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Relationship of metabolic syndrome and neurocognitive deficits in patients with schizophrenia



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ABSTRACT

This study aimed to evaluate the association of the metabolic syndrome (MS) and its components with neurocognition among patients with schizophrenia. 121 patients with schizophrenia from an outpatient service of two psychiatric centers were assessed on a neurocognitive battery and by metabolic measures. More than half (56.2%) of the patients fulfilled the consensus criteria for MS. After controlling/adjusting for various covariates (age, education in years, duration of illness, age of onset, Positive and Negative Symptom scale score and presence of smoking status), it was found that compared to patients without MS, those with MS had significantly poorer performance “in the cognitive domains” of cognitive processing and selective attention (Stroop effect percentile; p value 0.002; effect size-0.45) and auditory and verbal memory (AVLT; p value < 0.001; effect size 0.68). Patients with a higher number of abnormal parameters of MS had poorer functioning in the domains of cognitive processing and selective attention, auditory and verbal memory, and executive tasks. To conclude, this two center study suggests that MS has a negative impact on neurocognition in patients with schizophrenia. There is a need to identify and monitor metabolic abnormalities among patients with schizophrenia to minimize the negative effect of metabolic parameters on neurocognition.

1. Introduction

The metabolic syndrome (MS) is characterized by a clustering of at least three of the five risk factors for cardiovascular morbidity and mortality, i.e., abdominal obesity, hyperglycemia, hypertension, hypertriglyceridemia and low high-density lipoprotein (HDL) cholesterol levels (Grundy et al., 2005). MS is now a well-established risk factor for the development of coronary artery disease, cerebrovascular disease, and type II diabetes mellitus. Prevalence of MS in patients with schizophrenia has been extensively studied, with estimated prevalence rates ranging between 3.3 and 68% (Malhotra et al., 2013). The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) trial, which used the National Cholesterol Education Program- Adult Treatment Panel III criteria (NCEP-ATP-III) to define MS, reported prevalence of MS to be around 40% in patients with schizophrenia. This was significantly higher than the prevalence in the general population (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, 2001; McEvoy et al., 2005).

MS in patients with schizophrenia has been associated with several negative outcomes such as poor quality of life (Meyer et al., 2005),

higher residual psychopathology (Arango et al., 2008), higher depressive and anxiety symptoms (Maslov et al., 2009) and poor physical health status (Meyer et al., 2005). More recently, MS has been evaluated for its possible association with poor cognitive functions or neurocognitive deficits in patients with schizophrenia. Available studies suggest that presence of MS in patients with schizophrenia is associated with more significant cognitive impairments/deficits when compared to those without MS (Boyer et al., 2013; Lindenmayer et al., 2012). A recent meta-analysis of 18 studies, which included 2243 patients (854 patients with MS and 1389 patients without MS), concluded that presence of MS and/or abnormalities of its various components was associated with a significant negative impact on the cognitive functions (Bora et al., 2017).

MS has also been identified as an important risk factor for developing cognitive decline, and there is a growing body of evidence suggesting the association of various components of MS and adiposity with neuroinflammation, subsequently leading to cognitive impairment (Li et al., 2014; Panza et al., 2011; Ricci et al., 2017; Solfrizzi et al., 2010). Studies in patients with schizophrenia have suggested an association of MS with poor school performance between the ages of 12 and 16 years

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(de Nijs et al., 2016). Further, studies have strongly supported the linkage between obesity/MS and cognitive impairment (Case et al., 2002; Shefer et al., 2013; Yaffe et al., 2004). There is also evidence supporting improvement in cognitive domains following effective intervention for individual components of MS (Siervo et al., 2011). The pathogenic association of MS with Alzheimer's disease has been well-documented, and due to all these findings, nowadays, the concept of the metabolic-cognitive syndrome is being recognized (Frisardi et al., 2010).

It has been postulated that MS might aggravate the injury to cognitive functions in patients with chronic schizophrenia in almost all neurocognitive domains, especially in immediate memory, delayed memory, and attention (Li et al., 2014). Studies have also documented that the use of atypical antipsychotics cause insulin resistance (mostly due to the 5-HT_{2c} antagonist properties of second-generation antipsychotics such as olanzapine and clozapine), which is one of the central components of MS, suggesting that chronic treatment with these drugs is associated with the risk of developing MS and subsequent cognitive dysfunction (Cai et al., 2013; Houseknecht et al., 2007; Poa and Edgar, 2007; MacKenzie et al., 2018).

Significant relationship has also been established between hypertension and poor memory (immediate memory, delayed memory and recognition) (Friedman et al., 2010; Morra and Strauss, 2016), processing speed as well as visual and verbal learning (Morra and Strauss, 2016). Higher body mass index (BMI, >25) or obesity has been shown to be associated with poorer delayed memory (Friedman et al., 2010). Similarly, higher waist circumference has been shown to be associated with poorer attention/vigilance (Lindenmayer et al., 2012); and low HDL and high triglycerides have been shown to be associated with poorer attention/vigilance (Lindenmayer et al., 2012). A meta-analysis reveals a significant association between each component of MS (hypertension, dyslipidemia, waist circumference/obesity and diabetes mellitus) with cognitive deficits, more particularly on memory, attention, processing speed and executive functions (Bora et al., 2017). A meta-analysis reported a significant association between each component of MS (hypertension, dyslipidemia, waist circumference/obesity and diabetes mellitus) and some of the cognitive deficits (Bora et al., 2017).

Despite the widely prevalent use of anti-psychotics in India, the relationship between MS and cognitive deficits has not been studied systematically. This research is an attempt to evaluate the relationship of individual components of MS with cognitive impairment in patients with schizophrenia.

1.1. Materials and methods

This cross-sectional study was conducted at the psychiatric outpatient services of two centers, one being a tertiary care hospital in North India (Post Graduate Institute of Medical Education and Research, Chandigarh) and the second, an out-patient clinical services, Schizophrenia Research Foundation (SCARF), Chennai in South India during the period of May 2016– April 2017. The study included 121 patients diagnosed with schizophrenia as per Diagnostic and Statistical Manual of Mental Disorders-IV edition (DSM-IV) (American Psychiatric Association, 1994), recruited by purposive sampling.

To be included in the study, patients were required to fulfill the diagnosis of schizophrenia as per DSM-IV (American Psychiatric Association, 1994) (confirmed by MINI-Plus), to be right-handed as per the Edinburgh Handedness Inventory (Oldfield, 1971), of either gender, aged between 18 and 55 years, with a duration of illness of at least two years, able to read Hindi and/or English, and cooperative for cognitive testing. Those patients with comorbid organic brain syndrome, intellectual disability, head injury, past history of cerebrovascular accident or epilepsy or any demyelinating disease, co-morbid medically diagnosable and /or self-reported auditory impairment, co-morbid major depression or presence of current affective or schizoaffective

disorder, comorbid personality disorders, comorbid anxiety disorders, having received electroconvulsive therapy (ECT) in six months prior to assessment for the study and those with lifetime history of substance dependence (except for tobacco dependence) were excluded. Similarly, those with a history suggestive of color blindness were excluded.

The study was approved by the Local Ethics Committees of both the institutes, and the study participants were recruited after obtaining written informed consent.

1.2. Instruments used

Mini International Neuropsychiatric Interview-Plus (Sheehan et al., 1998) was used to confirm the clinical diagnosis of schizophrenia and to rule out other comorbid psychiatric disorders. Positive and Negative Syndrome Scale for Schizophrenia (PANSS; Kay et al., 1987) was used to grade the severity of psychopathology, and Global Assessment of Functioning Scale (GAF; Endicott et al., 1976) was used to assess the overall level of functioning of the participants.

1.2.1. Cognitive battery

- **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. It has been validated in the Indian population (Mukundan, 1996).
- **Controlled oral word association test (COWA) (Benton and Hamsher K, 1989):** This test is used to measure phonemic fluency. The subject is asked to generate words based on phonetic similarity. In the Indian adaptation, the subject is asked to generate words (in Hindi) commencing with consonants "pa," "a" and "ra" (Rao et al., 2004). The subject is expected to spontaneously produce words as instructed. Proper names, nouns and repetition of same words if used were excluded. The average number of new words generated over three trials forms the score.
- **Stroop test (Comalli et al., 1962; Golden JC, 1978):** The Stroop test is a measure of response inhibition. It contains names of different colours printed on a paper in different colors. The color of the print does not correspond with the color designated by the words. Reliability and validity of the Stroop test has been well established in children, adults and elderly (Strauss et al., 2005).
- **Rey auditory and verbal learning test (AVLT) (McMinn et al., 1988; Rey, 1958):** This instrument is used for evaluation of episodic declarative memory. It provides a detailed assessment of immediate memory, new verbal learning memory, delayed recall memory, and memory recognition. This test is quite sensitive to note neurological impairment and verbal memory deficits in a variety of disorders such as temporal lobe epilepsy, Alzheimer's disease, schizophrenia, Parkinson's disease, head injury, etc. and also the normal age-related memory impairment (Kreutzer et al., 2011). Reliability of the instrument has been well established, and normative data on different groups of populations are also available (Magalhães and Hamdan, 2010; Malloy-Diniz et al., 2007; McMinn et al., 1988). Studies have also found a strong positive association between verbal learning and verbal episodic declarative memory with executive functions (Duff et al., 2005; Malloy-Diniz et al., 2000).
- **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 two identical wooden boards, each fitted with three round pegs of different sizes and three wooden balls in red, green, and blue; going by respective height, the three pegs could hold three, two, and one 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.

1.3. Assessment of metabolic disturbances

A detailed assessment of metabolic disturbances was done, which included evaluation of anthropometric measures and physical investigations.

- a) *Physical examination* included measurement of height in meters, weight in kilograms on a standardized calibrated weigh scale, waist circumference (in centimeters) and blood pressure (systolic and diastolic) in mm of Hg using a standard mercury manometer. Waist circumference was measured by using a retractable measuring tape at the midpoint between the superior iliac crest and inferior costal margin in mid-expiration.
- b) *Laboratory investigations* included estimation of fasting blood glucose (FBS), triglycerides and high-density lipoproteins (HDL) from an overnight fasting venous blood sample.

MS was determined based on the consensus criteria. Based on the presence or absence of MS, the study sample was divided into Group I (Patients with MS) and Group II (Patients without MS). Similarly, for each abnormality, based on the Consensus criteria cut-offs, patients were divided into two groups, i.e., those with and without an abnormality. In case the patient was diagnosed with diabetes mellitus, hypertension, or dyslipidemia and was already on treatment, they were considered in the group of MS and with an abnormality.

Quality of data was ensured by carrying out random checks at the time of data collection and compilation.

1.4. Statistical analysis

Statistical Package for the Social Sciences Windows version 14 (SPSS version 14, SPSS Inc., Chicago) was used to analyze the data. The analysis included calculating frequency/percentage for categorical variables and mean and standard deviation for continuous variables. Comparisons were made by using Student's *t*-test, Mann-Whitney-U test, Chi-square test, and Fisher's exact test. Relationship between various metabolic parameters and clinical and neurocognitive variables were studied by Pearson's product moment correlation and Spearman's rank correlation coefficient. Comparison of clinical characteristics and neuropsychological test scores between the groups was performed using the McNemar's test and the Wilcoxon signed rank test, for categorical and continuous variables respectively. Multivariate analysis was performed by using ANCOVA, in which each neuropsychological variable was taken as dependent variable and age, education in years, total duration of illness, age of onset of psychosis, total PANSS positive score, total PANSS negative score, total general psychopathology score and presence of smoking status were taken as independent variables (covariates). Cohen's '*d*' effect sizes were calculated to present standardized magnitudes of between-group differences. In view of the multiple comparisons, Bonferroni correction was used, and for comparison of cognitive functions, a *p*-value of ≤ 0.003 (total of 17 comparisons $0.05/18 = 0.0027$) was considered as significant.

1.5. Results

The study included 121 participants with schizophrenia (71 patients from Centre 1 – Chandigarh and 50 patients from Centre 2 –Chennai). There were no significant differences in the demographic data, the clinical data or the metabolic data between the two centers for any of the variables. As per the Consensus criteria, 68 patients fulfilled the criteria for MS, giving a prevalence rate of 56.2%.

The demographic and clinical profile of the study sample is shown in Tables 1 and 2. No significant difference was seen between those

with (Group-I) and those without (Group-II) MS in terms of socio-demographic variables except for age, with patients with MS being older.

The patients with MS had a significantly longer duration of illness and were more often receiving clozapine when compared to those without MS. However, both the groups were comparable in terms of age of onset of illness, duration of current treatment, pharmacological profile (except for the group with MS, more often receiving clozapine) at the time of assessment, and psychopathology scores. There was no difference in the prevalence of hypertension and diabetes mellitus between the two groups (Table 2).

1.6. Metabolic profile

As expected, there were significant differences between the two groups on all the metabolic and the anthropometric parameters, except for systolic and diastolic blood pressure (Table 3). About one-third of the sample (34.7%) fulfilled the minimum three criteria, about one-fifth of the sample fulfilled four criteria, and only 2.5% of the sample fulfilled all the five criteria of MS.

1.6.1. Comparison of neurocognitive domains between those with and without MS

As is evident from Table 4, those with MS had significantly poorer neurocognitive functioning (*p* value < 0.003) in the domains of auditory and verbal memory and the executive functioning. To control for various possible confounding factors, ANCOVA was used by controlling for age, education in years, the total duration of illness, age of onset of psychosis, total PANSS positive score, total PANSS negative score, total general psychopathology score and presence of smoking status. Even after controlling for various covariates, patients with MS had significantly poorer performance in the domains of processing speed, poor cognitive processing and selective attention (effect size of 0.45), poor auditory and verbal memory (effect size of 0.68) and poor immediate recall memory, but had better executive functioning (significant effect sizes ranging between 0.48 and 0.77, Table 4).

1.6.2. Association of neurocognitive domains with metabolic parameters

As is evident from Table 5, in the entire sample, higher fasting glucose levels were associated with poorer performance in the auditory and verbal memory and on a few domains of executive functions. Similarly, higher systolic blood pressure was associated with poorer performance in the domains of executive functions, whereas higher diastolic blood pressure was associated with poorer processing speed and poorer auditory and verbal memory.

Patients with a higher number of abnormal components of MS had poorer functioning in the domains of cognitive processing and the selective attention (Stroop effect percentile), the auditory and verbal memory, and the executive functions (Table 5).

1.6.3. Comparison of individual metabolic abnormalities with the neurocognitive domains

Based on the cut-off values as determined by the consensus criteria for MS, the value of each component of MS was categorized as "abnormal" and "normal." The subjects were then categorized into two groups, i.e. subjects with and without the specific metabolic abnormality (waist circumference, FBS, triglycerides, HDL, systolic blood pressure, diastolic blood pressure), and the groups so raised were compared after controlling for all possible covariates.

When those with and without abnormal waist circumference were compared, no significant difference (*p* value < 0.003) was noted for any of the cognitive functions.

However, when those with abnormal and normal FBS as per the MS criteria were compared, it was seen that those with abnormal FBS had poorer auditory and verbal total memory (*F* value = 14.04; *p* < 0.001) and slightly better executive functions (*F* value for four mean moves percentile = 4.3; *p* < 0.001).

Table 1
Comparison of socio-demographic variables of Group I (schizophrenia with MS) with Group II (schizophrenia without MS).

Parameters	Whole sample (n = 121) Mean (SD)/ n (%)	Group I (N = 68) Mean (SD)/ n (%)	Group II (N = 53) Mean (SD)/ n (%)	T test/Chi square (P value)
Age	33.89 (9.86);19–54	35.61(10.15)	31.67 (9.10)	t = 2.213 (0.029)*
Gender: Male	66 (54.5%)	32 (47.1%)	34(64.2%)	$\chi^2 = 3.51(0.061)$
Education in years mean (SD);range	13.37 (3.05);4–22	13.29 (3.36)	13.47(2.63)	t = -0.316 (0.753)
Marital status: currently married	39 (24.8%)	24 (35.3%)	15 (28.3%)	$\chi^2 = 0.667 (0.414)$
Occupation: on paid employment	30 (24.8%)	18 (26.5%)	12(22.6%)	$\chi^2 = 0.234 (0.628)$
Locality: urban	88 (72.7%)	47 (69.1%)	41 (77.4%)	$\chi^2 = 1.02 (0.313)$

χ^2 = Chi-square value.

Table 2
Comparison of clinical variables of Group I (schizophrenia with MS) with Group II (schizophrenia without MS).

Parameters	Whole sample (n = 121) Mean (SD)/ n (%)	Group I (N = 68) Mean (SD)/ n (%)	Group II (N = 53) Mean (SD)/ n (%)	T-test/Chi-square (P value)
Age of onset (in years)	23.97 (7.85);12–43	24.50(7.89)	23.30 (7.83)	t = 0.831 (0.408)
Total duration of illness (in years)	9.91 (7.38);2–38	11.11(7.76)	8.37(6.61)	t = 2.053(0.042)*
Duration of current treatment (in months)	56.45 (31.45)	54.72(30.00)	58.67(33.38)	t = -0.685(0.495)
Diagnosed with hypertension	9 (7.4%)	6 (8.8%)	3 (5.7%)	0.013 (0.907)
Diagnosed with diabetes mellitus	6 (5.0%)	5 (7.4%)	1 (1.9%)	0.907 (0.341)
<i>Current Pharmacological profile</i>				
Olanzapine	19 (15.7%)	11 (16.2%)	8 (15.1%)	0.02(0.87)
Risperidone	22 (18.2%)	12 (17.6%)	10 (18.9%)	0.02(0.86)
Clozapine	56 (46.3%)	37 (54.4%)	19 (35.8%)	4.12(0.042)*
Aripiprazole	10 (8.3%)	3 (4.4%)	7 (13.2%)	3.03(0.08)
Quetiapine	3 (2.5%)	1 (1.5%)	2 (3.7%)	1.63(0.20)
Amisulpride	8 (6.6%)	4 (5.9%)	4 (7.5%)	0.13(0.71)
Haloperidol	1 (0.8%)	0 (0%)	1 (1.9%)	FE = 0.43
Trifluoperazine	3 (2.5%)	0 (0%)	3 (5.7%)	FE = 0.08
Fluphenazine depot	1 (0.8%)	1 (1.5%)	0 (0%)	FE = 1.00
Type of antipsychotics				$\chi^2 = 2.776 (0.095)$
Typical antipsychotics	5 (4.1%)	1 (1.5%)	4 (7.5%)	
Atypical antipsychotics	116 (95.9%)	67 (98.5%)	49 (92.5%)	
<i>PANSS</i>				
Total positive score	12.90 (5.68)	12.58 (5.35)	13.30(6.10)	-0.684(0.495)
Total negative score	17.33 (6.93)	17.07 (6.21)	17.67(7.80)	-0.475 (0.635)
Total GP score	29.04 (9.63)	28.92 (8.34)	29.18(11.15)	-0.148 (0.883)
Total PANSS score	59.28 (17.71)	58.58 (15.17)	60.16 (20.64)	-0.486 (0.628)
<i>Global assessment of functioning</i>				
GAF score	68.31(15.58)	68.54(15.50)	68.01(15.83)	0.183(0.855)
Co-morbid Tobacco dependence: present	13 (10.74%)	6(8.8%)	7 (13.2%)	0.597 (0.43)

χ^2 = chi-square value, FE = Fischer's exact value for Chi-square test.

Table 3
Metabolic profile of both groups.

Parameters	Whole sample (n = 121) Mean (SD)/ n (%)	Group I (N = 68) Mean (SD)/ n (%)	Group II (N = 53) Mean (SD)/ n (%)	T-test (p value)
Weight (kg)	70.19 (14.12)	73.13(12.62)	66.43(15.14)	2.652 (0.009)*
Waist circumference (cm)	91.82(11.72)	95.92(10.18)	86.56(11.56)	4.727(< 0.001)***
BMI (kg/m ²)	26.01(5.25)	27.35 (5.19)	24.30(4.84)	3.306(0.001)***
SBP (mm/hg)	117.19(13.31)	118.71(12.81)	115.25(13.80)	1.425(0.157)
DBP (mm/hg)	76.19(8.94)	77.98(9.30)	73.88(7.95)	2.559(0.012)
Triglycerides (mmol/dl)	155.28(60.69)	185.44(56.76)	116.59(40.39)	7.474(< 0.001)***
HDL (mmol/dl)	39.99(10.01)	36.60(7.82)	44.33(10.88)	-4.546 (< 0.001)***
FBS (mmol/dl)	103.19(23.28)	113.75(24.55)	89.64(11.88)	6.568(< 0.001)***
<i>Number of MS criteria met</i>				
0	9 (7.4%)	0(0%)	9 (18.86%)	
1	16 (13.2%)	0(0%)	16 (30.18%)	
2	28 (23.1%)	0(0%)	28 (52.83%)	
3	42 (34.7%)	42 (61.76%)	0(0%)	
4	23 (19.0%)	23 (33.82%)	0(0%)	
5	3 (2.5%)	3 (4.41%)	0(0%)	

BMI: Body Mass Index; SBP: systolic blood pressure; DBP: diastolic blood pressure; FBS: fasting blood glucose levels.

Table 4
Comparison of Group I (Schizophrenia with MS) with Group II (Schizophrenia without MS) on neurocognitive domains.

Neurocognitive domains	Whole sample (n = 121) Mean (SD)/ n (%)	Group I (N = 68) Mean (SD)/ n (%)	Group II (N = 53) Mean (SD)/ n (%)	T-test/Mann-Whitney (p-value)	Between-Group differences ANCOVA (co-variables listed as Q) F values (p value)	Effect size (Cohen's d)
<i>Processing speed</i>						
TMT -A percentile	42.16 (21.58)	39.39 (22.68)	45.71 (19.73)	- 1.608 (0.110)	2.401 (0.025)	0.29
<i>Verbal fluency</i>						
COWA average new words percentile	22.02(14.29)	21.23 (13.46)	23.03 (15.36)	- 0.687 (0.494)	1.053 (0.399)	0.12
<i>Cognitive flexibility</i>						
TMT -B percentile	27.42 (18.15)	25.42 (18.69)	29.98 (17.27)	- 1.374 (0.172)	2.042 (0.056)	0.25
<i>Cognitive processing & selective attention</i>						
Stroop score	155.44 (77.56)	155.87 (80.77)	154.89 (73.98)	0.069 (0.945)	1.022 (0.420)	0.01
Stroop effect percentile	33.31 (29.16)	38.94 (30.43)	26.09 (25.97)	2.454 (0.016)	3.457 (0.002)*	0.45
<i>Auditory and verbal memory</i>						
Total AVLT score percentile	21.61 (18.69)	16.25(16.69)	28.50(19.00)	U = 1177.5 (0.001)***	12.663 (<0.001)***	0.68
AVLT immediate recall percentile	7.23 (4.77)	6.82(5.74)	7.75 (3.09)	1.065(0.289)	2.861 (0.009)	0.20
AVLT delayed recall percentile	8.01 (4.02)	7.67 (4.41)	8.45 (3.45)	- 1.053 (0.295)	0.924 (0.491)	0.12
<i>Executive functioning-TOL</i>						
<i>2 moves problems</i>						
Mean time percentile	17.23 (22.23)	19.38 (22.38)	14.46 (21.94)	U = 1485.5 (0.096)	0.995(0.439)	0.22
Mean moves percentile	76.86 (34.92)	71.01 (38.64)	84.37 (28.64)	2.118(0.036)	2.507 (0.020)	0.39
<i>3 moves problems</i>						
Mean time percentile	25.83 (18.84)	29.63 (20.51)	20.94 (15.28)	2.577 (0.011)	3.126 (0.005)	0.48
Mean moves percentile	14.62 (15.39)	19.41 (17.06)	8.49 (10.16)	4.121 (<0.001)**	4.641 (<0.001)**	0.77
<i>4 moves problems</i>						
Mean time percentile	24.18 (20.50)	20.99 (15.87)	28.28 (24.80)	- 1.963(0.052)	1.336 (0.240)	0.35
Mean moves percentile	17.34 (17.58)	21.70 (20.19)	11.74 (11.46)	3.209 (0.002)*	3.444(0.002)*	0.60
<i>5 moves problems</i>						
Mean time percentile	19.87 (23.76)	14.16 (12.26)	27.19 (31.81)	- 3.098 (0.002)*	3.394 (0.003)*	0.54
Mean moves percentile	9.71 (9.15)	10.52 (10.97)	8.66 (6.03)	1.109 (0.270)	1.871 (0.081)	0.21
Total problems solved percentile	16.18 (18.50)	17.67 (20.33)	14.26 (15.82)	1.004 (0.317)	1.898 (0.076)	0.18

*p value <0.05; **p value <0.01; ***p value <0.001; Q = Co-variables included - age, education inyears, total duration of illness, age of onset of psychosis, total PANSS positive score, total PANSS negative score, total GP score, presence of smoking status.

Table 5
Relationship of metabolic parameters with neurocognition in patients with schizophrenia (N = 121).

Neurocognitive domains	Weight r (p)	WC r (p)	TG r (p)	HDL r (p)	FBS r (p)	SBP r (p)	Number of MS criteria met
<i>Processing speed</i>							
TMT -A percentile	0.038 (0.681)	-0.140 (0.126)	0.054 (0.556)	-0.083 (0.364)	0.026 (0.779)	-0.042 (0.649)	-0.091 (0.320)
<i>Verbal fluency</i>							
COWA average new words percentile	0.171(0.06)	0.035(0.706)	-0.007(0.937)	-0.143(0.116)	-0.061(0.506)	0.062(0.500)	0.011 (0.908)
<i>Cognitive processing & selective attention</i>							
Stroop score	-0.164 (0.072)	-0.160 (0.079)	-0.117 (0.201)	-0.132 (0.148)	-0.009 (0.925)	0.104 (0.256)	0.025 (0.782)
Stroop effect percentile	0.016 (0.246)	0.153 (0.093)	0.165 (0.07)	-0.150 (0.101)	0.187 (0.04)*	-0.025 (0.783)	0.194 (0.033)*
<i>Cognitive flexibility</i>							
TMT -B percentile	-0.028 (0.759)	0.071 (0.441)	-0.071 (0.439)	0.139 (0.129)	0.012 (0.892)	-0.049 (0.597)	-0.102 (0.265)
<i>Auditory and verbal memory</i>							
Total AVLT score percentile	0.035(0.704)	-0.153 (0.093)	-0.102 (0.268)	0.127 (0.165)	-0.307 (0.001)**	0.036(0.694)	-0.188 (0.038)*
AVLT immediate recall percentile	0.046 (0.613)	0.048 (0.598)	0.046(0.615)	0.108 (0.237)	0.072 (0.430)	0.091(0.321)	0.012(0.896)
AVLT delayed recall percentile	0.020(0.830)	0.048 (0.601)	0.042 (0.648)	0.132 (0.150)	-0.109 (0.234)	0.026(0.779)	-0.014(0.882)
<i>Executive functioning-TOL</i>							
<i>2 moves problems</i>							
Mean time percentile	0.123 (0.179)	0.045(0.621)	0.116(0.203)	-0.068(0.460)	0.137(0.135)	0.031(0.739)	0.056(0.540)
Mean moves percentile	0.010(0.910)	0.055 (0.550)	-0.109(0.233)	0.063(0.492)	-0.216(0.017)*	0.001(0.995)	-0.058(0.528)
<i>3 moves problems</i>							
Mean time percentile	0.056(0.540)	0.142(0.120)	0.116(0.204)	-0.090(0.328)	0.205(0.024)*	0.181(0.047)*	0.200(0.028)*
Mean moves percentile	0.081(0.376)	0.185(0.042)*	0.172 (0.059)	-0.171(0.06)	0.245(0.007)*	0.018(0.848)	0.249(0.006)*
<i>4 moves problems</i>							
Mean time percentile	-0.069(0.451)	-0.149(0.103)	-0.043(0.640)	-0.013(0.886)	-0.062(0.497)	0.202(0.027)*	-0.138(0.130)
Mean moves percentile	0.158 (0.084)	0.276(0.002)*	0.108(0.237)	-0.104(0.258)	-0.385 < 0.001)**	0.048(0.605)	0.280(0.002)*
<i>5 moves problems</i>							
Mean time percentile	-0.141(0.123)	-0.307(0.001)**	-0.062(0.503)	0.038(0.676)	-0.220(0.015)*	0.155(0.089)	-0.208(0.022)*
Mean moves percentile	0.023(0.800)	0.04(0.667)	0.121(0.186)	-0.062(0.500)	0.063(0.489)	0.109(0.236)	0.111(0.224)
Total problems solved percentile	-0.066(0.470)	0.041(0.657)	0.003(0.973)	-0.163(0.074)	0.133(0.146)	0.022(0.811)	0.045(0.623)

*p value < 0.05; **p value < 0.01; ***p value < 0.001; BMI: Body Mass Index; SBP: systolic blood pressure; DBP: diastolic blood pressure; FBS: fasting blood glucose levels; TG: triglyceride levels; HDL: high density lipoprotein levels.

When the association of neurocognition with serum triglyceride levels was evaluated, it was seen that those with higher triglyceride levels had better executive functions (F value for mean four moves percentile = 3.46; $p = 0.002$), but poorer auditory and verbal total memory and immediate recall memory (F value = 9.95; $p < 0.001$).

In terms of HDL levels, HDL values lower than cut-off for MS were associated with poorer cognitive processing and selective attention (F value = 3.26; $p = 0.003$) and auditory and verbal total memory (F value = 9.36; $p < 0.001$).

Systolic blood pressure higher than the cut-off for MS was associated with poorer cognitive functions in the domains of auditory and verbal total memory (F value = 8.8; $p < 0.001$). Similarly, abnormal diastolic blood pressure was also associated with poorer functioning in the domains of auditory and verbal total memory (F value = 9.01; $p < 0.001$).

When those with normal and abnormal blood pressure (i.e., those having either or both abnormal systolic and diastolic blood pressure) were compared, it was found that abnormal blood pressure was associated with poorer auditory and verbal total memory (F value = 8.74; $p < 0.001$).

1.7. Discussion

The prevalence of MS in this study, estimated at 56.2% is in the range reported by other studies (Cohn et al., 2004; Malhotra et al., 2013; McEvoy et al., 2005). However, previous Indian studies have found lower rates, in the range, 36.5–44.5% (Grover et al., 2014, 2012). The higher prevalence in the present study could be due to the longer duration of illness and a higher proportion of patients on clozapine which is known to be associated with higher rates of MS (Grover et al., 2011; Lamberti et al., 2006).

The hypothesis in this study was that MS will have no negative impact on cognitive deficits among patients with schizophrenia. However, we found that patients with MS have higher neurocognitive impairments in the domains of auditory and verbal memory and executive functioning. Other researchers have also found a strong association between MS and cognitive deficits (Bora et al., 2017; Boyer et al., 2013; Goughari et al., 2015; Lindenmayer et al., 2012). This implies the need for close monitoring for MS and cognitive functions in patients with schizophrenia.

Several individual components of MS too had a negative impact on domains of neurocognitive functions such as cognitive processing, selective attention, auditory and verbal memory, and executive functions. This study replicates the finding of high blood pressure being associated with poorer functioning in the cognitive domains of auditory and verbal total memory and verbal fluency (Botis et al., 2016; Depp et al., 2014; Friedman et al., 2010; Goughari et al., 2015). However, before making further conclusions, factors such as duration of hypertension/raised blood pressure, lifestyle, dietary factors, dose of antipsychotics and antihypertensives used, etc. have to be examined more closely (Bilder et al., 2002; Meltzer and McGurk, 1999; Sharma et al., 2003). Therefore routine clinical care should include serial measurements of BP in such patients.

Elevated fasting blood glucose levels seem to have a negative impact on the neurocognitive domains of auditory and verbal total memory, but are associated with slightly better executive functions (Bora et al., 2017). However, findings on the relationship between glucose levels and neurocognitive functions have not been very consistent (Takayanagi et al., 2012). The discrepancy in the findings could be due to methodological issues (different cutoff point for hyperglycemia used in some studies, i.e., 126 mg/dL) and duration of hyperglycemia/diabetes mellitus in study subjects across the studies.

Existing data is inconsistent with respect to association of raised waist circumference and neurocognitive functions, with some studies suggesting no negative effect (Goughari et al., 2015; Takayanagi et al., 2012) and other group of researchers suggesting a poorer functioning in the domains of attention/vigilance (Lindenmayer et al., 2012) and

processing speed (Boyer et al., 2013; Wysokiński et al., 2013). We found that abnormal waist circumference/abdominal obesity had no impact on cognitive functions.

Opinion on the role of dyslipidemia (abnormal triglycerides and HDL) is again divided (Goughari et al., 2015; Takayanagi et al., 2012). Poor attention and vigilance (Boyer et al., 2013; Lindenmayer et al., 2012; Wysokiński et al., 2013), processing speed (Boyer et al., 2013), verbal memory (Botis et al., 2016; Wysokiński et al., 2013) and executive functions (Boyer et al., 2013; Wysokiński et al., 2013) have been associated with raised triglyceride levels. We too found hypertriglyceridemia to co-exist with poor auditory and verbal memory and immediate recall memory, and better executive functioning.

From the findings of the present study, it needs to be stressed that psychiatrists should look for hypertension and lipid abnormalities and manage them. It is worth debating whether those with more cognitive deficits tend to develop metabolic abnormalities and subsequently MS, because of poor decision making and adopting unhealthy lifestyle (Bora, 2015) or vice versa. Additionally, the confounding effect of the impact of antipsychotics on the metabolic parameters, which is difficult to control, should be considered while interpreting the results.

The negative impact of MS on cognitive functioning can be an outcome of neuroinflammation caused by these abnormalities (Li et al., 2014; Panza et al., 2011; Ricci et al., 2017; Solfrizzi et al., 2010). This effect is possibly mediated by the insulin resistance, possibly arising as a result of chronic use of antipsychotics (Cai et al., 2013; Houseknecht et al., 2007; Poa and Edgar, 2007; MacKenzie et al., 2018).

Some of the limitations of this study are the relatively small sample size, a cross sectional design, and being restricted to a population on treatment. A few likely confounding factors such as number of psychotic episodes, time spent in psychosis, physical activities were not included in the analyses. In our future work, we will use the Brief Assessment of Cognition in Schizophrenia (BACS) which has been more widely used.

In conclusion, findings of the present study suggest that almost all the components of MS affect one or the other domain of neurocognition in patients with schizophrenia. The findings of this study have important clinical implications. There is a need to regularly monitor various metabolic parameters among patients with schizophrenia and to initiate appropriate intervention so as to minimize the negative impact on cognitive deficits which are already compromised in this group of patients.

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Supplementary materials

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