ORIGINAL RESEARCH PAPER

Psychiatry

A COMPARATIVE STUDY OF NEUROCOGNITIVE FUNCTIONING AMONG THE PATIENTS OF THE FIRST EPISODE OF SCHIZOPHRENIA AND BIPOLAR AFFECTIVE DISORDER IN REMISSION

KEY WORDS: schizophrenia, bipolar affective disorder, cognitive impairment, first episode

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ABSTRACT

Background- It is noted that cognitive deficits are found even in remitted state of the first episode of schizophrenia but inconsistent results are found in the case of other psychotic disorders like the first episode of bipolar affective disorder.
Aims & objectives - To examine and compare neurocognitive functioning of the first episode of schizophrenia and bipolar patients in remission.
Methods- A cross-sectional study was done at the tertiary care centre of north India from December 2019 to January 2021. Patients attending OPD were screened with a specially designed proforma comprising inclusion and exclusion criteria. Those fulfilling the criteria of first episode BAD and first episode SZ as per ICD 10 were recruited in the study. The sample included remitted 50 patients each of first episode BAD, first episode SZ and 50 healthy controls. Cognitive assessment was done by using various neuropsychological tools.
Results- Both the patient's group viz. schizophrenia and bipolar affective disorder were significantly impaired in all measured cognitive functions viz. visual attention, concentration, psychomotor speed, cognitive flexibility, executive functions, verbal learning and memory, visuospatial working memory, verbal working memory, verbal fluency, verbal attention, concentration, and short-term memory than the control group.
Conclusions- Cognitive impairment exists even in the patients of the first episode of bipolar affective disorder. Quantitative differences in cognitive functions between two patients groups reflect that both the disorders are on a neurobiological continuum and cognitive impairments in both groups can be considered as potential endophenotypes.

INTRODUCTION

Neuropsychological studies have provided evidence of cognitive impairment in similar cognitive domains in patients with multiple-episode schizophrenia (SZ) and bipolar affective disorder (BAD). The differences between impairments in these disorders are quantitative rather than qualitative. [1,2] Evaluation of cognitive functioning in the first episode, not only minimizes the selection bias but will also exclude the confounding effects of anti-psychotic medications used in multiple-episode patients.

There are strong genetic influences on the risk for BAD and SZ, and cognitive impairments have been proposed as potential endophenotypes for these disorders. Family studies of BAD suggest the executive function and processing speed as endophenotypes markers for the vulnerability to BAD. [3, 4] Linkage studies have identified candidate regions for susceptibility genes for each BAD and SZ with regions for SZ overlapping those for BAD. [5,6]

The array of studies showed interesting results with oligodendrocyte and myelin dysfunctions in prefrontal cortices in both BAD and SZ when compared to healthy controls. [7] Structural brain abnormalities in BAD are similar to those of SZ especially in the frontal lobe [8, 9] with cerebellar atrophies. [10]

In the present study, we examined whether cognitive impairment exists in the first-episode BAD patients and individuals with first episode SZ differ from individuals with the first-episode BAD with respect to the type and pattern of neurocognitive deficits.

MATERIAL &METHODS

Subjects-

Patients of first episode mania with psychosis (first episode BAD) with score < 6 (remission) on Young Mania Rating Scale (YMRS) [11], score < 8 on the Hamilton Depression Rating Scale (HDRS) [12], and patients of first episode SZ with Brief Psychiatric Rating Scale [13] (BPRS) score less than 30 (remission) [14] were included in this study. Patients were diagnosed as per ICD-10 criteria with the total duration of illness within 2 years. Patients were of age group 18-50 years of age of either gender with at least 8 years of school education. Patients who were not willing to participate, uncooperative, with significant physical or neurological illness, having dependence on any substance (except nicotine), colour blindness, learning disability, had electroconvulsive therapy during the last 6 months, and taking sedative/hypnotics except for insomnia were excluded from the study. Fifty subjects who were cooperative and willing to participate, matched for age, sex, and education were taken from the friends or other caregivers who were not relatives of patients. Subjects from the control group were excluded if they had significant physical or neurological illness, substance dependence (except nicotine), color blindness, history of any psychiatric illness in their first degree relatives, and if the score on the General Health Questionnaire (GHQ-12) was more than two. [15] GHQ used in this study is the shortest 12 items screening tool originally developed by Goldberg, to assess the risk of developing psychiatric illness. It is widely used across the Globe by researchers as it is reliable and well-validated. [16]

Study Design

It was a cross-sectional study done at the tertiary care centre

of north India during the period December 2019 to January 2021 after getting approval from the ethical committee of the institution. Patients attending OPD were screened with a specially designed proforma comprising inclusion and exclusion criteria. Those fulfilling the criteria of first episode BAD and first episode SZ as per ICD 10 were recruited in the study. The sample included 50 patients each of first episode BAD and first episode SZ with 50 healthy controls. The socio-demographic and clinical details of all subjects were noted. All the subjects including controls were rated on HDRS and YMRS. The patients with SZ were also rated on BPRS. The cases and controls were administered a battery of tests to assess their neurocognitive functioning. Six neuropsychological tests were used to assess various cognitive domains. Visual attention, concentration, psychomotor speed was assessed with Trail Making Test-A (TMT-A) and cognitive flexibility and executive functions were measured by Trail Making Test-B. [17] Verbal learning and memory were assessed by the Verbal Learning Memory Test in which a story containing 23 bits of information is being read by an examiner [18] visuospatial working memory was assessed by Visuospatial Working Memory Matrix (VWWM) test [19] verbal fluency by Controlled Oral word Association (COWA) test,(20) verbal attention, concentration by Forward Digit Span Test (FDST) and short term memory, verbal working memory was assessed by Backward Digit Span Test. [21] Response inhibition was assessed by Stroop Color Test. [22,23]

STATISTICAL ANALYSIS

Statistical analysis was done by using a statistical package for the social sciences (SPSS) version 20.0. Group comparison was done with the help of 'independent t-test' and 'chi squire test. One way ANOVA was applied for the group comparison of age. Group comparison of neurocognitive tests was done by using non-parametric test i.e. Independent-Samples Kruskal-Wallis Test. Further group differences were obtained with the help of post-hoc analysis.

RESULTS

Table 1 shows the sociodemographic details of all participants. All three groups were comparable regarding age distribution. Mean age for patients with SZ, BAD and control group was 28.5, 27.7, and 26.2 years respectively (df= 2.147; F=2.1, p=0.12). Most of the subjects were married, unemployed males with education above the middle class. For most of the subject's monthly income of the family was above 15,000 rs, most of them were Hindu from rural background.

Table 1: Socio-demographic details of SZ, BAD and control group

	SZ (n=50)	BAD (n=50)	Control (n=50)	X(df)	P value
Sex 1. Male 2. Female	34 (68%) 16(32%)	39(78%) 11(22%)	35(70%) 15(30%)	1.4(1)	0.49
Marital status 1. Married 2. Unmarried 3.Widow/ separated/ divorced	27(54%) 21(42%) 2(4%)	31(62%) 18(36%) 01(2%)	29(58%) 20(40%) 1(2%)	1.01 (4)	0.90
Occupation 1. Govt. service 2. Businessman 3. Semi/unskilled worker 4. Housewife/Student 5. Unemployed	6(12%) 1(2%) 13(26%) 5(10%) 25(50%)	19(38%) 1(2%) 10(20%) 9(18%) 11(22%)	25(50%) 1(2%) 12(24%) 6(12%) 6(12%)	4.9(8)	0.76
Education 1. Middle to secondary 2. Graduate/post graduate	37(74%) 13(26%)	19(38%) 11(22%)	38(76%) 12(24%)	1.6(2)	0.44
Monthly income of family (in rupees) 1. <6000 2. 6001-15000 3. >15000	32(4%) 10(20%) 8(76%)	2(4%) 3(6%) 45(90%)	1(2%) 4(8%) 45(90%)	6.2(4)	0.18
Religion 1. Hindu 2. Muslim 3. Others	42(84%) 7(14%) 1(2%)	44(88%) 5(10%) 1(2%)	41(82%) 7(14%) 2(4%)	1.03(4)	0.90
family type 1. Nuclear 2. Nuclear extended 3. joint	13(26%) 3(6%) 34(68%)	19(38%) 4(8%) 27(54%)	24(48%) 7(14%) 19(38%)	8.8(4)	0.063
Locality 1. Urban 2. Rural	15(30%) 35(70%)	13(26%) 37(74%)	13(26%) 37(74%)	0.26(1)	0.87

Abbreviations: BAD- Bipolar Affective Disorder, x- chi test, df- degree of freedom, p-Sig. (2-tailed); 0.05

Table 2 shows the Clinical details of the SZ and BAD groups. No significant differences among the groups were found in different clinical variables. Mean duration of illness for patients with SZ and BAD was 12.36±5.09 and 2.9±1.26 months respectively. Onset for most of the SZ patients was insidious while in BAD group it was acute in all cases. Patients with BAD needed more hospitalization than the patients with SZ in their first episode (p=0.06). Positive family history was present in almost half of the patients (53.33% of SZ and 45% of the bipolar group) though there was no group difference noted (p=0.36). Interestingly sixty-six percent of patients with BAD and 82% of patients with SZ contacted to a faith healer before seeking proper psychiatric treatment. Almost twelve percent were contacted to a physicians including a Neurologist. Only 0.09% of patients contacted psychiatrists directly. Antipsychotics used were olanzapine (48%), risperidone (41%), haloperidol (7%), and trifluoperazine (4%). Among the benzodiazepines, diazepam and clonazepam were used. Sodium valproate was the most commonly used mood stabilizer followed by lithium in cases of first episode BAD. Only ten patients of SZ were on sodium valproate.

Table 2: Clinical profile of Patients

	SZ (n=50)	BAD (n=50)	X(df)	P value
Type of onset 1. Acute 2. Insidious	2(4%) 48 (96%)	50(100%) 0(0%)	9.2(1)	0.001
Family history 1. Yes 2. No	28(56%) 22(44%)	21(42%) 29(38%)	1.9(1)	0.16
First contact 1. Faith healer 2. Physician/Neurologist 3. Psychiatrist	41(82%) 7(14%) 2(4%)	33(66%) 10(20%) 7(14%)	4.1(2)	0.12
Antipsychotic used 1. Olanzapine 2. Risperidone 3. Haloperidol 4. Trifluoperazine	22(44%) 20(40%) 5(10%) 3(6%)	26(52%) 21(42%) 2(4%) 1(2%)	2.6(3)	0.44
Mood stabilizer 1. None 2. Lithium 3. Sodium Valproate	41(82%) 0(0%) 9(18%)	0(0%) 18(36%) 32(64%)	71.2(2)	0.001

Abbreviations: BAD- Bipolar Affective Disorder, x- chi test, df- degree of freedom, p-Sig. (2-tailed); 0.05

Table 3 shows the comparison of cognitive functioning in all three groups. We found statistically significant difference in neurocognitive functioning among patients group and control group. On post hoc analysis, statistically significant difference was found among patients of schizophrenia and bipolar affective disorder only on four tests viz. TMT-A, COWA Total, SCT Total Error and VLMT.

Table 3- Comparison of cognitive functioning in all three groups

TEST	SZ (SD)	BAD(SD)	Control (SD)	Independent- Samples KruskalWallis Test, F	Post-hoc, P value
TMT-A	68.20(12.90)	66.17(17.9)	50.48(18.0)	41.8(2)	SZ–BAD **0.021** SZ–control 0.001 BAD-control 0.001
TMT-B	111.78(14.6)	107.65(26.7)	89.97(29.9)	40.22(2)	SZ–BAD 0.06 SZ–control 0.001 BAD-control 0.001
COWA Total	8.78(2.0)	9.91(1.2)	20.28(4.1)	113.9(2)	SZ–BAD **0.025** SZ–control 0.001 BAD-control 0.001
VWWM	1.28(1.13)	1.92(1.84)	4.87(2.2)	82.73(2)	SZ–BAD 0.074 SZ–control 0.001 BAD-control 0.001
SCT-1	31.45(5.4)	31.35(2.7)	26.82(4.7)	130.68(2)	SZ–BAD 0.40 SZ–control 0.001 BAD-control 0.001
SCT-2	34.90(6.7)	34.30(3.40)	30.07(5.7)	22.8(2)	SZ–BAD 0.55 SZ–control 0.001 BAD-control 0.001
SCT-3	42.30(10.7)	40.35(6.6)	34.82(6.9)	21.0(2)	SZ–BAD 0.98 SZ–control 0.001 BAD-control 0.001
SCT Total Error	6.6(3.0)	3.9(2.6)	2.33(2.1)	55.79	SZ–BAD **0.001** Sz–control 0.001 BAD-control 0.001
SCT Total Time	108(22.0)	106.02(11.9)	91.70(16.5)	27.11(2)	SZ–BAD 0.64 SZ–control 0.001 BAD-control 0.001
VLMT	9.8(1.7)	12.8(2.3)	15.47(2.2)	100.8(2)	SZ–BAD **0.001** SZ–control 0.001 BAD-control 0.001
FDST	4.0(0.5)	4.2(0.70)	6.18(.813)	115.47(2)	SZ–BAD 0.11 SZ–control 0.001 BAD-control 0.001
BDST	2.5(0.53)	2.8(0.89)	4.72(.715)	107.29(2)	SZ–BAD 0.27 SZ–control 0.001 BAD-control 0.001

Abbreviations:
TMT-A=trail making test-A, TMT-B=trail making test-B, SCT-1=stroop color test-1, SCT-2=stroop color test-2, SCT-3=stroop color test-3, VLMT=verbal learning & memory test, VWWM=Visuospatial working memory test, COWA= controlled oral word association, FDST=forward digit span test, BDST=backward digit span test

DISCUSSION

It was evident from past studies that a pattern of neuro cognitive impairment in remitted patients of SZ and BAD is not consistent. [24, 25] Cognitive impairment in patients with first-episode SZ and BAD is quantitative rather than qualitative. On application of neuropsychological tests on various domains like visual attention, concentration, psychomotor speed, cognitive flexibility, executive functions, verbal learning and memory, visuospatial working memory, verbal working memory, verbal fluency, verbal attention, concentration, and short-term memory, both the patient groups were impaired significantly in comparison to control group.

A meta-analysis done by Mesholam-Gately et al. (2009) and Bora and Pantelis et al. (2015) reported medium-to-large impairments in the first episode SZ group across 10 neurocognitive domains in comparison to the control group which supports our findings. [24,26]

Lee et al. (2014) in his meta-analysis reported medium to large deficits in psychomotor speed, attention and working memory, and cognitive flexibility and smaller deficits (ES 0.20-0.49) in the domains of verbal learning and memory, attentional switching, and verbal fluency in the first episode BAD patients compared to controls which corroborate our results. [25] Deficits in response inhibition were reported only in non-euthymic cases. There was no deficit reported in visual learning and memory and verbal fluency in acute as well as remission phase of patients of first episode BAD compared with controls that were contrary to our findings.

In our study, both the groups (SZ and BAD) performed similarly in most of the neuropsychological tests ($p \geq 0.05$) except for the test of visual attention, concentration, psychomotor speed (p-0.021), verbal fluency (p- ≈0.02), verbal learning, and memory (p- ≈0.001), and response inhibition (p-≈ 0.001). A meta-analysis (included 14 studies and 802 and 605 patients of the first episode of SZ and BAD respectively) done by Bora et al. (2015) found similar results in the domain of psychomotor speed, verbal fluency, verbal learning, and memory in his meta-analysis in which he included fourteen studies. [3]

We found that Patients with BAD performed significantly better than the SZ on verbal learning and memory, which was

consistent with the results of a study done by Hill et al. (2009) they reported that the performance on tests of executive functioning was poor in the SZ group than in the BD group [27,28] but Barrett et al. (2009) reported no significant difference between two groups which was contrary to our findings. [29] Barrett et al. (2009) found that the SZ group performed significantly poor than a BAD group on verbal fluency, which supports our study. However, the results of Zanelli et al. (2010) were contrary to our results. [30]

Barrett et al. (2009) and Dickerson et al. (2011) did not found any difference in cognitive flexibility in both the groups that were similar to the results of our study, though Hill et al., (2009) did found a difference in the same domain.

Pradhan et al. (2008) found that patients with multi-episode SZ consistently performed worse than patients with BAD. [2] On a direct comparison of the two groups, there was no significant difference found on neuropsychological performance except for semantic fluency and verbal learning and memory test.

Medial temporal and the frontal lobe are related to the underlying neurobiological substrates for deficits in verbal learning and memory and both of these brain regions are structurally and functionally impaired in SZ, as well as in patients with BAD but might be more in the SZ group [31], which may be a possible explanation of poor performance in verbal learning and memory test than the patients with bipolar disorder. Impaired encoding and retrieval implicate the abnormal involvement of the prefrontal cortex whereas accelerated forgetting implies impaired consolidation attributable to medial temporal lobe dysfunction. [32]

The similar neurocognitive impairment among patients of SZ and BAD was not unexpected. The notion that SZ and BAD are on same the neurobiological continuum, also supported by genetic, epidemiological, phenomenological, and neurobiological studies. So, it has been suggested that impaired cognitive functions in both disorders follow a common pathway. The similarities in cognitive de cits are thought to re ect common or converging neurobiological origins of SZ and BAD. [33] Goswami et al. (2006) suggested that frontal/prefrontal dysfunction appears to be the most likely mechanism that could account for the similarities in cognitive impairment among SZ and bipolar disorder. [34] Cognitive impairment in memory of both disorders could be explained based on similar pathology in the temporal lobe. However, the temporal lobe abnormality reported in the literature was not consistent in a bipolar group, so it may be possible that the temporal lobe dysfunction is more specific to the SZ group. [35]

Implications

It's always an interesting issue to know whether cognitive impairment in psychotic disorders is universal over all cognitive domains or to a particular domain. Results of this study showed generalized cognitive impairment across all domains in psychosis. Impairment in the cognitive domain indicates core deficits in underlying brain regions or specific neural pathways. Hence it has got a significant clinical implication in diagnosis, management, prognosis, and genetic research. It is now a well-established fact that poor neuropsychological functioning also leads to poor functional outcomes in SZ. [36] Recent researches in patients with BAD reported reduced functional outcomes with increasing neurocognitive deficits. [37, 38, 39] As neurocognitive deficits are the important cause of morbidity in psychosis, neurocognition should get more attention as the treatment target in patients with SZ and psychotic mood disorder.

Limitations and future directions

It was a cross-sectional study with a small sample size. The results would be better if we planned a longitudinal study. All the patients were on medication, so the effect of the medication cannot be denied. However, previous studies reported, there was no significant difference in cognitive impairment in drug-naive and patients who were on medication in SZ and bipolar group. [40, 41] The significant differences in the mean duration of illness in SZ and BAD groups (12.36±5.09 and 2.9±1.26 months respectively, p=0.001) could be a confounding factor. There should be a study including SZ, mood disorder with psychotic feature and mood disorder without psychotic feature, so that we can conclude that whether the nonpsychotic mood disorder is on the neurobiological continuum or not like the psychotic mood disorder. To substantiate the finding of this study neuroimaging studies are required.

CONCLUSION

Patients with SZ and BAD showed neurocognitive impairment in almost all neurocognitive domains. The significant difference in groups was noted in verbal learning and memory, semantic fluency, and response inhibition. Patients with SZ and BAD were showing a similar pattern of neurocognitive impairment with more impairment in SZ. The difference in neurocognitive impairment among groups was quantitative rather than qualitative which re ects that both disorders were on a continuum. The presence of existing cognitive deficits even in the first episode of BAD patients suggests that neurodevelopment factors play a crucial role not only in SZ but in BAD patients also. Cognitive impairments in SZ and BAD can be considered as potential endoph enotypes for these disorders.

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