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Neuropsychological function in euthymic patients with bipolar disorder

I. N. FERRIER, BIBA R. STANTON, T. P. KELLY and JAN SCOTT

Background The assumption that patients with bipolar disorder make a full inter-episode recovery has been challenged by limited evidence that suggests that neuropsychological dysfunction in bipolar disorder may persist beyond episodes of illness.

Aims To test the hypothesis that patients with euthymic bipolar disorder show neuropsychological impairment.

Method A battery of neuropsychological tests (assessed attention, working memory, learning and executive function) was administered to three matched groups of subjects: good-outcome patients with bipolar disorder (n=21); poor-outcome patients with bipolar disorder (n=20); controls (n=20). All patients were clinically euthymic, although some had low levels of depressive symptoms.

Results Patients performed worse than controls on a number of neuropsychological tests. When age, premorbid IQ and depressive symptoms were controlled for, the results indicated impairment of executive function.

Conclusions These findings provide good evidence for the existence of neuropsychological impairment in patients with euthymic bipolar disorder, although the possible effect of medication should not be overlooked. This may be of clinical relevance and raises questions about the course and outcome of the illness.

Declaration of interest None.

The view that patients with bipolar disorder make a full recovery between episodes of illness has been widely accepted despite a lack of systematic investigation. Neuropsychological impairment has been identified in depression and mania (Wolfe *et al*, 1987; Sackheim & Steif, 1988) but has always been thought to be entirely a state effect. Imaging studies have shown the presence of patchy white matter lesions (PWMLs) in the brains of patients with bipolar disorder, particularly those with poor outcome (Videbech, 1997). Such lesions may be associated with neuropsychological impairment (particularly of executive function) in healthy elderly subjects and in patients with unipolar depression or bipolar disorder (DeCarli *et al*, 1995; Dupont *et al*, 1995; Lesser *et al*, 1996). It has been suggested that cognitive deficits in bipolar disorder may persist after clinical recovery (Trichard *et al*, 1995) or in remitted patients (Coffman *et al*, 1990; Morice, 1990). However, there are no well-designed studies comparing adequate numbers of euthymic patients with controls. This study therefore aimed to test the hypothesis that patients with euthymic bipolar disorder show neuropsychological impairment, and that such impairment is greater in patients with poor-outcome illness.

METHOD

The study design involved the administration of a battery of neuropsychological tests to three groups of subjects. The two patient groups comprised patients with euthymic bipolar disorder defined as 'good' or 'poor' outcome on the basis of the course of their illness over the past five years. A control group of volunteers with no history of psychiatric illness was also tested. Groups were matched for age, gender and premorbid intelligence. Ethical approval for the study was granted by local research ethics committees. All subjects gave informed consent.

Patients

A number of consultants from the Northern Region were asked to compile lists of their patients with bipolar disorder. The notes of all these patients were then reviewed. A random sample of those who met the eligibility criteria for the study were approached to request participation. Of 54 patients approached, 41 (76%) agreed to take part. Inclusion criteria were:

(a) Conforming to DSM–IV criteria for Bipolar I Disorder (American Psychiatric Association, 1994).

(b) A minimum five-year history of illness from the first episode requiring treatment.

(c) Age 23–60 years.

(d) Currently euthymic.

Rigorous exclusion criteria were used to exclude subjects with other disorders that might cause neuropsychological impairment. These were evidence of a dementing disorder, learning disability, history of substance misuse, history of cerebrovascular disease, neurodegenerative disorders, history of head injury with concussion, clinical epilepsy, systemic illness with known cerebral consequences, severe hypertension, severe hepatic or renal disorder and endocrine disorders other than corrected hypothyroidism.

Good- and poor-outcome groups

No established method exists for the classification of outcome in bipolar disorder, so criteria were devised for the purpose of this study. Classification was based on the number of affective episodes in the last five years, because this information was obtainable easily and objectively from case notes. To be eligible for inclusion, patients had to meet the criteria for one of the following groups.

Good outcome. No more than two major affective episodes in the last five years, with recovery within 12 weeks of referral for specialist treatment.

Poor outcome. At least three major affective episodes in the last two years, or one year of unremitting illness in the last two years.

Although these criteria are essentially arbitrary, they were felt by experienced clinicians to have good face validity in distinguishing the two groups.

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Controls

A control group was recruited from the spouses and friends of patients so that they were as comparable as possible to the patient groups with respect to variables such as education and social class. Controls were subject to the same exclusion criteria as patients, with the addition of any past history of psychiatric illness and family history of bipolar disorder in a first-degree relative.

Testing

The test battery was administered in a standardised format, using instructions as published in the test manuals where these were available. It comprised evaluation of mood and premorbid intelligence in addition to the battery of neuropsychological tests. The complete test procedure took no more than two-and-a-half hours to complete, including a break halfway through the assessment.

Hamilton Rating Scale for Depression (HRSD; Hamilton, 1960)

Subjects scoring higher than eight points (a level representing clinically significant depressive symptoms) on the HRSD were excluded from the study.

Beck Depression Inventory (BDI)

The BDI (a self-rating scale for the assessment of depressive symptoms; Beck *et al*, 1961) was also administered in order to provide a subjective measure of symptom severity.

Manic State Scale (MSS)

The Manic State Scale (Beigel & Murphy, 1971) is an observer-rated scale for the measurement of manic symptoms. Bech *et al* (1975) developed a six-item sub-scale from the MSS that was found to be reliable and valid throughout the range of severity. A cut-off of 20 points on the MSS sub-scale (a level representing clinically significant hypomanic symptoms) was set as a criterion for inclusion.

Premorbid intelligence

The National Adult Reading Test (NART) was used to provide a measure of premorbid intelligence. It consists of a list of 50 short but irregularly spelled words that the subject is asked to read aloud. The NART score correlates highly with full-scale IQ measured by the Wechsler Adult Intelligence Scale (WAIS; Wechsler, 1981) but remains relatively stable following cerebral insult (Nelson & O'Connell, 1978).

Neuropsychological test battery

On the basis of existing research with patients with euthymic bipolar disorder and individuals with PWMLs, the areas of attention, working memory, learning and executive function were considered as the key areas for neuropsychological assessment. The tests used were selected to cover the four relevant areas of neuropsychological function and, where possible, to include tests tapping both verbal and non-verbal modalities. In order to facilitate replication, only tests readily available and frequently documented in the neuropsychological literature were employed. Details of all tests used are available in standard neuropsychological texts (Lezak, 1995; Spreen & Strauss, 1998). Tests that tapped a single cognitive function were often not available; the tests used are therefore ascribed to broad cognitive categories, acknowledging the need for multiple cognitive skills in their successful completion.

Attention

Digit Symbol. In this test, subjects fill in symbols beneath numbers according to a key. The score is the number of symbols correctly completed in 90 seconds. This test assesses visuomotor speed and attention.

Letter Cancellation. In this test the subject must cross out all the occurrences of a target letter in an array as quickly as possible. The score is the time taken to complete the task. It measures a number of functions, including visual scanning, response speed and sustained attention.

Trail-making Test. Part A requires the subject to draw a line to connect 25 consecutively numbered circles as quickly as possible. It assesses visuomotor speed and attention. In Part B the subject must connect 25 numbered and lettered circles by alternating between the two sequences. In addition to visuomotor speed and attention, Trail-making B requires an ability to shift strategy and so assesses executive function.

Working memory

Digit Span. In the 'Digits Forward' test, subjects must repeat back sequences of digits of increasing length read out by the examiner. It assesses immediate verbal memory span.

In the 'Digits Backward' test the subject has to repeat the sequences in reverse order. In addition to auditory attention and short-term retention capacity, this test assesses the ability to manipulate the information in verbal working memory.

Visual Memory Span (VMS). In the 'VMS Forward' test subjects are presented with a card showing nine squares and are asked to copy sequences indicated by the examiner. It assesses non-verbal memory span. In the 'VMS Backward' test the subject has to copy the patterns indicated in reverse order. This test therefore assesses non-verbal working memory.

Learning and memory

The Rey Auditory Verbal Learning Test (AVLT). The AVLT is a widely used test of verbal memory. The subject must recall a list of 15 nouns read out by the examiner after each of five trials. The score is the total number of words recalled correctly.

The Rey–Osterreith Complex Figure Test. The copy of visuoconstructional ability requires the subject to make an accurate copy of a complex figure. Scoring is carried out according to explicit criteria and has excellent interrater reliability. In the recall, after a delay of 30 minutes, subjects are asked to draw the figure as accurately as possible from memory. This recall test primarily assesses non-verbal memory, but normal visuospatial function is also required for accurate reproduction of the figure.

Executive function

'FAS' (Controlled Oral Word Association Test). In this the subject is asked to generate as many words as possible beginning with the letters F, A and S in three trials of 60 seconds. Verbal fluency is a sensitive measure of executive function, probably because it requires the subject to generate his or her own strategy. Patients with left frontal lesions show impairments on this test.

Tower of London. This non-verbal test of executive function (planning) requires the subject to move three coloured beads to new positions on three upright sticks in a specified number of moves. Successful performance requires the formation of a number of sub-goals on the way to the

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correct solution. Patients with frontal lobe lesions show impairment on this task.

Analysis

Analysis of variance was used to test the null hypothesis that the mean test scores in each group did not differ. Analysis of covariance (ANCOVA) was used to covary for the effects of age, premorbid intelligence and depressive symptoms (HRSD score). When significant group differences were found ($P<0.05$), *post hoc* comparisons were performed using independent sample *t*-tests with a Bonferroni correction for multiple comparisons (level of significance: $P<0.0167$).

RESULTS

Group characteristics

The characteristics of the three groups with respect to age, gender and premorbid intelligence (calculated from NART score) are given in Table 1. The three groups are well-matched for age and premorbid intelligence, although the gender composition of the groups differs slightly.

Table 1 also gives the number of patients in each group taking lithium, antidepressants, anticonvulsants and neuroleptics. The mean duration of recovery since the most recent episode of mania or depression was 21 months (range 1–91 months).

Mood

Two subjects were excluded from the study after scoring over eight on the HRSD and are not included in the analysis. No subjects were excluded on the basis of hypomanic symptoms. Scores on the HRSD, BDI and MSS sub-scale are given in Table 1. Although no subjects had clinically depressive symptoms, it is apparent that the two patient groups showed higher levels of depressive symptoms than controls. Analysis of variance of HRSD scores indicated that this difference was statistically significant (d.f.=2,58; F=9,34; $P<0.001$). *Post hoc* *t*-tests found a significant difference in the scores of each patient group as compared to controls (control *v.* good, P=0.001; control *v.* poor, $P<0.001$) but no difference between the patient groups (P=0.362). It is also notable that a few subjects scored very highly on the BDI despite having HRSD scores of eight or less.

Scores on the MSS showed no significant difference between the groups (ANOVA: d.f.=2,58; F=1,93; P=0.154).

Test results

Table 2 gives the mean and standard deviation of scores in each group for the test battery and the results of ANOVAs, ANCOVAs and *post hoc* *t*-tests.

Patients were found to perform less well than controls on a number of neuropsychological tests. After covarying for the effects of age, premorbid intelligence and depressive symptoms (HRSD score), patients were found to perform significantly worse than controls on trail-making A and B, FAS and Digits Backward. The same pattern of results was obtained when the BDI score was used in place of the HRSD score as a covariate.

DISCUSSION

Evidence of specific cognitive impairments in patients with bipolar disorder

The analysis of variance carried out on neuropsychological test results suggests fairly widespread impairment of cognitive function in the patients with bipolar disorder all of whom were clinically euthymic.

Immediate memory span, assessed by Digits Forward and Visual Memory Forward, was normal. No significant impairment was found on the copy test of the Rey Complex Figure, indicating normal visuoconstructional ability.

The results of the AVLT and Rey Complex Figure indicated significant impairment of new learning and recall. Poorer performance on FAS, Trail-making B, Digits Backward, Visual Memory Backward and Tower of London suggests an impairment of executive function (see below). Patients performed more slowly than controls on the Letter Cancellation test, suggesting a possible impairment of visuomotor speed or sustained attention.

Although no patients with HRSD scores of greater than eight were included, both patient groups showed higher levels of depressive symptoms than did controls. Analysis of covariance, with HRSD score as a covariate, thus provides a more rigorous test of the hypothesis that neuropsychological impairment is found in patients with euthymic bipolar disorder.

Impaired executive function is not attributable to depressive symptoms

The ANCOVA results showed highly significant differences between patients with bipolar disorder and controls on Digits Backward, Trail-making A and B and FAS. Differences on tests of new learning, visuomotor speed and sustained attention were no longer significant when depressive symptoms were covaried for.

These results are suggestive of a specific impairment of executive function, particularly working memory, in patients with euthymic bipolar disorder. There was no difference between groups on Digits

Table 1 Group characteristics[1]

	Controls (n=20)	Good-outcome patients (n=21)	Poor-outcome patients (n=20)
Age (years) (mean (s.d.))	42.0 (14.6)	45.7 (10.0)	43.7 (11.2)
Female	11	16	11
Male	9	5	9
Premorbid IQ (mean (s.d.))	112 (5.7)	110 (8.9)	110 (10.8)
Lithium	0	18	12
Antidepressants	0	9	3
Anticonvulsants	0	5	13
Neuroleptics	0	1	4
HRSD (mean (s.d.))	0.7 (1.1)	2.7 (2.1)	3.4 (2.6)
BDI (mean (s.d.))	2.4 (3.0)	7.1 (6.3)	8.3 (7.2)
MSS (mean (s.d.))	5.1. (1.4)	4.1. (1.9)	4.4 (1.7)

1. Age, gender and pre-morbid IQ (measured by the National Adult Reading Test) are given. The number of patients in each group on lithium, antidepressants (including tricyclics and selective serotonin reuptake inhibitors), anticonvulsants (carbamazepine, valproate and gabapentin) and neuroleptics is shown. Scores on the Hamilton Rating Scale for Depression (HRSD), Beck Depression Inventory (BDI) and Manic State Scale (MSS) are also given.

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Table 2 Analysis of neuropsychological test results for patients with good- and poor-outcome bipolar disorder and controls

	Controls[1] (*n*=20)	Patients[1]		ANOVA[2]		ANCOVA[3]		*t*-Tests[4]
		Good (*n*=21)	Poor (*n*=20)	*F*	*P*	*F*	*P*	
Trail-making A	28.5	34.7	41.9	2.86	0.065	**3.94**	**0.025**	P
	(8.11)	(20.1)	(21.9)					
Trail-making B	58.1	84.6	103	**6.04**	**0.004**	**4.47**	**0.016**	P
	(19.3)	(36.0)	(58.8)					G
Digit Symbol	54.5	45.6	46.5	2.44	0.096	1.56	0.218	
	(8.89)	(12.8)	(18.8)					
Rey Auditory Verbal Learning	52.8	43.2	47.4	**3.86**	**0.027**	1.87	0.164	G
	(5.93)	(13.3)	(12.2)					
Rey Figure Copy	35.1	33.3	33.1	1.82	0.171	1.08	0.348	
	(1.99)	(3.47)	(4.76)					
Rey Figure Recall	20.2	14.6	15.7	**4.06**	**0.022**	2.78	0.071	G
	(6.21)	(6.02)	(7.35)					
FAS	46.7	32.1	39.3	**4.21**	**0.020**	**4.32**	**0.018**	G
	(15.7)	(9.76)	(21.1)					
Tower of London	79.1	67.6	71.2	**4.53**	**0.015**	2.70	0.076	G
	(8.40)	(15.2)	(12.9)					
Digits Forward	9.90	9.43	9.60	0.348	0.708	0.070	0.934	
	(1.65)	(1.72)	(2.09)					
Digits Backward	8.00	5.81	6.95	**4.49**	**0.015**	**5.10**	**0.009**	G
	(1.84)	(2.09)	(2.96)					
Visual Memory Span Forward	7.20	6.57	7.00	0.865	0.426	0.660	0.522	
	(1.47)	(1.57)	(1.65)					
Visual Memory Span Backward	7.67	5.71	6.29	**5.15**	**0.009**	2.90	0.064	P
	(1.50)	(2.05)	(2.35)					G
Letter Cancellation	205	246	263	**4.38**	**0.017**	2.73	0.074	P
	(27.6)	(74.3)	(75.8)					

1. Data are given as the mean with s.d. in parentheses.
2. Degrees of freedom=2,58. Values in bold are significant results.
3. Degrees of freedom=2,3,55. Values in bold are significant results.
4. *Post hoc* t-tests using the Bonferroni correction were performed where ANOVA/ANCOVA showed a significant group difference. No differences between the good (G) and poor (P) outcome groups were shown, but in each case a patient–control comparison was significant. The groups performing significantly worse than controls on each test are indicated.

Forward, suggesting that the ability to attend to and immediately recall strings of digits is preserved. The impairment shown by patients on Digits Backward must therefore be attributable to the working memory component of this task (Lezak, 1995).

Although the results of Digit Symbol indicate normal visuomotor speed, Trail-making B performance was significantly impaired. This suggests the existence of an impaired ability to shift between the number and letter sequences. Shift is an aspect of executive function, closely allied to working memory. Trail-making A impairment can also be attributed to working memory impairment, because the ability to maintain one's position in a sequence depends on intact working memory. Electrophysiological evidence supports frontal lobe involvement in both parts of the Trail-making Test (Segalowitz *et al*, 1992).

The other test on which patients were shown to be significantly impaired was the Controlled Oral Word Association Test (FAS), which is a sensitive measure of executive function. Executive dysfunction would also be expected to result in impaired Tower of London performance, but this was not found. It may be that more sophisticated analysis of Tower of London performance is needed in order to detect such deficits.

It should be noted that the extent of overlap between the cognitive functions assessed by each test makes any interpretation of the pattern of results somewhat speculative. The assessment of executive function raises particular difficulties. By definition, executive function is concerned with the appropriate deployment and regulation of other cognitive functions. Consequently, tests of this domain necessarily rely on other cognitive functions being intact, whereas performance on all neuropsychological tests must rely on executive function to a greater or lesser degree.

It is also noteworthy that patients' test scores exhibited a large variance, with some showing considerable impairment but others performing well within the normal range.

Is neuropsychological impairment associated with poor outcome?

Post hoc *t*-tests showed no significant difference between patients with good and poor outcomes on any test of neuropsychological function. There is, therefore, no

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evidence that neuropsychological impairment in bipolar disorder is associated with poor outcome as defined in this study. The concept of outcome in bipolar disorder is very complex and no established definition exists. Aspects of outcome include the frequency of major and minor affective episodes, their duration and severity, the presence or absence of impaired inter-episode functioning and the wider psychosocial consequences of illness. Although the criteria used in this study had some face validity, they were essentially arbitrary and did not account for many important aspects of outcome. Given these difficulties, finding no difference between the two patient groups does not necessarily imply that neuropsychological function has no relationship with outcome.

Are the abnormalities related to medication?

The possibility that the observed impairment may reflect the cognitive side-effects of medication must be considered. There is controversy as to whether lithium causes cognitive impairment, with some studies suggesting deficits (Kocsis *et al*, 1993) but others showing no effect (Anath *et al*, 1981). One well-designed longitudinal study showed very little decline in neuropsychological performance over six years of treatment (Engelsmann *et al*, 1988). Furthermore, where impairment has been found, it is typically in the domains of psychomotor speed and memory rather than executive function (Squire *et al*, 1980).

Neuroleptics have been shown to cause impairment of sustained attention and visuomotor speed in normal volunteers (King, 1994), but only five patients in this sample were taking these drugs. Carbamazepine and sodium valproate probably cause little or no impairment of cognitive function in the therapeutic range (Devinsky, 1995) and most studies indicate that antidepressant treatment is not associated with cognitive impairment (Thompson, 1991). These data suggest that the impairments found are unlikely to be attributable to medication, but this possibility cannot be ruled out.

Despite limitations, the results of this study provide good evidence for the existence of neuropsychological impairment in patients with euthymic bipolar disorder. This population showed specific deficits, some of which remained even after controlling for depressive symptoms. The pattern of results suggests an impairment of executive function (particularly working memory), which is largely a function of the frontal lobes. The possible pathophysiological basis of a persistent abnormality of frontal function in bipolar disorder is unknown. (This may reflect frontal lobe damage or disruption of frontal, subcortical or fronto-mesolimbic circuits (Cummings, 1993).) These deficits may relate to the presence of PWMLs, which are associated with impaired executive function in normal volunteers (Schmidt *et al*, 1993). The PWMLs found in bipolar disorder have frequently been reported to have a relatively frontal distribution (Dupont *et al*, 1990, 1995), although this is not a universal finding. It has also been suggested that multi-focal lesions may particularly impair the integrative function of the frontal lobes (Mesulam, 1990). Persistent functional abnormalities could also be responsible. Positron emission tomography has shown that significant hypofrontality in patients with bipolar disorder may persist despite improvements in clinical state (Martinot *et al*, 1990). A recent study showed reduced blood flow to the subgenual area of the prefrontal cortex in bipolar and unipolar depression (Drevets *et al*, 1997), which was at least partly accounted for by a corresponding reduction in cortical volume.

Further investigation to confirm the existence and pattern of neuropsychological impairment in patients with euthymic bipolar disorder is clearly warranted. It would be particularly helpful to examine test performance in a group of patients who showed a comparable level of depressive symptoms to controls. More sophisticated testing procedures could help to clarify the domains of function involved. It is important to identify the variables that delineate those patients showing cognitive decline. Longitudinal studies to investigate the relationship with the course and outcome of the illness are required.

The existence of neuropsychological impairment in patients recovered from bipolar disorder is of clinical relevance, regardless of the mechanism by which this occurs. Frontal lobe damage is known to lead to severe difficulties in coping with everyday life, particularly in terms of goal-setting, self-regulation and decision-making. It is likely that even minor cognitive deficits may result in substantial social and occupational difficulties. An inability to cope with the demands of work or family could cause stress and thus contribute to relapse. Cognitive problems attributed, rightly or wrongly, to the side-effects of medication might lead to non-adherence. The recognition of such difficulties and the provision of appropriate advice on coping with these might be of considerable benefit to patients.

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CLINICAL IMPLICATIONS

- Neuropsychological testing may form a useful part of the assessment of patients with bipolar disorder.
- Impaired executive function may cause social and occupational difficulties. Recognition of this and advice on coping may be of benefit to patients.
- The possible negative impact of cognitive impairment on compliance and outcome remains to be determined.

LIMITATIONS

- The observed neuropsychological impairments may be the result of medication.
- The extent to which reduced test performance reflects a clinically significant impairment of cognitive function is not known.
- The complexity of defining 'outcome' in bipolar disorder makes the comparison between good- and poor-outcome groups of questionable significance.

I. N. FERRIER, FRCPsych, BIBA R. STANTON, BMedSci, T. P. KELLY, PhD, JAN SCOTT, FRCPsych, Department of Psychiatry, University of Newcastle, Newcastle upon Tyne

Correspondence: Professor I. N. Ferrier, School of Neuroscience, University of Newcastle upon Tyne, Division of Psychiatry, The Royal Victoria Infirmary, Queen Victoria Road, Newcastle upon Tyne NE1 4LP

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