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# A comparative study of childhood/adolescent and adult onset schizophrenia: does the neurocognitive and psychosocial outcome differ?

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ABSTRACT

*Aims & Objectives:* The present study aimed to evaluate the neurocognitive functioning and psychosocial outcome (in terms of social functioning, disability and internalized stigma) in patients with schizophrenia with childhood/adolescent onset (age of onset ≤18 years) and adult onset (> 18years) schizophrenia and to evaluate the effect of neurocognitive impairment on the outcome variables in patients with youth and adult onset schizophrenia.

*Methodology:* 34 patients with youth onset schizophrenia (Group-I) and 56 patients with adult onset schizophrenia (Group-II), who were currently in clinical remission were assessed on a comprehensive neurocognitive battery,Positive and Negative syndrome Scale (PANSS), Global Assessment of Functioning Scale (GAF), Indian Disability Evaluation and Assessment Scale (IDEAS),Social and Occupational Functioning Assessment Scale (SOFS) and Internalised Stigma of Mental Illness Scale (ISMIS).

*Results:* On neurocognitive domains (after adjusting for co-variates) significant differences were noted between the two groups in terms of processing speed (TMT-A; I > II; p-value -0.009), verbal fluency (COWA;I < II;p-value-0.001) and cognitive flexibility (TMT-B; I > II; p -0.031). Compared to patients with adult onset schizophrenia, patients with childhood & adolescent onset schizophrenia had significantly higher PANSS negative score, higher disability in all domains of IDEAS, poorer socio-occupational functioning, low global functioning and reported more stigma in the domains of alienation and discrimination.In patients with childhood & adolescent onset schizophrenia, higher deficits in the processing speed and verbal fluency were associated with significantly lower socio-occupational functioning and higher disability; higher executive dysfunction was associated with higher internalized stigma. Among patients with adult onset schizophrenia, higher disability was related to executive dysfunction only and higher stigma was associated with poor cognitive processing, selective attention and poor executive functioning.

*Conclusions:* The present study suggests that compared to adult onset schizophrenia, patients with childhood & adolescent onset schizophrenia have more deficits in neurocognition, have higher level of disability, poorer socio-occupational functioning and have higher level of self-stigma.

## 1. Introduction

Schizophrenia is a heterogeneous disorder with multiple facets to its presentation. Longitudinal studies have revealed that incidence of schizophrenia has two predominant peaks, i.e., prior to the age of 18 or 19 years, which is commonly known as childhood/adolescent onset schizophrenia and after the age of 19 years, which is commonly understood as adult onset schizophrenia(Buchanan and Carpenter, 2005).Among the various factors known to influence the outcome of patients with schizophrenia, there is lack of consensus regarding the influence of age of onset of psychosis on the outcome in schizophrenia. Some studies have found early onset to be associated with a positive/good outcome(Bland et al., 1976; Bland and Orn, 1978; Stefanopoulou et al., 2011; Stephens et al., 1997), while others report early onset to be associated withpoor outcome(Altamura et al., 2001; Juola et al., 2013) or age of onset to have no association with outcome in schizophrenia (Üçok et al., 2012). Some of the studies suggest that in long run, patients with early onset of schizophrenia are reported to have more severe form of illness (more severe positive and negative symptoms along with behavioral problems)(DeLisi, 1992; Pulver et al., 1990), higher disability (in all domains)(Hoff et al., 1996), lower probability of symptomatic remission (Juola et al., 2013), more number of hospitalizations (Rabinowitz et al., 2006), more cognitive impairment/deficits (Patiny et al., 2015), progressive loss of gray matter and decline in cerebellar volumes, more narrower posterior brain segments(Rapoport and Gogtay, 2011) and larger ventricles (Ordóñez et al., 2016) as

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compared to adult/late onset schizophrenia. Thereby, researchers have suggested age of onset of psychosis as a proxy marker of disease process (DeLisi, 1992; Gogtay et al., 2011; Golay et al., 2017).

However, over the years, outcome in schizophrenia has not been limited to symptomatic improvement, but has also been evaluated in terms of socio-occupational and vocational functioning, level of disability, quality of life, personal recovery, neurocognitive deficits, perceived/experienced stigmaetc (Davidson and McGlashan, 1997; Harrow et al., 1997; Jobe and Harrow, 2005; Meltzer, 1999; Meltzer et al., 1999).Cognitive impairment/neuropsychological deficits are now considered as a core feature of schizophrenia which possibly play an important role in the long term management/rehabilitation of patients with schizophrenia (Green et al., 2004; Green and Harvey, 2014; Heinrichs and Zakzanis, 1998; Rajji et al., 2009).Neurocognitive deficits are considered as the best predictors of functional outcome in schizophrenia (Bowie and Harvey, 2006, 2005).Neurocognitive domains have been found to be related with adaptive and social skills and deficits in these domains influence the socio-functional outcome (Bowie et al., 2006; Bowie and Harvey, 2006). Though, studies have found that cognitive deficits in patients with schizophrenia are stable over time with no deterioration or improvement in the course of illness (Davidson and McGlashan, 1997), yet it has been linked with disability and outcome in all domains. Majority of studies have found a definite association between age of onset and neurocognitive deficits in patients with schizophrenia (Frangou, 2013, 2010; Hoff et al., 1996; Tuulio-Henriksson et al., 2004). But some of the studies do not support the same(Heaton et al., 1994; Jeste et al., 1998; Sachdev et al., 1999).However, the nature of cognitive deficits have varied across the studies (Green et al., 2000; Rajji et al., 2009).Studies which have evaluated neurocognitive deficits in patients belonging to different age groups, suggest that compared to patients with adult onset schizophrenia, patients with early onset schizophrenia have more language/speech problems (van Beilen et al., 2004), more deficits in verbal and visual episodic memory(Fioravanti et al., 2012), visuo-spatial working memory (Rhinewine et al., 2005), selective attention and executive functions (difficulties in planning and learning new skills/abilities) (Frangou, 2010; Patiny et al., 2015).Further, no significant relationship has been found between the intelligence quotient (IQ) and age of onset of psychosis /disease evolution (Rajji et al., 2009; Zammit et al., 2004).

Another important outcome variable studied in patients with schizophrenia is internalized stigma/self-stigma. It has been reported that those with onset early in the course of their life with prolonged duration of illness face discrimination in all spheres and have higher degree of internalized stigma/self-stigma which further add on to the existing disability and lead to poor outcome (Firmin et al., 2018; Wong et al., 2009). Further recent studies have found strong association of poor neurocognitive function with higher self-stigma domains (stereotype endorsement and discrimination experience) (Chan et al., 2017; Shin et al., 2016) in patients with schizophrenia. Internalized stigma/self-stigma has been reported to act as a partial mediator between self-perceived/subjective cognitive deficits and social functioning as well as with quality of life (Pruß et al., 2012; Shin et al., 2016).

Existing literature on the association between age of onset and cognitions is mostly from the West and data is limited to studies with small sample sizes (Rajji et al., 2009). Existing data is inconsistent, with some studies reporting significant differences in various neurocognitive domains, whereas other studies suggest no difference in any neurocognitive domain among early onset and adult onset groups (Frangou, 2010).Moreover, only few studies from India have tried to substantiate if there are any specific differences on various neurocognitive domains between those with childhood/adolescent onset and adult onset schizophrenia from India(Biswas et al., 2006a, 2006b).However, these studies have not evaluated the relationship of neurocognitive functioning with other outcome variables like functioning and disability.

Further the existing literature on the impact of age of onset of psychosis and its relationship with various outcome variables have concluded that earlier age of onset of psychosis have overall poor outcome. However, the inter-relationship between different outcome measures has been poorly studied. In view of this, the present study aimed to evaluate the neurocognitive functioning and psychosocial outcome (in terms of social functioning, disability and internalized stigma) in patients with schizophrenia with childhood & adolescent onset (age of onset $\leq$18 years) and adult onset ($>$ 18 years) schizophrenia. Additional aim of the study was to evaluate the effect of neurocognitive impairment on the outcome variables in patients with childhood & adolescent and adult onset schizophrenia.

## 2. Methodology

This was a cross-sectional study carried out at the psychiatry outpatient services of a tertiary care teaching hospital in North India. The study was approved by the Ethics Committee of the Institute and the study participants were recruited after obtaining written informed consent.

The study sample was divided into two groups (I and II) based on age of onset of psychosis.There is lack of consensus in the literature with respect to age cut-off to categorize the patients with childhood & adolescent onset schizophrenia and adult onset schizophrenia, with some of the meta-analysis and reviews considering the age of 18 years and others considering 19 years as the cut-off (Díaz-Caneja et al., 2015; Rajji et al., 2009; Schimmelmann et al., 2007). Some of the studies from India, which have categorized patients into different age groups, have used age cut off of 16 years (Reddy et al., 1996) and 18 years (Biswas et al., 2006a, 2006b)for the same.For this study, we considered cutoff of 18 years to categorize the patients into childhood& adolescent onset and adult onset schizophrenia.

Group 1 included 34 patients with schizophrenia with age of onset of psychosis prior to or at 18 years of age and Group II included 56 patients with schizophrenia with age of onset of psychosis after 18 years of age. Participants were recruited by purposive sampling and both the groups were matched for gender.

The age of onset of the patients was determined on the basis of self report, report by the informants who were family members and review of the treatment records. Majority of the patients were on long term treatment from our centre. Hence, the information reported by the patient and the family members with regard to age of onset by ascertained by corroborating the same with the treatment records. In case of discrepancy, importance was given to the treatment records.

To be included in the study, the patients were required to fulfill the diagnosis of schizophrenia as per DSM-IV (confirmed by MINI Plus), right-handed as per the Edinburgh Handedness Inventory (Oldfield, 1971),aged between 18 and 65 years, with duration of illness of at least at least 2 years, score of less than 6 on Calgary depression rating scale, able to read Hindi and/or English and cooperative for cognitive testing. Patients with comorbid organic brain syndrome, intellectual disability, head injury, co-morbid medically diagnosable and /or self-reported and /or auditory impairment, history of receiving Electroconvulsive therapy (ECT) in last 6 months and substance dependence (except for tobacco

dependence) were excluded. Those patients who were co-operative for cognitive battery (as mentioned above) were recruited and subjected to the entire test battery in a quiet testing room in the same sequence as mentioned above with breaks given as per patient's preference. SS who was trained in the administration of all these tests by a qualified psychologist (RN) carried out the entire cognitive assessment. Both the study groups were matched on the variables of age and gender.

## 3. Instruments used

### 3.1. Mini international neuropsychiatric interview-plus (Sheehan et al., 1998)

It is a brief structured interview for diagnosis of psychiatric disorders that can be administered in 25–30 min. It is divided into modules corresponding to diagnostic categories. It elicits all the symptoms listed in the symptom criteria for DSM-IV and ICD-10 for major Axis I diagnostic categories, one Axis II disorder and for suicidality. Reliability ranges from good to excellent (kappa = 0.51 − 0.90) for various psychiatric disorders. It was used to confirm the clinical diagnosis of the psychiatric diagnosis.

### 3.2. Positive and Negative Syndrome scale for Schizophrenia (PANSS) (Kay et al., 1987)

This is one of the most commonly used scale to evaluate psychopathology in different studies evaluating the efficacy of medications and evaluating the outcome of psychopathology in patients with schizophrenia. It comprises of 30 items, divided into three subscales, i.e., positive, negative and general psychopathology. Each item is rated on a 7-point scale on the basis of a formal semi-structured clinical interview and data from other informational sources, pertaining to the previous one week. It has high inter-rater reliability as evident from the alpha coefficients of 0.73 to 0.83 ($p < 0.001$) for different subscales. Those in clinical remission as per Andreasen et al. (2005) criteria (Andreasen et al., 2005) were included in the study.

### 3.3. Calgary Depression Scale for Schizophrenia (CDSS) (Addington et al., 1990)

Depressive symptoms were assessed by using the Hindi version of Calgary Depression Scale for Schizophrenia. This scale was designed to assess depression exclusive of other dimensions of psychopathology in schizophrenia, such as negative and extrapyramidal symptoms. A score of 6 or more has been found to have 82% specificity and 85% sensitivity for predicting the presence of a major depressive episode. All those subjects who had scores more than 6 were excluded from the study.

## 4. Outcome was evaluated by

(1) Global Assessment of Functioning Scale (GAF) (Endicott et al., 1976): GAF was used to assess overall level of functioning of the participants.
(2) Indian Disability Evaluation and Assessment Scale (IDEAS) (Grover et al., 2014; The Rehabilitation Committee of the Indian Psychiatric Society, 2002): The IDEAS, evaluates disability in four areas (termed items in the scale), namely, self-care, interpersonal activities, communication and understanding and work. Each item is scored on a 5 point scale i.e., from no (0) to profound disability (4). The total disability score is obtained by summing up the ratings on each item. The global disability score is calculated by adding the 'total disability score' and score given for duration of illness (DOI). Global disability score of more than 7 signifies disability of > 40%. Internal consistency and concurrent validity of the scale is well established (Grover et al., 2014; Sahoo et al., 2017). The domains of disability captured by IDEAS are similar to the domains of disability captured by WHO-DAS and there is good concordance between the cut off levels of both scales to establish disability in patients with chronic psychiatric illness.(Basavarajappa et al., 2016).
(3) Social and Occupational Functioning Assessment Scale (SOFS) (Saraswat et al., 2006): It is a clinician rated 14 item scale, designed at India, which is used to assess level of social functioning. It has three main domains which includes adaptive life skills, social appropriateness and communication and interpersonal relationships. Each item is rated on a 5 point score ranging from 1 to 5, i.e. no impairment to extreme impairment. It is suitable for use in inpatient, outpatient and rehabilitation settings. It has adequate psychometric properties and can be used routinely by mental health professionals, family carers or professional care providers who are familiar with the patient for the functional assessment of persons with schizophrenia. Ratings should be based on patient's behavior during the last 1 month. The coefficient alpha is 0.91 for the total scale.
(4) Internalised Stigma of Mental Illness Scale (ISMIS) (Ritsher and Phelan, 2004): It is one of the widely used instruments for assessment of stigma associated with mental illnesses. This scale has been translated in multiple languages and has been used in many countries. It has 29 item which assesses subjective self-stigma/internalized stigma experienced by the person with mental illness. Each question has four options (strongly disagree-1, disagree-2, agree-3 and strongly agree-4), with higher scores indicating more stigma. Five domains - alienation, stereotype endorsement, perceived discrimination, social withdrawal and stigma resistance are conceptualized from the items. All sub-scale scores are calculated as averages with higher scores indicating more internalized stigma except for the items for stigma resistance which is scored in reverse direction. The scale has good reliability and validity (Ritsher et al., 2003; Ritsher and Phelan, 2004). The scale has been translated and validated in Hindi too (Singh et al., 2016).Usually, ascore of 2.5 is considered as a cut off to categorize the presence or absence of stigma by the authors of the scale (Ritsher et al., 2003; Ritsher and Phelan, 2004).
(5) Neurocognitive functions were assessed on a comprehensive cognitive battery which consists of the following tests:

**Trail making Test Part A and B** (Reitan et al., 1988): The test has two parts - Part A and Part B. A separate score for Part A and Part B, is evaluated which is the amount of time taken to complete each task. Both tests estimate the speed of attention, sequencing, mental flexibility, visual search and motor function. More specifically, Trail A tests visual scanning and psychomotor processing speed and Trail B tests cognitive flexibility and working memory. It has been validated in Indian population(Mukundan, 1996).

**Controlled Oral Word Association Test** (Benton and Hamsher, 1989):This test is used to measure phonemic fluency. The subject is asked to generate words based on phonetic similarity. In Indian adaptation, subject is asked to generate words (in Hindi) commencing with consonants "pa", "a" and "ra" (Rao et al., 2004).Subject is expected to spontaneously produce words as instructed. Proper names and nouns are excluded. The same word should not be repeated with a different suffix. Duration given for each consonant is 60 s and scoring is done by adding the total number of acceptable new words generated in the

stipulated time. The average new words generated over three trials form the score. This test is also used to find out number of perseverations, intrusions and variant words. Perseverated words are the number of repeated words, intrusion words are any words which are proper nouns like names or persons, any made up word or any word that does not begin with the given letter as asked and any alternate form of the word used already is regarded as a variant word.

**Stroop test**(Comalli et al., 1962; Golden, 1978):The Stroop test is a measure of response inhibition. It contains capital letters printed on a paper in different colours. The colour print does not correspond with the colour designated by the words. The words are printed in 16 rows and 11 columns and the test can be completed in around 20 min. The stimulus sheet is placed in front of the subject and in the first trial, subject is asked to column-wise read the word and in the second trial, name the colour in which the word was printed. Timings are recorded for both trials. Both reading time and naming time are recorded and the subtraction of the reading time from the naming time gives the stroop test effect score. Reliability and validity of stroop test has been well established in children, adults and elderly(Comalli et al., 1962; Strauss et al., 2005).

**Tower of London**(Krikorian et al., 1994):This test evaluates the ability to plan and anticipate the results of one's actions to achieve a predetermined goal. It consists of 2 identical wooden boards, each fitted with 3 round pegs of different sizes and 3 wooden balls in red, green, and blue; going by respective height, the 3 pegs could hold 3, 2, and 1 balls each. The subjects need to solve certain problems for which the time taken from start to finish is noted. The test score per problem is the number of moves (the subject lifting the ball). The usual completion time is about 30 min. It has been used to measure executive functions and has good inter-rater reliability and validity.

Statistical Package for the Social Sciences Windows version 14 (SPSS version 14, SPSS Inc., Chicago) was used to analyze the data. Analysis included calculating frequency/percentage for categorical variables and mean and standard deviation for continuous variables. Comparisons were done by using Student's t tests, Mann-Whitney-U tests, Chi-square test, Fisher's exact test, McNemar's test and the Wilcoxon signed rank test as per the requirement. Multivariate analysis was performed by using ANCOVA in which each neuropsychological variable was taken as dependent variable and age, gender, locality, total duration of illness, total PANSS positive score, total PANSS negative score andtotal PANSS general psychopathology score were taken as independent variables (covariates).These specific illness variables were used as co-variates as these can influence the neurocognitive functioning such as [Age – can affect neurocognitions (Salthouse, 2010); there exists significant gender differences with regard to schizophrenia course (Häfner, 2003);Urban living and urban upbrininging has been known to be associated with schizophrenia and urban living can affect neurocognitions too(Vassos et al., 2012) ;Total duration of illness has been shown to affect neurocognitive functioning (Cuesta et al., 1998); Severity of illness as assessed by total PANSS positive score, total PANSS negative score and total PANSS general psychopathology score can affect neurocognitions(Kuswanto et al., 2013)]. Previous studies which have compared neurocognitive deficits in early onset and late onset group have not controlled for these co-variates which can influence the results. Due to all these issues, we choose these variables as co-variates in the analysis so as to adjust for the confounders. Cohen's 'd' effect sizes were calculated to present standardized magnitudes of between-group differences. Relationship between neurocognitive domains and outcome variables were ascertained by using Pearson's and Spearman's correlation co-efficient.

## 5. Results

### 5.1. Demographic profile

The group-I (age of onset ≤18 years) included 34 participants and group-II included 56 participants. As is evident from Table 1, both the groups did not differ significantly in terms of gender and level of education. Both the groups also did not differ significantly in terms of other demographic variables like occupation, religion, type of family and locality. Compared to adult onset schizophrenia, those with childhood & adolescent onset schizophrenia were more likely to be single and were younger at the time of assessment.

### 5.2. Clinical profile

As shown in Table 2, both the groups did not differ significantly in terms of subtype of schizophrenia, duration of untreated psychosis, total duration of illness, type of onset of illness, overall longitudinal course of symptoms, comorbid tobacco dependence, comorbid obsessive compulsive disorder, mean chlorpromazine equivalent dose, PANSS positive, general psychopathology and total score. As expected the age of onset for childhood & adolescent onset schizophrenia was significantly lower and they were on treatment for longer duration of time, were more often receiving olanzapine and had significantly higher PANSS negative score.

**Table 1**
Comparison of Group I (age of onset ≤18yrs) with Group II (age of onset > 18yrs) on the socio-demographic variables.

| Parameters | Group I (N = 34) | Group II (N = 56) | T test/Chi square (P value) |
|---|---|---|---|
| Age :Mean (SD) | 28.61 (9.08)<br>Range : 17-54 | 36.75(9.55)<br>Range :22–63 | t= −3.986(< 0.001)*** |
| Sex : Male /Female | 22 (64.7%)/12 (35.3%) | 25 (44.6%)/31(55.4%) | $\chi^2$ = 3.413 (0.065) |
| Education in years Mean (SD);Range | 12.23 (3.29) | 13.35 (3.44) | t= −1.524(0.131) |
| Marital Status Currently single Currently married | 29 (85.8%) 5 (14.7%) | 37(66.1%) 19(33.9%) | $\chi^2$ = 3.997(0.046)* |
| Occupation | 8 (23.5%) | 16 (28.6%) | |
| On paid employment | 26 (76.5%) | 40 (71.4%) | |
| Not on paid employment | | | $\chi^2$ = 0.275(0.6) |
| Religion Hindu/Non-Hindu | 24 (70.6%)/10 (29.4%) | 41 (73.2%)/15(26.8%) | $\chi^2$ = 0.073(0.787) |
| Type of Family Nuclear/Non-Nuclear | 22 (64.7%)/12(35.3%) | 32 (57.1%)/24(42.9%) | $\chi^2$ = 0.504(0.478) |
| Locality Urban/Rural | 23 (67.6%)/11(32.4%) | 36(64.3%)/20(35.7%) | $\chi^2$ = 0.106 (0.745) |

$\chi 2$ = Chi-Square value.
* $p < 0.05$; *** $p < 0.001$

**Table 2**
Comparison of Group I (age of onset ≤ 18 yrs) with Group II (age of onset > 18 yrs) on the clinical variables.

| Parameters | Group I (N = 34)Mean (SD) | Group II (N = 56) Mean (SD) | T test/chi square (P value) |
|---|---|---|---|
| Type of Schizophrenia: | | | |
| Paranoid | 30(88.2%) | 52 (92.9%) | FE = 0.47 |
| Undifferentiated | 4(11.8%) | 4(7.1%) | |
| Age of onset (in Years) | 16.17(1.76)<br>Range : 10-18 | 25.07(5.98)<br>Range :19–44 | t = −8.42(< 0.001)*** |
| Duration of untreated Psychosis (in Months) | 18.64(22.25) | 17.71(23.13) | U = 933.0(0.874) |
| Total Duration of illness (in years) | 11.76(7.78)<br>(Range : 2–31) | 11.18(7.06)<br>(Range :2.5-38) | t = 0.361 (0.719) |
| Mode of onset : | | | |
| Acute/Subacute | 7(20.6%) | 15 (26.8%) | $\chi^2$ = 1.128 |
| Insidious | 27 (79.4%) | 41 (73.2%) | (0.569) |
| Course : | | | |
| Continuous | 33 (97.1%) | 53 (94.6%) | FE = 1.000 |
| Episodic | 1 (2.9 %) | 3 (5.4%) | |
| Co-morbid Tobacco dependence :Present | 4 (11.8%) | 4 (7.1%) | $\chi^2_b$ = 0.558 (0.455) |
| Co-morbid OCD: Present | 11 (32.4%) | 13 (23.2%) | $\chi^2$ = 0.903(0.342) |
| Duration of current treatment (in months) | 55.97(24.46) | 45.94(23.09) | t = 1.952(0.054) |
| Current Pharmacological profile | | | |
| Olanzapine | 7 (20.6%) | 1(1.8%) | $\chi^2_b$ = 13.269(0.039)* |
| Risperidone | 3 (8.8%) | 7 (12.5%) | |
| Clozapine | 23 (67.6%) | 42 (75%) | |
| Aripiprazole | 1(2.9%) | 4 (7.1%) | |
| Quetiapine | 0(0%) | 2 (3.6%) | |
| Mean Chlorpromazine (CPZ) equivalent dose(mg) | 455.88 (209.53) | 443.15<br>(243.41) | t=-0.253 (0.801) |
| PANSS | | | |
| Total Positive Score | 10.02(3.76) | 10.8(3.72) | t = −0.953(0.343) |
| Total Negative Score | 18.35(5.23) | 15.19(4.52) | t = 3.024(0.003)** |
| Total GP Score | 27.88(7.05) | 28.07(7.40) | t = −0.119(0.905) |
| Total PANSS Score | 56.26(13.25) | 54.07(14.42) | t = 0.721(0.473) |

$\chi$2= chi-square value; $\chi$2b = Chi-square with Yate's Correction; FE-Fischer's exact.

## 6. Comparison of neurocognitive functions

When both the groups were compared, in the initial analysis significant differences were seen between the two groups on verbal fluency and executive functions. However in view of multiple comparisons, p value of < 0.002 (total number of comparisons done-21; 0.05/21 = 0.002) was taken as significant. Accordingly, two groups differed significantly only for verbal fluency and one of the subsets of executive function (Table 3). However, when the data was controlled for covariates (age, sex, locality, total duration of illness, total PANSS positive score, total PANSS negative score, total GP score and total PANSS score), significant differences were seen between the two groups in terms of processing speed, verbal fluency and cognitive flexibility (Table 3). However, after controlling for multiple comparisons, significant difference was noted only for verbal fluency. The effect size was highest for the verbal fluency (1.02) and this was followed by effect size of cognitive flexibility (0.25) and processing speed (0.20).

## 7. Disability, social functioning, global functioning and internalized stigma

As is apparent from Table 4, patients with childhood & adolescent onset schizophrenia had significantly higher disability in all the 4 domains of IDEAS, although the proportion of patients with significant disability (i.e., > 40%) did not differ between the 2 groups. In terms of socio-occupational functioning, both the groups did not differ in any domain and overall socio-occupational functioning.GAF score for childhood & adolescent onset schizophrenia was also significantly lower. However, in view of multiple comparisons, p value of < 0.003 (total number of comparisons done-18; 0.05/18 = 0.003) was taken as significant. Still the differences between the two groups persisted for all the variables except for work domain of IDEAS and social withdrawal domain of stigma (Table 4). After controlling for co-variates, it was evident that childhood & adolescent onset schizophrenia had poor socio-occupational functioning and more disability in all domains. With regard to internalized stigma, patients with childhood & adolescent onset schizophrenia reported more alienation and social withdrawal as compared to patients with adult onset schizophrenia and when adjusted for the co-variates, patients with childhood & adolescent onset schizophrenia had more alienation, discrimination experience, social withdrawal and total ISMIS score. Additionally, it was seen that significantly higher proportion of patients with childhood & adolescent onset schizophrenia reported alienation (55.3%). In view of multiple comparisons, p value of < 0.003 (total number of comparisons done-18; 0.05/18 = 0.003) was taken as significant. Still the differences between the two groups persisted for all the variables except for work domain of IDEAS and all the domains of stigma (Table 4).

## 8. Association of Disability, social functioning and global functioning with Neurocognitive deficits

In the patients with childhood & adolescent onset schizophrenia, higher deficits in the processing speed and verbal fluency were associated with significantly lower global assessment of functioning and poorer socio-occupational functioning (Table 5). Executive dysfunction had few correlations with higher disability, poorer socio-occupational functioning and higher internalized stigma scores.

In contrast, in patients with adult onset schizophrenia, higher disability and socio-occupational dysfunction was related to executive dysfunction only. Poor global functioning was associated with poor executive functioning. Higher stigma was associated with poor cognitive processing and selective attention, poor cognitive flexibility and

**Table 3**
Comparison of Group I (age of onset ≤ 18yrs) with Group II (age of onset > 18yrs) on neurocognitive domains.

| Parameters | Group I (N = 34) Mean (SD) | Group II (N = 56) Mean (SD) | t-test/Mann-Whitney value (p-value) | Between Group differences ANCOVA (co-variates listed below) F values (p value) | Effect size Cohen's d |
|---|---|---|---|---|---|
| Processing Speed | | | | | |
| TMT –A percentile | 62.08(26.12) | 56.32(29.76) | t = 0.932(0.354) | 2.134(0.036)* | 0.20 |
| Verbal Fluency | | | | | |
| COWA average new words percentile | 13.67(7.51) | 30.53(22.08) | t = −4.294(< 0.001)*** | 3.934(< 0.001)*** | 1.02 |
| Mean no of perseveration words | 0.18(0.32) | 0.34(0.52) | U = 744.0(0.055) | 0.804(0.614) | 0.37 |
| Mean no of intrusion words | 0.60(0.59) | 0.57(0.74) | U = 885.0(0.566) | 1.017(0.434) | 0.04 |
| Mean no of variant words | 0.26(0.42) | 0.22(0.34) | U = 905.5(0.660) | 1.012(0.438) | 0.104 |
| Cognitive processing and Selective attention | | | | | |
| Stroop score | 130.35(54.49) | 134.16(73.22) | t = −0.262(0.794) | 1.367(0.217) | 0.059 |
| Stroop effect percentile | 56.79(28.79) | 54.30(27.79) | t = 0.407(0.685) | 1.687(0.106) | 0.088 |
| Cognitive flexibility | | | | | |
| TMT –B percentile | 39.64(31.80) | 31.83(29.66) | t = 1.178(0.242) | 1.816(0.03)* | 0.25 |
| Executive Functioning- TOL | | | | | |
| 2 Moves problems | | | | | |
| Mean Time percentile | 29.70(31.16) | 23.55(23.99) | U = 879.5(0.543 | 1.297(0.252) | 0.22 |
| Mean Moves percentile | 72.44(41.22) | 80.53(34.63) | ) | 0.994(0.452) | 0.21 |
| No of Problems solved with minimum moves percentile | 52.79(30.70) | 55.17(29.86) | t = −1.00(0.320)<br>t = −0.363(0.717) | 0.498(0.872) | 0.07 |
| 3 Moves problems | | | | | |
| Mean Time percentile | 16.52(12.53) | 24.67 (22.96) | t = −1.902(0.06) | 1.772(0.086) | 0.44 |
| Mean Moves percentile | 24.67(20.29) | 40.35(31.02) | t = −2.623(0.010)** | 1.343(0.229) | 0.59 |
| No of Problems solved with minimum moves percentile | 17.52(15.98) | 33.28(27.54) | t = −3.036(0.003)** | 1.449(0.182) | 0.69 |
| 4 Moves problems | | | | | |
| • Mean Time percentile | 17.58(16.09) | 30.18(24.33) | t = −2.681(0.009)* | 1.452(0.181) | 0.61 |
| • Mean Moves percentile | 26.85(20.78) | 40.08(26.73) | t = −2.468(0.016)* | 1.484(0.168) | 0.55 |
| • No of Problems solved with minimum moves percentile | 17.38(18.77) | 20.59(22.98) | U = 926.5(0.822) | 1.211(0.300) | 0.15 |
| 5 Moves problems | | | | | |
| • Mean Time percentile | 10.41(12.57) | 7.48(6.96) | U = 928.5(0.840 | 0.917(0.515) | 0.28 |
| • Mean Moves percentile | 8.76(9.43) | 6.96(7.89) | ) | 0.673(0.730) | 0.20 |
| • No of Problems solved with minimum moves percentile | 11.44(18.29) | 12.28(15.17) | U = 890.5(0.585)<br>U = 861.0(0.267) | 0.712(0.696) | 0.04 |
| Total No of Problems Solved With Minimum moves Percentile | 21.94(22.09) | 22.71(21.76) | U = 905.5(0.687) | 0.582(0.809) | 0.035 |

Co-variates included – age, sex, locality, total duration of illness, total duration of untreated psychosis, total PANSS positive score, total PANSS negative score and total GP score, total PANSS score.

* p value < 0.05.

** p value < 0.01.

*** p value < 0.001.

poor executive functioning in patients with adult onset schizophrenia (Table 5). However, when takes the multiple correlations into account, it can be said that most of these relationships were not very strong, when one considers the p values.

## 9. Discussion

The present study intended to evaluate the effect of age of onset of psychosis on neuropsychological functioning and outcome in schizophrenia. For this study, patients with schizophrenia were evaluated on a neurocognitive battery and outcome related scales.

Meta-analysis of studies which have evaluated the association of age of onset and outcome related variables suggest that age of onset has a small but significant impact on some of the outcomes of schizophrenia (Immonen et al., 2017). However, while reporting the impact of age of onset on outcome, many of the studies have not considered the impact of covariates on the outcome of schizophrenia(Immonen et al., 2017). Despite the common notion that those with earlier onset of illness in general have a poorer outcome, yet a clear view of the same is currently not present due to high variability across the studies. In the present study, due care was taken to match the subjects of both groups with regard to socio-demographic variables, duration of illness and severity of symptoms as assessed by PANSS. Accordingly, it can be said that the differences noted between the 2 groups with respect to the neurocognitive deficits and outcome variables were closer to the reality.

In the present study, patients with childhood & adolescent onset schizophrenia subjects had poorer verbal fluency and poor executive functioning when compared to patients with adult onset schizophrenia. However, after controlling for all co-variates and considering the multiple comparisons, only verbal fluency was found to be quite significantly low in childhood & adolescent onset schizophrenia. Several studies have suggested that verbal fluency can be regarded as an early trait marker of early/childhood/adolescent onset schizophrenia (Holmén et al., 2010; Landrø and Ueland, 2008; Phillips, 2004). More recently, verbal fluency has been understood as a neurocognitive endophenotype in schizophrenia(Liang et al., 2016), which has an impact on one's everyday functioning(Landrø and Ueland, 2008) as well as has been linked with failure of lateralization of language (Phillips, 2004). In the present study, difference in poor verbal fluency between the 2 groups was of large effect size (1.02) and it (verbal fluency) had definite association (negative) with poor socio-occupational functioning (as assessed by SOFS). Accordingly, it can be said that the present study supports the hypothesis of higher neurocognitive deficits in patients with childhood & adolescent onset schizophrenia and association of

**Table 4**
Comparison of Group I (age of onset ≤18yrs) with Group II (age of onset > 18yrs) on outcome variables.

| Parameters | Group I (N = 34)Mean (SD) | Group II (N = 56)Mean (SD) | t test/chi square (P value) | Between Group differences ANCOVA (co-variates listed below) F values (p value) |
|---|---|---|---|---|
| IDEAS Domains: | | | | |
| Self-care | 1.64(0.48) | 1.19(0.40) | 4.772(< 0.001)** | 4.074(< 0.001)*** |
| Interpersonal activities | 2.38(0.69) | 1.92(0.68) | 3.03(0.003)** | 4.629(< 0.001)*** |
| Communication and understanding | 2.50(0.61) | 2.03(0.57) | 3.632(< 0.001)*** | 4.050(< 0.001)*** |
| Work | 2.76(1.10) | 2.28(0.77) | 2.41(0.018)* | 2.174(0.033)* |
| Total score | | | | |
| Global score | 9.29(2.23) | 7.44(1.89) | 4.185(< 0.001)*** | 4.991(< 0.001)*** |
| (Total score + Duration of illness in years) | 12.5(2.40) | 10.66(2.12) | 3.787(< 0.001)*** | 6.634(< 0.001)*** |
| Disability as per GOI-IDEAS: Present/Absent | 31 (91.2%) | 44(78.6%) | 2.42(0.120) | |
| SOFS Domains: | | | | |
| Adaptive Skills | 10.94(3.22) | 10.35(2.26) | 1.006(0.317) | 4.022(< 0.001)*** |
| Social Appropriateness | 6.58(2.31) | 6.29(1.54) | 0.710(0.480) | 5.619(< 0.001)*** |
| Communication & Interpersonal relationships | 8.11(2.30) | 8.00(1.91) | 0.259(0.796) | 3.678(< 0.001)*** |
| Total SOFS score | 25.64(7.36) | 24.64(5.13) | 0.749(0.456) | 5.023(< 0.001)*** |
| GAF score | 65.05(12.60) | 74.17(13.88) | −3.126(0.002)** | 7.368(< 0.001)*** |
| Components of stigma as assessed by ISMIS scale | | | | |
| Alienation | 2.69(0.40) | 2.30(0.53) | 3.71(< 0.001)*** | 2.533(0.013)* |
| Stereotype endorsement | 2.44(0.56) | 2.43(0.51) | −0.001(0.999) | 1.879(0.067) |
| Discrimination experience | 2.50(0.47) | 2.34(0.55) | 1.426(0.157) | 2.989(0.004)** |
| Social withdrawal | 2.59(0.40) | 2.36(0.49) | 2.334(0.022)* | 2.885(0.005)** |
| Stigma resistance (reverse scoring) | 2.47(0.34) | 2.37(0.23) | 1.500(0.137) | 1.023(0.429) |
| Total ISMIS score | 2.44(0.35) | 2.35(0.35) | 1.171(0.245) | 2.669(0.009)** |
| Presence or absence of stigma as per the cutoff of 2.5 | | | | |
| Alienation | 19 (55.9%) | 14(25%) | $\chi^2$ = 8.688(0.003)** | |
| Stereotype endorsement | 15(44.1%) | 25(44.6%) | $\chi^2$ = 0.002(0.961) | |
| Discrimination experience | 19 (55.9%) | 21(37.5%) | $\chi^2$ = 2.895(0.089) | |
| Social withdrawal | 17 (50%) | 18 (32.1%) | $\chi^2$ = 2.83(0.092) | |
| Stigma resistance (reverse scoring) | 16(47.1%) | 17(30.4%) | $\chi^2$ = 2.541(0.111) | |
| Stigma (all 5 domains) | 19 (55.9%) | 20 (35.7%) | $\chi^2$ = 3.504(0.061) | |

Co-variates included – age, sex, locality, total duration of illness, total duration of untreated psychosis, total PANSS positive score, total PANSS negative score and PANSS general psychopathology score, total PANSS score.

* p value < 0.05.

** p value < 0.01.

*** p value < 0.001.

higher verbal fluency deficits with poor socio-occupational functioning.

Present study also suggests that patients with childhood & adolescent onset schizophrenia have poor psychosocial functioning, despite controlling for the presence of residual psychopathology. This finding also supports the existing literature (Díaz-Caneja et al., 2015; Leifker et al., 2009; Reichert et al., 2008). Accordingly, it can be said in patients with childhood & adolescent onset schizophrenia all efforts must be made to start rehabilitation measures at the earliest.

There is ample evidence to suggest that childhood & adolescent onset schizophrenia have more disability in all domains of life (self-care, interpersonal relationships, communication, adaptive skills and work)(Immonen et al., 2017). Though, meta-analysis have found no significant relationship between age of onset and employment status and general clinical outcome, but a definite association has been noted with regard to global outcome and socio-occupational functioning (Immonen et al., 2017). However, it is important to note that earlier studies have not controlled for the possible co-variates. In contrast, in the present study, difference between the 2 groups, persisted even after controlling for co-variates and multiple comparisons in all the domains of IDEAS (except for work domain), and global functioning. Both groups differed significantly after controlling for co-variates in all domains of socio-occupational functioning (poorer functioning in childhood & adolescent onset group). However, there was no difference between the 2 groups in the number of subjects scoring above the cutoff for disability. This lack of difference between the 2 groups could be due to inclusion of duration of illness (almost comparable total duration of illness) in calculating the global disability score. When we controlled for multiple comparisons, no significant difference emerged between the two groups with respect to stigma. This finding suggests that stigma is universal across patients, irrespective of age of onset.

It is in general said that neurocognitive deficits generally peak at the time of first episode of psychosis and after that in general remain stable (Bowie and Harvey, 2006; Green and Harvey, 2014). Considering this, based on the findings of the present study, it can be said that earlier onset of schizophrenia is associated with higher cognitive deficits and these deficits have influence upon the real world everyday living skills and social skills as has been found by some studies(Bowie et al., 2008; Leifker et al., 2009; Puig et al., 2012) i.e. these deficits affects the functional capacity of an individual with schizophrenia (Mantovani et al., 2015).

The limitations of the study include cross-sectional study design and absence of a healthy control group to compare the results of both groups. Some of the previous studies have used *Instrument for the retrospective assessment for onset of schizophrenia* (IRAOS) to estimate the age of onset. In contrast in the present study, age of onset was based upon retrospective recollection of the age of onset of by patient/family members or as documented in medical records. The study was limited to the hospital attending population which limits the generalibility of the results to the community. Intelligence quotient (IQ) was not assessed, although due care was taken to exclude those with intellectual disability. Although the sample size of the present study was larger than most of the previous studies, which have evaluated the effect of age on neurocognitive functioning in patients with schizophrenia, yet the sample can be considered relatively small. Future studies must attempt to overcome the limitations.

In conclusions, present study suggests that those with childhood & adolescent onset schizophrenia have more deficits in neurocognitive functioning which adversely affect their overall course and outcome in

**Table 5**
Association of neurocognitive domains with outcome variables with regard to age of onset of schizophrenia.

| Parameters | Group I (onset ≤18yrs) | | | | Group II(onset > 18yrs) | | | |
|---|---|---|---|---|---|---|---|---|
| | GAF Score r(p-value) | Total IDEAS scorer(p-value) | Total SOFS Scorer(p-value) | Total ISMISScore r(p-value) | GAF Score r(p-value) | Total IDEAS score r(p-value) | Total SOFS Score r(p-value) | Total ISMIS Score r(p-value) |
| Processing Speed | | | | | | | | |
| TMT –A percentile | 0.948 (0.012)* | −0.075 (0.673) | −0.859 (0.032)* | −0.127 (0.474) | −0.135 (0.321) | −0.20 (0.884) | −0.036 (0.798) | −0.193 (0.154) |
| Verbal Fluency | | | | | | | | |
| COWA average new words percentile | 0.063 (0.723) | 0.323 (0.062) | −0.665 (0.003)* | −0.199 (0.259) | −0.230 (0.088) | 0.089 (0.514) | 0.026 (0.852) | 0.070 (0.607) |
| Mean no of perseveration words | 0.197 (0.263)# | 0.985 (0.003)*,# | −0.106 (0.550)# | 0.208 (0.237)# | −0.022 (0.87)# | 0.006 (0.968)# | −0.052 (0.707)# | −0.015 (0.913)# |
| Mean no of intrusion words | −0.233 (0.185)# | 0.087 (0.626)# | 0.065(0.717)# | −0.019 (0.913)# | −0.166 (0.221)# | 0.131 (0.337)# | 0.209 (0.129)# | 0.013 (0.289)# |
| Mean no of variant words | 0.123 (0.487)# | 0.048 (0.787)# | 0.234 (0.184)# | −0.018 (0.921)# | −0.041 (0.762)# | −0.013 (0.926)# | 0.063 (0.651)# | 0.099 (0.467)# |
| Cognitive processing andSelective attention | | | | | | | | |
| Stroop score | 0.145 (0.413) | 0.179 (0.311) | −0.164 (0.354) | 0.024 (0.894) | 0.113 (0.409) | 0.028 (0.837) | 0.056 (0.689) | 0.211 (0.118) |
| Stroop effect percentile | −0.092 (0.606) | −0.093 (0.602) | 0.109 (0.539) | −0.048 (0.787) | −0.080 (0.556) | −0.173 (0.202) | −0.126 (0.365) | −0.375 (0.004)** |
| Cognitive flexibility | | | | | | | | |
| TMT –B percentile | −0.151 (0.395) | −0.060 (0.737) | −0.021 (0.967) | −0.077 (0.663) | −0.234 (0.083) | −0.024 (0.859) | −0.097 (0.486) | −0.294 (0.028)* |
| Executive Functioning- TOL | | | | | | | | |
| 2 Moves problems | | | | | | | | |
| Mean Time percentile | −0.207(0.240)# | 0.124(0.486)# | −0.207(0.240)# | 0.05(0.78) # | −0.009(0.949)# | −0.134(0.324)# | −0.213(0.121)# | −0.306(0.022)*,# |
| Mean Moves percentile | −0.101(0.570) | −0.139(0.432) | −0.225(0.201) | 0.232(0.188) | −0.010(0.939) | −0.009(0.950) | −0.097(0.486) | −0.091(0.503) |
| No of Problems solved with minimum moves percentile | −0.030(0.867) | −0.108 (0.544) | −0.188(0.286) | 0.316(0.068) | −0.101(0.458) | −0.066(0.627) | −0.062(0.627) | −0.131(0.335) |
| 3 Moves problems | | | | | | | | |
| Mean Time percentile | −0.042(0.814) | 0.196(0.266) | −0.980(0.004)* | 0.833(0.037)* | −0.216(0.111) | −0.046(0.738) | −0.010(0.944) | −0.263(0.051) |
| Mean Moves percentile | −0.040(0.820) | 0.194(0.273) | 0.622(0.088) | 0.261(0.136) | 0.127(0.352) | −0.254(0.059) | −0.027(0.848) | −0.241(0.073) |
| No of Problems solved with minimum moves percentile | 0.011(0.953) | 0.315(0.070) | −0.888(0.025)* | 0.789(0.048)* | −0.005(0.973) | 0.041(0.761) | −0.224(0.103) | −0.254(0.059) |
| 4 Moves problems | | | | | | | | |
| Mean Time percentile | 0.213(0.226) | 0.081(0.650 | 0.107(0.548) | 0.055(0.757) | −0.119(0.384) | −0.051(0.709) | −0.002(0.988) | −0.163(0.230) |
| Mean Moves percentile | 0.137(0.440) | −0.043(0.808) | 0.334(0.054) | 0.195(0.228) | −0.073(0.592) | −0.001 (0.996) | −0.05(0.72) | −0.125(0.360) |
| No of Problems solved with minimum moves percentile | −0.290(0.096)# | 0.167(0.346)# | 0.202(0.252)# | 0.051(0.773)# | −0.083(0.542)# | −0.011(0.935)# | −0.292(0.032)*,# | −0.156(0.251)# |
| 5 Moves problems | | | | | | | | |
| • Mean Time percentile | −0.099(0.579)# | −0.412(0.015)*,# | 0.123(0.487)# | 0.063(0.725)# | 0.864(0.023)*,# | 0.132(0.332)# | 0.168(0.226)# | 0.709(0.051)# |
| • Mean Moves percentile | −0.046(0.796)# | 0.212(0.229)# | 0.175(0.322)# | −0.258(0.141)# | 0.122(0.370)# | −0.879(0.021)*,# | 0.050(0.721)# | −0.115(0.399)# |
| • No of Problems solved with minimum moves percentile | −0.252(0.150)# | 0.107(0.549)# | −0.210(0.233)# | −0.03(0.867)# | 0.234(0.082)# | −0.314(0.018)**,# | −0.45(0.001)**,# | −0.071(0.601)# |
| Total No of Problems Solved With Minimum moves Percentile | −0.331(0.056)# | −0.914(0.019)*,# | 0.132(0.457)# | 0.110(0.536)# | −0.076(0.576)# | −0.010(0.942)# | −0.187(0.176)# | −0.220(0.103)# |

# Spearman rank correlation coefficients.

terms of disability in all domains, socio-occupational functioning and have high degree of self-stigma. Therefore, cognitive remediation strategies, psychosocial/occupational rehabilitationand stigma reduction strategies should be prioritized for patients with childhood & adolescent onset schizophrenia.

## Conflict of interest

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