Research Article

Neuro-cognition in patients of bipolar affective disorder (currently in remission) and their first degree healthy relatives

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Abstract

Background: Bipolar patients do complain of persistent difficulties in concentration, memory, inability to perform optimally in challenging tasks or even, in day-to-day functioning, whereas variety of factors may be responsible for persistent functional impairments, at least a subgroup of patients are likely to experience poor psychosocial outcomes as a result of cognitive dysfunction.

Objective: To assess the neurocognitive functions in patients of bipolar affective disorder currently in remission phase and their first-degree relatives.

Materials and Methods: This study was carried out on a total of 60 subjects. Of which, 30 subjects belonged to patient group, who were patients of BPAD (currently in remission phase) attending outpatient department and remaining 30 were their first-degree healthy relatives who were included in healthy relative groups.

Result: Mean age in both groups which was almost same, range between 42 and 45 years. Mean Hindi mini mental state examination (HMSE) test score obtained in patient group was 26.93 (SD = 2.066), in the healthy relative group 28.76 (SD = 1.278), and that in the control group was 29.133 (0.973). The performance of patient group and healthy relative group on the test of cognitive functions such as attention/psychomotor speed processing (Trail Making Test A), there was statistically significant difference in the TMT-A with patient. The performance of patient group and healthy relative group on the test of auditory verbal measure of simple span of attention (Digit Span Forward Test), there was statistically significant difference in the digit span forward test with patient group. The comparison of mean (2.60 ± 0.621 and 3.57 ± 0.568) between patients and healthy relative group was statistically significant (p = 0.00) in test of working memory (Digit span backward test). The comparison of mean (16.167 ± 1.839 and 19.00 ± 1.619) between patients and healthy relative group was statistically significant (p = 0.00) in test of immediate verbal memory and learning (VL and MT).

Conclusion: Patients of BPAD currently in remission phase performed poorly on measure of all domains of neurocognition such as executive functions, working memory, verbal memory, visuospatial memory than healthy relatives.

KEY WORDS: Neurocognition, bipolar affective disorder, first-degree healthy relatives, remission

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Introduction

Bipolar disorder (BD), formerly called manic depressive disorder, causes extreme mood swings that include emotional highs (mania or hypomania) and lows (depression). When one become depressed, he may feel sad or hopeless and lose interest or pleasure in most activities. When his mood shifts in the other direction, he may feel euphoric and full of energy.

Mood shifts may occur only a few times a year or as often as several times a week.[1]

Bipolar affecting disorder, currently in remission is that condition in which patient is not currently suffering from any significant mood disturbance, and has not done so for several months. The patient may, however, be receiving treatment to reduce the risk of future episodes.[2] Bipolar patients do complain of persistent difficulties in concentration, memory, inability to perform optimally in challenging tasks or even, in day-to-day functioning, while variety of factors may be responsible for persistent functional impairments, at least a subgroup of patients are likely to experience poor psychosocial outcomes as a result of cognitive dysfunction.[3] Bipolar disorder is highly heritable; family members of patients with bipolar disorder are at high risk of bipolar disorder. Cognitive deficits have been shown to be present in apparently healthy relatives of patients with bipolar disorder and thus they could be potential markers of familial vulnerability to bipolar disorder.[4] In order for a marker to be considered as a vulnerability marker (end phenotype), it must be associated with illness, must be present in asymptomatic patients, should be heritable, and must be served among unaffected relatives. Research over the past few years has revealed the presence of cognitive deficits in euthymic phase of bipolar disorder type 1. These cognitive deficits are independent of a mood state and have been proposed to a trait marker for BD. The first-degree relatives of bipolar sufferers have been shown to have a 10- to 20-fold increase in the risk of developing BD themselves. Various domain of cognition can easily be measured and are the key factors affecting the subject's ability to function occupationally, socially, and inter personally. The three cognitive domain of executive function, working memory, and attentional abilities are considered to be the most important cognitive domain for daily functioning.[5] the main objectives of this study were to assess the neurocognitive functions in patients of bipolar affective disorder currently in remission phase and their first-degree relatives and to compare and analyze the neurocognitive functions in patient group and their first-degree healthy relative group.

Materials and Methods

It is a cross-sectional study, which was conducted at the Department of Psychiatry, (DIMHANS) PBM Hospital, Bikaner. After taking permission from ethical committee and informed consent from patients of BPAD (currently in remission) attending outpatient department and their first-degree healthy relatives were included in the study. The selection criteria were made stringent to minimize the confounding factors in evaluation of cognitive functions. Such confounding factors could have been extremes of age, comorbid psychiatric or significant physical disorder, and significant substance use. Total of 60 subjects were included in the study. Of which, 30 subjects belonged to patient group, who were patients of BPAD (currently in remission phase) attending outpatient department and remaining 30 were their first-degree healthy relatives who were included in healthy relative group. Diagnosis of BPAD currently in remission phase firmly established by two separate psychiatrists.

Inclusion Criteria

1. Age between 18 and 60 years of both sex.
2. Patients of BPAD currently in remission phase of illness.
3. First-degree healthy relatives of patients of BPAD.
4. Literate enough to read and understand the questionnaires.
5. Grossly sociodemographically matched healthy control.

Exclusion Criteria

1. Substance abuse within past 6 months' period.
2. History of head injury with any documented cognitive sequel or with loss of consciousness.
3. Neurological disease or damage.
4. Mental retardation.
5. Medical illness that may significantly impair neurocognitive function.
6. Participants who refused to give informed consent.

Tools

1. Semi-structured sociodemographic profile sheet—includes age, gender, marital status, occupation, educational status, religion, family type, social status, and domicile.
2. Semi-structured clinical proforma—only for patient group and includes, past psychiatric illness history, total number of episodes, history of hospitalization, family history of psychiatric illness, current mental state examination, and treatment.
3. Neurocognitive tests includes:
    a) Hindi mini mental state examination (HMSE).
    b) Digit span test.
    c) Trail making test.
    d) Verbal learning and memory test (VL & MT).
    e) Visual learning and memory test (VL & MT).

Ethical Aspects

All the ethical aspects of the study were taken care of:

1. Only those subjects who are willing to participate in the study and given written consent were included in the study.
2. There was no discrimination or any other disadvantage to the subjects refusing to participate in the study.
3. The interview was conducted in privacy and the confidentiality of the information was ensured.

Statistical Analysis

Statistical product and service solutions (SPSS) 23 software was used for statistical analysis. For comparison of dichotomous variables χ^2-test and for comparison of two

groups Student's *t*-test were used. Difference was considered statistically significant when *p*-value was <0.05.

Result

According to sociodemographic profile details in patient group and healthy relative group most of the subjects were male in both groups. There was statistically no significant difference between both groups (*p*-value = 0.242). Mean age in both groups which was almost same, range between 42 and 45 years. Most of them were married as compared to unmarried and married single; difference was not statistically significant (*p*-value = 0.936). Most of subjects were farmer/clerical and unemployed in both groups. Difference was statistically insignificant with *p*-value 0.434. Most of participants were educated up to primary and high school, and minimum subjects were profession education status in both groups. There was statistically no significant difference in both with *p*-value 0.509. Maximum subjects were Hindu and there was statistically no significant difference found in religion (*p*-value 0.300). Maximum families were nuclear in both groups and *p*-value was 0.602. Most of the subjects were rural domicile and minimum were urban domicile in all two groups. There was no statistically significant difference in domicile with *p*-value = 0.347 [Table 1].

Mean Hindi mini mental state examination (HMSE) test score obtained in patient group was 26.93 (SD = 2.066), in the healthy relative group 28.76 (SD = 1.278), and that in the control group was 29.133 (0.973). There was statistically significant difference on HMSE with patient group performing poorly compared with healthy relative group, *p*-value being 0.00.

The performance of patient group and healthy relative group on the test of cognitive functions such as attention/psychomotor speed processing (Trail Making Test A), there was statistically significant difference in the TMT-A with patient. The comparison of mean (97.50 ± 17.781 and 48.73 ± 17.540) between patients and healthy relative group was statistically significant ($p = 0.00$).

The performance of patient group and healthy relative group on the test of auditory verbal measure of simple span

Table 1: Details of the socio-demographic profile both groups

Variables *N* (%)		Patient group	Healthy relative group	χ^2	df	Significance
		N (%)	*N* (%)			
Gender	Male	24(80)	20(66.7)	1.364	1	0.242
	Female	6(20)	10(33.3)			
Marital status	Married	25(83.33)	24(80.00)	0.132	2	0.936
	Unmarried	4(13.33)	5(16.67)			
	Married Single	1(3.33)	1(3.33)			
Occupation	Prof/Semi-Prof	1(3.33)	2(6.67)	3.794	4	0.434
	Farmer/Clerical	11(36.67)	10(33.33)			
	Skilled/Semi-Skilled	3(10.00)	8(26.67)			
	Unskilled	4(13.33)	2(6.67)			
	Unemployed/ Housewife	11(36.67)	8(26.67)			
Educational status	Profession/Graduate	2(6.67)	4(13.33)	4.28	5	0.509
	Post High School	3(10.00)	5(16.67)			
	High school	5(16.67)	6(20.00)			
	Middle school	5(16.67)	7(23.33)			
	Primary	11(36.67)	7(23.33)			
	Illiterate	4(13.33)	1(3.33)			
Religion	Hindu	29(96.7)	27(90)	1.071	1	0.300
	Muslim	1(3.33)	3(10.00)			
Family type	Nuclear	18(60.00)	16(53.33)	0.271	1	0.602
	Joint	12(40.00)	14(46.67)			
Domicile	Urban	8(26.7)	5(16.7)	0.884	1	0.347
	Rural	22(73.3)	25(83.3)			

of attention (Digit Span Forward Test), there was statistically significant difference in the digit span forward test with patient group. The comparison of mean (4.33 ± 0.660 and 5.03 ± 0.718) between patient groups and healthy relative group was statistically significant ($p = 0.00$).

According to performance of patient group and healthy relative group on the test of working memory (Digit Span Backward Test), there was statistically significant difference in the digit span backward test with patient group. The comparison of mean (2.60 ± 0.621 and 3.57 ± 0.568) between patients and healthy relative group was statistically significant ($p = 0.00$).

The performance of patient group and healthy relative group on the test of immediate verbal memory and learning (VL and MT), there was statistically significant difference in the verbal learning and memory test with patient group. The comparison of mean (16.167 ± 1.839 and 19.00 ± 1.619) between patients and healthy relative group was statistically significant ($p = 0.00$).

According to performance of patient group and healthy relative group on the test of visuospatial and visuoconstructional memory (VL & MT), there was statistically significant difference in the VL & MT with patient group. The comparison of mean (13.800 ± 1.827 and 16.97 ± 1.790) between patient group and healthy relative group was statistically significant ($p = 0.00$) [Table 2].

Discussion

This study was as designed to assess the neurocognitive functions in the patients of BPAD currently in remission and their first-degree healthy relatives of BPAD. Both groups had to satisfy rigorous selection criteria. Tests assessing neurocognition like executive functions, working memory, verbal memory, and visuospatial memory were chosen. HMSE for assessment of gross cognitive functions, Trial making test A for psychomotor speed processing, digit span forward test for auditory verbal measure of simple span of attention, digit span backward test for working memory, verbal learning and memory test for verbal memory, and VL and MT for visuospatial and visuoconstructional memory.

In our study both groups were comparable on basis of sociodemographic variable. Maximum subjects were male ($N = 44$) and most of the subjects were married ($N = 49$) as compared to that of single and unmarried. Mean age in all two groups range from 42 to 45 years. Maximum subjects were farmer/clerical ($N = 21$), followed by unemployed/house wife ($N = 19$) by occupation. Most of the subject belonged to lower middle class socio-economic status. The subjects included in our study were mostly educated up to primary ($N = 18$) and middle school ($N = 12$) and most of them ($N = 56$) belonged to Hindu religion and had nuclear family ($N = 34$) as compared to joint family and hailing from rural population ($N = 47$).

In our study, on comparing patient group with healthy relative group after applying HMSE, we found that patient group performed poorly as compared to that of healthy relative group. The finding is in consonance some of the previous studies in which significant deficits were found in executive functions verbal memory attention information processing speed and cognitive flexibility in the euthymic BD patients compared to healthy controls.[6] Savitz et al.[7] proposed that the neurocognitive and affective symptoms of BD are caused by functional changes associated with genetically driven population variation in critical neural networks. In other words, they suggested that neurocognitive dysfunctions found in BD patients do not simply occur as a result of the presence of the psychiatric disorder but may be due to premorbid developmental brain abnormalities. Savitz et al. argued that such abnormalities are genetically based, citing as support for their argument findings from studies involving premorbid functioning, twin studies, unaffected first-degree family members, and comparisons of cases with positive and negative familial histories of BD.[7-11] Although the work reviewed above is persuasive in arguing that there is impaired executing function in both BD patients and their non-affected relatives compared to healthy controls, it should be acknowledged that some studies of the euthymic BD population do not report similar results. For instance, McIntosh et al.[12] found no significant differences between BD patients and their non-affected relatives compared to healthy controls.

In our study, on comparing patient group with healthy relative group and control group on the test of attention/

Table 2: Comparison of patient group and healthy relative groups on neurocognitive test

Test	Patient group $N = 30$	Healthy relative group $N = 30$	*t*-value	df	*p*-Value
	Mean (SD)	Mean (SD)			
HMSE Test Score (Mean)	26.93 (2.07)	28.76 (1.278)	4.123	58	0.0001
Trail making test a score	97.50 (17.78)	48.73 (17.540)	10.695	58	0.0001
Digit span forward test score	4.33 (0.66)	5.03 (0.718)	3.931	58	0.0001
Digit span backward test score	2.60 (0.62)	3.57 (0.568)	3.487	58	0.0001
Verbal learning and memory test score	16.17 (1.84)	19.00 (1.619)	6.333	58	0.0001
Visual learning and memory test score	13.80 (1.83)	16.97 (1.790)	6.788	58	0.0001

HMSE, Hindi Mini Mental State Examination.

psychomotor speed processing after applying Trail Making Test - A, we found that patient group performed poorly as compared to that of healthy relative group and control group. Our findings are consistent with previous study Suwalska and Łojko[13] who claimed that patients in remission seem to be both affectively disturbed and cognitive impaired which may be a contributory factor to poor psychosocial outcome. During the last decade the result of numerous neurocognitive and neuroimaging studies on bipolar disorder have been reported. They have revealed various dysfunctions in bipolar disorder present during affective episodes and have demonstrated that many neurocognitive deficits persist in the period of clinical remission or euthymia. Patients during affective episode show significantly lower performances on several measures (test) of attention, executive function, learning and verbal memory, and psychomotor speed. Doruk et al.[14] investigated cognitive function in the manic, depressed, and remission period of bipolar disorder by comparing with a healthy control group and found that attention, memory, and learning functions were worse in the manic and depressive patients than healthy controls or patients in remission. No difference was found between patients in remission and healthy controls. Some attention subjects' scores were negatively related to the memory test and its subtest scores in manic and depressed patients and concluded that impairments in attention, memory, information processing, and learning functions of bipolar patients were specific to the depressive and manic periods of the disorder and no effect was present in the remission period.

In our study, on comparing patient group with healthy relative group and control group on the test of auditory verbal measure of simple span of attention after applying digit span forward test, we found that patient group performed poorly as compared to that of healthy relative group. The results of our study are consistent with those of Sole et al. who reported that euthymic bipolar patients showed significantly lower performance a several measure of attention, learning and verbal memory, and executive function compared with healthy controls. Goswami et al.[15] tested attention, memory and executive function in euthymic patients with bipolar disorder and controls. Test results on executive function and verbal memory (but not attention) were significantly poorer in euthymic bipolar patients.

In our study, on comparing patient group with healthy relative group and control group on the test of working memory (executive function) after applying digit span backward test we found that patient group performed poorly as compared to that of healthy relative group. Numerous other empirical studies have concluded that neurocognitive impairments are indeed evident in patients with euthymic BD compared to demographically matched healthy control.[16] For the present purposes, the results of interest in these studies are those related to the executive function deficit of the participants. In these studies, the most prominent test on which BD patients perform significantly more poorly than controls include the continuous performance test (CPT, which measure attentional impairment); the Digit Span Backward test (which measures working memory); and the Abstract Designs Self-Ordered Pointing Task (which measures non-special executive working memory.[16]

In our study, on comparing patient group with healthy relative group on the test of verbal memory and learning after applying verbal learning and memory test we found that patient group performed poorly as compared to that of healthy relative group and control group. Evidence suggests that cognitive impairments are present at first episode[17] and persist over time. The cognitive deficits particularly delayed verbal memory. Euthymic state was associated with impaired recall, though some other deficits were found to be better compared to the mood states. A number of comprehensive reviews and meta-analyses of neuropsychological performance indicated that euthymic patients with bipolar disorder show impairments on tests of attention, processing speed, verbal memory, and several aspects of executive function. While medium-to-large effect sizes have been detected for measures of certain aspects of executive function (especially response-inhibition and set-shifting tasks), not all executive functions are equally impaired in bipolar patients.[18] Verbal learning and memory deficits, for example, are frequently reported among euthymic bipolar patients. Robinson et al.[19] have also discussed about the potential overlap between executive functioning and verbal learning suggesting that executive deficits may affect memory performance.

In our study, on comparing patient group with healthy relative group and control group on the test of visuospatial and visuoconstructional memory after applying VL and MT, we found that patient group performed poorly as compared to that of healthy relative group. Robinson et al.[19] found that Euthymic BD patients often present with minor affective symptoms, which may adversely affect performance on cognitive measures. Few studies have tried to account for very mild dysphoric or depressive symptoms in otherwise euthymic patients and found that even after statistically controlling for these subsyndromal symptoms, there was still an impairment in visuospatial recognition memory, sustained attention, and executive function. It appears that euthymia is associated with at least some cognitive deficits despite carefully ruling out mood symptoms.[19]

Conclusion

Patients of BPAD currently in remission phase performed poorly on measure of all domains of neurocognition like executive functions, working memory, verbal memory, visuospatial memory than healthy relatives.

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