Neuropsychological dysfunction, soft neurological signs and social disability in euthymic patients with bipolar disorder

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Background Neurocognitive deficits exist in euthymic patients with bipolar disorder, but relationships between symptoms, psychosocial and neurological factors remain uncertain.

Aims To measure neurocognitive function in bipolar disorder and explore links to sub-syndromal mood symptoms, soft neurological signs and psychosocial impairment.

Method Attention, memory and executive function were tested in 37 euthymic patients with bipolar disorder and 37 controls. Psychosocial functioning, soft neurological signs and residual mood symptoms were assessed.

Results Performances on tests reflecting executive function and verbal memory (but not attention) were significantly poorer in the bipolar disorder group. Sub-syndromal mood symptoms produced small cognitive effects, predominantly on verbal memory. Soft neurological signs, especially frontal signs, were marked; some patients showed marked social disability which correlated strongly with soft neurological signs but weakly with executive dysfunction, which was linked to illness episodes.

Conclusions Cognitive dysfunction, social dysfunction and soft signs occur in euthymic patients with bipolar disorder and may represent trait deficits.

Declaration of interest None. Funding detailed in Acknowledgements.

Several studies have identified neurocognitive dysfunction in euthymic individuals with bipolar disorder, suggesting that these deficits represent trait abnormalities (Ferrier & Thompson, 2002). Poorer performance has been reported in a range of cognitive tests, with deficits especially evident on tests reflecting executive function and memory (e.g. Thompson *et al*, 2005). Investigators have reported that such deficits are related to sub-syndromal mood symptoms and indices of illness progression or severity (Dupont *et al*, 1995; Tham *et al*, 1997; Zubieta *et al*, 2001). Soft neurological signs, well established in schizophrenia, have been observed in patients with bipolar disorder in America (Nashrallah *et al*, 1983) and in India (Goswami *et al*, 1998). Recently, Negash *et al* (2004) reported a link to poor social conditions in Ethiopia. It might be expected that soft neurological signs would be related to neurocognitive performance in bipolar disorder, but this has not yet been examined.

We compared neurocognitive function in a group of euthymic patients with bipolar disorder and a control group. We predicted that those with the disorder would exhibit an impaired neurocognitive performance that would be significantly related to sub-syndromal mood symptoms, soft neurological signs and social disability.

METHOD

The study took place in the Department of Psychiatry and Drug De-addiction Centre, Lady Hardinge Medical College and Associated Hospitals, New Delhi, India, and was submitted successfully (A.S.) for the degree of MD to the University of Delhi. It involved the administration of a battery of neurological and neuropsychological tests to patients with bipolar disorder who were currently in remission and to healthy controls matched for age, gender and years of education. Approval was obtained from the institutional ethics committee for conducting the study and all participants gave written informed consent.

Participants

Forty-five consecutive patients who fulfilled the DSM–IV criteria for bipolar I disorder (American Psychiatric Association, 1994) and were currently euthymic were screened in the out-patient clinic of the Lady Hardinge Medical College Hospitals. Of these, 37 were finally recruited into the study. To be included, participants had to:

(a) be aged 17–65 years, of either gender;

(b) meet criteria for bipolar I disorder but have no other Axis I or Axis II condition;

(c) be euthymic at the time of inclusion in the study and at testing 1 month later.

One month after recruitment the participants were re-examined by the original assessor and an independent psychiatrist to ensure that they conformed to the diagnosis and that they remained euthymic in the intervening period before administration of the neuropsychological test battery. The study's exclusion criteria were similar to those reported by Moore *et al* (2001), to ensure that the participants did not have any illness with psychiatric consequences (other than treated hypothyroidism), did not misuse drugs or alcohol and did not display learning disabilities. Specifically, the following conditions were grounds for exclusion.

(a) Psychiatric: evidence of cognitive decline; other Axis I comorbid condition; bipolar disorder other than type I; learning disabilities.

(b) Neurological: cerebrovascular disease; neurodegenerative disorders; head injury with concussion; epilepsy; idiopathic parkinsonism; systemic illness with cerebral consequences; focal neurological signs on examination.

(c) Medical: hepatic disorder; cardiovascular disorder; renal failure; hypertension (blood pressure over 150/100 mmHg untreated, or treated hypertension); endocrine disorder (excluding corrected hypothyroidism).

(d) Pharmacological: medication (corticosteroids, antihypertensives); alcohol dependence or misuse; illicit drug use or solvent misuse.

The control group consisted of 37 healthy individuals recruited from hospital

https://doi.org/10.1192/bjp.188.4.366 Published online by Cambridge University Press

staff and from friends and relatives of the participating patients. They were examined to ensure they were free from Axis I and Axis II psychiatric disorders and conformed to the same exclusion criteria as the group with bipolar disorder. They were matched individually for age, gender and length of education.

Mood assessment

The mood of participants at recruitment and immediately prior to testing 1 month later was assessed using the Hamilton Rating Scale for Depression (HRSD; Hamilton, 1960) and Bech's modification of Beigel's Manic State Rating Scale (MSRS; Bech *et al*, 1975). Using a structured pro forma, life charts were constructed as suggested by Post *et al* (1998). An assessment of residual disability was made using the Schedule for Assessment of Psychiatric Disability (SAPD; Thara *et al*, 1988), a modification of the Disability Assessment Schedule II. Behaviour, social role, occupational and overall disability were rated on four separate scales, which are designed to be independent of culture.

Neurological assessment

All participants underwent a detailed neurological assessment. The presence and severity of soft neurological signs were assessed using a modification of the Kolakowska battery (Kolakowska *et al*, 1985). The original 12-point scale was increased by three items to include the grasp reflex, the suck reflex and the glabellar tap. Each item was rated 0–4 (absent, mild, moderate and severe); severe dysfunction was identified by a score of 15 or more. Movement disorders (dyskinesia, parkinsonism and akathisia) were assessed using the Abnormal Involuntary Movement Scale (AIMS; Guy, 1976) and the Simpson–Angus Scale (Simpson & Angus, 1970). The akathisia item on the latter scale was reported separately, as well as the total score.

Neuropsychological test battery

A battery of neuropsychological tests (see Appendix) was designed to encompass the four areas believed to be affected by bipolar disorder, namely attention, working memory, learning and executive function, by assessing verbal and visuospatial abilities. Tests included in the battery were well established and for purposes of comparison included many reported earlier. Details of the tests may be found in standard texts (Lezak, 1995; Spreen & Strauss, 1991). The tests were administered in a fixed order using, where available, standard guidelines. The tests began at noon and lasted for 2 h; two breaks of 10–15 min were allowed but the intake of stimulant drinks was prohibited.

Data analysis

Prior to analysis, data were checked for normality using the Anderson–Darling method (Stephens, 1980). Group and demographic data were subjected to analysis of variance (ANOVA). Data failing tests of normality (the Porteus Maze Test, the Trail Making Test Part B and the Five Point Test) were log transformed or, failing this, analysed by non-parametric methods. Data that failed to normalise after transformation were subjected to analysis by Mann–Whitney tests. To reduce the risks of false positives from repeated hypothesis testing, a significance level of $P \leqslant 0.01$ was adopted, with $0.05 \geqslant P > 0.01$ regarded as a trend. Associations between socio-demographic data, illness variables and neurocognitive performance were explored using the Pearson product-moment correlation coefficient, r. Because of recent discussions in this journal about the best method to analyse data (see Clark *et al*, 2002), both methods of assessing the influence of subsyndromal mood scores, namely analysis of covariance (ANCOVA) or partial correlations, were used and results compared.

RESULTS

Sample characteristics

Forty-five patients were recruited into the study and 37 completed it. Four patients were excluded because they developed an affective episode during the 1-month run-in period of monitored euthymia. Two patients were withdrawn when it was discovered that they had histories of alcohol dependency and seizures, and a further two withdrew for personal reasons. All 37 persons who were recruited into the control group completed the study.

The principal illness and demographic characteristics of the participants are shown in Table 1. Patients and controls were well matched for age, gender and years of formal education. The ages of participants (patients and controls) were uniformly distributed across the third (35%), fourth (26%) and fifth (36%) decades of life, with only 11% exceeding 50 years of age. The sample comprised mainly well-educated individuals: most (53%) had received more than 14 years of education, 21% had received 10–13 years and only 16% had received less than 10 years. Accurate assessment of premorbid IQ using the National Adult Reading Test (Nelson, 1982) was not possible because Hindi is the first language of many Delhi residents. As an alternative, participants were matched by time spent in formal education.

All patients were euthymic for a minimum of 1 month at the time of testing. Their mean HRSD score was 2.35 (s.d.=1.48) and no patient's individual score exceeded 7. The mean MSRS score was 7.91 (s.d.=4.88) with no patient's score exceeding 19. At the time of testing, patients had been clinically euthymic for a considerable period (mean 22 months, s.d.=35) and 66% had been euthymic for more than 6 months. Most patients reported histories of predominantly manic episodes each with a mean duration of approximately 3 months. This reflects the cultural trend in India to seek help less readily for depressive mood swings. The proportion of patients with a family history of affective disorders was high (68%) compared with the UK. This probably reflects larger family sizes in New Delhi compared with the UK, rather than any geographical difference in morbid risks to relatives.

Of the 37 participants with bipolar disorder, 15 were drug-free during the 4 weeks of euthymia prior to testing. The mean HRSD and MSRS scores of drug-free patients (2.79 and 8.86 respectively) were not significantly different from those of treated patients (2.19 and 8.19 respectively) and all scores were within study clinical norms. The treated patients (n=22) were receiving mood stabilisers (lithium 22%, valproate 16%, carbamazepine 11%); only 11% required the combination of lithium and valproate. In addition, some patients received benzodiazepines (n=1), antipsychotics (n=6) or antidepressants (n=2). Participants in the control group had not taken any psychoactive drugs during the month prior to testing.

Despite the participants being euthymic, their SAPD scores (mean 9.95) indicated that three-quarters of the patient group showed a degree of social impairment (threshold score $\geqslant$6). In 56% the impairment was mild, but 19% showed substantial impairment (Thara *et al*, 1988).

https://doi.org/10.1192/bjp.188.4.366 Published online by Cambridge University Press

Table 1 Sample characteristics

	Patient group	Control group	P^1
Age, years			
Mean (s.d.)	34.89 (9.89)	34.18 (11.06)	0.16
Range	20–52	20–53	
Gender, *n*			
Male	20	20	
Female	17	17	
Years educated: mean (s.d.)	12.95 (3.37)	12.95 (3.27)	0.9
Assessment scores: mean (s.d.)			
HRSD	2.35 (1.48)	1.55 (1.64)	0.02
MSRS	7.91 (4.88)	4.02 (2.07)	<0.001
SAPD	9.95 (6.75)		
Family history of affective disorder, %	67.6		
Family history of BPD, %	59.5		
Medication, %			
Drug-free	40 (n=15)		
Lithium	22		
Valproate	16		
Carbamazepine	11		
Lithium+valproate	11		
Duration euthymic, months			
Mean (s.d.)	21.68 (34.76)		
Range	1–89		
Age at onset, years			
Mean (s.d.)	25.81 (8.54)		
Range	15–46		
Number of episodes			
Mean (s.d.)	4.83 (2.67)		
Range	2–12		
Duration of illness, months			
Mean (s.d.)	17.82 (12.13)		
Range	2–22		
Number of manic episodes			
Mean (s.d.)	3.19 (1.79)		
Range	1–9		
Months manic			
Mean (s.d.)	12.43 (9.16)		
Range	1–42		
Number of depressive episodes			
Mean (s.d.)	1.62 (1.44)		
Range	1–6		
Months depressed			
Mean (s.d.)	5.34 (6.04)		
Range	0–27		

BPD, bipolar disorder; HRSD, Hamilton Rating Scale for Depression; MSRS, Manic State Rating Scale; SAPD, Schedule for Assessment of Psychiatric Disability.
1. Analysis of variance.

Neuropsychological testing

The results of neuropsychological testing are given in Table 2. Analysis of variance revealed differences between patients and controls in tests of specific neurocognitive functions. The group with bipolar disorder scored less well on tests reflecting executive function. Performances in the Categories Test, the Porteus Maze and the Five Point Test were significantly reduced ($P \leqslant 0.001$ in all). While performing these tests, patients perseverated more frequently. Reduced executive function was mirrored by poor performances in the Trail Making Test Part B – but not Part A – and the Shift Index.

The Forward Digit Span Test measures short-term memory, whereas the Reverse Digit Span requires additional manipulation of data in the working memory. Significantly lower scores in the reverse test indicate reduced executive function. Patients performed less well (P=0.004) on the Forward Digit Span Test but this reduced to a trend (P=0.04) when residual mood symptoms were controlled. This may indicate a short-term verbal memory deficit. Significantly lower scores on lists A1–A5 of the Rey Auditory Verbal Learning Test (AVLT) indicated reduced learning, although this was the only component of the tests in which significant differences were apparent. Coupled to the poorer performance on the Forward Digit Span, this may indicate a reduction in verbal memory. However, the scores on the latter test were influenced strongly by residual mood symptoms, so evidence of differences in verbal memory must be regarded as preliminary. Within the limitations of sample size, participants with bipolar disorder did not manifest an attention deficit. Performances on the Letter Cancellation Test and the Symbol Digit Modalities Test were similar between the bipolar disorder and control groups. After residual mood symptoms were controlled for, the trend for the participants with bipolar disorder to perform less well on Part A of the Trail Making Test (Trail A) was lost (P=0.04).

Controlling residual mood symptoms by ANCOVA or partial correlations

The influence of residual mood symptoms on performance can be seen by comparing group differences by ANCOVA with residual mood symptoms as covariates (see Table 2). The correct method of controlling for residual symptoms has been discussed in this journal by Clark *et al* (2002). It has been suggested that ANCOVA is invalid because those tested could not be randomly assigned to an experimental group, in this case patient or normal control groups (Clark *et al*, 2002). Partial correlations were proposed as an alternative. Our data have been analysed using both methods to

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Table 2 Neuropsychological test results: comparison of patients and controls

	Controls		Patients		ANOVA		ANCOVA			
	Mean	(s.d.)	Mean	(s.d.)	*F*	*P*	*F* (group)	*P* (group)	*P* (HRSD)	*P* (MSRS)
Letter Cancellation Test	131.7	(18.4)	135.5	(32.1)	0.4	0.53	0.88	0.35	0.46	0.23
Omissions	9.3	(3.9)	9.3	(4.7)	0.05	0.83	0.24	0.63	0.18	0.20
Commissions	0.6	(0.7)	0.5	(1.1)	0.06	0.80	0.05	0.83	0.17	0.51
Symbol Digit Modalities Test	13.6	(1.8)	13.2	(2.4)	2.3	0.07	0.83	0.36	0.67	0.50
Trail Making Test										
Part A	82.5	(22.6)	97.1	(31.1)	4.6	0.04	1.67	0.20	0.035	0.77
Part B	95.1	(26.0)	198.9	(69.0)	75.1	<0.001	64.7	<0.001	0.27	0.16
Trail shift index	12.6	(13.1)	101.9	(52.5)	98.0	<0.001	97.3	<0.001	0.16	0.85
Porteus Maze	48.0	(28.9)	149.3	(69.6)	66.6	<0.001	45.8	<0.001	0.17	0.85
Five Point Test	27.1	(6.9)	13.5	(6.2)	87.0	<0.001	63.0	<0.001	0.77	0.88
Rotation	4.0	(2.8)	12.1	(5.0)	79.0	<0.001	64.3	<0.001	0.09	0.27
Perseveration	2.2	(1.8)	7.8	(6.9)	23.0	<0.001	18.7	<0.001	0.60	0.90
Categories Test	40.5	(10.6)	24.3	(6.3)	72.4	<0.001	56.5	<0.001	0.27	0.48
Perseverations	1.8	(1.5)	6.6	(2.6)	97.2	<0.001	64.9	<0.001	0.71	0.31
Reverse Digit Span	5.5	(1.0)	3.1	(1.1)	116.7	<0.001	93.8	<0.001	0.54	0.70
Forward Digit Span	6.6	(1.1)	6.1	(0.9)	7.5	0.004	4.39	0.04	0.07	0.09
Rey Auditory Verbal Learning Test										
Lists A1–A5	48.7	(9.0)	41.4	(12.0)	12.2	<0.001	8.4	0.005	0.31	0.86
List A6	9.7	(3.0)	8.8	(3.1)	2.8	0.1	1.58	0.24	0.08	0.86
List A7	9.5	(2.9)	8.3	(2.9)	4.6	0.04	2.11	0.15	0.47	0.56
Checklist										
Correct A	12.7	(2.1)	12.8	(2.1)	0.03	0.87	0.54	0.46	0.37	0.35
Correct B	10.5	(2.9)	9.5	(3.5)	1.8	0.19	0.92	0.34	0.28	0.95

ANCOVA, analysis of covariance; ANOVA, analysis of variance; HRSD, Hamilton Rating Scale for Depression; MSRS, Manic State Rating Scale.

compare results: these are seen in Table 2 (ANCOVA) and Table 3 (partial correlations). Comparison of ANCOVA (with MSRS and HRSD covariates) and partial correlations (controlling for MSRS and HRSD) reveals that these methods give similar results for our data. Furthermore, the influence of residual symptoms is small and occurs most markedly in Trail A, Rey AVLT list A7 and Forward Digit Span scores. Thus, the major finding of the study – impaired executive function tests in euthymic patients with bipolar disorder – is supported, as is the absence of an attention deficit and the presence of a possible reduction in verbal memory, irrespective of the method used to control residual mood symptoms.

Soft neurological signs and movement disorders

The results of assessment of soft neurological signs and the movement disorder scales are shown in Table 4. Soft signs were present in 36 patients and 33 controls. The signs found in controls were minor and isolated, whereas in patients they were substantial and commonplace. This is reflected in the significantly different ($P<0.001$) mean scores on the modified Kolakowska battery of 13.8 (s.d.=6.65) for patients and 3.56 (s.d.=2.67) for controls. Half of the patients were markedly affected, with scores greater than 15. Thus, soft neurological signs are highly prevalent in euthymic patients with bipolar disorder.

Movement disorders, especially parkinsonism and akathisia, were also prevalent in bipolar disorder. Using the Simpson–Angus Scale, parkinsonism was found in 54% and akathisia in 27% of the patient group. Dyskinetic movements, including tardive dyskinesia, were recorded in 11% of patients. The presence of dyskinetic movements may reflect the use of antipsychotic drugs to treat mania prior to the widespread use of anticonvulsants; however, the illness duration of the four participants with dyskinesia was 4 years, 4 years, 18 years and 19 years respectively.

Correlates of neuropsychological performance

A correlation, albeit weak, links neuropsychology, the presence of soft neurological signs, social disability and illness history. Trail B and Porteus Maze scores correlate well with soft neurological signs ($r=0.4$ for each). The Porteus Maze scores correlate with the number of manic episodes ($r=0.3$) and the number of depressive episodes ($r=0.3$) rather than with total time unwell. This suggests that executive function declines with increasing number of illness episodes, rather than with the duration of the episodes. Many studies of affective disorder have reported links between cognitive deficits and illness-related variables (see, for example, Kessing, 1998; Cavanagh *et al*, 2002), and it seems probable that deficits increase with the burden of illness accumulated during life.

Correlates of soft neurological signs and social disability

Social dysfunction was strongly correlated ($r=0.57$) with the severity of soft neurological

https://doi.org/10.1192/bjp.188.4.366 Published online by Cambridge University Press

Table 3 Values of *P* corresponding to the partial correlation coefficient of test performance on illness status when manic (MSRS), depressive (HRSD) and both (MSRS+HRSD) residual symptoms are controlled

Test	*P* MSRS+HRSD	*P* MSRS	*P* HRSD
SNS	⩽0.001	⩽0.001	⩽0.001
Letter Cancellation Test	0.351	0.280	0.648
Omissions	0.628	0.467	0.933
Commissions	0.825	0.640	0.943
Trail Making Test			
Part A	0.201	0.103	0.112
Part B	⩽0.001	⩽0.001	⩽0.001
Trail Shift Index	⩽0.001	⩽0.001	⩽0.001
Porteus Maze	⩽0.001	⩽0.001	⩽0.001
Five Point Test	⩽0.001	⩽0.001	⩽0.001
Perseveration	⩽0.001	⩽0.001	⩽0.001
Rotations	⩽0.001	⩽0.001	⩽0.001
SDMT	0.366	0.319	0.186
Themes test	⩽0.001	⩽0.001	⩽0.001
Perseveration	⩽0.001	⩽0.001	⩽0.001
Rey AVLT			
A1–A5	0.005	0.003	0.002
A6	0.240	0.139	0.221
A7	0.151	0.112	0.062
Correct hits A	0.464	0.557	0.694
False positives A	0.708	0.645	0.442
Forward Digit Span	0.040	0.080	0.003
Reverse Digit Span	⩽0.001	⩽0.001	⩽0.001

AVLT, Auditory Verbal Learning Test; HRSD, Hamilton Rating Scale for Depression; MSRS, Manic State Rating Scale; SDMT, Symbol Digit Modalities Test; SNS, soft neurological signs.

Table 4 Neurological dysfunction

	Patients	Controls	*P*
Soft neurological signs			
Mean score (s.d.)	13.8 (6.65)	3.56 (2.67)	<0.001
Score > 15, *n* (%)	18 (49)	0 (0)	<0.001[1]
AIMS			
Mean score (s.d.)	0.78 (2.56)		
Patients scoring > 0, %	11		
Simpson–Angus Scale			
Total score			
Mean (s.d.)	2.14 (2.98)		
Patients scoring > 0, %	54		
Akathisia score			
Mean (s.d.)	0.42 (0.73)		
Patients scoring, > 0, %	27		

AIMS, Abnormal Involuntary Movement Scale.
1. Fisher's exact test.

signs. Soft neurological signs were correlated with executive function tests. A loose picture emerges of a link between soft neurological signs, neuropsychological deficits and impaired psychosocial functioning. The link between these domains must be regarded as preliminary and needs to be explored by carefully designed research.

Family and genetic influences

Genetic influences, as reflected in a family history of affective disorder, were absent from the study findings. Although 59.5% of the group with bipolar disorder had a family history of mood disorder, there was no influence of family psychiatric history on neurocognitive performance or the presence of soft neurological signs.

DISCUSSION

Neuropsychological deficits

The principal neuropsychological finding of the study is a significant impairment in euthymic participants with bipolar disorder of performance on cognitive tests regarded as measures of executive function. This result is seen consistently across a range of neuropsychological tests and, in the main, agrees well with our other studies (El Badri *et al*, 2001; Thompson *et al*, 2005). Thompson *et al* used comparable definitions of euthymia and similar inclusion and exclusion criteria in a UK study based in Newcastle, and found comparable deficits in executive tasks and declarative memory. The remarkable similarity of neurocognitive deficits found in Delhi and Newcastle indicate that the deficits do not result from cultural factors.

In our study participants were euthymic for at least 4 weeks when tested and residual mood symptoms were controlled, suggesting a trait deficit in executive function. Patients performed less well on the Porteus Maze, Five Point Test, Categories Test, Reverse Digit Span, Trail B and the Shift Index (Trail B minus Trail A). These tests require patients to shift sets or to generate new cognitive sets and strategies. When faced with some of these tasks, those with bipolar disorder perseverated more than controls. Segalowitz *et al* (1992) suggested that several of these tests are linked to abnormal frontal lobe electrophysiology. Van Gorp *et al* (1998) reported limited executive dysfunction in people with bipolar disorder but only in those with comorbid alcohol dependence. Alcohol misuse may worsen executive function, but it was specifically excluded from our study.

Two studies have failed to find impaired executive function in people with bipolar disorder (Cavanagh *et al*, 2002; Clark et *al*, 2002). These studies encompassed a broad range of executive tasks which differed from our own tests. The discrepancy is of concern and may have arisen for many

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reasons. The power of both studies was modest. The probability of type II errors was high, making the evaluation of negative findings difficult. Premorbid IQ, to which executive function makes an explicit and implicit contribution, could have influenced the results. Thus, a high IQ could lead to ceiling effects in simple executive tests, whereas a lower IQ might mask illness effects in patients. In many recent studies including those of Cavanagh *et al* (2002) and Clark *et al* (2002), mean IQs have been relatively high (about 115), but ceiling effects were not reported. Links between the IQs (of patients and controls) and executive dysfunction warrant investigation. A further and more significant source of the discrepancy may lie in the concept or definition of executive function (see Lezak, 1995). A discussion of these issues is beyond the scope of this paper. Nevertheless, executive function encompasses a broad range of components and not all are influenced equally by the presence of bipolar disorder. For example, Martinez-Aran *et al* (2004) have reported deficiencies in performance of the Reverse Digit Span and Wisconsin Card Sort tests in euthymic participants with bipolar disorder, but not in performance of the Controlled Word Association Test unless the participant was depressed. Executive abilities in bipolar disorder and control groups may have different profiles. Meta-analyses of individual tests might elucidate a profile of executive deficits in bipolar disorder and, importantly, limit type II errors when identifying cognitive functions unaffected by the disorder.

In our study verbal memory was impaired in the group with bipolar disorder. They performed less well on the Forward Digit Span and on Rey AVLT lists A1–A5 (immediate recall). Verbal memory has been reported to be abnormal in many studies. Most commonly, short-term verbal memory, as monitored by the California Verbal Learning Test or the Rey AVLT, is reduced in euthymic patients with bipolar disorder. Immediate memory as assessed by the Forward Digit Span Test is often reported to be reduced. Both immediate and short-term verbal memory are influenced by residual depressive symptoms, and the reduction is supported by studies that control statistically for residual affective symptoms. The evidence today favours a trait deficit in short-term verbal memory or learning, but higher-powered studies are needed to confirm these findings and also the link between poor verbal memory and time spent with depression (Van Gorp *et al*, 1998).

It is uncertain whether attention and psychomotor speeds are grossly reduced in euthymic individuals with bipolar disorder. In this study, tests of these domains – the Letter Cancellation Test and the Symbol Digit Modalities Test – did not differ significantly between the bipolar disorder and control groups, nor did Trail A after controlling for residual mood symptoms. Some studies (Van Gorp *et al*, 1998) have not reported deficits in these domains, whereas others have (Tham *et al*, 1997; Krabbendam *et al*, 2000; Rubenstein *et al*, 2000; Zubieta *et al*, 2001). With increasing complexity of the attention task, differences between patients and controls may become manifest, for example during sustained attention or extradimensional–intradimensional shifting (Clark *et al*, 2002). The lack of evidence of simple attention deficits or psychomotor slowing facilitates the interpretation of timed tests in other cognitive domains which are underpinned by attention. However, in common with memory and executive function, larger, higher-powered studies or meta-analyses are needed to resolve uncertainties surrounding attention.

Neurological dysfunction

An important result of our study is the widespread presence and considerable severity of soft neurological signs in euthymic patients with bipolar disorder. This occurred in the absence of reported birth injuries or other neurological dysfunction, and was independent of drug usage (see below). Soft signs are regarded as indicators of neurological impairment and are frequently seen in schizophrenia and neurodegenerative disorders. We believe that this is the first report of soft signs and neurocognitive performance in euthymic participants with bipolar disorder (with up to half being markedly affected). Recently, these signs have been reported in a group of euthymic and symptomatic patients with bipolar disorder in rural Ethiopia (Negash *et al*, 2004), reinforcing earlier observations in symptomatic people with this disorder (Nashrallah *et al*, 1983). Detailed comparison of the studies is hampered by the use of different test batteries and different mood states of participants. Nevertheless, the studies confirm the presence of soft signs in bipolar disorder. However, the localisation of soft signs is problematic (see discussion by Lishman, 1998). Signs that occurred most frequently in people with bipolar disorder (suck reflex, grasp reflex and to a lesser extent the glabellar tap) are regarded as pointers to frontal lobe dysfunction.

Other evidence of neurological dysfunction in bipolar disorder is the presence of movement disorder, which was recorded in both treated and drug-free participants. About a third of the sample (n=11) were found to have parkinsonism, with scores ranging from 3 to 12 on the Simpson–Angus Scale; of these five were free of neuroleptics for more than 1 month when examined. Similarly, four patients showed significant akathisia. Dyskinetic movements were recorded on the AIMS in 11% (n=4) of participants; these movements were most common in the face and upper limbs. An earlier Delhi-based study (Goswami *et al*, 1998) reported a prevalence of 15%. These rates are lower than Western estimates (Mukherjee *et al*, 1984) and may reflect an ethnic insensitivity to dyskinesias or the generally lower dosages of neuroleptics used in India (Goswami *et al*, 1998). Nevertheless, the presence of spontaneous movement disorder in bipolar disorder indicates that the basal ganglia are involved in the disease process in addition to any secondary impairment resulting from neuroleptic use.

Indicators of structural and functional frontal lobe abnormalities in bipolar disorder come from several sources. The neurocognitive deficits, especially those in executive function, point to dysfunction in the dorsolateral prefrontal cortex (Thompson *et al*, 2005). The soft neurological signs reported here also point to frontal dysfunction. Recently, magnetic resonance imaging (MRI) structural studies (Lopez-Larsen *et al*, 2002) have reported significant grey-matter (but not white-matter) reductions in specific prefrontal areas, compatible with neurocognitive findings. Thus, there are good indicators of frontal lobe involvement in bipolar disorder, although the primary pathology remains elusive. Alexander *et al* (1986) have described fronto-striato-thalamic circuits linked to several functions including eye movements and cognitive abilities and the extrapyramidal motor system. The prefrontal MRI results were compatible with abnormalities in these circuits (Lopez-Larsen *et al*, 2002). Our results indicate that in bipolar disorder other components of these circuits are impaired or dysfunctional, which would

https://doi.org/10.1192/bjp.188.4.366 Published online by Cambridge University Press

provide supporting evidence for a role of these circuits in the pathogenesis of bipolar disorder.

Social disability in bipolar disorder

The link between bipolar disorder and the important outcome measure of social disability is underresearched. On the SAPD, a test specifically developed for use in India, 54% of patients showed mild to moderate disability (score 6–15), 8% marked disability and 11% severe impairment in psychosocial functioning, whereas only 27% showed minimal or no impairment. Limited studies in Western populations (e.g. Tsuang *et al*, 1979) have reported higher levels of severe dysfunction, often in the range 20–30%. Comparisons of social variables between cultures are problematic, but in India even patients who are euthymic carry a significant disability which, like symptoms of this disorder, demands active management.

The correlates of social dysfunction have been little researched. In Ethiopia an unexpected association between soft neurological signs and poor accommodation was noted (Negash *et al*, 2004). Many of the higher functions tested in the battery (e.g. facial recognition) would be expected, if impaired, to lead to social disability. Our study finds a strong correlation (r=0.57, r^2=0.33) between soft signs and social dysfunction scores. The more frequently observed signs were markers of frontal lobe dysfunction, and the presence of soft neurological signs correlates, albeit quite weakly, with deficiencies in certain frontal executive tasks. Similar soft signs are commonplace in the neurodegenerative disorders, Parkinson's disease and Alzheimer's disease, in which social disability is frequently marked and progressive. If the severity of soft neurological signs in older patients with bipolar disorder was found to increase more rapidly with ageing than in controls, this would support a neurodegenerative view of the disorder. The links between soft neurological signs, social dysfunction, cognitive deficits and ageing merit detailed investigation.

CLINICAL IMPLICATIONS

- Even when euthymic, people with bipolar disorder have neurocognitive (trait) deficits which occur across cultures. Executive function and verbal memory are impaired.
- Neurological abnormalities, the appearance of primitive reflexes and spontaneous dyskinesia coupled to neurocognitive abnormalities suggest that fronto-striatal and thalamic pathways may be dysfunctional in bipolar disorder.
- Bipolar disorder, even in euthymic patients, is associated with considerable social disability; this needs to be considered when an individual's care plan is written.

LIMITATIONS

- The study was conducted on the Indian subcontinent, and cultural influence may modify the presentation and progression of bipolar disorder.
- The power of the study was relatively limited and, to limit type II errors, negative results should not be over-interpreted.
- The lack of an examination of the control group for movement disorder is a significant omission.

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(First received 19 January 2004, final revision 18 May 2005, accepted 3 June 2005)

ACKNOWLEDGEMENTS

The study was supported by Lady Hardinge Hospital and Medical School, University of Delhi, India. The Department of Psychiatry, University of Newcastle upon Tyne receives generous support from the Stanley Medical Research Institute. The authors sincerely thank Mrs M. Cheek for her skill and patience in typing the manuscript.

APPENDIX

Neuropsychological test battery

The following neuropsychological tests were used (for further details see Lezak, 1995; Spreen & Strauss, 1991);

(a) Letter Cancellation Test (attention, visuomotor speed);

(b) Symbol Digit Modalities Test (attention, visuomotor speed);

(c) Trail Making Test Parts A (attention, visuomotor speed); and B (attention, visuomotor speed and executive function);

(d) Porteus Maze (executive function);

(e) Five Point Test (executive function, non-verbal fluency);

(f) Categories Test (executive function, verbal fluency);

(g) Reverse Digit Span (executive function, short-term verbal memory);

(h) Forward Digit Span (short-term verbal memory);

(i) Rey Auditory Verbal Learning Test (verbal memory)

REFERENCES

Alexander, G. E., DeLong, M. R. & Strick, P. L. (1986) Parallel organisation of frontally segregated circuits linking basal ganglia and cortex. *Annual Review of Neurosciences*, **9**, 357–381.

American Psychiatric Association (1994) *Diagnostic and Statistical Manual of Mental Disorders* (4th edn) (DSM–IV). Washington, DC: APA.

Bech, P., Boewig, T. G., Dein, E., *et al* (1975) Quantitative rating of manic states. *Acta Psychiatrica Scandinavica*, **59**, 1–6.

Cavanagh, J. T. O., van Beck, M., Muir, W., *et al* (2002) Case–control study of neurocognitive function in euthymic patients with bipolar disorder: an association with mania. *British Journal of Psychiatry*, **180**, 320–326.

https://doi.org/10.1192/bjp.188.4.366 Published online by Cambridge University Press

Clark, L., Iversen, S. D. & Goodwin, G. M. (2002) Sustained attention deficit in bipolar disorder. *British Journal of Psychiatry*, **180**, 313–319.

Dupont, R. M., Jernigan, T. L., Heindel, W., *et al* (1995) Magnetic resonance imaging and mood disorders: localization of white matter and other subcortical abnormalities. *Archives of General Psychiatry*, **52**, 747–755.

El Badri, S. M., Ashton, C. H., Moore, P. B., *et al* (2001) Electrophysiological and cognitive function in young euthymic patients with bipolar disorder. *Bipolar Disorder*, **3**, 79–87.

Ferrier, I. N. & Thompson, J. M. (2002) Cognitive impairment in bipolar affective disorder: implications for the bipolar diathesis. *British Journal of Psychiatry*, **180**, 293–295.

Goswami, U., Basu, S., Khastgir, U., *et al* (1998) Neurobiological characterization of bipolar affective disorders: a focus on tardive dyskinesia and soft neurological signs in relation to serum dopamine beta hydroxylase activity. *Indian Journal of Psychiatry*, **40**, 201–211.

Guy, W. (1976) *ECDEU Assessment Manual for Psychopharmacology (Revised)*. Bethesda, MD: US Department of Health, Education and Welfare.

Hamilton, M. (1960) A rating scale for depression. *Journal of Neurology, Neurosurgery and Psychiatry*, **23**, 56–62.

Kessing, L. V. (1998) Cognitive impairment in the euthymic phase of affective disorder. *Psychological Medicine*, **28**, 1027–1038.

Kolakowska, T., Williams, A. O., Jambor, K., *et al* (1985) Schizophrenia with good and poor outcome. III: Neurological 'soft' signs, cognitive impairment and their clinical significance. *British Journal of Psychiatry*, **146**, 348–357.

Krabbendam, L., Honig, A., Wiersma, J., *et al* (2000) Cognitive dysfunctions and white matter lesions in patients with bipolar disorder in remission. *Acta Psychiatrica Scandinavica*, **101**, 274–280.

Lezak, M. D. (1995) *Neuropsychological Assessment* (3rd edn). Oxford: Oxford University Press.

Lishman, W. A. (1998) *Organic Psychiatry* (3rd edn), pp. 94–126. Oxford: Blackwell.

Lopez-Larson, M. P., DelBello, M. P., Zimmerman, M. E., *et al* (2002) Regional prefrontal gray and white matter abnormalities in bipolar disorder. *Biological Psychiatry*, **52**, 93–100.

Martinez-Aran, A., Vieta, E., Reinares, M., *et al* (2004) Cognitive function across manic or hypomanic, depressed and euthymic states in bipolar disorder. *American Journal of Psychiatry*, **161**, 262–270.

Moore, P. B., Shepherd, D. J., Eccleston, D., *et al* (2001) Cerebral white matter lesions in bipolar affective disorder: relationship to outcome. *British Journal of Psychiatry*, **178**, 172–176.

Mukherjee, S., Shukla, S. & Rosen, A. (1984) Neurological abnormalities in patients with bipolar affective disorder. *Biological Psychiatry*, **19**, 337–345.

Nashrallah, H. A., Tippin, J. & McCalley-Williams, M. (1983) Neurological soft signs in mania patients; a comparison with schizophrenia and control groups. *Journal of Affective Disorders*, **5**, 45–50.

Negash, A., Kebede, D., Alem, A., *et al* (2004) Neurological soft signs in bipolar I disorder patients. *Journal of Affective Disorders*, **80**, 221–230.

Nelson, H. E. (1982) *National Adult Reading Test (NART). Test Manual*. Windsor: NFER–Nelson.

Post, R. M., Roy-Byrne, P. P. & Uhde, T. W. (1998) Graphic representation of the life course of illness in patients with affective disorder. *American Journal of Psychiatry*, **145**, 844–848.

Rubinstein, J. S., Michael, A., Paykel, E. S., *et al* (2000) Cognitive impairment in remission in bipolar affective disorder. *Psychological Medicine*, **30**, 1025–1036.

Segalowitz, S. J., Unsal, A. & Dywan, J. (1992) CNV evidence for the distinctiveness of frontal and posterior neural processes in a traumatic brain-injured population. *Journal of Clinical and Experimental Neuropsychology*, **14**, 545–565.

Simpson, G. M. & Angus, J. W. S. (1970) A rating scale for extrapyramidal side effects. *Acta Psychiatrica Scandinavica*, **46** (suppl. 212), 11–16.

Spreen, O. & Strauss, E. (1991) *A Compendium of Neuropsychological Tests*. Oxford: Oxford University Press.

Stephens, M. (1980) Tests based on EDF statistics. In *Goodness-of-Fit Techniques* (eds R. B. D'Agostino & M. A. Stephens), pp. 97–105. New York: Marcel Dekker.

Tham, A., Engelbrektson, K., Mathe, A. A., *et al* (1997) Impaired neuropsychological performance in euthymic patients with recurring mood disorders. *Journal of Clinical Psychiatry*, **58**, 26–29.

Thara, R., Rajkumar, S. & Valecha, V. (1988) The schedule for assessment for psychiatric disability – a modification of DAS–II. *Indian Journal of Psychiatry*, **30**, 47–53.

Thompson, J. M., Gallagher, P., Hughes, J. H., *et al* (2005) Neurocognitive impairment in euthymic patients with bipolar affective disorder. *British Journal of Psychiatry*, **186**, 32–40.

Tsuang, M. T., Woolson, R. F. & Fleming, J. A. (1979) Long-term outcome of major psychoses. *Archives of General Psychiatry*, **36**, 1295–1304.

Van Gorp, W. G., Altschuler, L., Theberge, D. C., *et al* (1998) Cognitive impairment in euthymic bipolar patients with or without prior alcohol dependence. *Archives of General Psychiatry*, **55**, 41–46.

Zubieta, J. K., Huguelet, P., O'Neil, R. L., *et al* (2001) Cognitive function in euthymic bipolar I disorder. *Psychiatry Research*, **102**, 9–20.

https://doi.org/10.1192/bjp.188.4.366 Published online by Cambridge University Press