STUDY ON EXECUTIVE DYSFUNCTION IN EUTHYMIC PHASE OF PATIENTS WITH BIPOLAR AFFECTIVE DISORDER

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ABSTRACT

BACKGROUND: Although classically conceptualised as a disorder of mood, a consensus is emerging that patients with bipolar disorder show cognitive deficits both during the acute phase of illness and during remission (Savitz et al., 2005). The cognitive dysfunction seen in bipolar disorder may also be a key to longterm disability, which in turn is likely to adversely affect psychosocial functioning, insight and treatment adherence.

AIM
To assess the executive functions in euthymic phase of bipolar affective disorder subjects and study the relationship between cognitive functions and illness variables.

MATERIALS AND METHODS
30 BPAD patients were assessed in the euthymic phase for executive dysfunction on four tests- verbal fluency, Trail making tests, Stroop colour word tests and Wisconsin card sorting tests and compared with controls. An intragroup analysis was then done to determine the effect of illness variables. Statistical analysis of the data has been done using the Statistical Package for Social Sciences.

RESULTS
Executive function was significantly impaired in the bipolar group when compared to normal controls. On analysing the relation of executive dysfunction with illness variables, only number of episodes had a significant effect, that too on a subtest of Stroop.

CONCLUSION
The presence of executive dysfunction may be a trait marker of bipolar illness and its relation with progression of illness need to be assessed.

KEYWORDS
Executive Dysfunction, Frontal Lobe Dysfunction, Prefrontal Cortex, Neuropsychological Tests, Euthymic Phase, Bipolar Disorder, Affective Disorder, Mood Disorder.

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INTRODUCTION: Emil Kraepelin (1896), the famous German psychiatrist and father of modern diagnostic nosology, delineated insanity into 'Dementia praecox' (Schizophrenia) and 'Manic-depressive psychosis (Bipolar affective disorder). This delineation was made on the basis that patients suffering from dementia praecox did not remit completely and patients suffering from manic-depressive psychosis tended to experience full remission in between episodes. Emerging research is beginning to show that impaired cognition is also an important factor in bipolar disorder. While apparently not as severe as that seen in schizophrenia, the cognitive dysfunction seen in bipolar disorder may also be a key to longterm disability, which in turn is likely to adversely affect psychosocial functioning, insight and treatment adherence.

With the potential for full recovery in bipolar disorder much more likely than in schizophrenia, small decrements in cognitive functioning may make the difference between a normal life and chronic disability. Given the importance of this issue, only few studies have specifically assessed bipolar affective disorder and its impact on neurocognitive functions, despite the fact that 30-50 percent of largely remitted patients fail to attain premorbid levels of psychological functioning and much of the disability may be linked to the neurocognitive impairment (Goodwin and Jamison, 1990)[1]. Studies in euthymic phase have shown that there are some neurocognitive deficits that persist even in the absence of clinical symptomatology, which in turn cause significant impairment in psychosocial functioning (Atre-Vaidya et al, 1998)[2]. In addition to the impact of cognitive dysfunction on an individual's quality of life, it may have implications for treatment. The demonstrated association between cognitive impairment and number of affective episodes suggests that early diagnosis and active treatment potentially could reduce the cognitive morbidity associated with bipolar disorder.

AIMS AND OBJECTIVES:

1. To study the executive functions in euthymic phase of bipolar affective disorder subjects and compare with those of controls.

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2. To study the relationship between cognitive functions and illness variables.

MATERIALS AND METHODS: Subjects fulfilling the ICD-10 diagnostic criteria for "Bipolar Affective Disorder" (n=30) confirmed by two consultants were recruited among the patients attending the Psychiatry Outpatient Department, Medical College, Kottayam after informed consent. Control group (n=30) was selected from general population, matched for age, gender and education after informed consent.

Calculation of Sample Size: Pairs of Cases and Controls matched 1:1 on defined characteristics are evaluated for exposure to a risk factor and distributed. The counts represent Pairs containing 1 case and 1 control rather than individual cases. The Proportion exposed in the control group is 0.3 (30%), Anticipated Odds Ratio from previous literatures is 3, and considered 95% as confidence level. Power (1- beta) is 80% and type 1 error fixed at 5%. Based on sample size calculation, minimum number of required cases are 30 and 30 controls.

STUDY GROUP:

Inclusion Criteria:

- Diagnosis of bipolar affective disorder according to ICD-10.
- Either sex in the age group between 15 and 40.
- At least 7 years of formal education.
- Subjects who are euthymic.
  a) In clinical remission for the past 2 months.
  b) Young Mania Rating Scale score of less than 7.
  c) Hamilton Rating Scale for Depression of less than 7.

Exclusion Criteria:

- Presence of colour blindness.
- Presence of other psychiatric illness.
- H/O ECT in the past 6 months.
- H/O substance dependence in the past 3 months.
- Presence of Medical/neurological illness (Mental Retardation, Epilepsy, Head Injury, CVA, Thyroid Dysfunction Etc.).
- Subjects with self-reported visual/auditory impairment.
- Patients who did not give informed consent for the study.

CONTROL GROUP:

Inclusion Criteria:

- No history or cross sectional evidence of psychiatric illness.
- Both sexes of age group 15 to 40 years.
- At least 7 years of formal education.

Exclusion Criteria:

- Presence of colour blindness.
- Family history of bipolar/psychiatric illness in first degree relatives.
- Presence of visual or auditory impairment.
- Presence of medical/neurological illness as for the study group.

INSTRUMENTS:

A. Specially Designed Intake Proforma:

Socio-Demographic Details: To Record the Subject's Age, Gender, Education, Occupation, Marital Status, Religion, Type of Family, Income.

Clinical Profile: Information on the following variables was recorded.

a) Age at onset of illness.
b) Total duration of illness.
c) Number of episodes.
d) Average duration of episode.
e) Number of episodes of mania, depression and mixed type.
f) Treatment details.
g) Family history of bipolar illness in first degree relatives.

B. Hamilton Rating Scale for Depression

C. Young Mania Rating Scale (YMRS)

D. Ishihara's Isochromatic Charts

E. Neuropsychological Tests to Assess Executive Function: Trail making test, Stroop colour word test, controlled oral word association test and Wisconsin card sorting tests were employed.

PROCEDURE: Patients attending the Outpatient Department of Psychiatry Unit, Medical College, Kottayam were screened. The subjects and relatives/caregivers were explained about the nature and purpose of the study and informed consent was taken. Subjects meeting the inclusion criteria for diagnosis of bipolar affective disorder, age and education were selected. Those with any other psychiatric illnesses were excluded. Colour blindness was ruled out using Ishihara's chart. Clinical examination was conducted to rule out medical illness. The subjects' euthymic state was established based on the available clinical records, cross sectional unstructured clinical interview and scoring on Young Mania Rating Scale and Hamilton Rating Scale for Depression. Only those who scored less than 7 on both these scales were recruited for further study.

Similarly, normal controls were taken from general population and those fulfilling the selection criteria were recruited after getting informed consent. After noting down the sociodemographic details, the bipolar disorder subjects and the control subjects were administered the neuropsychological tests in the same order, carried out under similar conditions for the all the subjects. All the procedures followed in this study were approved by the ethical committee of our institution.

STATISTICAL ANALYSIS: Statistical analysis of the data has been done using the Statistical Package for Social Sciences (SPSS- Windows version 10). For interval/ratio level data, mean was computed and used for comparison. For nominal level measurements, the differences are compared

in terms of percentages. For interval/ratio level data, t test is used to study the difference between main values. When there were wide variations in data, as reflected in Standard Deviation, equivalent non-parametric test (Mann Whitney U) was applied. For continuous data, when more than two means were involved ANOVA (F test) was used. For qualitative data, to study the differences in observations, Chi square test was used. Spearman's rho correlation analysis was also used to examine the relationship between scores on tests and age at onset, duration of illness, number of episodes and duration of episodes. For all these tests, the statistical significance was fixed at 5% level.

RESULTS: The aim of the present study was to assess executive function in bipolar patients in euthymic phase and to find if it has any relation with illness variables. Executive functioning was assessed using Controlled Word Association Test (Verbal fluency), Trail Making Tests, Stroop Colour Word Test (SCWT) and Wisconsin Card Sorting Test (WCST) in 30 euthymic bipolar patients and compared with 30 matched normal controls.

CLINICAL CHARACTERISTICS:

Age: The mean age of cases was 29.5 years which shows a patient group of younger age as against earlier studies which were conducted in higher age group (more than 40 years) [Altshuler et al., 2004; Martinez –Aran et al., 2004; Thompson et al., 2005][3,4,5]. Increased age could be one of the confounding factors as normal ageing can lead to cognitive deficits or there may an underlying dementing process ongoing as some of the dementias have their onset during the same age.

Sex: Majority of cases and controls were females (73% and 80% respectively). The gender matching has been done so as to rule out the differences in neurocognitive functions between genders.

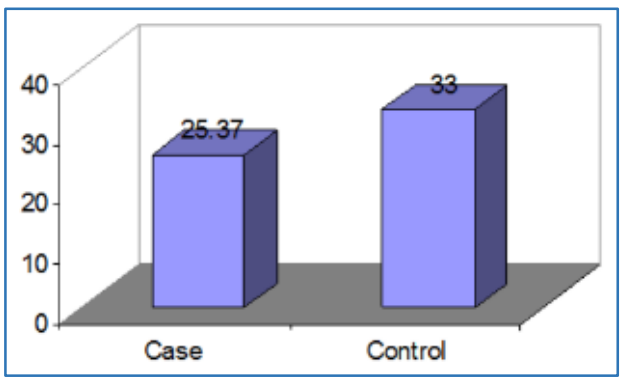
Education: The mean number of years of education is 11.4 years in cases and 11.2 years in controls. A minimum number of years of formal education was sought to be included in the study since premorbid IQ could not be assessed, and was matched between the groups.

Medication Status: All except one among the 30 patients were on psychotropic medications at the time of study. 73% were on Sodium Valproate. The effect of medications on cognitive functions could not be controlled in the present study. As in earlier studies (Bearden et al., 2001; Goswami et al., 2002),[6,7] cognitive deficits in bipolar illness are unlikely to be primary effect of medication. Nonetheless, many patients with this disorder take several psychotropic medications at varying doses and the effect of combined therapy is unknown.

NEUROPSYCHOLOGICAL TESTS:

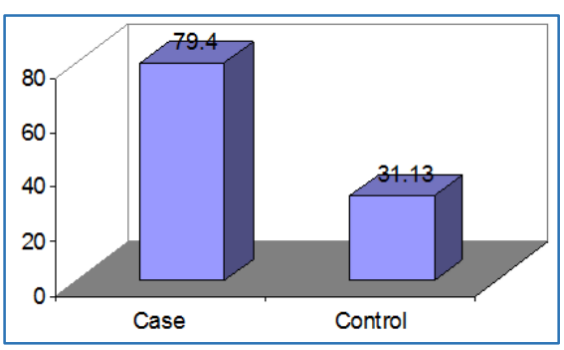
1. **Verbal Fluency:** The total mean score of verbal fluency was only 25.37 (cases) whereas the mean score for controls was higher (33). The difference is statistically significant. (p=0.01). On analysing the component letters, although clinical difference was observed for all three letters, statistical significance was found only for Sa.

This deficit of verbal fluency of cases is in agreement with earlier studies like Atre-Vaidya et al. 1998; Ferrier et al. 1999 El Badri et al. 2001; Thompson et al. 2005[2,8,9,5].



The mean score for verbal fluency was 25.39 for cases & 33 for controls, showing significant difference. (Significance = 0.014)*.

2. **Trail Making Test:** The time taken for TMT Part B showed a mean of 140.87 seconds for cases whereas the controls took significantly lesser time for completion, i.e. 67.9 seconds (p=0.00). The time difference between Part B and A also showed significant difference between the two groups, a mean of 79.4 seconds for cases and 31.13 seconds for controls. (p =0.00). This finding is similar to other studies which have shown deficits on TMT (Jones et al., 1994; Ferrier et al., 1999; El Badri et al., 2001; Altshuler et al., 2004; Martinez-Aran et al., 2004; U S Kolur et al., 2006).[10,8,9,3,11]



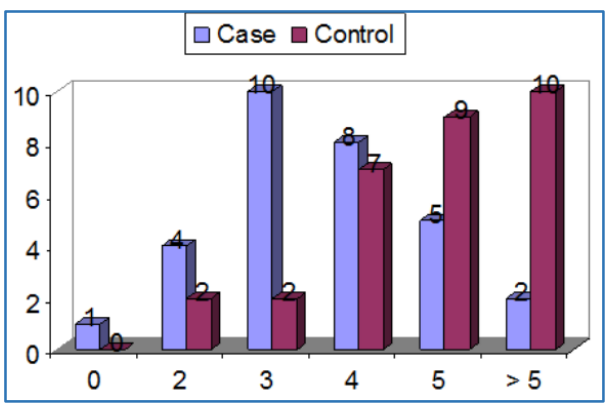
3. **Stroop Test:** The parameters assessed were reading time, naming time, the difference between the two and errors made in reading and naming. Time taken for reading and naming was significantly higher for cases than controls (p=0.04 and 0.00 respectively). The time difference between naming and reading was also significantly increased for cases (Mean for cases 228.33 sec; 118.9 sec for controls; p=0.00).

The errors made on naming was more for cases than controls and the difference was statistically significant. (p=0.03). The findings in Stroop test in the study is consistent with those in earlier studies. (Martinez-Aran et al., 2002, 2004; Zalla et al., 2004; Thompson et al., 2005).[11,12,5]

SCWT	Category	Mean (SD) Time in seconds	Mann- Whitney U	Significance
Reading time (RT)	Case Control	103.73 (23.33) 94.43 (21.81)	310.5	0.04*
NT – RT	Case Control	228.33 (121.81) 118.9 (44.7)	112.0	0.00*

Statistically significant differences were found for reading time, naming time & difference between the two.

4. **Wisconsin Card Sorting Test:** The number of categories completed and the number of perseverative errors were assessed.



The majority of the patient group 33.3% made only 3 categories whereas the majority of controls (30%) could complete 5 categories. (p=0.03). Cases made more perseverative errors than controls and the difference was statistically significant. (p =0.04). This finding is in accordance with earlier studies that had shown deficits in Wisconsin Card Sorting Test. (Coffman et al., 1990; Martinez-Aran et al., 2002; Altshuler et al., 2004; Ritu Nehra et al., 2006).[13,4,3,14]

Perseverative Error	Case n (%)	Control n (%)
< 30	4 (13.3)	12 (40)
30 – 40	8 (26.7)	8 (26.7)
> 40	18 (50)	10 (33.3)
$\chi^2 = 6.3$, p = 0.04*		

Cases made more perseverative errors than controls, the difference being statistically significant (*Significance at values less than or equal to 0.05). Thus, executive function was significantly impaired in the bipolar group when compared to normal controls. The relationship between executive dysfunction and illness variables was assessed. The illness variables included in the study are age at onset of illness, total duration of illness, total number of episodes, number of depressive episodes, duration of episodes and family history of bipolar illness in first degree relatives.

Age at Onset: The patients were divided into two groups, those who had an onset at age less than 20 years and those with onset after 20. No significant difference was observed in their performance on any of the four tests and no correlation was found between age at onset and executive function. This is in agreement with earlier studies (El Badri et al., 2001; Zubeita et al., 2001; Thompson 2005; U S Kolur et al., 2006).[9,15,5]

Duration of Illness: Comparison was made between the performance of cases with duration of illness less than 5 years, 6-10 years and more than 10 years. None of the tests showed significant difference between the groups. No relation was found between executive function and duration. This is in accordance with earlier studies by Kessing 1998 and Zubeita et al., 2001.[15] But in a study by Thompson et al (2005)[5] a significant negative correlation was found in executive functioning with regard to duration of illness. The sample size was more in that study and more tests for executive functioning was employed than in the present study. Moreover, the tests which showed negative association were different from that used in this study and the tests common in both studies showed no correlation with illness duration. Thus, the negative finding of this study could be a type II error and needs further replication.

Number of Episodes: The cases were divided into three groups, those with number of episodes less than 2, 3 to 5 and more than 5 episodes. Though correlation analysis showed no statistical significance between number of episodes and any of the four tests, a significant difference in one subtest of Stroop test was found between patients with 3-5 episodes and more than 5 episodes (p=0.04) revealing a significant lowering of performance in patients with more number of episodes. Studies by Kessing et al (1998)[16], Zubeita et al (2001)[15], El Badri et al (2001)[9] showed a significant negative correlation of executive functioning with the number of episodes. The lack of a significant correlation on Spearman's Rho in the present study could be due to smaller sample size.

Number of Depressive Episodes: No significant correlation was found between increasing number of depressive episodes and executive dysfunction. This is similar to findings of Van Gorp et al., 1998[17]. But, in the present study, 13 patients out of 30 came with a history of

depressive episode and the maximum number of depressive episodes was 3 and that too was only for a single patient.

This could reflect the general trend of manic episodes being detected more often because of the disruptive behaviour and missing the depressive episode. Thus, poor representation of depressive episodes in this sample may underlie this negative result and needs further replication.

Duration of Episodes: Patients with average duration of episodes less than 2 months and more than 2 months were compared. An apparent difference in performance was seen in TMT B-A (mean time 73.6 seconds for <2 months duration and a mean of 108 seconds for patients with more than 2 months duration) and Stroop Naming Time and difference between Naming time and Reading time. But these were not statistically significant. This is in consistence with the finding of Goswami and Ferrier et al., 2006.[7,8]

Family History of Bipolar Illness: Performance of patients with and without family history of bipolar affective disorder in first degree relative was compared and found no significant difference between the two on any tests. This is in agreement with the study by US Kolur et al (2006).

Presence of Depressive Episodes: No significant difference was found between patients with manic episodes only and those with both manic and depressive episodes.

Drugs: Though the effect of medication could not be eliminated in the study, a comparison was done between patients taking Lithium and those taking Valproate. This revealed no significant difference. (Verbal fluency p=0.87; TMT B minus A p =0.88; Stroop NT – RT p = 0.76 and Number of Categories in WCST p=0.06). Patients on antipsychotics and without antipsychotics also showed no significant difference in performance.

DISCUSSION: When compared to controls, bipolar group in euthymic phase showed significant impairment in executive functioning. On analysing the association of executive dysfunction with illness variables in the bipolar group, number of episodes, alone, had a significant effect, that too on a subtest of Stroop. As the sample size in this study is small, there is a need for further replication of results. A systematic review done by Robinson and Ferrier, 2006[18,8] also suggests that executive dysfunction was less consistently related to illness features when compared to verbal memory. This could be due to the broad range of executive tests used in the various studies.

Our finding that executive dysfunction worsens with the number of episodes has been replicated in studies by Zubeita et al, 2001, Clark et al, 2002, Cavanagh et al, 2002 and MacQueen et al, 2001[15,19,20,21]. This led to postulates that repeated episodes result in an accumulation of neurobiological abnormalities and also proposal that stress induced hypercortisolaemia during an affective episode may result in neurotoxicity in hippocampal cells and its connection. It has a significant implication in treatment as it can be posited that by preventing further relapses, further decline in executive functioning can be prevented.

Progression of Cognitive Impairment: There has been many studies examining this particular aspect. But, most of these were cross sectional in design. Studies by Kessing et al (1998),[16] Zubeita et al (2001),[15] and El Badri et al (2001)[9] showed a significant negative correlation of executive functioning with the number of episodes; but not with duration of illness. In a study by Thompson et al (2005),[5] a significant negative correlation was found in executive functioning with regard to duration of illness. One of the few studies to conduct a longitudinal assessment of bipolar patients (Dhingra et al, 1991)[22] has also found some evidence for cognitive deterioration over the course of the disorder.

In our study, no correlation has been found with the duration of the illness, but there was a negative correlation with the number of episodes. As ours was a cross sectional one, a prospective analysis of cognitive impairment needs to be undertaken to comment about progression of the impairment.

State or Trait Marker: Chowdhury et al (2003)[23] have reported a selective deficit in the executive control of working memory in first-degree relatives of bipolar probands with intact verbal learning and memory. Interestingly, this profile accords with that observed in euthymic bipolar subjects providing further support for a selective 'Trait-deficit' in executive control of working memory. Thus, the same neurocognitive deficits in bipolar subjects and their healthy first-degree relatives may represent phenotypic markers of genetic vulnerability. Therefore, the presence of executive dysfunction observed may be thought as a trait marker rather than a state dependent variable. However, whether it progresses with the illness needs to be assessed further with longitudinal studies rather than cross sectional ones.

LIMITATIONS:

1. The patients in the present study were on multiple psychotropics and the effects of these drugs on cognition could not be excluded.
2. The sample size is 30 and there are more of women than men in this study, thus the results cannot be generalised. Even though gender matching has been done, the effect on each test has not been examined. A larger sample size with a more equal representation of gender would be required for better generalizability of the results.
3. Only executive functions were assessed in the study. Attention and verbal memory which are also impaired in euthymic bipolar disorder were not included.
4. The association with illness characteristics like presence of psychotic symptoms and type of BPAD (type 1 or 2) has not been assessed in this study.
5. The study design was cross sectional and the longitudinal course of these deficits needs to be assessed.

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