Cognitive functions in stable schizophrenia & euthymic state of bipolar disorder

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**Background & objectives**: Some cognitive deficits in schizophrenia and bipolar disorders persist after the subsidence of active symptoms. We carried out this study to assess and compare the cognitive functioning of patients with stable schizophrenia and bipolar disorder.

**Methods**: Fifteen each of stable maintained schizophrenic patients and euthymic bipolar-I patients attending outpatient clinic in a tertiary care psychiatric hospital in north India were included in the study as also equal number of age and education matched control subjects. Cognitive assessments were done using Wisconsin’s Card Sorting Test (WCST), Spatial Working Memory Test (SWMT) and Continuous Performance Test (CPT).

**Results**: Stable schizophrenia patients performed poorly on all the neurocognitive parameters as compared to both controls and bipolar euthymic patients. Euthymic bipolar patients showed significant difference on executive functions with normal controls. Patterns of cognitive disturbances in tasks of executive function are similar in both groups but are quantitatively more marked in schizophrenia.

**Interpretation & conclusions**: Our results showed that stable schizophrenia patients performed significantly worse on cognitive measures than patients of euthymic bipolar disorder which was consistent with their poorer functional outcome. The results further indicated that stable schizophrenia and euthymic bipolar disorders may be distinguished qualitatively in neuropsychological terms with different profiles of cognitive impairment.

**Key words** Cognitive functions - euthymic state in bipolar disorder - schizophrenia

Many neuropsychological studies have been performed on bipolar disorder that attempted to separate it from other psychiatric disorders, such as unipolar depression\(^1^,2\) and schizophrenia\(^3,4\) and also to define the cognitive profile across the three distinct phases of the illness viz., mania, depression and euthymia\(^5,6\). Although it has previously been assumed that euthymia equates to ‘recovery’, there are emerging trends of disruptions in verbal memory\(^7\), phonemic verbal fluency, complex problem solving, abstract concept formation and attentional set-shifting\(^8\). The disruptions observed are frequently subtle, and suggest inefficiency in how tasks
are performed, rather than what can be achieved. In addition, difficulties in social and occupational functioning are also reported in up to one-third of euthymic bipolar disorder patients. The existence of such deficits (both cognitive and social) during normal mood may indeed point to an underlying pathology of bipolar disorder.

Cognitive deficits in schizophrenia have been the focus of psychiatric research in recent years. Cognitive deficits persist during the stable phase of schizophrenia. Patients with schizophrenia perform systematically worse than patients with affective disorders. One previous study suggested that both euthymic bipolar subjects and relatively stable schizophrenic subjects differed from control subjects in neurocognitive function. Among schizophrenic subjects, a generalized cognitive impairment was observed, and the degree of impairment was greater in the schizophrenics compared with the bipolar subjects. Subjects with bipolar disorder were impaired in two specific domains - verbal memory and executive function.

Comparisons of cognition between these patient groups are problematic due to the fact that differences in illness characteristics and current symptoms are not always assessed and many confound neuropsychological test performance. Bipolar disorder patients show comparatively less impairment in cognitive functions during the euthymic phase. Most researchers have reported deficits in the areas of executive functioning, episodic memory, working memory, learning and attentional abilities in schizophrenia and bipolar I disorder. These are also the cognitive functions most consistently needed for the better functioning of a person.

Various domains of cognition can easily be measured and are the key factors affecting the subject’s ability to function occupationally, socially and interpersonally. The three cognitive domains of executive functions, working memory and attentional abilities included in our study are considered as the ‘core features’ in schizophrenia. The importance of cognition in the daily life of a person and also the large number of psychiatric patients catered by the general practitioners, underscore the importance of this knowledge to all the medical personnel and not just to psychiatrists. Many a times such patients are not able to communicate their medical problems to the physicians because of their cognitive limitations, making it frustrating for the doctor.

Substantial evidence now exists to show that cognitive deficits occur in patients of schizophrenia and bipolar disorder, and some of the cognitive deficits persist to the stable phase of schizophrenia and euthymic state of bipolar disorder. But the deficits in the remitted phase of both the illnesses are not essentially similar forming a basis for the differentiation of the illnesses, in the etiology as well as, the management.

We based our study on the hypothesis that schizophrenia patients show more impairment during their stable phase, as compared to the euthymic bipolar patients and more cognitive deficits in such patients could be one of the plausible explanations for this observation. The aim of the present study was therefore to assess and compare the neurocognitive functions in the domains of executive functions, vigilance and working memory, in stable schizophrenic and euthymic bipolar patients, and also in normal healthy controls.

**Material & Methods**

This single-center study was carried out from January to November 2005. Subjects were screened consecutively from the Adult Psychiatry Out Patients Department of King George Medical University, Lucknow, on specified days.

**Subjects:** Fifteen patients diagnosed to be suffering from bipolar affective disorder currently euthymic and fifteen patients fulfilling the criteria of stable schizophrenia according to Diagnostic and Statistical Manual of Mental Disorders (DSM IV) were included, all the patients were in age group 18-45 yr, formally educated for a minimum of 8 yr and had at least 4 months of euthymia for affective disorder and, at least 6 months period free from active symptoms for schizophrenia. Euthymia was ascertained by scores on Young’s Mania Rating Scale (YMRS score < 7) and Hamilton Depression Rating Scale (HAM-D score < 7), while stable schizophrenia was ascertained by Positive and Negative Symptom Scale (PANSS score < 60) and also by HAM-D (score < 7). All patients with bipolar disorder were on a single mood stabilizer, while the schizophrenia patients were taking a single antipsychotic and dosages in both the groups were stabilized for the period of euthymia or stability, respectively. Subjects having YMRS score > 7, HAM-D score > 7, PANSS score > 60, co-morbid psychiatric illness, concurrent major illness or systemic dysfunction (including seizures), history of head injury severe enough to cause unconsciousness, history of substance abuse or dependence, history of electroconvulsive
therapy (ECT) in the past 6 months and patients taking benzodiazepines for any indication other than insomnia were excluded from the study. All the subjects were clinically assessed for intellectual capacity and those who were doubted to be mentally retarded, were subjected to formal IQ assessment by clinical psychologist and subjects with IQ < 70 were excluded from the study.

The potential cases were interviewed by a psychiatric resident, and their medical records were reviewed whenever relevant. Secondly, a consultant psychiatrist audited the first phase results and confirmed or rejected the diagnosis. Finally, two psychiatrists set the diagnosis, blind to each others classification, using written information collected about the patients. Only the patients, who received the diagnosis of stable schizophrenia or euthymic state of bipolar disorder from both the investigators, were taken. Retrospective assessments in both the groups were based on records and history given by reliable informants –patients without records or informants were not included.

Fifteen age, sex and education matched controls were taken from the friends, not the relatives of the patients, so as to provide a control sample as close to the patient group as possible, in their demographic profile. They were excluded if they ever had a history of any psychiatric illness, or a history of any substance abuse or dependence, or a history of any psychiatric illness in any of their first degree relatives and if their score on General Health Questionnaire (GHQ) was more than three.

Protocol and procedure: Informed consent was taken from all the subjects and the study protocol was approved by the ethics committee of the institution.

All the computer based cognitive tests were used and standardized for the Indian population during a multicenter pilot study and published results. The psychologist, who administered the tests in our study, was formally trained in their usage during the previous multicenter study. The patients were explained about the tests at the start and all possible queries were answered promptly. They were made to relax and asked to concentrate on the tests, as much as possible. To accomplish this, the tests were administered in a quiet room, with minimal disturbance. Each test is preceded by a mock test series to check the understanding and involvement of the patient in the test. In both the groups cognitive assessments were done between 1200 and 1600 h for all the subjects, to minimize the confounding factors of drowsiness or withdrawal symptoms, patient had not taken benzodiazepines in the preceding 8 h of cognitive assessments but had taken all other medicines as usual. The tests were conducted in a single sitting, sequentially with an interval of 15 min between each test.

Assessment was done on a semi-structured socio-demographic proforma which required patient information regarding demographic and personal details of the patients and informants, complaints of the patients, history of present illness, details of medical or surgical interventions, past history, family history, personal history, premorbid personality, details of physical examination, mental status examination and diagnostic formulation. The diagnosis was made using DSM-IV. The patients were then screened on various rating scales like Hamilton Depression Rating Scale (HAM-D), Positive and Negative Symptom Scale (PANSS) (applied only in stable schizophrenia patients) and Young’s Mania Rating Scale (YMRS) (applied only in euthymic patients) and, inclusion and exclusion criteria were applied. The patients who were included were assessed on computer based neurocognitive tests. These included Wisconsin Card Sorting test (WCST), Continuous Performance Test (CPT) and Spatial Working Memory Test (SWMT).

The controls were assessed using 12 item General Health Questionnaire (GHQ) and computer based neurocognitive tests viz., WCST, CPT and SWMT.

Spatial Working Memory Test (SWMT) – In the SWMT, which is a test of memory for spatial locations, the subject views a brief presentation of black circle on computer screen and then asked to point the location of circle after a delay of ‘0’ sec and 20 sec, randomly. During the 20 sec delay, the subject is engaged in a distraction task by asking to repeat continuously a 3 digits number, appearing on the screen.

The result in SWMT is obtained as number of correct responses and number of non-adjacent errors at 0 sec and at 20 sec delay respectively.

Continuous Performance Test (CPT) –Sustained attention, vigilance and impulse control is assessed by CPT. The test requires a participant to respond to a specified target when it is presented spontaneously within a stream of interfering visual stimuli. The task involves monitoring a random series of geometrical figures. The results obtained are in terms of correct responses, wrong responses, missed responses and the reaction or response time. In the test, target stimulus is
rare in frequency and presentation latency is brief. A total of 328 stimulus are presented, of which 28 are for practice. Stimulus duration and interstimulus latency are 50 and 1000 milliseconds respectively.

Wisconsin Card Sorting Test (WCST)25 - The WCST can be considered a measure of executive function requiring the ability to develop and maintain an appropriate problem-solving strategy across changing stimulus conditions in order to achieve a future goal. There are 4 stimulus cards which cards reflect three stimulus parameters- colour, form and number. The response cards display figures of varying forms (crosses, circles, triangles or stars), colours (red, blue, yellow or green) and number of figures (one, two, three or four). These cards are numbered from 1 to 64 on the lower left corner of the reverse side to ensure a standard order of presentation. It can be applied on subject in the age group of 6½ to 89 yr25.

Data analysis: The mean scores of the patients and the controls were compared using Student’s t - test (two tailed), \( P <0.05 \) was considered significant. Chi-square test was used to compare the socio-demographic variables of the two groups.

Results

A total of 212 patients of schizophrenia and bipolar disorder were screened and patients diagnosed as euthymic bipolar affective disorder (n=81) or stable schizophrenia (n=71) were subjected to the selection criteria. Of these, 15 patients each with stable schizophrenia, and euthymic bipolar disorder and 15 healthy controls were included. The control group (A) (n=15) had a mean age of 34.26±11.17 yr, 80 per cent of them were males and had mean years of education of 10.80 ± 2.49 yr. The bipolar euthymic group (B) (n=15) had a mean age of 34.43 ± 10.71 yr, 82 per cent of them were males and had mean years of education of 11.52 ± 2.31 yr. The stable schizophrenia group (C) (n=15) had a mean age of 34.98 ± 10.63 yr, with 11.92 ± 3.81 yr as mean years of education. There was no statistically significant difference in the three groups among these variables. In the schizophrenia group, 8 had an urban background, 2 were married, and family income of 8 patients was below Rs. 5000 / month, while the rest had more than Rs. 5000 monthly income. Of the 15 bipolar patients, 9 were urban, 5 were married and 9 had less than Rs. 5000/month family income. In the controls, 8 were urban, 5 married, and 9 had family income less than Rs. 5000/month. None of the parameters were significantly different, between any of the groups, when analysed by the chi-square test. The bipolar group had a mean duration of illness of 3.70 ± 1.23 yr, while the mean duration of illness in the schizophrenia group was 3.43±1.52 yr. There was no significant difference in the mean duration of illness among the two groups.

On WCST test the mean differences regarding categories completed and perseverative errors were found statistically significant (\( P<0.01 \)) suggesting that control subjects completed more categories and committed less perseverative errors on WCST, than the euthymic bipolar group and the stable schizophrenia group. The euthymic bipolar group completed more categories and committed less perseverative errors than the schizophrenia group and perseverative errors, but the difference was not significant (Table I).

On CPT test the mean differences show that patients with stable schizophrenia responded less correctly, committed more wrong responses and also took more time to respond as compared to the control group, as well as, the euthymic bipolar group and the difference was statistically significant (\( P<0.01 \)). The control group and the euthymic bipolar group did not show significant difference (Table II).

| Table I. Comparison of scores of different groups on Wisconsin Card Sorting Test (WCST) |
|---------------------------|---------------------------|---------------------------|
|                          | Controls (A)              | Euthymic psychiatric patients (B) | Stable schizophrenia (C) |
|                          | N=15                      | N=15                      | N=15                      |
| Perseverative errors     | 26.06±6.30                | 38.9±9.46*                | 36.93±14.18*              |
| Categories completed     | 4.70±1.81                 | 2.30±1.69*                | 2.13±1.73*                |
| Values are mean ± SD     |
* \( P<0.01 \) compared to control

| Table II. Comparison of scores on Continuous Performance Test (CPT) of different groups |
|---------------------------------|---------------------------|---------------------------|
|                                | Control psychiatric patients (A) | Euthymic psychiatric patients (B) | Stable schizophrenia (C) |
|                                | N=15                      | N=15                      | N=15                      |
| Correct responses              | 34.07±3.33                | 34.86±4.11                | 11.13±7.36**              |
| Wrong responses                | 5.27±2.41                 | 6.92±4.13                 | 10.4±12.2**               |
| Missed responses               | 10.00±3.39                | 12.5±5.01                 | 23.4±07.45**              |
| Response time                  | 74±0.09                   | 0.77±0.05                 | 91±0.22**                 |
| Values are mean ± SD * \( P<0.001 \) compared to control * \( P<0.01 \) compared to group B
On SWMT at immediate delay there was no difference in committing non adjacent errors among the three groups. At 20 sec delay, the stable schizophrenia group made less correct responses than normal controls and euthymic bipolar patients, and also committed more non adjacent errors than both the other groups (Table III).

**Discussion**

The present study was designed to assess the neurocognitive functions in euthymic patients with bipolar disorder and stable schizophrenia patients and to compare them with that of an age, gender and education matched normal control group. Patients and controls had to satisfy rigorous selection criteria for entering the study. The control group was selected from healthy volunteering friends of the patients. They were well matched for age, gender and education status so that the confounding factors for assessment of cognitive functions and functional disability may be minimized. The matching also allowed the use of raw scores of tests like WCST.

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, co-morbid psychiatric or significant physical disorders, significant substance use, use of medications associated with cognitive changes. Likewise a minimum level of cognitive functioning was ascertained by including only those patients who were formally educated for more than 8 yr. None of the patients had taken any medications on the day of cognitive assessment, so that it was ensured that the patient’s psychomotor activity and reaction was not impaired and they were not sedated.

Computer methods of assessment of cognitive function have greater reliability and objectivity.

Findings of our study showed that patients of schizophrenia had persistent cognitive deficits in all the domains viz., executive functions, sustained attention and working memory, even during the stable phase. The patients of bipolar disorder in euthymia performed poorly on the tests for executive functions. On the tests for executive functions the bipolar group was comparable to the schizophrenic group but they were qualitatively different. In SWMT and CPT, the bipolar group performed significantly better than the schizophrenic group and in fact, this group was comparable to the control group. These findings are consistent with the previous study by Altshuler et al, where stable schizophrenic subjects demonstrated a generalized cognitive impairment across most domains compared with control subjects, while euthymic bipolar subjects were significantly impaired compared with control subjects only in executive functioning (Wisconsin Card Sorting Task) and verbal memory (California Verbal Learning Test) domains. The degree of impairment was greater in the schizophrenic group compared with the bipolar subjects, in that study as well as in our study. The deficits highlight the impaired ability for planning, set shifting and problem solving in schizophrenics and bipolar patients, even during their otherwise asymptomatic phases; thus affecting their daily life. While, both the groups showed deficits; the schizophrenia patients were more affected than the bipolar patients. The deficit may be associated with a functional neuropathology in the lateral prefrontal cortex. The extradimensional shifting stage is selectively impaired by lateral prefrontal cortex lesions.

Impairment in attention or immediate memory can interfere with almost every facet of human life. Stable schizophrenic patients were specifically impaired in comparison to controls as well as euthymic subjects on continuous task (i.e. attention and concentration), however euthymic subjects performed similarly to a tightly matched normal controls on attention-concentration abilities. These findings are consistent with the previous studies. Impaired attentional ability in schizophrenia patients underscore important aspects like impaired mathematical abilities, social skills.
deficits and missing medicine dosages. No significant deficits in the attention in bipolar patients can be a possible explanation of their better interepisodic functioning, as compared to the schizophrenia patients.

Impairments in the spatial working memory are found as a core feature of schizophrenia across all phases of the illness, chronic, 1st episodes, prodromal and patients who are stable and high functioning in other cognitive domain⁴. In our study, on SWMT all the subject groups i.e., stable schizophrenic, euthymic and normal controls, were comparable at 0 sec. delay. Specific impairment was seen for correct responses and commission of non adjacent errors after a delay of 20 sec. (delayed recall) in schizophrenia. On executive function test (WCST), schizophrenic patients showed the worst performance while that of the bipolar patients was somewhat between schizophrenic and controls. The patient groups, schizophrenic as well as euthymic completed less categories i.e., performed poorly on set shifting and committed more perseverative errors than controls. Both the groups were however comparable with each other regarding these variables⁴. Spatial working memory is needed in day to day activities like walking, driving, social interactions and routine daily work. This impairment, along with the other cognitive impairments, in schizophrenics make them vulnerable to frustration and social underfunctioning.

In this study, as many confounding factors were ruled out, as possible. The patients were meticulously screened for substance use, head injury, comorbid psychiatric illness, systemic illness, electro convulsive therapy and obvious clinical intellectual impairment. The current status of the illness was ascertained by using standard tools and strict cut-offs were used to ascertain euthymia or ‘stable’ phase of schizophrenia. Moreover, the diagnostic procedure was made rigorous to avoid any diagnosis bias. The controls were also carefully chosen and they were matched for age, sex and education with the patient group. A major limitation was difference in medication regimes. Patients with bipolar disorder were taking mood stabilizers, while those with schizophrenia were taking antipsychotics, which are known to affect cognition. But the drugs were stabilized for a substantial period of time and the patients were assessed for any overt sedation or side effects due to the effect of the drugs. Though the drugs may have been affecting cognition, it was ethically not possible to take the drugs off these patients, as it increases the chances of relapse. Another limitation of the study was limited sample size. As three different groups of patients were to be assessed and the selection criteria were rigid, only 15 subjects were included in each group.

In conclusion, our study supported the view that schizophrenia and bipolar disorders are distinguishable disorders rather than being different phases of a same continuum³¹. The differences in the cognitive profiles of the two patient groups during their stable phases suggested that even after the subsidence of active symptoms, some illness process continued, which might be more marked in schizophrenia, as compared to bipolar disorders.

Our findings also indicated that cognitive deficits can serve as the endophenotype markers for these disorders as has been established recently³². Further, our study suggested cognitive dysfunctions as a possible explanation for the poorer functional outcome of patients with schizophrenia, as compared to the patients of bipolar disorders. Schizophrenia patients may thus require more intensive therapeutic plans.

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