Research Report

FACTORS AFFECTING COGNITIVE FUNCTIONING IN INDIVIDUALS WITH BIPOLAR DISORDER IN EUTHYMIC PHASE

Mareen Benjamin[1], Roy Abraham Kallivayalil[1]*

[1]Department of Psychiatry, Pushpagiri Institute of Medical Sciences & Research Centre, Thiruvalla
*Corresponding address: Professor and HOD, Department of Psychiatry, Pushpagiri Institute of Medical Sciences & Research Centre, Thiruvalla, Kerala. Email: roykalli@gmail.com

ABSTRACT

Background: Neurocognitive studies during the euthymic phase of bipolar disorder have shown persistent cognitive deficits in 32% of patients. There is limited evidence in the Indian literature regarding this area. Neurocognitive impairment can significantly affect the overall functional recovery of these individuals. Understanding potential factors contributing to neurocognitive impairment in bipolar disorder is essential to develop prevention strategies and effective treatments. **Methods**: A total of 50 patients with bipolar disorder currently in euthymic phase for the last three months with a minimum duration of illness of two years and current Young Mania Rating Scale<11 and Hamilton Depression Rating Scale <8 currently on medications were administered various cognitive tests namely digit span test forward and backward, digit symbol substitution test and Trail making test A and B. The study was completed within a period of 6 months after getting approval from the institutional ethics committee. **Results**: Patients with bipolar disorder, in remission, have cognitive impairment in attention, memory and executive functioning. More than 50% of the patients could perform digit span test forward more than five digits, and in the case of the digit span test backwards, more than 50% of patients could perform only less than or equal to three digits. In the Trail Making tests A and B, 66% of the patients could perform within </=78seconds, and 62% could perform within </=273 seconds, respectively. Only 4% of the patients could complete 49 squares in the Digit symbol substitution test. **Conclusion**: Findings of the current study shows evidence of cognitive impairment in euthymic bipolar patients.

Keywords: Bipolar disorder, cognitive impairment, euthymic, executive functioning

INTRODUCTION

Bipolar disorder is characterised by repeated (i.e. at least two episodes in which the patient's mood and activity levels are significantly disturbed, this disturbance consisting on some occasions of an elevation in mood and increased energy and activity and on others of a lowering of mood and decreased energy and activity.[1] Lifetime prevalence of bipolar disorder is estimated as about 1 percent.[2] Patients with Bipolar disorder are known to have better functional outcomes than Schizophrenia.[3] Studies have shown low functioning in bipolar patients even when they are in a state of clinical remission.[4]

Cognitive deficits are impairments in cognitive ability that is closely linked to the functioning of specific brain areas, neural pathways, or cortical networks.[5] Studies have shown that during the euthymic phase, patients with Bipolar disorder show deficits in executive

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functioning, verbal and visual memory, and sustained attention.[6,7] In fact, 40%–60% of euthymic patients present with neurocognitive disturbances. Cognitive dysfunction may affect everyday activities and the ability to work.[8] Therefore, neurocognition has an important role in functional outcomes of patients with bipolar Affective disorder.[5] Most of the studies have focused on cognitive impairments in subjects during an episode, and very few studies have examined neurocognitive impairments in euthymic patients. Very few studies are available to comment on neurocognitive functions in Indian patients with Bipolar Affective Disorder (BPAD) during the euthymic phase. Hence the study was done to determine the factors affecting cognitive functioning in individuals with bipolar disorder in the euthymic phase and to find out the association between illness-related factors and cognitive functions.

MATERIALS &METHODS

Study design

The present study was a cross-sectional analytic study exploring the factors affecting the cognitive functioning of individuals with bipolar disorder in the euthymic phase. Patients with Bipolar Affective Disorder in euthymic phase for at least three months with a minimum of two years of illness duration in the age group of 18-60 years of any gender and those who gave informed consent were included in the study. Patients in the euthymic phase were selected as per scores on the Hamilton Rating Scale for Depression (HDRS; SCORE<8) and Young Mania Rating Scale(YMRS; SCORE<11). Patients who were unwilling, with cerebrovascular disease, neurodegenerative disorders, head injury with concussions, epilepsy, any other organic disease, intellectual disability and history of substance use except nicotine were excluded from the study.

Data collection

A total of 80 patients who attended the outpatient department of Psychiatry, Pushpagiri Institute of medical sciences and research centre were screened. Out of which 50 patients who met the study criteria were enrolled. The study was completed within a period of 6 months from December 2019-June 2020 after getting approval from the Institutional Ethics and Research Committee.

TOOLS FOR ASSESSMENT

1. A semi-structured proforma was used for sociodemographic and illness-related data.
2. Hamilton Depression Rating Scale (HDRS)[9]: Most widely used clinician-administered depression assessment scale. Score 0-7 is within the normal range, and a score of 20 or higher is required for entry into clinical trial. It was used to diagnose depression and to assess the state of remission. Those patients who gave a score of <6 were included in the study.
3. Young Mania Rating Scale (YMRS)[10,11,12] is one of the most frequently utilised rating scales to assess manic symptoms. The scale has 11 items based on the patient's subjective report of their clinical condition over the previous 48 hours. It was used to diagnose mania and to assess the state of remission. Those who gave a score of <7 were included in the study
4. Each participant in the study was subjected to cognitive assessment with the use of the following:
   a) **Digit Span Test: forward and backward[13]**: It is a test for attention and vigilance. The patient is verbally presented with an increasing series of random digits at a rate of one digit per second (beginning with two digits and increasing until failure on two successive trials) and is requested to repeat the digit string exactly as heard. Similarly, random digits are given, and the patient is asked to repeat the digits backwards. A normal person can do five digits forward and three digits backward.

   b) **Digit Symbol Substitution test[14]**: The DSST is a pencil and paper test of psychomotor performance[14] in which the subject is given a key grid of numbers and matching symbols, and there is a test section with numbers and empty boxes. The test requires filling as many empty boxes as possible with a symbol matching each number. The score is the total number of correct number symbol matches achieved in 90 seconds, and this test has high test-retest reliability.[15] Studies visuomotor speed and attention.[16]

   c) **Trail making test A & B (TrailA, Trail B)[13]:** This test, which is included in the Halstead-Reitan Battery, is a popular measure of visual searching, visual sequencing, perceptuomotor speed, the

ability to make alternating conceptual shifts efficiently, and attention. Part A of the test merely requires the patient to draw a line sequencing the numbers 1 through 25. Part B includes an element of conceptual shifting, requiring the sequencing of numbers and letters in alternating fashion (e.g., l-A-2-B- 3-C-4 ...).

Statistical analysis

Descriptive and inferential statistical methods were used with the help of Statistical Package for Social Sciences (SPSS)version 21.0. Mean and Standard deviation was used for demographic variables, frequency and percent to explore the nature of cognitive functioning. Spearman's correlation was used to study the relationship of illness related variables with cognitive functioning. Mann Whitney U test and Kruskal Wallis test were used to compare two and more than two group means, respectively.

RESULTS

Table-1. Sociodemographic variables

Variable	Frequency (%)
Occupation	
Home maker	23(46)
Student	7(14)
Skilled	14(28)
Non-skilled	6(12)
Monthly income	
</=10,000	24(48)
10,000-20,000	12(24)
20,000-30,000	7(14)
30,000-40,000	1(2)
40,000-50,000	3(6)
>50,000	3(6)

The total sample collected was 50. Patients in the euthymic phase were included in the study. The mean age among the study group was 42.14years. Out of 50 patients, 29 of them belonged to 40-60years. Thirty-four of them were females, and 16 were males. Nine of them completed higher secondary education, ten were postgraduates, 15 of them were educated up to Xth standard, 16 of them were graduates.

The performance in the various cognitive tests among the study group is given in Table 3. From the table, we understand that more than 50% of the patients could perform digit span test forward more than five digits, and in the case of the digit span test backwards, more

Table-2. Illness-related variables

Illness related variable	Frequency (%)
Number of episodes	
1-5	32(64)
5-10	11(22)
10-15	5(10)
>15	2(4)
Family history	
Nil	28(56)
Yes	2(244)
Medical history	
Nil	24(48)
Yes	26(52)

Table-3. Performance in various cognitive tests among the study group

Cognitive tests	Frequency (%)	Mean (SD)
Digit span test forward		
</=5	22(44)	5.54(1.25)
>5	28(56)	
Digit span test backward		
</=3	32(64)	3.02(0.89)
>3	18(36)	
Digit span test total		
</=8	26(52)	8.56(1.86)
>8	24(48)	
Trail-A		
</=78sec	33(66)	75.88(43.58)
>78sec	17(34)	
Trail-B		
</=273sec	31(62)	203.42(105.73)
>273sec	19(38)	
Digit symbol substitution test		
</=29	26 (52)	
30-39	11(22)	29.10(13.30)
40-49	11(22)	
>49	2(4)	

than 50% of patients could perform only less than or equal to three digits backward. In the Trail Making tests A and B, 66% of the patients performed within </=78 seconds, and 62% performed within </=273 seconds. Only 4% of the patients could complete 49 squares in the Digit symbol substitution test. Cognitive functions of attention, vigilance, visual tracking and psychomotor speed were impaired from the above results.

The association between sociodemographic variables and cognitive function tests and that between illness-related variables and cognitive function tests were done, and p values <0.05 were considered significant. (Tables 4,5). A significant relation was seen between the educational status of the study group with the performance of cognitive tests, seen with digit span test backwards, trail A, B and DSST. Occupational status and cognitive test performance were analysed, significance was noted for digit span test backward, trail-A, B and DSST. Our study group had 46% homemakers, 28% skilled workers, 14% students and 12% non-skilled workers.

Table-4. Correlation between sociodemographic variables and cognitive functions

Sociodemographic variables	Cognitive tests	p-value**
Education	Digit span test backward	0.047*
	Trail-A	0.006*
	Trail-B	<0.001*
	DSST	<0.001*
Occupation	Digit span test backward	0.016*
	Trail-A	0.005*
	Trail-B	0.008*
	DSST	0.001*

DSST- Digit Symbol Substitution Test **Kruskal Wallis test *p value<0.05 is statistically significant

Among the illness-related variables, age of onset of the illness and duration of illness were statistically significant with the performance of cognitive tests. The majority of the patients had an age of onset of illness between 20-30 years, and the duration of illness was between 10-20 years.

Table - 5. Correlation between illness-related variables and cognitive functions

Illness related variable	Cognitive tests	P-value	Spearman's correlation
Age of onset	Digit span test forward	0.026	-0.315
	Digit span test total	0.013	-0.348
	DSST	0.006	-0.384
Duration of illness	Trail-A	0.003	0.415
	Trail-B	0.035	0.299
	DSST	0.012	-0.353

p-value <0.05 is statistically significant

DISCUSSION

Bipolar Disorders are characterised by repeated (at least two) episodes in which the mood and activity levels are significantly disturbed. The episodes may be manic, depressive or mixed. The euthymic phase of the bipolar disorder indicates a normal range of mood and neither depressed nor elevated mood. Although there is clinical recovery between the episodes in bipolar disorder, neurocognitive impairments have been noted. The presence of subclinical psychopathology would probably account for the observed residual deficits. Neurocognitive impairment can significantly affect the functional recovery of individuals with bipolar disorder.

The study shows that sociodemographic and illness-related factors significantly contribute to cognitive functions. Impairment was seen in the digit span test backward and digit symbol substitution test. These results clearly show impairment in attention, vigilance, visual tracking, psychomotor speed and executive functions.

Education and occupation had a significant relationship with cognitive function tests among the sociodemographic variables. Very few studies have shown an association between sociodemographic factors and cognitive functions.

The current study has shown that the age of onset of the illness and duration of illness has a significant relation with the performance of the cognitive tests. Previous studies[3,17,18] have shown a cognitive decline with increasing duration of illness, and the current study has also produced similar results. The increasing number of episodes was not shown to have significant relations with cognitive functions. This was against the findings of the previous studies.[3,19]

Thus, it is evident that cognitive function impairment can occur in the euthymic phase of bipolar disorder. There are multifactorial causes for the same. The current study has considered limited factors. The effect

of medications, psychosocial stressors, residual depressive or manic symptoms has not been considered. The sample size of the study was small, and the study was a cross-sectional one conducted for a very short period of duration. Only a few cognitive tests have been performed on the study group.

It is worth mentioning that cognitive function impairment needs to be considered a therapeutic clinical target to improve psychosocial functioning and quality of life of patients with bipolar disorder. (Grande et al., 2016).[20] Thus, prevention and treatment of cognitive dysfunction is vital for relapse prevention and improving the overall quality of life in patients with bipolar disorder. There are both pharmacological and non-pharmacological approaches for preventing and treating cognitive dysfunction in patients with bipolar disorder. Different drugs with potential beneficial effects for treating neurocognitive impairment have been examined (e.g., some cholinesterase inhibitors, glutamate receptor antagonists, glucocorticoid receptor antagonists, dopaminergic agonists, intranasal insulin, some antioxidants, erythropoietin, etc.). There is no well-established pharmacological treatment for cognitive impairment since studies have yielded mixed results.[21] Functional remediation is an innovative intervention aimed at restoring psychosocial functioning, and it is designed explicitly for bipolar patients.[21] In 21 weekly sessions, functional remediation provides several neurocognitive strategies and techniques for daily life to tackle the main neurocognitive deficits associated with Bipolar Disorder (e.g. attention, memory, and executive functions). The intervention includes both individual and group format tasks in an ecologic setting. They help establish a connection between the learned skills and strategies with daily life situations of patients (as work, autonomy, etc.). The efficacy of functional remediation was proven in a randomised controlled trial that compares functional remediation with psychoeducation and treatment as usual (Torrent et al., 2013).[22] Patients receiving the functional remediation program improved the overall psychosocial outcome the interpersonal and occupational functioning.

CONCLUSION:

The present study shows that more than half of the study population has impairment in cognitive functions, especially in attention, vigilance, visual tracking, executive functions, and psychomotor speed. There is a significant association between the duration of illness and impairment of cognitive functions, which emphasises the need for prompt early diagnosis and treatment. The association of illness-related factors and cognitive functioning is helpful to predict the high-risk population and early initiation of cognitive remediation measures. It is better to elucidate the determinants of cognitive impairment, which can pave the way for further research in other possible factors influencing cognition.

Nevertheless, not all patients with bipolar disorder suffer from cognitive dysfunction. So, research on cognitive heterogeneity is an important issue to explore, which would aid to obtain more valid and homogeneous neurocognitive phenotypes and a better understanding of those factors that may influence cognition and contribute to its variability.

In future, longitudinal studies with multiple factors taken into consideration should be done to understand better the cause for cognitive decline in these individuals. This can also be combined with neuroimaging to find out the target areas of cognitive decline. Also, novel neuromodulatory techniques deserve further research to be considered potential treatments to mitigate cognitive deficits in patients with bipolar disorder.

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Nil

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