Effect of symptoms on executive function in bipolar illness

T. DIXON, E. KRAVARITI*, C. FRITH, R. M. MURRAY AND P. K. McGUIRE

Division of Psychological Medicine, Institute of Psychiatry, London; Department of Imaging Science, Institute of Neurology, London

ABSTRACT

Background. The relationship between cognitive function and symptomatology in bipolar disorder is unclear. This study assessed executive function during the manic, depressed and remitted stages of bipolar I disorder.

Method. Tasks assessing phonological and semantic verbal fluency, the Hayling Sentence Completion Test, the Stroop Neuropsychological Screening Test and the Cognitive Estimates Test were administered to manic ($n=15$), depressed ($n=15$), and remitted ($n=15$) bipolar I patients, and to healthy controls ($n=30$). Multiple regression analyses and analyses of covariance were used to identify potential determinants of executive dysfunction in the three bipolar groups.

Results. Executive function deficits were particularly associated with the manic state. In general, manic patients performed less accurately than the remitted and depressed groups, and their performance deficit was related to the severity of positive thought disorder. The depressed and remitted bipolar groups showed a less widespread pattern of impairment. Deficits in response initiation, strategic thinking and inhibitory control were evident in all the bipolar groups.

Conclusions. Executive function deficits in bipolar I disorder are most evident during mania, and are particularly associated with formal thought disorder. However, deficits in response initiation, strategic thinking and inhibitory control may be more related to the underlying disorder than a particular symptom profile.

INTRODUCTION

Bipolar disorder is characterized by persistent cognitive impairments (Bearden *et al.* 2001), but it is not clear how these relate to the different affective states of the disorder. There is a growing consensus that cognitive function is least impaired during periods of euthymia, but still differs from that in healthy controls (Bearden *et al.* 2001). Less is known about the effect of episodic exacerbations on cognition. Many direct comparisons of bipolar mania and depression have failed to detect cognitive differences (see for review Murphy & Sahakian, 2001). However, Sweeney *et al.* (2000) observed

widespread cognitive disturbances during manic and mixed affective states of the disorder, which contrasted with more limited and less severe deficits in depression. Similarly, sub-optimal decision making, increased number of errors and reduced ability to inhibit responses in an affective shifting task have been identified in manic bipolar patients, but not depressed patients (Murphy *et al.* 1999, 2001). Depressed subjects were impaired in their ability to reverse the focus of attention (Murphy *et al.* 1999), while both groups showed slow deliberation times during decision making and impaired performance on tasks of planning (see for discussion Murphy *et al.* 2001).

To clarify the relationship between cognitive ability and affective state in bipolar disorder, we examined executive function in manic,

* Address for correspondence: Dr Eugenia Kravariti, Institute of Psychiatry, Division of Psychological Medicine, Box 63, De Crespigny Park, London SE5 8AF.

depressed and remitted bipolar patients, and healthy controls. Our selection of neuropsychological tasks was influenced by evidence that the cognitive dysfunction of bipolar disorder during episodic exacerbations and clinical remission is related to structural and functional abnormalities of the pre-frontal cortex and basal ganglia (Martínez-Arán *et al.* 2000; Bearden *et al.* 2001). These regions are critically involved in error monitoring, inhibitory control, response generation and mental speed, as well as affect regulation. Based on previous findings (Murphy *et al.* 1999, 2001; Bearden *et al.* 2001), we predicted that (1) relative to the other subject groups, manic patients would show evidence of increased error intrusion and reduced inhibitory control; (2) patients with depression would show reduced verbal output and mental speed compared to the other subject groups; and (3) patients in remission would show the least degree of impairment relative to healthy controls.

METHOD

Subjects

Patients were recruited from the South London and Maudsley NHS Trust, following referral by their clinicians. The investigators had previously explained the purpose and inclusion criteria of the study to the clinicians. The inclusion criteria were: (1) A diagnosis of bipolar I disorder according to DSM-IV (APA, 1994), (2) age 18–60 years, (3) English as first language, and (4) appropriate current symptomatology: either predominantly manic, predominantly depressed or in remission. Healthy control subjects were recruited through local press advertisements and job centres.

Potential recruits were excluded if they had a personal history of drug/alcohol abuse or neurological disorder (all subjects), a personal or family history of psychiatric illness (controls), or if their symptoms were too severe, or their level of cooperation was too low to be likely to provide valid data (patients). The patients' suitability for testing was based on the clinician's recommendation, and on their actual ability to participate in the testing process as judged by the examiner (T. D.). Fifteen referrals who met inclusion criteria were too unwell to comply with the assessment requirements.

The final sample ($n = 75$) contained 15 patients in each of the manic, depressed and remitted groups, and 30 healthy controls.

Approval by the local Research Ethical Committee, informed consent by all subjects and permission from the patients' clinical teams were obtained prior to the study.

Assessment of handedness and socio-demographic characteristics

Handedness was assessed by the Annett Handedness Questionnaire (Annett, 1970). Paternal occupation provided an index of socio-economic status and was classified according to three condensed categories of the Standard Occupational Classification (Office of Population Censuses and Surveys, 1991) (1 = professional or intermediate; 2 = skilled; 3 = semi-skilled, unskilled or unemployed). The remaining socio-demographic characteristics (Table 1) were ascertained through subject interviews.

Assessment of clinical and treatment characteristics

Age of onset (defined as age at first diagnosis of bipolar disorder), illness duration and treatment characteristics were ascertained through information provided from the medical notes. These sources were further used to determine predominant symptomatology, which was confirmed *a posteriori* through the use of rating scales. In doing so, we addressed two concerns. Firstly, the presence of predominant symptoms can be ascertained on a relative basis (presence of the symptom cluster of interest, in the relative absence, or lesser severity, of the competing cluster). Secondly, the use of different rating scales for mania and depression does not allow comparison of severity across them. Therefore, we examined whether each patient's score on his/her (pre-defined) representative cluster lay at a higher quartile of distribution (based on the scores of the total patient sample) than their corresponding score on the competing cluster. All but one patient in each of the manic and depressed groups fulfilled this criterion. These two exceptions scored within the same quartile on both mania and depression. However, we decided to include them in the analyses, as their position within the quartile was higher for the predominant cluster of their pre-allocated sub-group.

Table 1. *Socio-demographic, handedness and clinical/treatment (patients only) characteristics of the subject groups*

Variable	Manic ($n=15$)	Depressed ($n=15$)	Remitted ($n=15$)	Control ($n=30$)
Male/female (n)	7/8	6/9	8/7	17/13
Years old at testing: mean (S.D.)	34·3 (11·6)	33·9 (8·2)	35·7 (9·3)	35·2 (9·8)
White/African(-Caribbean)/other (n)	7/6/2	9/6/0	11/3/1	15/13/2
Right-handed/left-handed (n)	12/3	11/4	12/3	25/5
Years of education at testing: mean (S.D.)	13·0 (2·7)	13·9 (2·6)	15·6 (2·6)	12·8 (2·0)
Socio-economic status: 1/2/3 (n)	4/7/4	7/7/1	8/6/1	7/10/13
Years old at illness onset: mean (S.D.)	23·6 (6·5)	27·7 (9·5)	26·4 (6·9)	N.A.
Years ill at testing: mean (S.D.)	10·7 (10·0)	6·3 (5·8)	9·3 (8·1)	N.A.
% on lithium	67	60	100	N.A.
% on antidepressants	0	100	53	N.A.
% on antipsychotic medication	100	27	67	N.A.
% on anticholigergic medication	13	7	13	N.A.

N.A., Not applicable.

The four rating scales were also administered to the healthy control participants in order to exclude the presence of any psychiatric symptoms.

Mania and depression were assessed using the total scores of Young's Mania Rating Scale (Young *et al.* 1978) (0–5 = normal; 6–12 = mild; 13–19 = moderate; 20–29 = severe; 30+ = very severe) and the Beck Depression Inventory (Beck *et al.* 1961) (0–9 = normal; 10–19 = mild/moderate; 20–29 = moderate/severe; 30+ = severe) respectively.

Thought disorder was reflected in the Index for the Assessment of Bizarre-Idiosyncratic Thinking (Marengo *et al.* 1986) (1 = absent; 2 = mild; 3 = definite; 4 = severe; 5 = very severe), a mean score derived from the Gorham Proverbs Test (Gorham, 1956), and the Comprehension subtest of the Wechsler Intelligence Scale-Revised (WAIS-R; Wechsler, 1981).

Negative symptoms were measured using the global score of the Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1981) (0–4 = none; 5–9 = questionable; 10–14 = mild; 15–19 = moderate; 20–24 = marked; 25+ = severe).

Assessment of executive function

Phonological and semantic verbal fluency (VF) was examined using the 'FAS' (Benton & Hamsher, 1976) and Set (Isaacs & Kennie, 1973) tests respectively. Total number of responses and percentage (%) of correct responses were analysed.

Cognitive inhibition was assessed using the colour-word score (number of correct responses minus number of incorrect responses) of the Stroop Neuropsychological Screening Test (SNST; Trenerry *et al.* 1989).

Response initiation/suppression and strategy use were examined using the Hayling Sentence Completion Test (HSCT; Burgess & Shallice, 1996). This required subjects to finish incomplete sentences using contextually relevant (part A: straightforward completion condition) or contextually irrelevant (part B: anomalous completion condition) words. The following measures were analysed: response initiation latency (total response time for part A); response suppression latency (total response time for part B minus total response time for part A, a measure of the ability to suppress salient or habitual responses); percentage of patients (%) using strategy (response pattern in part B, e.g. listing objects in the testing environment), and error scores (parts A and B).

Cognitive estimation was assessed using the Cognitive Estimates Test (CET; Shallice & Evans, 1978). This required participants to generate reasonable estimates of quantifiable attributes of common objects or familiar concepts. The test yielded one error score based on the accuracy of estimates.

As rate of articulation and integrity of semantic store can confound verbal productivity in timed tasks, these factors were assessed using an articulation rate task (Belleville *et al.* 1992) and the Vocabulary subtest of the WAIS-R (Wechsler, 1981) respectively. In the former paradigm, subjects were timed while counting from 1 to 10 as quickly as possible in each of five consecutive trials, and 'total time/50' was used

as an index of articulation rate. Vocabulary required subjects to define 35 words of increasing difficulty.

Statistical analysis

The data were analysed using the statistics package Intercooled Stata 7.0 for Windows (StataCorp, 2001).

Between-group differences in socio-demographic, clinical and treatment characteristics were explored by (1) simple linear regression analyses, using robust standard errors to safeguard against potential violations of the standard ANOVA assumptions (age, years of education, age of onset, duration of illness, symptom scores), (2) Pearson's χ^2 (gender), and (3) Fisher's exact test (ethnicity, socio-economic status, handedness).

The relationship between group status and each cognitive variable was examined by simple linear (continuous response variables) or logistic (binary response variables) regression analyses, using robust standard errors where applicable (linear regression analysis). This step (1) was used to identify significant between-group differences in the various cognitive variables.

In a second exploratory analysis (step 2), response variables that gave rise to significant group effects or trends (step 1) were examined using multiple regression analyses with symptom scores (mania, depression, thought disorder, negative symptoms), medication dose (antipsychotic dose, lithium dose) and possible confounding factors (years of education, vocabulary score: see Results) as explanatory variables. This approach was used as a preliminary assessment of the likely importance of each explanatory variable in relation to cognitive performance, as reflected in the standardized regression coefficients and their associated statistics (using a conventional 5% criterion). The variance inflation factors in these models were generally satisfactory, suggesting that multi-collinearity was not a reason for concern. The robust standard option was again used where applicable.

In a third step (step 3), those baseline comparisons which gave rise to significant differences or trends (step 1) were repeated while adjusting separately for each explanatory variable that emerged as a significant predictor [using a liberal threshold of significance (0·1) to ensure that no important explanatory variables were missed. This was higher than the one used for all remaining analyses: 0·01] of neuropsychological performance in step 2.

Variables that both emerged as significant predictors of cognitive function in steps 2 and 3, and effectively removed statistical significance/trends from the between-group comparisons of interest (those significant or near-significant in step 1), were tentatively identified as determinants of cognitive dysfunction in the manic, depressed and remitted states of the bipolar illness.

Due to the large volume of analyses, the present study reports on the outcomes of steps 1 and 3.

As the modest group sizes increased the likelihood of type II errors, we did not correct for multiple pair-wise comparisons, but opted for a relatively stringent statistical threshold of cognitive impairment, at or below the 0·01 level. Trends (referred to below as near-significant group differences) were set at the 0·05 level. Those findings that would also have remained significant had a Bonferroni correction (0·05 divided by 6 pair-wise comparisons) been applied, are marked with two or three asterisks in Table 4.

RESULTS

Socio-demographic characteristics

Table 1 presents the socio-demographic and handedness characteristics of the four subject groups. These were matched for age [$F(3, 71) = 0·12$, $p = 0·95$], gender ($\chi^2 = 1·25$, $p = 0·74$), ethnicity ($\chi^2 = 4·83$, Fisher's exact $p = 0·57$), socio-economic status ($\chi^2 = 12·16$, Fisher's exact $p = 0·06$), and handedness ($\chi^2 = 0·63$, Fisher's exact $p = 0·92$), but differed significantly in years of education [$F(3, 71) = 4·92$, $p < 0·01$]. Further analyses revealed that the remitted bipolar sample had significantly more years of education than the control (coef. = 2·83, 95% CI 1·31–4·35, $p < 0·001$) and manic (coef. = 2·60, 95% CI 0·69–4·51, $p < 0·01$) groups.

Clinical and treatment characteristics

The clinical and treatment characteristics of the patient groups are presented in Tables 1 and 2.

The three groups did not differ in age of onset [$F(2, 42) = 1·16$, $p = 0·32$], duration of illness [$F(2, 42) = 1·41$, $p = 0·26$], or lithium dose [$F(2, 42) = 0·49$, $p = 0·62$] (manic: mean = 353·3 mg,

Table 2. *Mean (S.D.) symptom scores of the subject groups*

	Mania	Depression	Thought disorder	Negative symptoms
Manic	15·1 (6·2)d***, r***, c*** (1)	9·1 (6·1)c* (2)	2·20 (1·2)d**, r*, c*** (3)	0·2 (0·3)
Depressed	4·1 (2·2)c*** (4)	29·7 (10·1)m***, r***, c*** (5)	1·31 (0·4)c* (6)	6·5 (3·5)m***, r***, c*** (7)
Remitted	2·7 (2·2)	6·5 (4·3)	1·40 (0·5)c* (8)	0·9 (1·2)m* (9)
Controls	1·4 (2·1)	5·3 (3·1)	1·08 (0·2)	0·6 (0·7)m** (10)

m Higher than the manic group; d higher than the depressed group; r higher than the remitted group; c higher than the control group.
* <0·05; ** <0·01; *** <0·001.
(1) *v.* depressed: coef.=11·00, 95% CI 7·64–14·36; *v.* remitted: coef.=12·40, 95% CI 9·04–15·76; *v.* control: coef.=13·67, 95% CI 10·41–16·92; (2) *v.* control: coef.=3·80, 95% CI 0·46–7·14; (3) *v.* depressed: coef.=0·89, 95% CI 0·25–1·53; *v.* remitted: coef.=0·80, 95% CI 0·14–1·46; *v.* control: coef.=1·12, 95% CI 0·51–1·73; (4) *v.* control: coef.=2·67, 95% CI 1·29–4·04; (5) *v.* manic: coef.=20·60, 95% CI 14·57–26·63; *v.* remitted: coef.=23·20, 95% CI 17·61–28·79; *v.* control: coef.=24·40, 95% CI 19·13–29·67; (6) *v.* control: coef.=0·23, 95% CI 0·02–0·45; (7) *v.* manic: coef.=6·35, 95% CI 4·55–8·15; *v.* remitted: coef.=5·67, 95% CI 3·78–7·56; *v.* control: coef.=5·95, 95% CI 4·14–7·76; (8) *v.* control: coef.=0·32, 95% CI 0·05–0·59; (9) *v.* manic: coef.=0·68, 95% CI 0·05–0·31; (10) *v.* manic: coef.=0·40, 95% CI 0·08–0·72.

S.D.=415·5; depressed: mean=506·7 mg, S.D.=465·2; remitted: mean=383·3 mg, S.D.=436·6), but differed in antipsychotic dose (chlorpromazine equivalents) $[F(2, 42)=50·65, p<0·0001]$ (manic: mean=633·3 mg, S.D.=171·6; depressed: mean=106·7 mg, S.D.=193·5; remitted: mean=131·7 mg, S.D.=107·1): The manic group received higher doses than the depressed (coef.=526·67, 95% CI 391·91–661·43, $p<0·001$) and remitted (coef.=501·67, 95% CI 396·28–607·05, $p<0·001$) subjects.

As expected, each of the manic and depressed groups scored higher on their defining symptom cluster than all the other subject groups (Table 2). In addition, the manic and depressed subjects displayed, or tended to display, higher degrees of thought disorder and negative symptoms respectively, than all the other groups (Table 2). Although significant or near-significant differences were also noted between the manic and control subjects in depression and negative symptoms, between the depressed and control groups in mania and thought disorder, between the remitted and control subjects in mania and thought disorder, and between the manic and remitted subjects in negative symptoms (Table 2), all respective group means fell within the normal ranges (Table 2). No other between-group difference reached or approached statistical significance.

Between-group differences in executive function

Table 3 presents the means and standard deviations of the raw scores obtained by the bipolar and control groups on the neuropsychological battery. Table 4 presents the results of the statistical comparisons between each bipolar group

and the healthy controls on the variables examined. Fig. 1 presents a summary of the neuropsychological findings based on the t/z scores obtained in the various comparisons between each bipolar group and the healthy controls. The order of variables along the *x*-axis in this figure is based on how much they discriminated the patients from the controls.

Comparisons across diagnostic categories

Relative to the healthy controls, the manic patients showed significant or near-significant deficits on nine variables: Phonological VF: (%) Correct; Semantic VF: (%) Correct; Hayling: Response Initiation Latency, Error Scores (straightforward and anomalous completion) and (%) Using Strategy; Stroop Colour–Word Score; CET Error Score, and Vocabulary Score (Tables 3 and 4).

Compared to the controls, the depressed patients displayed significant deficits on four variables: Hayling: Response Initiation Latency, Error Score (anomalous completion) and (%) Using Strategy, and Stroop Colour-Word Score (Tables 3 and 4).

Relative to the control group, the remitted bipolar patients displayed significant or near-significant deficits on five variables: Semantic VF: Total Responses; Hayling: Response Initiation Latency, Error Score (straightforward completion) and (%) Using Strategy; and Stroop Colour–Word Score (Tables 3 and 4).

As Fig. 1 shows, the big effects are mainly seen in measures of erroneous responding or inhibitory control (Error Scores in the Hayling and CET tests, (%) Correct in the VF tests, Stroop Colour–Word Score) and strategy use,

Table 3. *Mean (s.d.) raw scores of the subject groups in the neuropsychological battery*

Variable	Manic ($n=15$)	Depressed ($n=15$)	Remitted ($n=15$)	Controls ($n=30$)
Phonological Verbal Fluency				
Total responses across trials	37·3 (13·3)	32·3 (18·5)	38·0 (16·3)	40·3 (11·6)
% correct	76·1 (20·2)[r**, c** (1)]	87·5 (10·6)	90·9 (10·2)	92·7 (6·6)
Semantic Verbal Fluency				
Total responses across trials†	38·8 (2·5)	39·3 (1·6)	39·1 (1·6)[c* (2)]	39·6 (1·7)
% correct	87·1 (12·5)[d*, r*, c** (3)]	95·4 (5·9)	95·1 (7·0)	97·2 (3·3)
Hayling Test				
Response Initiation Latency (total sec)	34·0 (39·8)[c* (4)]	28·8 (20·3)[c** (5)]	28·4 (19·8)[c** (6)]	13·6 (3·7)
Response Suppression Latency (total sec)	11·7 (17·5)	31·2 (35·7)	23·5 (27·4)	20·4 (13·9)
Error Score (straightforward completion)	2·7 (3·8)[d*, r*, c** (7)]	0·3 (0·6)	0·6 (0·9)[c* (8)]	0·0 (0·0)
Error Score (anomalous completion)	18·3 (8·8)[c** (9)]	20·5 (11·4)[r*, c** (10)]	13·2 (8·5)	10·5 (5·2)
% using strategy†	20 %[c*** (11)]	33 %[c** (12)]	33 %[c** (13)]	83 %
Stroop Test: Colour–Word Score	51·3 (35·6)[r**, c*** (14)]	70·8 (31·6)[c** (15)]	81·7 (24·4)[c* (16)]	97·5 (16·2)
Cognitive Estimates Test: Error Score	12·0 (5·4)[c** (17)]	8·9 (5·1)	9·4 (5·5)	6·9 (4·3)
WAIS-R Vocabulary: Age Scaled Score	7·9 (3·3)[r*, c* (18)]	9·5 (2·8)	11·0 (4·4)	10·0 (2·2)
Rate of articulation: mean sec per word	0·2 (0·1)	0·3 (0·2)	0·3 (0·2)	0·2 (0·1)

[d] Impaired relative to the depressed group; [r] impaired relative to the remitted group; [c] impaired relative to the control group.

* <0.05; ** <0.01; *** <0.001.

† Analysed as a binary variable (Semantic Verbal Fluency: 'perfect score or less'; Hayling Test: 'any use of strategy *versus* no use of strategy').

[1] *v.* control: see Table 4; *v.* remitted: coef. = −14·73, 95 % CI −26·30 to −3·16; [2] *v.* control: see Table 4; [3] *v.* depressed: coef. = −8·28, 95 % CI −15·35 to −1·20; *v.* remitted: coef. = −8·04, 95 % CI −15·38 to −0·69; *v.* control: see Table 4; [4-6] *v.* control: see Table 4; [7] *v.* depressed: coef. = 2·47, 95 % 0·50–4·44, $t = 2·50$; *v.* remitted: coef. = 2·13, 95 % CI 0·13–4·13; *v.* control: see Table 4; [8-9] *v.* control: see Table 4; [10] *v.* remitted: coef. = 7·33, 95 % CI 0·07–14·60; *v.* control: see Table 4; [11-13] *v.* control: see Table 4; [14] *v.* remitted: coef. = −30·4, 95 % CI −52·49 to −8·31; *v.* control: see Table 4; [15-17] *v.* control: see Table 4; [18] *v.* remitted: coef. = −3·07, 95 % CI −5·88 to −0·26; *v.* control: see Table 4.

Table 4. *Statistical differences between the bipolar and control groups in the neuropsychological variables*

Variable	Manic *v.* control Coefficient/OR (95 % CI)	Depressed *v.* control Coefficient/OR (95 % CI)	Remitted *v.* control Coefficient/OR (95 % CI)
Phonological Verbal Fluency			
Total responses across trials	−3·07 (−11·10 to 4·97)	−8·00 (−18·40 to 2·40)	−2·33 (−11·68 to 7·02)
% Correct	−16·57 (−22·17 to −5·97)**	−5·20 (−11·12 to 0·71)	−1·84 (−7·60 to 3·92)
Semantic Verbal Fluency			
Total responses across trials†	0·20‡ (0·03 to 1·23)	0·29‡ (0·04 to 1·93)	0·14‡ (0·24 to 0·86)*
% Correct	−10·15 (−16·68 to −3·63)**	−1·87 (−5·11 to 1·36)	−2·12 (−5·91 to 1·68)
Hayling Test			
Response Initiation Latency (total sec)	20·36 (−0·04 to 40·77)*	15·21 (4·74 to 25·68)**	14·75 (4·52 to 24·97)**
Response Suppression Latency (total sec)	−8·68 (−18·99 to 1·64)	10·84 (−8·11 to 29·78)	3·14 (−11·78 to 18·06)
Error Score (straightforward completion)	2·73 (0·79 to 4·68)**	0·27 (−0·04 to 0·57)	0·60 (0·13 to 1·07)*
Error Score (anomalous completion)	7·87 (2·98 to 12·75)**	10·07 (3·96 to 16·18)**	2·73 (−2·03 to 7·50)
Strategy use†	0·05‡ (0·01 to 0·25)***	0·1‡ (0·02 to 0·43)**	0·1‡ (0·02 to 0·43)**
Stroop Test: Colour–Word Score	−46·20 (−65·37 to −27·03)***	−26·67 (−43·87 to −9·46)**	−15·80 (−29·65 to −1·95)*
Cognitive Estimates Test: Error Score	5·10 (1·93 to 8·27)**	2·03 (−0·99 to 5·06)	2·50 (−0·71 to 5·71)
WAIS-R Vocabulary: Age Scaled Score	−2·03 (−3·89 to −0·18)*	−0·43 (−2·09 to 1·23)	1·03 (−1·37 to 3·43)
Rate of articulation: mean sec per word	0·00 (−0·06 to 0·07)	0·05 (−0·03 to 0·13)	0·01 (−0·04 to 0·06)

* <0.05; ** <0.01; *** <0.001.

† Analysed as a binary variable (Semantic Verbal Fluency: 'perfect score or less'; Hayling Test: 'any use of strategy *versus* no use of strategy').

‡ Odds ratio.

and are most obvious in the manic group. By contrast, the small effects are seen in measures of latency, speed and number of responses, with the exception of Response Initiation Latency (Hayling), which showed moderate to big effects in all the bipolar groups.
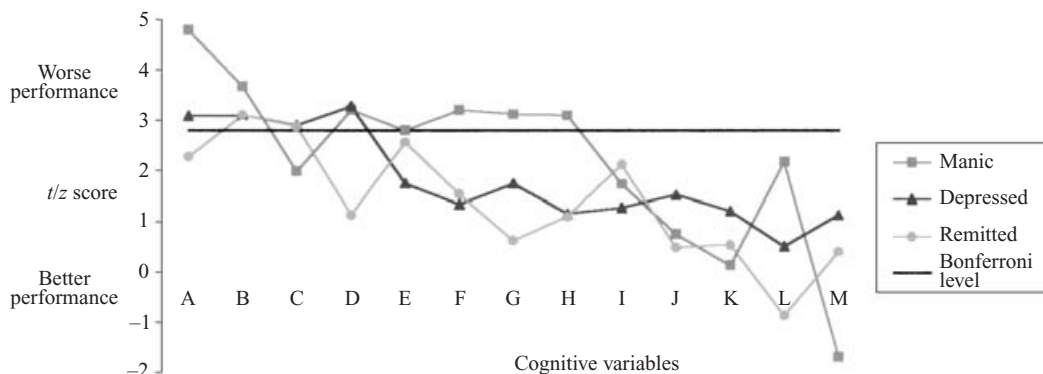
FIG. 1. Plot of *t/z* scores for all the neuropsychological variables. A, Colour–word score on the Stroop Neuropsychological Screening Test (SNST); B, strategy score on the Hayling Sentence Completion Test (HSCT); C, Response Initiation Latency on the HSCT; D, error score on the HSCT (part B); E, error score on the HSCT (part A); F, error score on the Cognitive Estimates Test (CET); G, mean % of correct responses on the FAS Verbal Fluency Test; H, mean % of correct responses on the Semantic Verbal Fluency Test; I, mean no. of responses on the Semantic Verbal Fluency Test; J, mean no. of responses on the FAS Verbal Fluency Test; K, rate of articulation (ROA); L, WAIS-R Vocabulary Age Scaled Score; M, Response Suppression Latency on the HSC.

Comparisons within the bipolar diagnostic category

Compared to the remitted bipolar group, the manic patients showed less accurate, or trends towards less accurate, performance in Phonological VF: (%) Correct, Semantic VF: (%) Correct, Hayling: Error Score (straightforward completion), and Vocabulary Score; they were also more impaired in Stroop Colour–Word Score (Table 3).

Compared to the depressed group, the manic patients tended to perform less accurately in Semantic VF: (%) Correct, and Hayling: Error Score (straightforward completion) (Table 3).

Compared to the remitted group, the depressed patients tended to perform less accurately in Hayling: Error Score (anomalous completion) (Table 3).

No other between-group comparisons within the bipolar diagnostic category reached or approached statistical significance.

Putative determinants of executive dysfunction in the manic, depressed and remitted states of bipolar illness

Five explanatory variables satisfied the twin criteria of emerging as significant predictors of cognitive performance in the exploratory (step 2) and adjusted (step 3) regression analyses, and effectively removing statistical significance/trends from various baseline comparisons of interest

(those significant or near-significant in step 1): thought disorder score (14 pair-wise comparisons), vocabulary score (4 pair-wise comparisons), mania score (3 pair-wise comparisons), antipsychotic dose (2 pair-wise comparisons) and lithium dose (1 pair-wise comparison).

Manic group

Six cognitive variables failed to show significant or near-significant differences between the manic and control subjects after adjusting for thought disorder score: Phonological VF: (%) Correct ($p = 0.44$), Semantic VF: (%) Correct ($p = 0.34$), Hayling: Response Initiation Latency ($p = 0.54$) and Error Score (straightforward completion) ($p = 0.72$), CET Error Score ($p = 0.54$), and Vocabulary Score ($p = 0.95$).

Adjusting for thought disorder removed the trends for differences in the comparisons between the manic and depressed subjects in Semantic VF: (%) Correct ($p = 0.62$), and Hayling: Error Score (straightforward completion) ($p = 0.40$).

Adjusting for thought disorder removed the trends for differences in the comparisons between the manic and remitted subjects in Phonological VF: (%) Correct ($p = 0.29$), Semantic VF: (%) Correct ($p = 0.50$), Hayling: Error Score (straightforward completion) ($p = 0.50$), Stroop Colour–Word Score ($p = 0.12$), and Vocabulary Score ($p = 0.37$).

Adjusting for Vocabulary Score removed the statistical trends from the baseline comparisons

between the manic and remitted subjects in three variables: Phonological VF: (%) Correct ($p = 0.09$), Semantic VF: (%) Correct ($p = 0.27$), and Stroop Colour–Word Score ($p = 0.07$).

After adjusting for mania score, the difference in Phonological VF: (%) Correct between the manic and control subjects ($p = 0.68$) and between the manic and remitted subjects ($p = 0.22$) no longer reached or approached significance.

After adjusting for lithium dose and anti-psychotic dose respectively, the differences between the manic and control subjects in Hayling: Error Score (anomalous completion) ($p = 0.22$) and (%) Using Strategy ($p = 0.08$) were no longer significant.

Depressed group

After adjusting for mania score, the difference between the depressed and control subjects in Hayling: Error Score (anomalous completion) was no longer significant ($p = 0.10$). Adjusting for Vocabulary Score removed the statistical trend from the baseline comparison between the depressed and remitted subjects in Hayling: Error Score (anomalous completion) ($p = 0.12$).

Remitted group

The difference in Stroop Colour–Word Score between the remitted and control subjects no longer approached significance after adjusting for either thought disorder score ($p = 0.28$) or antipsychotic dose ($p = 0.96$).

The remaining significant or near-significant between-group differences could not be accounted for in terms of any single predictor of neuropsychological performance, suggesting the presence of small additive effects of more than one explanatory factors.

DISCUSSION

Previous studies of cognitive function in bipolar disorder have largely focused on one or two phases of the illness, studied mixed affective groups, or failed to specify the patients' affective state. A strength of the present study was that it investigated executive function across the three phases of bipolar disorder, studying well-matched groups of patients and healthy controls. In addition, by selecting neuropsychological paradigms that allowed fractionation

of executive ability, we were able to examine the relationship between symptoms and deficits in the productivity, latency and accuracy of responses.

Various characteristics distinguished the bipolar groups of the present study. The manic patients showed the most widespread impairment, with deficits in areas that were preserved in the other bipolar groups, greater dysfunction in some areas of shared deficit, and, as predicted, increased error intrusion relative to all the other groups. The depressed patients found it difficult to comply with the task requirements in the anomalous, but not the straightforward, condition of the sentence completion task, a pattern that was not evident in the manic (impaired in both conditions) or remitted (impaired in the straightforward condition) patients, and may reflect difficulties with reversing the focus of attention or changing cognitive set. These findings are consistent with reports of cognitive differences (Murphy *et al.* 1999; Sweeney *et al.* 2000) and differential pre-frontal activation (Drevets *et al.* 1997) in mania and depression. In contrast to the other patient groups, the remitted subjects showed preserved accuracy in the anomalous condition of sentence completion, and reduced verbal output in semantic fluency.

All the bipolar groups showed compromised ability to inhibit a pre-potent reading response in favour of a less rehearsed one (Stroop colour naming), and displayed delayed response initiation and impaired strategy use in the sentence completion task. Contrary to our predictions, the manic patients were not more impaired than the depressed patients on the inhibitory control index of the Stroop task, and signs of mental slowness (prolonged response initiation) were not confined to the depressed patients, but were evident in all the bipolar groups. This pattern of shared dysfunction across the three patient groups suggests that deficits in strategic thinking, inhibitory control, and response initiation are dissociable from symptom state and may represent trait markers of bipolar illness. Our findings provide indirect support to the proposition that a stable dys-regulation of prefrontal function or the subcortical-frontal circuitry may underlie the cognitive disturbances of bipolar disorder (Martínez-Arán *et al.* 2000; Bearden *et al.*

2001). They are also consistent with an association between measures of executive function and trait-related anomalies in monoaminergic systems that regulate basal ganglia and thalamocortical activity (Zubieta *et al.* 2000). Moreover, they corroborate evidence that psychomotor slowing may be a trait marker of bipolar illness. Thus, a number of studies of clinically stable bipolar patients have reported impairments in measures of response latency, rapid visual information processing and fine motor skills (Rubinsztein *et al.* 2000; Wilder-Willis *et al.* 2001; Clark *et al.* 2002), which contrast with findings of recovered accuracy in measures of executive function (Rubinsztein *et al.* 2000). Psychomotor speed deficits in bipolar disorder seem to persist even with full remission (Rubinsztein *et al.* 2000), and to be unrelated to medication and symptom severity (Wilder-Willis *et al.* 2001).

Our data corroborate earlier findings that cognitive deficits in bipolar disorder are evident during euthymia (Kessing, 1998; Van Gorp *et al.* 1999; Rubinsztein *et al.* 2000; Bearden *et al.* 2001; El-Badri *et al.* 2001; MacQueen *et al.* 2001; Zubieta *et al.* 2001; Cavanagh *et al.* 2002; Clark *et al.* 2002), although preserved performance on the Stroop, Hayling and verbal fluency tasks has also been reported (Bearden *et al.* 2001; Cavanagh *et al.* 2002). However, the present findings only partly support the view that cognitive impairment in bipolar disorder is least pronounced during periods of euthymia (Bearden *et al.* 2001). Compared to the manic patients, the remitted subjects were less impaired in five performance indices, and showed fewer cognitive deficits relative to healthy controls. However, the remitted and depressed groups could not be clearly differentiated in the extent of cognitive dysfunction. Although the depressed patients were more impaired than the remitted subjects in one function (performance accuracy during anomalous sentence completion), the latter group showed deficits in five cognitive domains relative to healthy controls, while the depressed patients were impaired in only four. Hence, our prediction that patients in remission would show the least degree of impairment relative to healthy controls was not supported.

While cognitive deficits in the remitted patients of the present study may represent trait markers of bipolar disorder, we cannot exclude the possibility that they were related to other features of this group, independent of mood, such as thought disorder or medication. Both emerged as probable determinants of executive dysfunction in a small number of comparisons. Mood stabilisers have previously been reported to produce minor decrements in psychomotor performance, learning and decision time (Martínez-Arán *et al.* 2000; Goldberg & Burdick, 2001). The influence of medication on cognitive function could be addressed through comparison of medication-free bipolar subgroups, although this would be logistically difficult.

Most of the cognitive deficits shown by the manic patients relative to the other subject groups were largely explicable in terms of thought disorder, although the core affective component of the manic state, as well as confounding factors (e.g. differences in vocabulary) played a lesser role. This corroborates earlier reports of associations between thought disorder and cognitive deficits in bipolar disorder (Martínez-Arán *et al.* 2000). None of the defining or predominant clinical symptoms of the depressed patients could singly explain their executive function deficits, suggesting that a combination of smaller effects operated in this group. Paradoxically, the symptoms that did appear to solely account for a proportion of the neuropsychological deficits in the depressed, as well as the remitted, groups, were mania and thought disorder, features usually associated with the manic state.

Previous studies have reported associations between cognitive function in bipolar disorder and duration of illness (Goldberg *et al.* 1993; Clark *et al.* 2002), number or duration of hospitalizations (Rubinsztein *et al.* 2000; Zubieta *et al.* 2001), and number of previous episodes (Kessing, 1998; El-Badri *et al.* 2001; MacQueen *et al.* 2001; Zubieta *et al.* 2001; Cavanagh *et al.* 2002). However, these associations have not been evident in other studies (Zihl *et al.* 1998; Ferrier *et al.* 1999; Krabbendam *et al.* 2000; Verdoux & Liraud, 2000; Liu *et al.* 2002). Nevertheless, assessment of the number and duration of previous manic/depressed episodes in the present study may have helped with the interpretation of the findings and allowed better control of potential confounders.

The present investigation was restricted to measures of executive function, and we cannot exclude the possibility that a different pattern of findings would have emerged if we had assessed memory or other cognitive processes. A further caveat is that the tasks had different psychometric properties, and a failure to detect deficits in one particular cognitive domain may have been due to the low sensitivity of the instrument used, rather than the actual absence of impairment. This issue could be examined by repeating the study using different tasks that engaged the same set of cognitive processes.

In conclusion, our data suggest that executive dysfunction in bipolar disorder is particularly associated with the manic state, and is largely explicable in terms of the formal thought disorder that is a feature of mania. At the same time, deficits in response initiation, strategic thinking and inhibitory control appeared to be independent of affective state, and may represent trait markers of bipolar illness. The relationship of cognitive impairments in bipolar disorder to state and trait factors could be clarified by testing the same patients in different phases of the illness in a prospective design, although this would be logistically difficult.

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