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Sustained attention and executive functions in euthymic young people with bipolar disorder

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Background Persistent neuropsychological impairments have been reported in the euthymic phase of bipolar affective disorder. However, the findings have been confounded by multiple episodes, chronic illness and residual mood symptoms.

Aims To assess sustained attention and executive functioning in euthymic young people with bipolar I disorder who had had no more than two affective episodes.

Method Thirty euthymic patients (with illness duration of less than 5 years and no more than two affective episodes) and 30 matched healthy individuals were assessed for sustained attention and executive functioning.

Results The bipolar group (mean age 22.4 years, s.d.=2.52; duration of illness 20.87 months, s.d.=14.72), showed impairment on tasks of attention and executive functioning. Multivariate logistic regression analysis demonstrated that deficits in executive functioning differentiated cases from controls. There was no correlation between residual depressive symptoms and neuropsychological performance.

Conclusions Deficits in attention and executive functioning were present in young people who had experienced only a few episodes of bipolar disorder, suggesting that the deficits are possibly trait abnormalities. Whether these deficits worsen with progression of illness needs to be examined in longitudinal studies.

Declaration of interest None.

Persistent neuropsychological deficits present in the euthymic state of bipolar affective disorder, particularly impairment in sustained attention, suggest that such deficits could be vulnerability trait markers of the illness (Clark *et al*, 2002, 2005*a*; Clark & Goodwin, 2004; Thompson *et al*, 2005). However, previous studies included older participants with chronic illness and multiple episodes. It is demonstrated that the deficits correlate with both the duration of illness and the number of affective episodes (McKay *et al*, 1995; Denicoff *et al*, 1999; Clark *et al*, 2002; Savitz *et al*, 2005). Our study examined attention and executive functions in young euthymic patients with fewer episodes (maximum two) and shorter duration of illness (<5 years) to confirm that the deficits are not necessarily the result of chronicity of illness and multiple affective episodes. We predicted that attention and executive function deficits would be demonstrable in young people with bipolar disorder in the euthymic state compared with matched healthy controls.

METHOD

The study was conducted in compliance with the guidelines of the ethics committee of the institute, and all participants gave written informed consent.

Sample

Thirty persons who fulfilled the inclusion criteria were recruited into the study from the out-patient services of the National Institute of Mental Health and Neurosciences, Bangalore, India, during the period September 2003 to February 2005. None of them withdrew from the study. The inclusion criteria were a DSM–IV diagnosis of bipolar I disorder (American Psychiatric Association, 1994); illness duration of less than 5 years; a history of no more than two affective episodes; age below 30 years; right-handedness; at least 7 years of formal education; and euthymic state. Euthymic status was defined as a score of less than 6 on the Young Mania Rating Scale (YMRS; Young *et al*, 1978) as well as on the 17-item Hamilton Rating Scale for Depression (HRSD; Hamilton, 1960). Participants had to be free from active symptoms for at least 8 weeks preceding the assessment and did not fulfil DSM criteria for an affective episode. This was established by obtaining information from the patient, a close relative of the patient, and the clinical charts. Exclusion criteria included a Mini-Mental State Examination (MMSE; Folstein *et al*, 1975) score below 25; presence of any other comorbid Axis I disorder including lifetime alcohol and substance misuse; evidence of organic brain disorder or neurological disorder; history of treatment with electroconvulsive therapy; and presence of colour blindness and any auditory or visual impairment.

Control group

Thirty healthy individuals, individually matched with participating patients for age (±2 years), gender and years of education (±2 years), were recruited by word of mouth. They did not have any lifetime Axis I disorder, had had at least 7 years of formal education and were right-handed. Controls conformed to the same exclusion criteria as the participants with bipolar disorder. They also had no family history of major psychiatric illness (psychosis, affective disorder, suicide or alcohol and substance misuse) in a first-degree relative. This was confirmed by unstructured clinical interview of those recruited.

Clinical assessment

A diagnosis of bipolar disorder was established from several sources – clinical charts and unstructured clinical interviews of the participants and their immediate family members – and confirmed by administration of the Operational Criteria for Research (OPCRIT; McGuffin *et al*, 1991; Williams *et al*, 1996) and the Mini International Neuropsychiatric Interview (MINI; Sheehan *et al*, 1998). Global functioning was assessed using the Global Assessment of Functioning (GAF; American Psychiatric Association, 1994). Members of the control group also completed the MINI to rule out the presence of any Axis I psychiatric disorder. Handedness was determined with the 10-item Edinburgh Handedness Inventory

(Oldfield, 1971) and colour blindness was ruled out using the Ishihara isochromatic charts. Demographic and clinical characteristics of the participants are shown in Table 1. At the time of assessment, 19 participants (63%) were taking an antipsychotic drug (olanzapine 8, risperidone 6, chlorpromazine 5); 27 (90%) were taking a mood stabiliser (lithium 23, carbamazepine 2, valproate 2); 1 (3%) was taking an antidepressant; and 9 (30%) were taking trihexyphenidyl. Sixteen patients (53%) were receiving a combination of a mood stabiliser and other drugs and the remaining 14 (47%) were receiving monotherapy with either a mood stabiliser or an antipsychotic.

Table 1 Demographic and clinical characteristics of the sample

Variable	Bipolar group (n=30)	Control group (n=30)	P
Gender, *n* (%)			
Male	21 (70)	21 (70)	–
Female	9 (30)	9 (30)	
Age, years: mean (s.d.)[1]	22.40 (2.52)	22.50 (2.32)	0.81
Years of education: mean (s.d.)	11.57 (1.94)	11.50 (1.85)	0.41
Marital status, *n* (%)			
Single	24 (80)	28 (93)	0.22
Married	6 (20)	2 (7)	
Religion, *n* (%)			
Hindu	26 (87)	28 (93)	0.69
Muslim	2 (7)	1 (3)	
Christian	2 (7)	1 (3)	
Occupation, *n* (%)			
Self-employed	4 (13)	0	0.04
Unemployed	13 (43)	9 (30)	
Private job	5 (17)	14 (47)	
Government job	1 (3)	0	
Home-maker	7 (23)	7 (23)	
Background, *n* (%)			
Urban	8 (27)	14 (47)	0.24
Rural	22 (73)	16 (53)	
Age at illness onset, years: mean (s.d.)	20.7 (2.53)		
Duration of illness, months: mean (s.d.)[2]	20.87 (14.72)		
Number of episodes, *n* (%)			
Single episode	13 (43)		
Two episodes	17 (57)		
Time spent in episodes, weeks: mean (s.d.)	18.70 (11.15)		
History of psychotic symptoms, *n* (%)	25 (83)		
History of hospitalisation, *n* (%)	19 (63)		
Number of admissions: mean (s.d.)	0.77 (0.68)		
Duration of euthymia, weeks: mean (s.d.)[3]	40.80 (38.50)		
Mood rating score: mean (s.d.)			
HRSD[4]	0.53 (0.77)	0	0.001
YMRS	0	0	
GAF score: mean (s.d.)	84.83 (5.49)		
Family history of bipolar disorder, *n* (%)	10 (33)		

GAF, Global Assessment of Functioning; HRSD, Hamilton Rating Scale for Depression; YMRS, Young Mania Rating Scale.
1. Age range for whole sample 18–26 years.
2. Median duration 14 months.
3. Median duration 27 weeks.
4. Five patients had a score of 2, six had a score of 1 and the others scored 0.

Neuropsychological assessment

Neuropsychological assessment lasted from 1 h 15 min to 2 h. Assessments were performed in a fixed order in a quiet room by a trained psychiatrist (U.S.K.). If needed, a short break halfway through the assessment was permitted. The tests administered included the following: the Continuous Performance Test (Cornblatt *et al*, 1988) for sustained attention and executive function; the Trail Making Test (Reitan & Wolfson, 1985) part A for attention and psychomotor speed and part B for attention, psychomotor speed and executive function; the Wisconsin Card Sorting Test (Heaton *et al*, 1993) for cognitive flexibility, working memory, problem-solving and set-shifting abilities; the Stroop colour–word association test for selective attention and executive function (Comalli *et al*, 1962); and the Tower of London test for forward planning and working memory (Shallice, 1982). These are well-established tests and detailed descriptions of them are found in standard texts (Lezak, 1995; Spreen & Strauss, 1998). The Tower of London test (Rao *et al*, 2004) and the Trail Making Test (Mukundan, 1996) have been validated in the Indian population. The remaining tests are routinely used in the institute for clinical and research purposes. The tests were administered in the Kannada language to 12 participants in the bipolar group and 7 in the control group, and in English to the remaining participants.

Statistical analysis

The data were tested for normal distribution using the Shapiro–Wilk test. Since most of the neuropsychological variables were not normally distributed, non-parametric analysis was carried out. As the patients and controls were individually matched, between-group comparisons were made using the Wilcoxon signed rank test for continuous variables along with effect size for log-transformed values for matched pair design. Effect size (d) is given by $d=\mu_y/\sigma_y$, where μ_y is the mean of the differences and σ_y the standard deviation of the differences (Cohen, 1988). Categorical variables were analysed by McNemar's test for dependent samples. Subgroup analyses among patients were performed using the Mann–Whitney U-test.

Spearman's correlation analysis was employed to examine the relationship between the scores on neuropsychological tests and certain illness-related clinical variables and the HRSD score. To identify significant neuropsychological variables in

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Table 2 Neuropsychological performance

Measure	Bipolar group (n=30) Mean (s.d.)[1]	Control group (n=30) Mean (s.d.)[1]	Z	P	Effect size[2]
Continuous Performance Test					
Total correct responses	29.63 (8.77)	39.20 (4.79)	−4.076	<0.001	0.79
Total commission errors	21.40 (29.91)	12.73 (7.15)	0.936	0.349	0.21
Total omission errors	17.33 (8.74)	7.80 (4.79)	4.097	<0.001	0.99
Response time, s	0.80 (0.20)	0.60 (0.20)	3.209	0.001	0.33
Trail Making Test					
Part A time, s	68.60 (20.67)	44.53 (15.69)	3.785	<0.001	0.86
Part B time, s	129.47 (40.20)	68.07 (19.97)	4.639	<0.001	1.72
Stroop test					
Colour card time, s	110.53 (29.71)	72.60 (12.27)	4.701	<0.001	1.35
Word card time, s	69.77 (17.14)	50.30 (7.67)	4.361	<0.001	1.07
Interference time, s	168.77 (39.36)	113.70 (14.04)	4.454	<0.001	1.30
Wisconsin Card Sorting Test					
Categories	2.10 (1.30)	5.40 (1.25)	−4.706	<0.001	1.69
Perseverative errors	30.30 (10.40)	13.67 (5.99)	4.456	<0.001	1.32
Tower of London test					
Problems solved in minimum number of moves	8.90 (1.54)	10.00 (0.79)	−3.138	0.001	0.68
Four-move problems	6.58 (2.42)	5.39 (1.03)	2.511	0.012	0.44
Five-move problems	8.25 (1.94)	6.37 (0.76)	4.077	<0.001	1.03

1. Untransformed means are reported for clarity.
2. Calculated for matched pair design based on log transformation.

differentiating cases and controls, the forward conditional logistic regression for matched case–control design was used (Dunlop *et al*, 1996). Even though non-parametric tests were used, for clarity the data were expressed as mean and standard deviation for continuous variables and number and proportion for categorical variables. Statistical analysis was carried out using Stata version 7.0 for Windows, and all reported P values are two-tailed. All results at $P<0.05$ were considered to be significant.

RESULTS

The two study groups were comparable on most demographic variables (Table 1). Neuropsychological performance in the two groups is shown in Table 2. The results suggest that the participants with bipolar disorder had impaired sustained attention and executive functioning. Because of the large effect sizes on some of the variables, we performed further subgroup analyses in the patient group. Neuropsychological performance did not differ significantly between subgroups based on number of episodes (single episode, n=13 *v.* two episodes n=17), and presence (n=10) or absence (n=20) of family history of bipolar disorder except on the Continuous Performance Test commission errors ($Z=-2.682$, P=0.007 for number of episodes; $Z=-2.154$, P=0.031 for family history). There was also no significant difference based on other subgroupings such as gender, and intensity of current treatment (combination of a mood stabiliser and other drugs *v.* monotherapy).

In the multivariate analysis, scores on the Stroop test (interference) (coefficient 0.074, s.e.=0.034, Z=2.14, P=0.033) and Tower of London minimum moves (coefficient −1.982, s.e.=1.122, $Z=-1.77$, P=0.077) differentiated cases from controls after controlling for the possible confounding effects of years of education, residual depressive symptoms (HRSD score) and urban/rural residence. The two variables accounted for 81% of the variance (R_2=0.8172).

To examine the effect of residual depressive symptoms on neuropsychological performance in the patient group, the HRSD score was correlated with all the neuropsychological variables. No significant correlation was found. However, years of education correlated with the Continuous Performance Test total correct responses (r=0.475, $P<0.001$) and omission errors ($r=-0.485$, $P<0.001$) and the time taken for the Stroop word card ($r=-0.563$, $P<0.001$). Average response time in the Continuous Performance Test and time taken for the Stroop colour and interference cards correlated with the time spent in affective episodes (Table 3). The number of episodes correlated with Continuous Performance Test commission errors. Global functioning measured by the GAF correlated with the Trail Making Test part A and Stroop colour card times.

DISCUSSION

Our study has demonstrated significant impairment in sustained attention and executive functions in young, euthymic people with bipolar disorder compared with well-matched healthy controls, even after controlling for the effects of residual depressive symptoms.

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Table 3 Correlation (Spearmans's rho) of illness characteristics and neurocognitive performance in patients with bipolar disorder.

Measure	Age at onset	Duration of illness	Current euthymia	Number of episodes	Time spent in episodes	Number of admissions	GAF score
Continuous Performance Test							
Correct responses	0.287	0.005	0.299	−0.058	−0.275	0.110	−0.064
Commission errors	0.088	−0.120	−0.121	0.498**	0.114	−0.014	0.016
Omission errors	−0.290	−0.005	−0.286	0.062	0.283	−0.113	0.057
Average response time, s	0.081	0.055	−0.197	−0.109	0.462*	−0.093	−0.041
Trail Making Test							
Part A time, s	0.071	0.068	−0.172	−0.226	0.078	−0.058	−0.388*
Part B time, s	0.096	−0.062	−0.056	0.101	0.236	−0.349	−0.094
Stroop Test							
Colour card time, s	−0.122	−0.025	−0.019	0.187	0.414*	0.136	−0.390*
Word card time, s	−0.123	−0.024	−0.031	0.292	0.159	−0.148	−0.207
Interference time, s	0.061	−0.149	−0.115	0.284	0.516**	−0.162	−0.225
Wisconsin Card Sorting Test							
Categories completed	−0.103	0.194	0.064	−0.074	−0.152	0.031	0.150
Perseverative errors, %	−0.230	−0.009	−0.045	0.062	−0.293	0.002	0.152
Tower of London test							
Problems solved in minimum number of moves	0.008	0.055	0.063	−0.088	−0.258	0.058	0.029
Four-move problems	−0.230	−0.134	−0.212	0.254	0.125	−0.107	−0.163
Five-move problems	−0.012	−0.179	−0.004	0.078	0.047	0.012	0.111

GAF, Global Assessment of Functioning.
*$P < 0.05$, **$P < 0.01$.

Comparison with previous studies

Our findings are largely consistent with those of previous studies (for review, see Savitz *et al*, 2005), including a recent study from India (Goswami *et al*, 2006). Our study differed from the latter study in that their participants were much older and had multiple episodes. In addition, soft neurological signs and social disability were also measured in that study. Our findings are complementary to those of recent studies implicating impairment not just in sustained attention but also in executive functions (McKay *et al*, 1995; Ferrier *et al*, 1999; Martinez-Aran *et al*, 2004*a*,*b*; Savitz *et al*, 2005; Thompson *et al*, 2005). However, some earlier studies demonstrated deficits in sustained attention (Ferrier *et al*, 1999; Clark *et al*, 2002; Clark & Goodwin, 2004), whereas two others did not (Robertson *et al*, 2003; Goswami *et al*, 2006).

Although our findings are similar to those of previous studies, effect sizes exceeded 1 on several of the neuropsychological variables. The effect sizes in previous studies usually ranged between 0.3 and 1 (Robinson *et al*, 2004). We examined patient subgroups based on number of episodes, family history of bipolar disorder, gender and intensity of current treatment to identify whether the large effect sizes could be explained by any of these parameters. However, largely the differences were not significant. In the correlation analysis too, there was no correlation between age at onset, duration of illness and number of admissions with neuropsychological performance. None of these could explain the variations in the effect size. However, the medication status and the nature of the sample might have some bearing on the performance. The sample was recruited from a tertiary care setting, which essentially caters for severely ill patients.

Are neuropsychological deficits the result of the disease process or trait-related?

Most previous studies included people who were much older than our sample and who experienced multiple relapses with long-term exposure to psychotropic medication (Savitz *et al*, 2005). Our findings suggest that the deficits are possibly trait-related, considering that they were detected in young euthymic individuals with few episodes of the disorder. Cognitive deficits could be the endophenotype of mood disorders (Clark *et al*, 2005*b*). However, it is likely that they could worsen with progression of illness. It has been shown that neuropsychological deficits in bipolar disorder correlate with both the number of affective episodes and the overall duration of illness (Savitz *et al*, 2005). In our study we found only modest evidence for this (Table 3). There was some indication of greater impairment with longer time spent in affective episodes. It is possible that with progression of the illness, greater correlation between neuropsychological deficits and severity of illness would be seen, as in other studies. Such associations are often considered to be indicators of a progressive disease process. However, one needs to be cautious in arriving at such conclusions because the direction of causality cannot be determined from correlational analysis. The result may well be interpreted to mean that those with neurocognitive deficits are more vulnerable to spending a greater time ill due to longer episodes and frequent relapses.

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Confounding factors

Previous studies have highlighted the confounding effects of minor affective symptoms on neurocognitive performance (Ferrier *et al*, 1999; Clark *et al*, 2002). However, a majority of our participants had no mood symptoms (Table 1) and there was no correlation between neuropsychological performance and HRSD score. Our sample was also much 'cleaner'; there was no evidence of any other Axis I disorder, including 'lifetime' alcohol and substance misuse.

A confounding effect of psychotropic drugs on neuropsychological performance cannot be ruled out. A majority of the patient group were taking lithium and atypical antipsychotic agents. Nearly a third of our patients were also taking trihexyphenidyl. Adverse effects of lithium (Kocsis *et al*, 1993; Honig *et al*, 1999), anticonvulsants (Thompson & Trimble, 1982), antipsychotics (King, 1994) and trihexyphenidyl (Gold *et al*, 1991; Sweeney *et al*, 1991; Heinik, 1998) on cognitive functions are well documented, although there is some evidence that lithium may not cause cognitive deficits (Engelsmann *et al*, 1988; Joffe *et al*, 1988; Goswami *et al*, 2002), and that anticonvulsants (Drevets, 2000; Manji *et al*, 2000) and atypical antipsychotics (Bilder *et al*, 2002) may even improve cognitive performance. The confounding effect of psychotropic medication on neuropsychological performance remains in most studies. It would be ideal to study people with bipolar disorder who were drug-naïve or not undergoing any treatment. However, this is not a possibility since it raises ethical dilemmas, and such drug-naïve patients are perhaps not representative of the actual population of people with bipolar disorder who seek help.

Limitations

The sample size was relatively small and the study was cross-sectional. We did not have any measure of premorbid IQ. Not all the tests used in the study have been validated in the Indian population, but this is unlikely to be a major limitation since the tests are routinely used in clinical services and are well validated in other populations. Moreover, the study had a matched control group. The definition of euthymia was not prospective, as in some other studies (Thompson *et al*, 2005; Goswami *et al*, 2006). Participants in our study were not drug-free and a significant proportion of them were taking trihexyphenidyl.

Implications for future research

Our findings demonstrate that neuropsychological deficits are possibly trait-related. The deficits in the long run can cause considerable impairment in psychosocial and occupational functioning (Martinez-Aran *et al*, 2004*a*,*b*; Thompson *et al*, 2005); therefore, greater emphasis should be placed on routine assessment of cognitive function in patients with bipolar disorder. Early intervention in the form of neuropsychological rehabilitation may be particularly important, as there is some evidence that these deficits may increase with disease progression. The role of available pharmacological agents in the amelioration of neurocognitive deficits needs to be systematically studied. More research on people with first-episode disorder, high-risk populations and long-term assessments are needed to elucidate further the nature of neuropsychological deficits in bipolar disorder, and whether these constitute a stable endophenotype of this condition.

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