST, Drevets *et al.* (1997) have identified a region of the vmpfc, just beneath the genu of the corpus callosum, which is activated during periods of mania and underactivated in unipolar and bipolar depression. This finding is also interesting in the light of anatomical and functional distinctions between ventromedial and dorsolateral regions of the prefrontal cortex. While the dorsolateral region has numerous connections with cortical systems involved in information processing, the ventromedial region is more extensively connected with the limbic system (Pandya & Yeterian, 1996).

Relation between neuropsychological profile and clinical descriptions

The contrasting patterns of performance observed on the affective shifting task in manic and depressed patients are consistent with clinical descriptions of these two patient groups. First, the affective biases for happy and sad stimuli are congruent with the euphoric and depressed moods characteristic of these two patient groups. Secondly, the difficulty manic patients had inhibiting behavioural responses is reminiscent of the disinhibited behaviour frequently observed during manic episodes. Finally, the negative affective bias and impaired ability to shift the focus of attention in depressed patients are consistent with the perseverance of low mood and persistent ruminations that are so characteristic of depression. Indeed, Teasdale has suggested that one of the goals of psychotherapy is to give depressed individuals greater control over switching in and out of different 'minds-in-place' (Teasdale, 1997).

In the light of these commonalities, it is surprising that correlations between clinical characteristics and neuropsychological performance, particularly on the affective shifting task, did not approach significance. The severity rating scales used are not comprehensive, and such scales may not be sensitive enough to detect changes in mood and cognition with the same sensitivity as those detected by the affective shifting task used here. In depressed patients, perhaps a cognitive rating scale such as the BDI would have provided a better index. In manic patients, the window during which testing could occur was very narrow (i.e. due to severity of illness and the need for treatment these patients could not be assessed immediately upon admission, and testing could not be too much delayed due to the potential for early discharge; thus, patients were tested approximately 2 weeks post-admission), perhaps resulting in reduced variance in severity of manic symptoms and failure to find significant correlations with cognitive measures.

Constraints on interpretation: medication and research design

Recent reviews of the effects of benzodiazepines on psychomotor ability and memory (Stein & Strickland, 1998) and of antipsychotics and mood stabilizers on general cognitive functioning (see King, 1990; and Mortimer, 1997 for discussion) have emphasized the potential for medication confounds in studies assessing mood disorder-related impairments. Comparisons of patient subgroups receiving and not receiving

these medications in the present study failed to show marked differences in accuracy or latency measures across all tasks administered. In order to gauge the potential influence of prior substance abuse on neuropsychological functioning, data were reanalysed following removal of three patients who had received diagnoses of alcohol or drug abuse; the profile of impairment in manic patients was not affected. It thus seems unlikely that patient medication or substance abuse factors account for the full range of neuropsychological deficits demonstrated in the present manic sample. It seems even more unlikely that the specific and contrasting patterns of performance observed in manic and depressed patients on the affective shifting task could be due to medication alone.

The preceding discussion – and indeed the experimental design itself – is based on the assumption that the affective shifting task involves various components of inhibitory control over cognitive processing. This task was modelled after other neuropsychological tasks thought to involve inhibitory control (e.g. Iabonia *et al*. 1995; Dias *et al*. 1996), but with an added emotional, or affective, component. As with many designs of a similar complexity, it is possible that processes other than those targeted may explain, at least in part, the observed phenomena. It could not be unreasonable to attribute the observed patterns of performance in the affective shifting tasks to different speed-accuracy trade-off biases in the three subject groups. For example, it is possible that depressed patients place a greater emphasis on accuracy relative to speed than other subjects. Similarly, even assuming that the observed biases do stem from interference based on attention to mood-congruent stimuli, inhibitory control may not be implicated. Given the preponderant convergence of theoretical, experimental, neuroanatomical, and clinical evidence, however, we believe that a failure of inhibitory control represents the most parsimonious explanation for the results obtained.

Conclusion

The findings of the present study suggest that manic patients are impaired on conventional neuropsychological tasks that tap a range of cognitive functions subserved by different neural substrates. Although the deficits observed on these tasks appear similar to those previously observed in depressed patients, the two patient groups in this study exhibited dissociable impairments in distinct levels of inhibitory control in the novel affective shifting paradigm; manic patients were impaired in their ability to inhibit behavioural responses and focus attention, while depressed patients were impaired in their ability to shift the focus of their attention. In addition, affective biases congruent with current mood were found in manic and depressed patients. We suggest that these differences in performance might be related to differences in the functioning of neural circuits involving the vmpfc in manic and depressed patients.

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