Do executive functions predict outcome in remitted bipolar patients? A case control study

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Abstract

Background: Bipolar disorder patients have cognitive deficits even during periods of remission particularly in domains of executive functions and verbal memory that contribute to poor functional recovery. The present study aims to identify the executive function deficits in bipolar patients in remission, and its influence on overall functioning.

Methods: Twenty consenting patients with diagnosis of a bipolar disorder (YMRS scores<11 and HRSD scores<8) and twenty healthy controls satisfying the inclusion and exclusion criteria were recruited for the study. All participating subjects were administered the Color Trail test, Stroop test, fluency test and Tower of London test. Functioning was rated on Global assessment of functioning scale.

Results: Cases and controls were comparable with respect to socio-demographic data. Remitted bipolar patients performed significantly worse than controls on, Fluency test, Color Trail test, and Stroop (C-W) scores and had significantly lower GAF scores compared to healthy controls ($p<0.05$). In the multiple regression analysis, executive functions contributed to 10.9% of the variance in GAF scores (after controlling for illness duration).

Conclusion: Remitted Bipolar disorder patients have significantly more executive dysfunction than healthy controls and executive functions significantly predict global functioning.

Keywords: Bipolar Disorder, Executive functions, Global functioning.

Introduction

Bipolar disorder affect approximately 2% of the general population.(1) Recent evidence suggests that a large proportion of patients with Bipolar disorders have poor functional outcomes. Studies have also shown that patients with Bipolar disorders continue to have executive function deficits even after remission from acute episodes of illness. However, the euthymic state is associated with less impairment.(2)

If components of executive functions are impaired it may have distressing effects on everyday life activities, including the ability to work and attend school, to develop and maintain appropriate social relations or function independently at home.(3)

There is little evidence about the unique effects of impairment in specific executive functions to adaptive functioning in bipolar disorder. Our study hypothesized that remitted Bipolar patients would have more executive deficits than healthy controls and that executive function deficits would predict poor functioning independently of other clinical and demographic variables.

Review of Literature

The modern psychiatric concept of bipolar disorder has its origins in the nineteenth century. In 1851 and 1854 Falret, on the basis of longitudinal observations categorized bipolar disorder as an illness and developed the entity of "folie circulaire"(circular madness), defined by episodes of mania and melancholia separated by symptom-free intervals. Baillarger used the term folie a double forme to describe cyclic (manic–melancholic) episodes.

The term bipolar disorder (1980) replaced manic-depressive disorder as a diagnostic term in the Diagnostic and Statistical Manual of the American Psychiatric Association (DSM-III).(4)

1. **Recovery in bipolar affective disorder:** Functional recovery is defined as the ability to achieve a level of functioning that existed prior to the most recent episode.(5) Kraepelin in 1921 noted that manic or depressive episodes were periodic in nature, and typically were followed by a return to normal functioning. This was supported by earlier studies on functional outcomes in bipolar disorder patients, which have shown a favorable outcome with almost more than 90% recovering from the initial episode.(6) However, more recent studies do not describe such a favorable outcome in patients with bipolar disorder.(7)

A review study by Bauer and colleagues, found that among the various factors associated with poor functional, poor premorbid functioning, longer duration of illness, residual depressive symptoms, psychotic features, substance abuse, and neurocognitive deficits were consistently associated with major occupational, social and other dysfunctions observed in bipolar disorder patients.(8) Presence of neurocognitive deficits during euthymia and its implications in functional recovery in BPD patients, is an important scientific and clinical question.

2. **Neurocognitive deficits**: Cognitive deficits are known to occur during acute phases of mania and depression in patients with bipolar disorder. Recent studies have shown that patients with bipolar disorder, irrespective of the mood state continue to have cognitive deficits.[9] However the remitted state is associated with lesser impairment than acute states. Maximum impairment was seen in the domains of executive functions and verbal memory [10]. Various other studies have also shown that executive functions is one of the major neurocognitive domain affected in remitted bipolar disorder patients.[11,12]
3. **Executive Functions:** The International Neuropsychological Society (INS) described executive functions as: "Cognitive abilities necessary for complex goal-directed behavior and adaptation to a range of environmental changes and demands. Executive function includes the ability to plan and anticipate outcomes (cognitive flexibility) and to direct attentional resources to meet the demands of non-routine events. Many conceptualizations of executive function also include self-monitoring and self-awareness since these are necessary for behavioral flexibility and 'appropriateness".[13]

Levin and Hanten (2005) defined executive functions as the ability of the individual to plan and to organize behavior over time; to use reflexivity in problem solving; to maintain goal direction and set future goals; to conform to societal rules; to strategize; to learn and regulate according to reward and punishment; and to self-monitor and regulate his/her behavior.[14]

Etiology of Executive functions: Executive function is associated with frontal cortex, particularly the dorsolateral prefrontal cortex (DLPFC) involved in cognitive flexibility and working memory, and with the Ventrolateral and orbital prefrontal cortex (PFC), involved in emotional processing, acquisition, and reversal stimulus– reward associations.[15,16]

Apart from frontal–cortical areas several other brain areas like limbic region of the medial temporal lobe are involved in executive functions.[17,18] Most recent studies have shown that the caudate nucleus is involved in active planning of a novel action[19] and in cognitive manipulation[20] hence, playing a key role in executive function particularly set shifting. There is altered connectivity between the caudate nucleus and prefrontal cortex in patients with bipolar disorder when compared to healthy controls[21,22,23] which may contribute to the executive dysfunction in bipolar patients.

4. **Relationship of executive functions to everyday functioning:** Brissos et al (2008) proposed that, the core dysfunction in BD during euthymia is executive in nature and is associated with poorer academic performance, worse vocational outcomes, reduced social adjustment, and diminished quality of life.[24] Executive function is part of all domains in terms of independent living and also day-to-day social functioning from planning and fixing goals to solving problems.[25] It has been found by Jaramillo et al (2009) that there are substantial differences between patients with and without cognitive deficits in areas such as work and vocational functioning like lack of ability to plan, to prioritize activities, and to use problem-solving skills.[26]

There are only few studies looking at cognitive deficits in remitted bipolar patients in India. The present study differs from other studies conducted, in aiming only at executive functions in remitted bipolar patients in comparison to healthy controls and studying its influence on overall functioning that may result in substantial social and occupational difficulties.

Aim

This study aimed to examine executive functions and Global functioning amongst a group of remitted Bipolar disorder patients in comparison with healthy controls. In particular, the study looked at whether executive function deficits predicted poor global functioning.

Methods

1. The study was conducted at the OP department of the Institute of Medical Psychology, Asha hospital, Hyderabad over a period of 12-months.
2. The design is a Case-Control design, and involved comparing 20 cases with 20 controls.
3 Twenty consenting patients who met the inclusion criteria set out below were recruited from the OP department for the study.

Inclusion criteria

- Patients providing informed consent.
- Patients of either sex between ages of 20-50 years.
- Subjects with at least 7 years of formal education.
- Patient who satisfy the criteria of bipolar affective disorder anytime during the longitudinal course of illness according to ICD-10
- Minimum of 5 years' duration of illness from the first episode
- Currently in remission as per scores on the Hamilton Rating Scale for Depression (HRSD; score <8) and Young Mania Rating Scale (YMRS; score <11)

Exclusion criteria

- Psychiatric diagnosis other than patients of bipolar affective disorder.
- Patients with a history of mental retardation, epilepsy, head injury with loss of consciousness, substance abuse, cerebrovascular disease, neurodegenerative disorders, and systemic illness with known cerebral consequences

4 The control group comprised of 20 healthy subjects with no past, present or family history of psychiatric illness. They were recruited from amongst hospital staff and unrelated attendants of patients.

5 All recruited subjects were administered a study questionnaire that included information about background socio-demographic details, illness related data, YMRS (Young mania rating scale) and HRSD (Hamilton rating scale for depression) to assess psychopathology, and GAF (Global assessment of functioning) for overall functioning.

6 Executive function was assessed by a neuropsychological battery which included

a. **Fluency test:** It measures initiation, psychomotor speed, fluency, cognitive flexibility and working memory.[27,28,29]

Phonemic fluency:[30] The subject is asked to generate words for 1 minute in the case of each consonant starting with the consonant i.e. F, A, S or in their mother tongue starting with Ka, Pa, Ma. The average new words generated forms the score.

Category Fluency:[31] The subject is asked to generate the names of as many animals as possible in 1 minute excluding the names of fish bird and snakes. The number of names generated forms the score.

b. **The Color trails test1:** It measures attention and psychomotor speed.[27,28,29] It consists of numbers 1-25 that are randomly spread, with odd numbers in pink circles and even numbers in yellow ones. The subject is asked to point to successive numbers in ascending order 1 to 25.The time taken to complete the test is noted.

c. **The Color trails 2:** It measures working memory, and set shifting.[27,28,29] It consists of numbers from 2 through 25 printed twice, once on pink circles and once on yellow circles. These are randomly arranged on the test sheet. The subject is asked to point to numbers in alternating colors with the successive numbers. The time taken to complete the test is noted.

d. **Stroop test:** It assess working memory and response inhibition[27,28,29] The color names blue, green, red and yellow are printed in 16 rows and 11 columns. The subject is asked to read the stimuli column- wise as fast as possible. The time taken to read all the 11 columns is noted down. Next the subject is asked to name the color in which the word is printed. The reading time was subtracted from the naming time to get the Stroop effect score. The number of errors committed were also noted.

e. **Tower of London Test:**[32] It measures planning and sequencing.[27,28,29]

The subject is presented with a goal state of arrangement of the 3 balls on one of the boards placed near the examiner. The subject has to arrive at the goal state in the board placed on his side. The test has total of 12 problems. Overall total number of problems solved with minimum number of moves was noted.

Statistics: All data was systematically collected in a study proforma, and was analyzed using a statistical package (SPSS version 23). As a first step, the data was tested for its distribution characteristics, and was found to be normally distributed. Therefore, parametric statistics were used for further analysis. Descriptive statistics for the entire sample included frequencies, means and standard deviations. The cases and controls were compared using an independent samples t-test (for continuous data) or a chi-square test (for nominal data). The association of GAF scores with other variables was done using a Pearson's correlation coefficient- this helped to identify which variables could be included the Multiple regression analysis to predict GAF scores. It also helped to test for multicollinearity. In order to ascertain whether executive functions independently predicted GAF, the independent variables were entered hierarchically, with illness duration entered in the first block and the rest of the executive test scores in the second block. Significance was set at $p<0.05$.

Results

The study sample consisted of 20 subjects (cases) who had Bipolar disorders and were in remission, and 20 healthy controls. Amongst the cases, there were 12 males and 8 females. The mean age of this group was 32.8 (SD 8.1). The mean duration of illness was 10.8 years (SD 5.5). The average of number of affective episodes (manic +depressive) was 3.2 (SD 1.6). Their mean YMRS score was 2.5 (SD 2.7) and HRSD score was 3.4 (SD 2.3).

In the control group, there were 13 males and 7 females. None of the control subjects had any past, present or family history of psychiatric illness. The mean age of the study group was 32 (SD 7.9)

The cases and controls groups did not differ with respect to age, sex, education and other demographic variables (**Table 1**). Clinical variables of the study group is shown in **Table 2**. The mean GAF score which assessed overall functioning of the study group was 70.3 (SD 11.9) which was significantly less than controls 92.8 (SD 5.3).

Table 1: Socio-demographic details of the study sample

Variable	Sample N=40	Cases N=20	Controls N=20	Significance
Age	32.4 (SD 7.9)	32.8 (SD 8.1)	32(SD 7.9)	NS
Sex				NS
Male	25	12	13	
Female	15	8	7	
Education				NS
UG	7	3	4	
G	26	13	13	
PG	7	4	3	

Marital Status				NS
Single	17	8	9	
Married	18	9	9	
Divorced	5	3	2	
Residence				NS
Urban	37	18	19	
Rural	3	2	1	

Table 2: Clinical variables (in the Cases)

Illness duration in years	10.8(5.5)	
Number of episodes	3.2(1.6)	
Time since last episode in months	28.4(21.6)	
History of substance abuse	Yes	4
	No	16
Past h/o psychotic symptoms	Yes	6
	No	14
Family h/o psychiatric illness	Yes	5
	No	15

Executive Function Tests: The two groups were compared with each other with respect to executive functions. Subjects in the case-group performed significantly poorly ($p<0.05$) than the controls on the Fluency test, Color trail test 1 and 2 and Stroop test (**Table 3**). These are measures of fluency, attention and psychomotor speed, set shifting and response inhibition.

Table 3: Executive function test

Executive Functions	Total sample (N=40)	Cases (N=20)	Controls (N=20)	Sig
Verbal fluency (no.)	9.5(2.4)	8.7(2.7)	10.2(1.8)	0.05*
Animal fluency (no.)	12.6(4.0)	11(4.1)	14.2(3.3)	0.01*
CTT1 (sec)	54.6(14.3)	63.2(15.4)	46.1(5.5)	0.00**
CTT 2 (sec)	119(34.1)	136.5(35.6)	101.3(21.5)	0.001**
Stroop color-word (sec)	92(26.2)	104.5(30.3)	79.5(12.9)	0.002**
Stroop errors (no.)	1.07(0.97)	1.5(1)	0.65(0.74)	0.004**
TNMM	7.07(1.16)	7.0(1.23)	7.1(1.11)	0.89

CTT- color trail test, TNMM- total number of minimum moves
P< 0.05=*. P<0.01=**

Regression Analysis: On Bivariate Correlational analysis, longer illness duration and executive function deficits were both significantly associated with poorer global functioning ($p<0.05$). Other clinical and socio-demographic variables were not found to have a significant association with GAF scores. The duration of illness was also significantly associated with performance on executive functions ($p<0.05$).

Illness duration was entered in the first block of the Multiple Regression analysis. Results show that nearly 60% of variance in GAF scores was contributed by illness duration. Executive function deficits accounted for further 10.9% of the variance (after controlling for illness duration) **(Table 4)**.

Table 4: Multiple regression analysis

Model	R	R2	Adjusted R2	SE	R^2 Δ	F	Sig
1	0.775	0.600	0.590	9.3	0.600	52 (1,38)	0.000
2.	0.842	0.709	0.666	8.4	0.108	3.1 (1,34)	0.026

Model 1- illness duration alone
Model 2- illness duration+ animal fluency+ CTT1+ CTT2+ Stroop color-word

Discussion

This was a case-control study looking at the relationship between executive function deficits and global functioning. The study design is broadly similar to other studies that have addressed similar research questions. However, to the best of our knowledge, this is the only study conducted in an Indian setting. Further, most of the prior studies comparing executive functioning deficits in remitted bipolar patients with healthy controls had a sample size between 30 and 60. Our study sample of 40 subjects also matches with them. Overall therefore, our study design is broadly comparable with earlier western studies addressing the same research question.

Executive functions: Our study has shown that remitted bipolar disorder patients differed significantly on tests of executive functions, when compared to healthy controls. Various studies have used combination of different test of executive functions. In our study, executive functions were assessed in both cases and controls using a neurocognitive battery which included Stroop Test, CTT 1 and 2, Fluency test and Tower of London. The procedure of all the tests was according to NIMHANS neuropsychology battery-2004 manual.

On constructs of response inhibition and cognitive flexibility as assessed by Stroop test, the difference in time taken to name the color and to read the word was higher in cases, which was statistically significant ($p=0.002$). Thompson (2005) in his study, found that remitted bipolar disorder (n=63) patients performed worse than controls (n=63) on Stroop test ($p=0.002$) which is consistent with the finding of our study.[33]

Studies by Mubeentaj and Padmavathi (2005) and Ryan et al (2012)have shown that time taken by the remitted bipolar patients to complete trial making test 1 and 2 was significantly higher than healthy controls. In our study we used color trial test which is similar to trial making test and is cross culturally more acceptable.[34] The mean time taken by the cases to

complete CTT was significantly higher than of controls (CTT1 p=0.00, CTT2 p=0.001).

On fluency test, cases produced less number of words than controls for both phonemic fluency (p=0.05) and categorical fluency (p=0.01). Results are in line with study by Palsson et al (2013).

Results of study by Thompson et al (2005) have shown that on TOL test, total number of problems solved with minimum number of moves was lower in remitted BD patients when compared to healthy controls.[33] However, our study did not find any significant difference in TOL test (p= 0.89).

Functioning in remitted bipolar patients: Overall functioning in the present study was assessed by Global assessment of functioning scale which measures psychological, social and occupational functioning. Though test retest reliability and validity of GAF scale is low, we used GAF scale to measure overall functioning to make our study comparable to previous other studies.

Review study by Wingo et al (2009) found that out of 22 studies reviewed, 11 studies have shown a consistent associations of executive functions with functional outcomes.[35] Specific cognitive domains that were associated with functioning in various other studies included verbal fluency (Martinez- Aran 2002), working memory (Dittman et al 2007), set shifting and response inhibition (Martinez- Aran 2007, Gildeners 2007). In particular, prior studies showed that measures of set-shifting as assessed by color trial test was related to everyday functioning (driving). Stroop test and fluency tests were related to level of independent living.[36] In contrast to the above findings, study by Malhi 2007 showed no significant association of cognitive domains with functioning.[37]

In the present study, we found that executive deficits account for nearly 11% of the variance in Global functioning, even after controlling for illness duration. It is likely that deficits around response inhibition, fluency and set-shifting influence different aspects of day-to-day activities (e.g., interpersonal interactions, social interactions, grooming, etc) thus contributing to the overall impairment in functioning found in this study.

There are important clinical implications to the findings of our study. It opens up newer therapeutic programs involving cognitive remediation for remitted bipolar patients, which could have a positive impact upon the patients' functioning, and possibly their Quality of life too.

Limitations

Our study is however, limited by the fact that we only had 40 subjects included. Perhaps a larger sample might have improved the validity of our findings, as well as improved the power of the results. Also, the study group were on medications like mood stabilizers and antipsychotics which can potentially have an impact on cognitive deficits. Premorbid intelligence was not assessed which significantly affects the performance on tests of executive functions. Future studies need to address these limitations in order to arrive at more robust conclusions about this research question in an Indian population.

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