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Effect of metabolic abnormalities on cognitive performance and clinical symptoms in schizophrenia

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Summary

Aim. The objective of this study is to determine whether and how metabolic abnormalities are associated with clinical symptoms and cognitive performance in schizophrenia.
Methods. 46 adult patients with schizophrenia taking first- or second generation antipsychotics were included in the study. The following data were collected: BMI, abdominal circumference, lipid panel and blood glucose, blood pressure and treatment of comorbidities. Clinical symptoms were assessed using PANSS, CDSS, CGI and SAS scales. Cognitive performance was assessed using CNS Vital Signs computerized battery of tests: Verbal Memory test, Visual Memory test, Finger Tapping Test, Symbol Digit Coding, Stroop Test, Shifting Attention Test, and Continuous Performance Test.
Results. Dyslipidemia, raised LDL and raised blood glucose levels were the best predictors of more severe clinical symptoms (PANSS, PANSS P, PANSS G, CGI) and lower neurocognitive index, worse cognitive flexibility, executive functions, complex attention composite memory, verbal memory, slower reaction time and worse performance in SAT, CPT, ST tests. Obesity was associated with worse results in VBM, VIM, FTT, SDC tests. Raised blood pressure was associated with improvements in all cognitive domains and better performance in SAT, CPT, ST tests.
Discussion. There are several weak associations between severity of clinical symptoms and metabolic abnormalities. Most of these were for blood glucose levels and raised blood glucose. Lipids and glucose abnormalities are the best predictors of deteriorated cognitive performance. Contrary to previous observations, raised blood pressure was associated with better results in cognitive tests.
Conclusions. These findings indicate that cognitive impairment and metabolic abnormalities may be linked in patients with schizophrenia.

metabolic syndrome / obesity / schizophrenia / cognitive functions

INTRODUCTION

Schizophrenia is a mental disorder causing significant public health problems. Its course (onset in early adult life and recurring course), poor prognosis and excessive morbidity and mortality, as well negative personal, familial, social, occupational and educational consequences emphasize the importance of proper diagnosis and effective treatment. Antipsychotics remain the primary therapeutic option for schizophrenia and other psychotic disorders. They are effective, yet current researches indicate that metabolic abnormalities (usually named as metabolic syndrome) may be more frequent in patients treated with antipsychotics (particularly of second-generation) comparing to general population [1]. However, this applies not only to antipsychotics, but also to mood stabilizers [2] and antidepressants [3], so these are common consequences for all major psychopharmacological drugs used nowadays. Therefore, patients with

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psychiatric disorders may have increased mortality resulting from increased risk of cardiovascular events (e.g. myocardial infarction, sudden cardiac death and stroke) [4].

Metabolic syndrome (MetS) is a complex clinical condition. It is a cluster of metabolic disorders comprising central (abdominal) obesity, dyslipidemia, hypertension and abnormal blood glucose levels. Various criteria are used to diagnose MetS. International Diabetes Federation (IDF) criteria are the most widely used in European studies [5]. These are slightly more restrictive than American ATPIII criteria [6]. The presence of MetS increases the risk of death due to cardiovascular diseases [7].

Cognitive impairment is a core pathophysiological feature of schizophrenia. Deficits include the domains of attention, executive functioning, memory, verbal skills, and processing speed impairments [8] and have been found in first episode patients, as well as first-degree relatives of schizophrenia patients [9, 10].

Both metabolic abnormalities and cognitive impairment are common in patients with schizophrenia. It is however unclear, whether these two phenomena are related to each other. Therefore, the present study was undertaken with the purpose to determine whether and how strongly various metabolic abnormalities are associated with clinical symptoms and cognitive performance in subjects with schizophrenia.

METHODS

Forty six European Caucasian adult in-hospital patients with paranoid schizophrenia (diagnosed using ICD-10 criteria) treated with first and/or second generation antipsychotics were included in the study. Antipsychotic treatment (class - first or second generation, drug name and daily dose) and treatment of comorbidities (diabetes, arterial hypertension and hyperlipidemia) were also registered. All subjects gave written informed consent in accordance with ethical committee approval.

Clinical symptoms of schizophrenia were assessed using the Positive and Negative Syndrome Scale (PANSS), severity of depression - using the Calgary Depression Scale for Schizophrenia (CDSS), general illness severity - using the Clinical Global Impressions (CGI), while extrapyramidal symptoms were measured using the Simpson-Angus Scale (SAS). All assessments were performed once, after participants finished CNSVS tests. CGI items were defined from 1 = among the most extremely ill to 7 = normal, not at all ill.

The blood samples for the chemistry panel that included fasting plasma glucose and lipid panel (total cholesterol (TC), high density lipoproteins (HDL), and low density lipoproteins (LDL) as well as triglycerides (TGA)) were collected between 7 am and 8 am, after ensuring at least 8 h of overnight fasting. The samples were immediately transferred to the central laboratory where they were analyzed. Plasma glucose and serum lipids were estimated using a Dirui CS-400 Auto-Chemistry Analyzer (Dirui, China).

Height was measured with a wall-mounted height measure to the nearest 1 cm. Weight was measured with a spring balance that was kept on a firm horizontal surface. Subjects wore light clothing, stood upright without shoes and weight was recorded to the nearest 0.5 kg. Body mass index (BMI) was calculated as body weight in kilogram divided by the height in meter squared (kg/m^2). Abdominal circumference was measured using a non-stretchable fiber measuring tape, at a level midway between the lowest rib and the iliac crest.

MetS and its components were defined according to the International Diabetes Federation (IDF) criteria (5). These include: (1) central obesity (waist circumference): men ≥94 cm, women ≥80 cm (for Europeans); (2) raised blood pressure or specific treatment: ≥130/≥85 mm Hg or treatment of previously diagnosed hypertension; (3) reduced HDL level: men <40 mg/dL, women <50 mg/dL, or specific treatment; (4) raised TGA level: ≥150 mg/dL or specific treatment; (5) raised FPG level or specific treatment: ≥100 mg/dL or previously diagnosed type 2 diabetes. MetS is present if central obesity (obligatory) if found and additional 2 criteria are met. Raised blood glucose was defined as fasting plasma glucose level >100 mg/dL. Normal weight, overweight and obesity were defined as BMI <25 kg/m^2, 25-30 kg/m^2 and ≥30 kg/m^2, respectively. Raised TGA level ≥150 mg/dL and/or TC ≥200 mg/dL and/or reduced HDL level <40 mg/dL for men and <50 mg/dL for women and/or raised LDL

level ≥135 mg/dL and/or current treatment with statins or fibrates were interpreted as dyslipidemia. Raised blood pressure and central obesity were defined according to IDF criteria for Europeans (see above).

Cognitive performance was assessed using CNS Vital Signs (CNSVS) (CNS Vital Signs LLC, Morrisville, USA) computerized battery of tests. This battery of tests includes the following tests: Verbal Memory test (VBM), Visual Memory test (VIM), Finger Tapping Test (FTT), Symbol Digit Coding (SDC), Stroop Test (ST), Shifting Attention Test (SAT), and Continuous Performance Test (CPT). The test was performed once, during in-hospital treatment.

Statistical procedures were performed with STATA 12.1 for OS X (StataCorp, College Station, Texas, USA). Simple descriptive statistics (means, standard deviations and 95% confidence interval) were generated for all continuous variables. For discrete variables number of patients and percentages are given. For inter-group comparisons t-test was used. Associations were measured using logistic regression for discrete variables and linear regression for continuous variables. The significant level was set at P≤0.05. The study protocol was approved by the local Bioethics Committee. There was no financial involvement from the industry.

RESULTS

Demographic and clinical details are shown in Tab. 1.

All subjects were right-handed. The majority of subjects was taking second generation antipsychotics, of which clozapine, quetiapine, risperidone and olanzapine were most frequent. There were more men in the study group (35 (76.1%) vs. 11 (23.9%). All subjects were right-handed. On average severity of schizophrenia symptoms was moderate (PANSS total: 75.8±22.3 points, with more pronounced negative symptoms - PANSS P 15.5±5.5 vs. PANSS N 25.5±9.1 points, CGI points: 3.5±1.2). Patients were not severely depressed (CDSS: 5.0±4.5 points) and had no severe extrapyramidal symptoms (SAS: 1.9±3.2 points).

We have found several associations between all clinical scales used and the presence of MetS, abdominal obesity, abnormal fasting plasma glucose, hypertension, dyslipidemia, values of BMI, abdominal circumference, fasting plasma glucose and diastolic blood pressure. No associations were found for the number of MetS criteria met, BMI≥25 kg/m^2, systolic blood pressure, and levels of total cholesterol, HDL, LDL and triglycerides. All significant associations between metabolic parameters and clinical symptoms are shown in Tab. 2 – *page 17.*

We have also found several significant associations between metabolic parameters (the presence of MetS, obesity, abdominal obesity, abnormal fasting plasma glucose, hypertension, dyslipidemia, values of fasting plasma glucose, systolic and diastolic blood pressure, total cholesterol and LDL cholesterol) and neurocognitive index (primary score for the CNSVS test, calculated as an average score derived from domain scores,

Table 1. Demographic and clinical details.

Men Women	35 (76.1) 11 (23.9)
Age [years]	31.7±10.9
Education [years]	13.3±2.6
Tobacco smoking	24 (52.2)
Treatment duration [months]	105.0±89.5
PANSS total [points]	75.8±22.3
PANSS P [points]	15.5±5.5
PANSS N [points]	25.5±9.1
PANSS G [points]	34.0±10.1

table continued on next page

CDSS [points]	5.0±4.5
CGI [points]	3.5±1.2
SAS [points]	1.9±3.2
Patients taking FGAs	4 (8.7)
Patients taking SGAs	46 (100.0)
Number of APs	1: 18 (39.1) >1: 28 (60.9)
BMI [kg/m^2]	28.2±5.1
AC [cm]	100.4±14.1
TC [mg/dL]	194.4±40.2
HDL [mg/dL]	38.2±11.2
LDL [mg/dL]	122.8±31.0
TGA [mg/dL]	171.0±76.5
FPG [mg/dL]	103.1±28.2
SBP [mm Hg]	119.4±15.5
DBP [mm Hg]	80.0±11.9
Patients with MetS ‡	27 (58.7)
MetS – number of criteria met ‡	0: 2 (4.3) 1: 6 (13.0) 2: 8 (17.4) 3: 8 (17.4) 4: 14 (30.4) 5: 8 (17.4)
Patients with antihypertensive treatment	12 (26.1)
Patients with dyslipidemia treatment	7 (15.2)
Patients with antidiabetic treatment	4 (8.7)
Patients with normal body weight Patients with overweight Patients with obesity	14 (30.4) 16 (34.8) 16 (34.8)
Patients with abdominal obesity ‡	31 (67.4)
Patients with raised blood pressure	25 (54.3)
Patients with raised blood glucose	20 (43.5)
Patients with dyslipidemia	40 (87.0)

Data given as mean ± standard deviation for continuous variables or n (%) for discrete variables.

‡ IDF – defined.

PANSS = Positive and Negative Syndrome Scale; PANSS P = PANSS positive symptoms subscale; PANSS N = PANSS negative symptoms subscale; PANSS G = PANSS general symptoms subscale; CDSS = Calgary Depression Scale for Schizophrenia; CGI = Clinical Global Impressions; SAS = Simpson-Angus Scale; APs = antipsychotics; FGAs = first generation antipsychotics; SGAs = second generation antipsychotics; BMI = body mass index; AC = abdominal circumference; TC = total cholesterol; HDL = high density lipoproteins; LDL = low density lipoproteins; TGA = triglycerides; FPG = fasting plasma glucose; SBP = systolic blood pressure; DBP = diastolic blood pressure; MetS = metabolic syndrome; NS = not significant.

which reflects general neurocognitive performance), all nine major cognitive domains (Composite Memory, Psychomotor Speed, Reaction Time, Cognitive Flexibility, Executive Function, Verbal Memory, Visual Memory, Complex Attention, Processing Speed), as well as total test

Table 2. Associations between metabolic parameters and clinical symptoms

	MetS(+) (n=27) vs MetS(-) (n=19)	Abd(+) (n=31) vs Abd(-) (n=15)	BMI [kg/m^2]	AC [cm]	GLU(+) (n=20) vs GLU(-) (n=26)	FPG [mg/dL]	HA(+) (n=25) vs HA(-) (n=21)	DBP [mm Hg]	LIP(+) (n=40) vs LIP(-) (n=6)
PANSS	NS	NS	NS	NS	83.5±20.7 69.9±22.0 p=0.02 OR=1.03	β=0.29 p=0.01 η^2=0.14	NS	NS	NS
PANSS P	NS	NS	NS	NS	17.5±5.9 13.9±4.7 p=0.01 OR=1.14	β=0.07 p<0.01 η^2=0.16	NS	NS	NS
PANSS N	23.1±9.0 29.0±8.1 p=0.01 OR=0.92	23.9±9.2 28.9±8.1 p=0.04 OR=0.94	β=-0.68 p<0.01 η^2=0.15	β=-0.19 p=0.05 η^2=0.09	NS	NS	NS	NS	NS
PANSS G	NS	NS	NS	NS	36.9±10.8 31.7±9.2 p=0.04 OR=1.05	β=0.14 p<0.01 η^2=0.15	NS	NS	NS
CDSS	NS	NS	NS	NS	NS	NS	3.8±3.9 6.4±4.8 p=0.02 OR=0.87	NS	4.5±4.3 8.0±5.4 p=0.04 OR=0.85
CGI	NS	NS	NS	NS	3.2±1.0 3.8±1.3 p=0.04 OR=0.61	β=-0.01 p<0.04 η^2=0.09	3.9±1.3 3.1±0.9 p=0.02 OR=1.8	NS	NS
SAS	NS	NS	NS	NS	NS	NS	NS	β=0.1 p=0.01 η^2=0.14	NS

Data given as mean±standard deviation.
OR = odds ratio; β = regression coefficient; η^2 = effect size; NS = not significant.
MetS(+) = with metabolic syndrome; MetS(-) = without metabolic syndrome; Abd(+) = with central obesity; Abd(-) = without abdominal obesity; BMI = body mass index; AC = abdominal circumference; GLU(+) = with raised blood glucose; GLU(-) = without raised blood glucose; FPG = fasting plasma glucose; HA(+) = with raised blood pressure; HA(-) = without raised blood pressure; DBP = diastolic blood pressure; LIP(+) = with dyslipidemia; LIP(-) = without dyslipidemia.

time (measured in seconds). Tab. 3 – *next page* shows all significant associations between metabolic parameters and major cognitive domains. For better clarity, only significant results were shown. Tab. 4 – *page 19.*

Table 3. Associations between metabolic parameters and major cognitive domains

	MetS(+) (n=27) vs MetS(-) (n=19)	Obs(+) (n=32) vs Obs(-) (n=14)	Abd(+) (n=31) vs Abd(-) (n=15)	GLU(+) (n=20) vs GLU(-) (n=26)	FPG [mg/dL]	HA(+) (n=25) vs HA(-) (n=21)	SBP [mm Hg]	DBP [mm Hg]	LIP(+) (n=40) vs LIP(-) (n=6)	TC [mg/dL]	LDL [mg/dL]
NCI	NS	NS	NS	NS	NS	70.8±19.4 58.5±25.0 p=0.03 OR=1.03	β=0.6 p<0.01 η^2=0.18	β=0.7 p=0.01 η^2=0.14	NS	NS	β=-0.3 p<0.01 η^2=0.18
Composite Memory	NS	NS	NS	85.1±9.5 90.4±9.2 p<0.03 OR=0.94	β=-0.1 p=0.04 η^2=0.08	NS	β=0.2 p=0.02 η^2=0.11	β=0.2 p=0.05 η^2=0.08	NS	NS	NS
Psychomotor Speed	NS	126.5±26.6 142±14.7 p=0.02 OR=0.97	NS	124.7±22.4 136.4±25.3 p=0.05 OR=0.98	NS	NS	β=0.5 p=0.04 η^2=0.1	NS	NS	NS	NS
Reaction Time*	815.7±120.6 893.5±170.9 p=0.04 OR=1.0	NS	NS	NS	β=1.6 p=0.04 η^2=0.1	NS	β=-3.5 p=0.01 η^2=0.14	β=-3.8 p=0.04 η^2=0.09	863.0±142.8 746.3±144.9 p=0.03 OR=1.0	NS	NS
Cognitive Flexibility	NS	NS	NS	NS	NS	24.4±18.6 11.9±26.2 p=0.04 OR=1.02	β=0.5 p=0.02 η^2=0.12	β=0.6 p=0.03 η^2=0.1	16.1±21.7 34.4±26.8 p=0.03 OR=0.95	NS	β=-0.3 p<0.01 η^2=0.20
Executive Function	NS	NS	NS	NS	NS	26.2±17.6 14.9±24.8 p=0.04 OR=1.02	β=0.5 p=0.02 η^2=0.11	β=0.6 p=0.04 η^2=0.01	18.8±20.5 36.0±25.7 p=0.03 OR=0.95	NS	β=-0.3 p<0.01 η^2=0.19
Verbal Memory	NS	NS	NS	45.1±6.5 49.1±6.0 p=0.02 OR=0.90	β=-0.1 p=0.05 η^2=0.08	NS	β=0.2 p<0.01 η^2=0.17	β=0.2 p=0.03 η^2=0.1	NS	NS	NS
Visual Memory	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Complex Attention*	NS	NS	NS	NS	NS	15.4±10.5 21.4±12.1 p=0.04 OR=0.95	β=-0.2 p=0.02 η^2=0.11	NS	NS	β=0.1 p=0.04 η^2=0.1	β=0.2 p<0.001 η^2=0.26
Processing Speed	NS	36.7±10.9 43.0±10.3 p=0.4 OR=0.94	NS	NS	NS	NS	β=0.3 p=0.01 η^2=0.13	NS	NS	NS	NS
Total Test Time*	NS	1858.6±153.1 1736.0±138.9 p<0.01 OR=1.01	1862.8±162.9 1735.5±108.1 p<0.01 OR=1.01	NS	NS	NS	NS	β=4.0 p=0.04 η^2=0.09	NS	β=1.2 p=0.03 η^2=0.1	NS

Data given as mean±standard deviation.

OR = odds ratio; β = regression coefficient; η^2 = effect size; NS = not significant.

* Lower is better.

MetS(+) = with metabolic syndrome; MetS(-) = without metabolic syndrome; Obs(+) = BMI ≥25 kg/m^2; Obs(-) = BMI<25 kg/m^2; Abd(+) = with central obesity; Abd(-) = without abdominal obesity; AC = abdominal circumference; GLU(+) = with raised blood glucose; GLU(-) = without raised blood glucose; FPG = fasting plasma glucose; HA(+) = with raised blood pressure; HA(-) = without raised blood pressure; SBP = systolic blood pressure; DBP = diastolic blood pressure; LIP(+) = with dyslipidemia; LIP(-) = without dyslipidemia; TGA = triglycerides; TC = total cholesterol; LDL = low density lipoproteins; HDL = high density lipoproteins.

Table 4. Verbal Memory Test (VBM)

	MetS(+) (n=27) vs MetS(-) (n=19)	Obs(+) (n=32) vs Obs(-) (n=14)	BMI [kg/m2]	AC [cm]	GLU(+) (n=20) vs GLU(-) (n=26)	FPG [mg/dL]	HA(+) (n=25) vs HA(-) (n=21)	SBP [mm Hg]	DBP [mm Hg]	LIP(+) (n=40) vs LIP(-) (n=6)	TGA [mm Hg]
Correct Hits - Immediate	NS	NS	NS	NS	NS	NS	NS	NS	NS	10.4±2.9 12.7±1.5 p=0.04 OR=0.6	NS
Correct Passes - Immediate	NS	NS	β=-0.06 p=0.02 η2=0.12	β=-0.02 p=0.05 η2=0.08	NS	NS	NS	NS	NS	NS	NS
Correct Hits Reaction Time - Immediate	NS	NS	NS	NS	NS	NS	NS	β=-4.9 p=0.01 η2=0.13	NS	NS	NS
Correct Hits - Delay	NS	NS	NS	NS	6.6±3.5 9.0±2.9 p=0.01 OR=0.8	β=-0.04 p=0.02 η2=0.11	NS	β=0.12 p<0.001 η2=0.27	β=0.12 p<0.01 η2=0.17	NS	NS
Correct Passes - Delay	NS	NS	NS	NS	13.8±1.1 14.4±1.1 p=0.04 OR=0.6	NS	NS	NS	NS	NS	NS
Correct Hits Reaction Time - Delay	893.7±139.1 1006.2±189.7 p=0.01 OR=1.0	NS	NS	NS	NS	NS	900.0±141.4 988.0±190.3 p=0.04 OR=1.0	NS	β=-6.5 p=0.001 η2=0.21	NS	β=-1.0 p<0.01 η2=0.19

Data given as mean±standard deviation.

OR = odds ratio; β = regression coefficient; η^2 = effect size; NS = not significant.

MetS(+) = with metabolic syndrome; MetS(-) = without metabolic syndrome; Obs(+) = BMI ≥25 kg/m^2; Obs(-) = BMI<25 kg/m^2; BMI = body mass index; AC = abdominal circumference; GLU(+) = with raised blood glucose; GLU(-) = without raised blood glucose; FPG = fasting plasma glucose; HA(+) = with raised blood pressure; HA(-) = without raised blood pressure; SBP = systolic blood pressure; DBP = diastolic blood pressure; LIP(+) = with dyslipidemia; LIP(-) = without dyslipidemia; TGA = triglycerides.

We have also analyzed relationship between metabolic abnormalities and individual cognitive tests and their sub-scores. We have found there were associations for each of the CNSVS test and many (but not all) sub-scores with several metabolic parameters. Tab. 4–10 show all significant associations for individual CNSVS tests. Again, for better clarity, only significant results were shown.

DISCUSSION

Clinical symptoms

Our results indicate there are several weak associations between severity of clinical symptoms and metabolic abnormalities. Most of these were for blood glucose levels and raised blood glucose. We find these results relatively consistent

Table 5. Visual Memory Test (VIM)

	MetS(+) (n=27) vs MetS(-) (n=19)	Abd(+) (n=31) vs Abd(-) (n=15)	BMI [kg/m^2]	DBP [kg/m^2]
Correct Hits – Immediate	NS	NS	NS	NS
Correct Passes – Immediate	NS	NS	NS	NS
Correct Hits Reaction Time - Immediate	NS	NS	NS	NS
Correct Hits – Delay	8.8±2.3 7.6±2.7 p=0.05 OR=1.2	8.8±2.6 7.4±2.2 p=0.04 OR=1.2	β=0.14 p=0.04 η^2=0.09	β=0.07 p=0.03 η^2=0.1
Correct Passes – Delay	NS	10.4±2.7 12.1±2.0 p=0.02 OR=0.7	NS	NS
Correct Hits Reaction Time – Delay	NS	NS	NS	β=-4.9 p=0.02 η^2=0.12

Data given as mean±standard deviation.

OR = odds ratio; β = regression coefficient; η^2 = effect size; NS = not significant.

MetS(+) = with metabolic syndrome; MetS(-) = without metabolic syndrome; Abd(+) = with central obesity; Abd(-) = without abdominal obesity; BMI = body mass index; DBP = diastolic blood pressure.

Table 6. Finger Tapping Test (FTT)

	Obs(+) (n=32) vs Obs(-) (n=14)
Right Taps Average	45.4±10.5 50.8±5.2 p=0.04 OR=0.93
Left Taps Average	NS

Data given as mean±standard deviation.

OR = odds ratio; β = regression coefficient; η^2 = effect size; NS = not significant.

Obs(+) = BMI ≥25 kg/m2; Obs(-) = BMI<25 kg/m2.

Table 7. Symbol Digit Coding (SDC)

	Obs(+) (n=32) vs Obs(-) (n=14)	SBP [mm Hg]	LIP(+) (n=40) vs LIP(-) (n=6)
Correct Responses	37.2±11.1 43.8±10.5 p=0.03 OR=0.94	β=0.26 p=0.01 η^2=0.13	NS
Errors*	NS	NS	0.5±0.9 1.3±1.5 p=0.03 OR=0.52

Data given as mean±standard deviation.

OR = odds ratio; β = regression coefficient; η^2 = effect size; NS = not significant.

* Lower is better.

Obs(+) = BMI ≥25 kg/m^2; Obs(-) = BMI<25 kg/m^2; SBP = systolic blood pressure; LIP(+) = with dyslipidemia; LIP(-) = without dyslipidemia.

T**able 8.** Stroop Test (ST)

	MetS(+) (n=27) vs MetS(-) (n=19)	Obs(+) (n=32) vs Obs(-) (n=14)	FPG [mg/dL]	SBP [mm Hg]	DBP [mm Hg]	LIP(+) (n=40) vs LIP(-) (n=6)	TGA [mg/dL]	LDL [mg/dL]
Simple Reaction Time*	338.6±80.5 433.4±187.4 p=0.01 OR=1.0	NS	NS	NS	β=-3.6 p=0.04 η^2=0.09	NS	β=-0.5 p=0.05 η^2=0.09	NS
Complex Reaction Time Correct*	715.0±112.5 814.1±186.0 p=0.01 OR=1.0	702.1±104.5 784.6±168.8 p=0.04 OR=1.0	β=1.9 p=0.01 η^2=0.13	β=-2.9 p=0.05 η^2=0.09	NS	NS	β=-0.6 p=0.04 η^2=0.09	NS
Reaction Time Correct*	NS	NS	NS	β=-4.2 p=0.01 η^2=0.14	NS	957.3±173.3 816.2±147.0 p=0.03 OR=1.0	NS	β=2.0 p=0.02 η^2=0.13
Commission Errors*	NS	NS	NS	β=-0.05 p=0.01 η^2=0.14	NS	NS	NS	β=0.03 p=0.01 η^2=0.13

Data given as mean±standard deviation.

OR = odds ratio; β = regression coefficient; η^2 = effect size; NS = not significant.

* Lower is better.MetS(+) = with metabolic syndrome; MetS(-) = without metabolic syndrome; Obs(+) = BMI ≥25 kg/m^2; Obs(-) = BMI<25 kg/m^2; FPG = fasting plasma glucose; SBP = systolic blood pressure; DBP = diastolic blood pressure; LIP(+) = with dyslipidemia; LIP(-) = without dyslipidemia; TGA = triglycerides; LDL = low density lipoproteins.

Table 9. Shifting Attention Test (SAT)

	HA(+) (n=25) vs HA(-) (n=21)	SBP [mm Hg]	DBP [mm Hg]	LIP(+) (n=40) vs LIP(-) (n=6)	LDL [mg/dL]
Correct Responses	NS	β=0.3 p=0.03 η^2=0.11	β=0.3 p=0.05 η^2=0.08	33.3±12.2 46.3±16.9 p=0.01 OR=0.9	β=-0.18 p<0.01 η^2=0.16
Errors*	11.6±7.6 16.7±9.6 p=0.02 OR=0.9	β=-0.2 p=0.03 η^2=0.1	β=-0.2 p=0.03 η^2=0.1	NS	β=0.13 p=0.001 η^2=0.21
Correct Reaction Time*	NS	NS	NS	1324.35±172.6 1076.0±268.2 p<0.01 OR=1.0	NS

Data given as mean±standard deviation.

OR = odds ratio; β = regression coefficient; η^2 = effect size; NS = not significant.

* Lower is better.

HA(+) = with raised blood pressure; HA(-) = without raised blood pressure; SBP = systolic blood pressure; DBP = diastolic blood pressure; LIP(+) = with dyslipidemia; LIP(-) = without dyslipidemia; LDL = low density lipoproteins.

Table 10. Continuous Performance Test (CPT)

	GLU(+) (n=20) vs GLU(-) (n=26)	FPG [mg/dL]	SBP [mm Hg]	TC [mg/dL]	LDL [mg/dL]
Correct Responses	38.4±2.3 39.4±1.1 p=0.03 OR=0.68	β=-0.02 p=0.04 η^2=0.09	NS	NS	β=-0.02 p=0.03 η^2=0.1
Omission Errors*	1.5±1.8 0.6±1.1 p=0.03 OR=1.47	β=0.2 p=0.04 η^2=0.09	NS	NS	β=0.02 p=0.03 η^2=0.1
Commission Errors*	NS	NS	NS	β=0.01 p=0.03 η^2=0.11	β=0.01 p=0.01 η^2=0.14
Choice Reaction Time Correct*	494.6±58.1 448.6±73.4 p=0.01 OR=1.01	β=0.9 p=0.02 η^2=0.12	β=-1.5 p=0.03 η^2=0.1	NS	β=0.72 p=0.03 η^2=0.1

Data given as mean±standard deviation.

OR = odds ratio; β = regression coefficient; η^2 = effect size; NS = not significant.

* Lower is better.

GLU(+) = with raised blood glucose; GLU(-) = without raised blood glucose; FPG = fasting plasma glucose; SBP = systolic blood pressure; TC = total cholesterol; LDL = low density lipoproteins.

with our hypothesis. Total PANSS score, as well as PANSS P and PANSS G scores (which measure the severity of positive and general symptoms) were positively correlated with glucose abnormalities (OR=1.03 and 1.05, respectively). CGI scores (which reflects general impression; higher scores represent better results) were negatively correlated with glucose abnormalities (OR=0.61) and the presence of hypertension (OR=1.8).

Interestingly, PANSS N scores (which reflects negative symptoms) were negatively correlated with the presence of MetS (OR=0.92), obesity (β=-0.68), abdominal obesity (OR=0.94) and abdominal circumference (β=-0.19), while CDSS scores (which reflects the severity of depression, so a phenomenon somewhat similar to negative symptoms) were negatively correlated with the presence of hypertension (OR=0.87) or dyslipidemia (OR=0.85).

As it was previously reported [11] our hypothesis was that increased BMI, abdominal obesity and other metabolic abnormalities would rather be associated with more severe negative symptoms (e.g. more lethargic, apathetic, anhedonic and depressed patients should have less active life-style, less healthy diet and care less about proper treatment of metabolic abnormalities). Our results could be explained by the fact that usually for such patients non-sedating antipsychotics ares used (amisulpride, aripiprazole, ziprazidone), which have less frequent metabolic side-effects [12]. Therefore, we assume that there are some, at most moderate, associations between metabolic parameters and clinical symptoms of schizophrenia.

Cognitive performance

Similar to previous observations (e.g. for patients with bipolar disorder [13]), we found that metabolic abnormalities are correlated with worse cognitive performance. It seems that lipid and glucose abnormalities were the best predictors of worse results in most of CNSVS major cognitive domains.

Lipid parameters were associated with: lower neurocognitive index (general assessment of the overall neurocognitive status of a patient) (β=-0.3 for LDL), lower cognitive flexibility (how well subject is able to adapt to rapidly changing and increasingly complex set of directions and/or to manipulate the information) (β=-0.3 for LDL), lower executive functions (how well a subject recognizes rules, categories, and manages or navigates rapid decision making) (β=-0.3 for LDL), lower complex attention (ability to track and respond to information over lengthy periods of time and/or perform mental tasks requiring vigilance quickly and accurately) (β=0.2 for LDL; β=0.1 for TC; in this test lower scores are better) and longer total test time (β=1.2 for TC). The presence of dyslipidemia was also associated with slower reaction time (how quickly the subject can react, in milliseconds, to a simple and increasingly complex direction set) (OR=1.0), lower cognitive flexibility (OR=0.95) and lower executive functions (OR=0.95).

Raised blood glucose was associated with lower composite memory (how well subject can recognize, remember, and retrieve words and geometric figures) (β=-0.1), lower verbal memory (how well subject can recognize, remember, and retrieve words) (β=–0.1) and slower reaction time (β=1.6). The presence of raised fasting plasma glucose was associated with lower composite memory (OR=0.94), lower psychomotor speed (which measures how well a subject perceives, attends, responds to visual-perceptual information, and performs motor speed and fine motor coordination) (OR=0.98) and lower verbal memory (OR=0.90).

The presence of general obesity was associated with longer total test time (OR=1.01), slower processing speed (how well a subject recognizes and processes information) (OR=0.94) and slower psychomotor speed (OR=0.97), the presence of abdominal obesity was associated with longer total test time (OR=1.01). Interestingly, the presence of metabolic syndrome was associated with better reaction time (OR=1.0).

Giving that elevated blood pressure is associated with cognitive decline (at least in long-term observations) [14], it is particularly interesting that the presence of hypertension, as well as values of systolic or diastolic blood pressure were associated with improvements in all but one (total test time, which was positively (β=4.0) correlated only with diastolic blood pressure) cognitive domains. One hypothesis that may explain this finding is that, at least in older patients,

higher blood pressure improves cerebral blood flow and therefore - cognitive performance [15]. However, we have studied a group of younger patients and there this may not apply to our group.

Obese subjects achieved worse results in the following tests: Verbal Memory (VBM, which measures recognition memory for words) - only in two sub-scores, Visual Memory (VIM, which measures recognition memory for figures) - again only in two sub-scores, Finger Tapping (FTT, which measures motor speed and fine motor control) for a dominant hand and Symbol Digit Coding (SDC, which measures information processing speed and complex attention). However, these observation is somewhat inconsistent since in the Stroop Test (ST, which measures executive function, information processing speed, and inhibition / disinhibition) patients with MetS and/or obesity achieved better results in two sub-scores.

For several sub-scores we have observed that raised systolic or diastolic blood pressure was associated with improvements, while the presence of glucose and lipid abnormalities correlated with worse results. These tests were: Shifting Attention Test (SAT, which is a measure of ability to shift from one instruction set to another quickly and accurately), Continuous Performance Test (CPT, which is a measure of vigilance or sustained attention or attention over time) and Stroop Test. Finally, we have found no associations with any of metabolic variables for visual memory performance.

These results indicate that of all analyzed metabolic variables, lipids and glucose abnormalities are the best predictors of deteriorated cognitive performance in schizophrenia patients. Contrary to previous observations, raised blood pressure was associated with better results in cognitive tests.

Detrimental effects of metabolic disorders on cognitive functioning were previously established both in healthy people [16], as well as in patients with schizophrenia. Friedmann et al. found that hypertension and BMI are associated with recognition and delayed memory impairments in schizophrenia [17]. Guo et al. found that higher BMI was associated with lower scores on the Wechsler Memory Scale-Revised (WMS-R) Visual Reproduction subscale, the Wechsler Adult Intelligence Scale-Revised (WAIS-R) Digit Symbol subscale and obese patients with schizophrenia had significantly lower scores than normal weight patients on the Trail Making Test B, the WMS-R Visual Reproduction subscale, and the WAIS Digit Symbol subscale [18]. Our results seem to be in agreement with these terms.

Our results confirms that there may be an association between metabolic abnormalities and both clinical symptoms and cognitive performance in patients with schizophrenia. While we cannot clearly explain the mechanisms linking metabolic abnormalities with cognitive dysfunctions, there are several hypothesis explaining this issue. Obesity and hypertension are well-established risk factors of atherosclerosis and this is one of the risk factors of age-related or neurodegenerative cognitive decline [19]. Antipsychotic-induced obesity is associated with leptin-resistance [20] and previous studies support a role of leptin in cognition [21]. We also cannot exclude that schizophrenia patients with impaired cognitive functioning are more likely to become obese due to less healthy diet, limited activity, and more limited access to health care.

Limitations

There are several limitations to this study. First, low number of study subjects limited the probability of finding inter-group differences due to lack of statistical power. Therefore, these results should be considered as preliminary and require further studies with larger groups. Second, the participants were not randomly selected so the study sample may not be representative of individuals with schizophrenia. Third, due to the cross-sectional study design causal relationships cannot be established. Fourth, BMI and abdominal circumference may not be the most appropriate measures of obesity. In order to get more accurate results, more sophisticated techniques, such as dual-energy X-ray absorptiometry (DXA) or body impedance analysis (BIA), to measure body composition and percentage of fat are needed.

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