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A Comparative Study of Cognitive Flexibility Among First Episode and Multi-Episode Young Schizophrenia Patients

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Abstract

Background: Although cognitive deficits are not yet included in the diagnostic criteria for schizophrenia, they are considered a core feature of schizophrenia symptomatology. Cognitive flexibility is a core executive function. This study was planned to assess and compare impairment in cognitive flexibility in young first episode (FE) and multi episode (ME) schizophrenia patients.
Methods: We recruited 100 young (aged from 18 to 35 years) schizophrenic outpatients of either sex (diagnosed as per ICD-10 criteria) and 50 control subjects for this cross-sectional study. The cases were assessed with study instruments like the PANSS for psychopathology and the Trail Making Test-B (TMT-B) for cognitive flexibility.
Results: FE patients had significantly more negative symptom scores (p=0.039) and general psychopathology scores (p=0.0001) than ME patients. FE patients performed better than ME patients on TMT-B, but there was no significant difference between the two groups. Control group performed significantly better than both patient groups (p=0.0001).
Conclusion: Deficits in cognitive flexibility, which is a core executive function, are already present in first episode schizophrenics and may be the intrinsic part of schizophrenia. This supports a neurodevelopmental origin of schizophrenia (German J Psychiatry 2013; 16(4): 130-136).

Keywords: cognitive flexibility; trail making test; schizophrenia

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Introduction

Schizophrenia is a debilitating and poorly understood psychiatric disorder of uncertain aetiology. It affects 26 million people worldwide, is the cause of moderate to severe disability in 60% of cases (Eaton et al., 2008) and ranks fifth among men and sixth among women as a cause of years lived with disability (Lora et al., 2012).

It has been observed that patients suffering from schizophrenia show a generalized impairment across a range of cognitive abilities. The evidence also strongly supports the view that social deficits and functional outcome in schizophrenia directly relate to impairment in cognitive abilities. Although cognitive deficits are not yet included in the diagnostic criteria for schizophrenia (APA, 2000), they are considered a core feature of schizophrenia symptomatology (Elvevag & Goldberg, 2000). The DSM-IV-TR and ICD-10 descriptions of schizophrenia include several references to cognitive impairment, but neither the diagnostic criteria nor the sub-typology of schizophrenia includes a requirement of cognitive impairment.

It has been repeatedly found that patients with schizophrenia show a generalized impairment across a range of cognitive abilities including attention, processing speed, verbal learning and memory, working memory and executive functions (Elvevag & Goldberg, 2000; Heinrichs & Zakzanis, 1998; Mesholam-Gately et al., 2009).

One core skill of executive functions is cognitive flexibility. It is the ability to nimbly adjust to changing demands and priorities as per situation and requires considering new or different perspectives, adjusting to change (Scott et al., 1962).

The mechanisms underlying cognitive flexibility have been explored extensively using various methods. Studies using functional magnetic resonance imaging (fMRI) have revealed a variety of distinct regions of the brain that work in concert from which flexibility could be predicted reliably, including the prefrontal cortex (PFC), basal ganglia, anterior cingulate cortex (ACC), and posterior parietal cortex (PPC) (Leber et al., 2008; Morice et al., 1990).

Cognitive flexibility is important for creativity, for learning and redirecting our attention. It is intimately related to social cognition and interpersonal relationship. As social cognition includes functions such as ability to understand other peoples´ beliefs and intentions, social perception, emotional processing, and working memory (Burns, 2006; Green et al., 2005), any change in cognitive flexibility might reflect upon changes in social cognition. Therefore, hypothetically, improvement in cognitive flexibility may improve social cognition in patients suffering from schizophrenia and vice versa. In this backdrop, we planned this study to assess impairment in cognitive flexibility in young schizophrenics and to compare it in First episode (FE) and multi-episodes (ME) schizophrenia patients.

The main objectives for this study were formulated to assist in the development of phase-appropriate cognitive remediation interventions.

Methods

In this cross-sectional study, we recruited 100 young schizophrenic outpatients (aged from 18–35 years and diagnosed as per ICD-10 criteria) and 50 control subjects (aged from 18–35 years)

The first study group included 50 patients with schizophrenia who were experiencing their first psychotic episode (the FE schizophrenia group) and had received less than 12 weeks of cumulative life-time neuroleptic treatment in the past (Liebermann, 1993; Hutton et al., 1998). The second group included 50 patients with schizophrenia who had experienced more than one acute episode of psychosis and had been treated as inpatient more than once for an acute relapse in past (the ME schizophrenia group). Their first admission to hospital for a psychotic episode had taken place more than 3 years before study entry. An "acute episode" necessitating hospitalization was defined as a psychotic episode by a senior psychiatrist (Addington & Addington, 1999).

Only those patients who were on regular medication intake during the preceding month (as verified by the clinical staff and/or a family member) and having a positive symptom score ≤20 on the Positive and Negative Syndrome Scale (PANSS) for schizophrenia were included (to eliminate patients in acute psychotic state).

The PANSS (Kay et al., 1987) is used for the assessment of positive and negative symptoms of schizophrenia. The PANSS includes 30 items on three subscales: seven items covering positive symptoms (e.g. delusions and hallucinations), seven covering negative symptoms (e.g. blunted affect) and 16 covering general psychopathology (e.g. guilt, uncooperativeness). Each item scored on a seven point. The positive and negative subscales each range from 7 to 49, and the general psychopathology scale ranges from 16 to 112. Reliability for each scale is fairly high, with excellent internal consistency and inter-rater reliability. The validity is also good, based on correlation with other symptom severity measures and factor analytic validation of the subscales.

Patients having history of any significant medical and neurological illness, history of significant head injury, any co-morbid psychiatric illness, mental retardation (based on medical records or clinical assessment conducted prior to inclusion in study), current & past history of substance dependence were excluded.

The control group included 50 normal and healthy young subjects of either sex who were recruited from hospital staff and bystanders of hospitalized patients. A careful history of lifetime psychiatric disorder in any of the first-degree relatives of controls was taken to ensure that there was no genetic loading in the subjects.

The study was approved by the institutional ethics committee. Written informed consent was taken from all subjects prior to inclusion in the study. A screening performa was used to satisfy all selection criteria (including the PANSS for patient groups). Sociodemographic data (name, age, sex, marital status, education, occupation, monthly income, religion, type of family, locality and address of the participant) and clinical profile including total duration of illness, type of onset, age of onset, history of past psychiatric illness, family history, first contact for treatment, treatment status, type of treatment given and response were recorded. Subjects were assessed by using the Trail Making Test-B (TMT-B; Army Individual Test Battery, 1944; Reitan et al., 1958; Tombaugh, 2004).

The TMT-B assesses an individual's cognitive flexibility (Reitan & Wolfson, 1985). Participants connect alternate letters with increasing numbers (e.g., 1, A, 2, B, 3, C….). Performance is indexed using the time to complete the task in comparison to a similar age, years of education, and gender comparison group (Lezak et al., 2004).

Statistical analysis was done by using SPSS 20.0. A group comparison for sociodemographic variables was done by using the t test for independent samples and the chi-square test. For the group comparison of age, one way ANOVA was applied.

Table 1. Comparison of age in FE schizophrenia, ME schizophrenia and controls

Variable	Mean ± SD	F	*p*
Age			
FE (n=50)	27.5 ± 4.9		
ME (n=50)	28.1 ± 4.4	2.73	0.068
Control (n=50)	25.9 ± 5.6		

SD, standard deviation

Table 2. Sociodemographic profile of FE, ME schizophrenic patients and controls

Variables	FE (n=50)	ME (n=50)	Controls (n=50)	X^2 (df)	*p*
Sex					
Male	37	43	48	2.46 (2)	0.292
Female	13	7	12		
Marital Status					
Married	29	25	25	6.79 (4)	0.148
Unmarried	21	22	25		
Divorced/Separated	0	3	0		
Occupation					
Unemployed (including house wives)	16	16	16		
Retired Pensioners					
Professional	0	0	0	0.26 (6)	1.000
Businessmen	8	7	8		
Farmer / Skilled worker / Semi skilled	4	5	5		
worker / unskilled worker	22	22	21		
Education					
Up to Middle	9	15	10	2.81 (4)	0.590
Middle to Sr. Secondary	28	26	27		
Graduate / Post Graduate	13	9	13		
Income					
Nil – 6000	16	19	15	2.10 (4)	0.717
6001 – 15000	16	19	18		
>15000	18	12	17		
Religion					
Hindu	44	44	44	7.20 (4)	0.126
Muslim	6	3	6		
Others	0	3	0		
Family					
Nuclear	25	25	26	0.43 (4)	0.931
Nuclear Extended	2	2	3		
Others	23	23	21		
Locality					
Urban	19	20	20	0.56 (2)	0.972
Rural	31	30	30		

X^2, chi-square; df, degrees of freedom

We could not apply an ANOVA for statistical analysis of the TMT-B because basic assumption of the ANOVA was violated (i.e., normal distribution and homogeneity of variance). Therefore, group comparisons for TMT-B were done by using a non-parametric test, the independent samples Kruskal-Wallis test. Further group differences were obtained by using a *post hoc* analysis.

All groups were comparable regarding age distribution. The mean age of the first episode schizophrenia (FE), the multi-episode schizophrenia (ME) and the control group was 27.54, 28.10 and 25.86, respectively. On application of one-way ANOVA, no significant differences were found between groups (p=0.068; Table 1). The groups were comparable on all the sociodemographic variables, as shown in Table 2. There were no significant differences between the groups regarding the use of antipsychotics (olanzapine and risperidone), trihexyphenidyl and benzodiazepines.

On group comparison, a significant difference was found between all three groups (FE, ME and control group; p=0.0001). Further, on *post hoc* analysis we found that the FE group performed better than the ME patients but there was no significant difference (p=0.361). The control group performed significantly better than both patient groups (FE group and ME group; p=0.0001).

Table 3. Comparison of clinical variables between FE and ME schizophrenic patients

Variable	Mean ± SD		t (df)	*p*
	FE (n=50)	ME (n=50)		
Total duration of Illness (months)	11.4 ± 5.52	79.6 ± 41.57	11.49 (50.73)	0.0001**
Age at onset (years)	26.3 ± 4.82	21.5 ± 4.46	5.19 (98)	0.0001**
Duration of untreated illness (months)	8.9 ± 5.49	7.8 ± 8.46	0.79 (84.01)	0.434
Total No. of episodes	-	2.8 ± 1.57	7.92 (49)	0.0001**

df, degrees of freedom; SD, standard deviation

Table 4. Comparison of clinical variables between FE and ME schizophrenic patients

Variables	FE (n=50)	ME (n=50)	Value (df)	*p*
Type of Onset				
Acute	22	19	0.37 (1)	0.542
Insidious	28	31		
Past History				
Present	5	48	74.23 (1)	0.0001**
Absent	45	2		
Family History				
Present	8	9	0.07 (1)	0.790
Absent	42	41		
Type of Therapy				
Atypical	50	50		
Typical	0	0		

**p value<0.001; df, degrees of freedom

Table 5. Comparison of PANSS scores between FE and ME schizophrenic patients

Variable	Mean ± SD		t (df)	*p*
	FE (n=50)	ME (n=50)		
Positive score	14 ± 2.54	13 ± 3.85	1.59 (84.79)	0.114
Negative score	16.9 ± 4.82	14.8 ± 5.32	2.089 (98)	0.039*
General psychopathology score	32.9 ± 7.61	27.5 ± 6.07	3.94 (98)	0.0001**
Total score	63.9 ± 11.28	55.3 ± 12.40	3.62 (98)	0.0001**

df, degrees of freedom; SD, standard deviation; *p value<0.05; **p value<0.001

Discussion

The main focus of present study was to assess impairment in cognitive flexibility in young FE and ME schizophrenics and to compare it with controls.

The three groups in the study were comparable on sociodemographic data. No significant differences were found on age, sex, marital status, education, occupation, income, socioeconomic status, family type, religion and locality. Although matching on education is a debatable issue, as noted in a meta-analysis (Snitz et al., 2006) that assuming schizophrenia as a neurodevelopmental disorder, matching patients and normal controls on education may cause mismatching of theoretically expected cognitive ability. However, in our study, it was found comparable by default.

There was a statistically significant difference between both groups in age of onset (Table 3).The mean age of onset in the ME group (21.52 ± 4.46) was earlier as compared to the FE group (26.34 ± 4.82). This may be due to outliers in the sample, but several studies have depicted that early age of onset correlates well with more severe psychopathology and more psychotic episodes (Hoff et al., 1996; Johnstone et al., 1989; Rajji et al., 2009). However, we cannot comment on the future course of patients in the FE group.

No significant difference was found in both patient groups for duration of untreated illness (p=0.434). Hoff et al. (1996) observed no significant correlations between duration of untreated illness and the severity of either cognitive or structural brain deficits at baseline. However, a study suggested that untreated psychosis compromises some aspects of cognitive function and early treatment of psychosis could help to reduce the prominent cognitive deficit in first-episode schizophrenia (Amminger et al., 2002).

No statistically significant difference was found in type of onset between groups (p=0.542; Table 4). There was no family history of any psychiatric illness in most of patients and difference found in both the groups in this regard was insignificant (p=0.749).

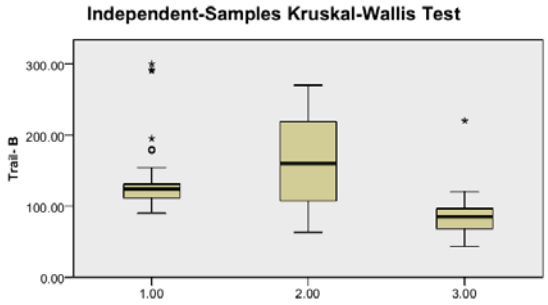
On comparison of the Positive and Negative Syndrome Scale (PANSS) scores, statistically significant differences were found in negative scores, general psychopathological scores, total PANSS scores. All mean scores were higher in the FE group (Table 5). No significant differences were found for the positive scores between both groups (p=0.114), but patients in the FE group scored higher.

Table 6. Comparison of medication exposure between FE and ME schizophrenia

Medications	FE (n=50)	ME (n=50)	X^2 (df)	*p*
Olanzapine				
Yes	20	17	0.39	0.534
No	30	33	(1)	
Risperidone				
Yes	30	29	0.04	0.839
No	20	21	(1)	
Trihexyphenidyl				
Yes	37	36	0.05	0.822
No	13	14	(1)	
Benzodiazepines				
Yes	30	35	1.09	0.295
No	20	15	(1)	
Fluoxetine				
Yes	6	9	0.71	0.401
No	44	41	(1)	

df, degrees of freedom; X^2, chi square

Figure 1. Box-plot diagram for the TMT-B test. 1.00 – FE, 2.00 – ME, 3.00 – controls



These findings support a study by Maurer et al. (1993) who used a new standardized interview for the retrospective assessment of onset and early course of schizophrenia (IRAOS) to study the influence of age and sex on time of onset and psychopathology before first admission in 267 schizophrenic patients admitted for the first time. They found that schizophrenia began with negative symptoms in 70% of cases, appearing two to six years before admission. Both positive and negative symptoms accumulate exponentially. They also found a longer period of negative symptoms before first admission in late-onset schizophrenia in women.

On the domain of cognitive flexibility in both patient groups, there was significant impairment as compared to healthy controls (Table 7). Similar results were found in several studies, which compared cognitive flexibility, planning and sequential behavior (Braw et al., 2008; Chan et al., 2006; Gonzalez-Blanch et al., 2007; Hutton et al., 1998; Mohammed et al., Moritz et al., 2002; 1999; Rajji et al., 2009; Riley et al., 2000; Rubin et al., 1995; Sobizack et al., 1999; Williams et al., 2008;). However, no group differences were also found by Saykin et al. (1994).

Very few studies have compared executive function, particularly cognitive flexibility, between first episode and multiple episode schizophrenia patients. Researchers have reported superior performance among first episode patients on the Wisconsin Card Sorting Test (WCST; Braw et al., 2008; Townsend & Norman, 2004), while Rubin et al. (1995) described equal performance between patient groups when comparisons were made using the WCST and the TMT-B. In our study, the FE group performed better on the TMT-B than the ME group patients; however, the difference was not significant (p=0.36; Table 8).

Table 7. Independent samples Kruskal-Wallis test for TMT-B in FE, ME schizophrenic patients and controls

Groups (N)	Mean ± SD	Test Statistics	df	Asymp. Sign. (2 sided Test)
FE (50)	132.6±46.34			
ME (50)	164.9±62.56	67.80	2	0.0001**
Control (50)	84.6±27.18			

SD, standard deviation; df, degrees of freedom

Table 8. Post hoc analysis

Sample1–Sample2	Test Statistic	Std. Error	Std. Test Statistic	p	Adj. p
Control–FE	54.1	8.7	6.2	0.0001	0.0001**
Control–ME	67.6	8.7	7.8	0.0001	0.0001**
FFE–ME	-13.5	8.69	-1.6	0.12	0.36

SE, standard error

This suggests that certain cognitive deficits are intrinsic to schizophrenia and present in first episode of illness itself. Secondly, the insignificant difference in performance of both groups on TMT-B as a test of cognitive flexibility implies that such deficits remain relatively stable over the course of schizophrenia. These findings of our study appear to be consistent with the view of schizophrenia being a static encephalopathy rather than a degenerative process and lend support to neurodevelopmental hypothesis of schizophrenia (Jindal & Keshavan, 2008; Marenco & Weinberger, 2000).

Another important implication of our study is that, as cognitive flexibility has been implicated in social cognition, any magnitude of improvement in cognitive flexibility may indirectly improved social cognition, which is largely impaired in schizophrenia. Cognitive remediation therapies like specific cognitive flexibility rehabilitation (Delahunty et al., 1993) might help in achieving this in schizophrenia patients. However, our small sample size and the cross-sectional study design limit the generalization of our results.

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