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ORIGINAL ARTICLE

Relationship between changes in metabolic syndrome constituent components over 12 months of treatment and cognitive performance in first-episode schizophrenia

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Abstract

Few studies have investigated the longitudinal effects of treatment-emergent metabolic syndrome changes on cognitive performance in first-episode psychosis. The aim of the present study was to determine the associations between changes in metabolic syndrome constituent component over 12 months of treatment and end-point cognitive performance in schizophrenia spectrum disorders. This single site-cohort study included 72 minimally treated or antipsychotic-naïve first-episode patients. Cognitive performance was evaluated using the MATRICS Consensus Cognitive Battery (MCCB). Our primary objective of interest was the relationship between metabolic syndrome constituent component changes over 12 months of treatment and end-point cognitive performance. Secondary objectives included investigating whether this relationship was affected by age, sex, antipsychotic dose, treatment duration and substance use. Weight gain predicted better overall cognition ($p = 0.02$) at end-point, adjusting for age, sex, substance use, baseline cognitive score and BMI, modal antipsychotic dose and treatment duration. Weight loss ($p = 0.04$) and substance use ($p = 0.01$) were both associated with poorer working memory performance at end-point. Low baseline BMI showed differential effects on end-point working memory performance in substance users (unfavorable) compared to non-users (favorable) ($p < 0.05$). In conclusion, weight gain over the course of antipsychotic treatment is associated with better overall cognitive performance and the working memory domain in first-episode schizophrenia spectrum disorder patients. In contrast, low baseline BMI may represent an unfavorable marker in substance users, who demonstrated weight loss compared to non-users.

Keywords First-episode schizophrenia spectrum disorders · Cognitive performance · Working memory · MCCB · Weight gain

Introduction

In patients with schizophrenia, metabolic syndrome is associated with cognitive impairments, including executive dysfunction, poor working memory and altered attention/vigilance (Guo et al. 2013; Bora 2016). This is important, given the increased risk for development of metabolic syndrome in schizophrenia patients (Mitchell et al. 2013).The impact of metabolic syndrome on cognitive dysfunction is pronounced in patients with severe negative symptoms, and increases in parallel with the number of metabolic syndrome risk factors present (Lindenmayer et al. 2012; Boyer et al. 2013; Botis et al. 2016; Bora et al. 2017a). Meta-analyses have further confirmed the effects of metabolic syndrome and type II diabetes mellitus (DM II) as determinants of poor overall cognition in schizophrenia (Bora et al. 2017b). Better cognitive performance at baseline has also been associated with a favorable metabolic profile at follow-up in schizophrenia (Storch-Jakobsen et al. 2018).

Individual metabolic syndrome constituent components may exert distinct effects on specific cognitive domains in schizophrenia. For example, elevated waist circumference

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has been correlated with decreased motor speed (Botis et al. 2016) and attention/vigilance (Lindenmayer et al. 2012), while hypertension and elevated triglycerides have been associated with poorer verbal memory (Friedman et al. 2010; Goughari et al. 2015). On the other hand, opposing literature suggests certain metabolic syndrome features such as hypertension, hyperglycemia and dyslipidaemia may be associated with better performance in certain cognitive domains affected in schizophrenia (Goughari et al. 2015; Wysokinski et al. 2013). Interestingly, several prospective studies have reported that changes in certain metabolic syndrome constituent components including elevated lipids predict cognitive improvement in schizophrenia (Krakowski and Czobor 2011; Nasrallah and Blom 2015). These findings are in keeping with studies showing an association between high cholesterol levels and better performance on verbal fluency, reasoning, motor speed and attention/concentration in population-based cohorts (Elias et al. 2005).

In contrast to a well-documented association with psychopathology improvement in schizophrenia (Raben et al. 2018), the relationship between weight gain and cognitive performance over the course of antipsychotic exposure remains poorly described. Indeed, there is a paucity of evidence from longitudinal studies of well-characterized first-episode patients investigating the relationship between changes in antipsychotic-induced metabolic syndrome constituent components and cognitive performance in schizophrenia. In response to this knowledge gap, the aim of the present study was to determine the associations between changes in metabolic syndrome constituent component over 12 months of treatment and end-point cognitive performance in schizophrenia spectrum disorders. Our primary objective was to investigate the relationship between change in body mass index (BMI) over 12 months of treatment and end-point cognitive performance. Secondary objectives included to determine whether this relationship is affected by age, sex, antipsychotic dose, treatment duration and substance use.

Firstly, we hypothesized that increased BMI would be associated with better overall cognition at end-point, adjusting for modal antipsychotic dose, treatment duration and substance use, in accordance with our previous finding that weight gain predicted global psychopathology improvement in first-episode patients independent of these covariates (Luckhoff et al. 2018). Secondly, we anticipated that substance use would affect the relationship between weight gain and end-point performance in specific cognitive domains, given our previous finding that patients who used cannabis, unlike their non-using counterparts, did not gain significant weight when treated with antipsychotics (Scheffler et al. 2018). In addition, our focus on working memory in particular was motivated by its importance in the control of appetite and weight gain (Higgs and Spetter 2018) as well as recent evidence that ongoing substance use is associated with poorer working memory performance in first-episode or early psychosis (Bogaty et al. 2018; Sanchez-Gutierrez et al. 2018).

Materials and methods

Study design and ethics approval

The present single-site longitudinal study, which recruited minimally treated or antipsychotic-naive first-episode schizophrenia patients, was conducted as part of a larger parent project (N06/08/148), with ethical approval obtained from the Health and Research Ethics Committee (HREC) at Stellenbosch University (SU). Written, informed consent was obtained from all participants, and in the case of participants younger than 18 years of age, we obtained written, informed consent from parents or legal guardians.

Selection of study participants

Study participants were selected from first admissions to hospitals and community clinics in the metro and rural areas of North Eastern Cape Town, the Winelands and West Coast over a 4 year period (2007–2011). Inclusion criteria were men and women, in- or outpatients, aged 18 to 45 years, with a first psychotic episode meeting Diagnostic and Statistical Manual of Mental Diseases, Fourth Edition, Text Revisions (DSM-IV TR) (American Psychiatric Association 1994) criteria for schizophrenia, schizophreniform or schizoaffective disorder. Exclusion criteria included lifetime exposure to more than 4 weeks of antipsychotic medication, serious or unstable medical condition, and substance-induced psychosis.

Antipsychotic treatment

Patients were treated according to a fixed protocol with flupenthixol decanoate, a depot antipsychotic. There was a lead-in period of 7 days with oral flupenthixol 1–3 mg/day followed by flexible doses of flupenthixol decanoate intramuscular injections 2-weekly. Permitted concomitant medications included lorazepam, anticholinergics, propranolol, antidepressants and medications for medical conditions. Prohibited medications included other antipsychotics, mood stabilizers and psychostimulants.

Patient assessments

Clinical assessments

Patients were assessed with the Structured Clinical Interview for DSM-IV (SCID) (First et al. 1994). The MATRICS Consensus Cognitive Battery (MCCB) was utilized as a tool specifically designed and validated for the assessment of

cognitive functioning in schizophrenia (Nuechterlein and Green 2006). The MCCB comprises seven domains and a composite score. The individual domains are: 1) speed of processing, 2) attention/vigilance, 3) working memory, 4) verbal learning, 5) visual learning, 6) reasoning and problem solving, and 7) social cognition. The MCCB was administered at baseline, month 6 and month 12 by trained psychologists under supervision of an experienced clinical psychologist and psychiatrist. The MCCB computer program was used to transform raw scores into individual domain and composite T-scores. Age- and sex-corrected norms were used according to the guidelines outlined in the MCCB manual (Nuechterlein and Green 2006). We compared metabolic syndrome constituent component change scores with MCCB end-point scores rather than the MCCB change scores, as the baseline cognitive tests were performed while patients were acutely psychotic and this may have confounded the scores. The end-point MCCB scores therefore assessed cognitive performance in clinically stable patients.

Metabolic assessments

A physical examination was performed at baseline, follow-up and study completion. Body weight was measured at baseline and months 3, 6, 9 and 12. Study participants removed all surplus clothing including socks and shoes and were weighed on an electronic scale calibrated throughout the study. Height was measured using a pre-fixed wall-mounted measuring tape.BMI was also calculated as the patient's body weight in kilograms (kg) divided by their height in meters squared (m^2). Clinically significant weight gain was defined as >7% increase in body weight from baseline to end-point (McIntyre et al. 2003). A peripheral venous blood sample was collected from participants following an 8 hour fasting period and 10 minute rest prior to venepuncture. Biochemical testing was performed at baseline and again at months 3, 6, 9 and 12, and included assessment of the fasting lipid profile (triglycerides, total, LDL and HDL cholesterol) and glucose levels.

Urine toxicology

Urine toxicology was performed at baseline and again at months 3, 6 and 12 to assess use of cannabis, methaqualone and methamphetamine over the course of the study. Patients who tested positive were classified as substance use positive.

Statistical analysis

Statistical analyses were performed using the R Studio software package (version 3.2.4) and confirmed by a biostatistician using the IBM SPSS software program (version 25). All participants with at least one baseline and one follow-up measure were included for analysis. End-point scores were calculated by last observation carried forward, and metabolic change scores were calculated by subtracting the baseline score from the end-point score. Categorical characteristics were described using cross-tabulation and frequency tables and compared between study groups using the Pearson's Chi-Squared or Fisher's exact tests. For normally distributed data, quantitative phenotypes are given as means and the standard deviation (SD). Linear correlations between metabolic change scores and MCCB end-point scores were described using Pearson's correlation analysis. Winsorized data were utilized for triglyceride and HDL cholesterol change scores in order to minimize the potential effects of outliers, and a significance level of $p < 0.10$ was used to identify predictor variables for subsequent linear regression analyses. In all other analyses, statistical significance was defined as a p value <0.05.

Results

Characteristics of study population

From an initial group of 126 patients, we included 72 largely treatment-naive, first-episode schizophrenia spectrum disorder patients (53 males, 19 females; mean age = 24.2 years) for whom sufficient data were available to calculate metabolic syndrome constituent component change scores (baseline and at least one follow-up visit) as well as composite MCCB score at end-point. In total, 57 patients (79%) had a DSM-IV diagnosis of schizophrenia, while 15 patients (21%) were diagnosed with schizophreniform disorder. The sample consisted mostly ($n = 53$; 74%) of patients of Mixed Ancestry, and further included 11 Caucasian (15%) and eight Black African (11%) patients. The majority of males tested positive for use of illicit substances ($n = 31$, 58%) compared to a minority ($n = 4$, 21%) of females. In total, 35 patients (49%) tested positive for substance use, of which 28 (80%) were positive for cannabis use. Modal 2-weekly dose of depot flupenthixol decanoate was 10 mg in 47 (65%) patients, 15 mg in 15 (21%) patients, 20 mg in seven (10%) patients, and 5 mg in three (4%) patients.

The baseline and end-point scores for the cognitive and metabolic outcomes of interest are presented and compared in Table 1. There was a significant increase in MCCB composite score ($p = 0.04$) as well as the attention/vigilance ($p < 0.01$) and reasoning/problem-solving domains ($p = 0.01$) from baseline to end-point. In addition, a significant increase in mean BMI ($p < 0.01$) and triglycerides ($p < 0.01$) as well as a decrease in HDL cholesterol ($p < 0.01$) was noted from baseline to end-point. Glucose ($p = 0.18$), total cholesterol ($p = 0.39$) and LDL cholesterol ($p = 0.30$) did not change significantly over the course of the study.

Table 1 Comparison of baseline and end-point scores for cognitive performance and metabolic status for total study group, provided along with corresponding unadjusted *p* values

Cognitive and metabolic characteristics	Baseline scores Mean (SD)	End-point scores Mean (SD)	Comparison baseline to end-point (unadjusted *P* value)
MCCB Composite score	21.06 (13.33)	26.40 (14.43)	0.04**
MCCB Working memory	27.91 (12.40)	31.51 (12.34)	0.11
MCCB Speed of processing	23.22 (11.11)	27.27 (13.20)	0.07
MCCB Reasoning/problem solving	32.81 (9.25)	37.40 (10.41)	<0.01**
MCCB Attention/vigilance	24.64 (11.64)	31.86 (9.93)	<0.01**
MCCB Visual learning	31.96 (13.51)	36.49 (12.90)	0.06
MCCB Verbal learning	33.61 (8.52)	34.36 (7.78)	0.61
MCCB Social cognition	46.25 (15.22)	49.57 (18.96)	0.28
Body mass index (kg/m^2)	21.72 (4.18)	24.66 (5.36)	<0.01**
Glucose (mmol/L)	4.81 (0.76)	5.10 (1.61)	0.18
HDL cholesterol (mmol/L)	1.16 (0.51)	0.96 (0.25)	<0.01**
Triglycerides (mmol/L)	0.85 (0.41)	1.22 (0.84)	<0.01**
Total cholesterol (mmol/L)	4.22 (1.06)	4.36 (0.87)	0.39
LDL cholesterol (mmol/L)	2.71 (0.89)	2.85 (0.82)	0.30

HDL high-density lipoprotein, *LDL* low-density lipoprotein, *MCCB* MATRICS Consensus Cognitive Battery, ** statistically significant

Effects of baseline BMI and weight change on end-point cognitive scores

Baseline BMI was not associated with the composite MCCB score or any specific cognitive domains at end-point ($p > 0.05$). A total of 45 patients (63%) experienced clinically significant weight gain, which was not significantly associated with the composite MCCB end-point score or any of the specific cognitive domains at end-point ($p > 0.05$). In total, 14 patients (19%) lost weight over the course of the present study. These patients had poorer end-point working memory scores (mean = 25.43) compared to the rest of the patient group (mean = 32.98) ($p = 0.04$). Weight loss was not significantly associated with poorer cognitive performance at end-point for the composite MCCB score or other specific domains ($p > 0.05$).

Correlations between metabolic syndrome change scores and end-point cognitive scores

Pearson correlation coefficients were calculated to assess the linear relationship between 1) the composite MCCB score/specific cognitive domains at end-point, and 2) metabolic change scores where a significant increase (i.e. BMI, triglycerides) or decrease (i.e. HDL cholesterol) was noted from baseline to end-point, as shown in Table 2. BMI change scores were significantly positively correlated with the MCCB working memory domain at end-point ($r = 0.28$; $p = 0.02$). A similar trend was noted towards a positive association between BMI change scores and the composite MCCB score at end-point ($r = 0.20$, $p = 0.09$). In addition, HDL change scores were inversely associated with the reasoning/problem solving domain ($r = -0.23$; $p = 0.05$) at end-point, although this

Table 2 Results from correlation analysis evaluating the linear relationship between metabolic change scores and MCCB composite score and specific cognitive domains at end-point, presented as the Rho-value and corresponding unadjusted *p* values

	Composite MCCB end-point score	WM end-point score	SOP end-point score	RPS end-point score	AV end-point score	VISL end-point score	VERBL end-point score	SC end-point score
BMI change score (kg/m2)	0.20; 0.09	0.28; 0.02	0.19; 0.12	0.02; 0.89	0.07; 0.56	0.10; 0.40	0.16; 0.19	0.17; 0.16
HDL cholesterol change score (mmol/L)	−0.19; 0.12	−0.15; 0.22	−0.14; 0.25	−0.23; 0.05	−0.07; 0.53	−0.07; 0.57	−0.19; 0.10	−0.14; 0.25
Triglycerides change score (mmol/L)	0.08; 0.52	0.02; 0.86	−0.02; 0.86	0.07; 0.54	−0.03; 0.81	0.12; 0.31	0.05; 0.69	0.12; 0.31

Predictor variables were identified using a significance level of $p < 0.10$

AV attention/vigilance, *BMI* body mass index, *HDL* high-density lipoprotein, *MCCB* MATRICS Consensus Cognitive Battery, *RPS* reasoning/problem solving, *SC* social cognition, *SOP* speed of processing, *VERBL* verbal learning, *VISL* visual learning, *WM* working memory

correlation did not remain significant when outliers ($n = 3$) were removed ($r = -0.12$, $p = 0.33$). Based on results from initial exploratory correlation analyses, we therefore identified the composite MCCB end-point and working memory domain as our dependent variables of interest, and the BMI change score as our metabolic predictor of interest.

Linear regression analyses

Linear regression models were constructed to assess the relationship between BMI change scores and the composite MCCB score as well as working memory domain at end-point, incorporating clinical (age, sex, substance use, baseline cognitive score and BMI) and treatment-related (modal antipsychotic dose, treatment duration) factors as covariates (Table 3). Increase in BMI ($\beta = 1.17$, $p = 0.02$) significantly predicted a higher composite MCCB score at end-point, adjusting for age, sex, substance use, modal antipsychotic dose, treatment duration, baseline composite score and BMI as covariates. In addition, weight gain ($\beta = 0.89$, $p = 0.02$) predicted better working memory performance at end-point, adjusting for age, sex, modal antipsychotic dose, treatment duration, baseline composite score and BMI as covariates (Table 3). The effect of increased BMI as a predictor of end-point working memory performance was however non-significant ($\beta = 0.63$, $p = 0.13$) when substance use was also incorporated into a linear model ($R^2 = .58$, $F(8,46) = 8.24$, $p < 0.01$) adjusting for the same covariates (i.e. age, sex, modal antipsychotic dose, treatment duration, baseline composite score and BMI). We therefore performed subsequent sub-analyses to further explore the effects of substance use on inter-relationship between baseline BMI, weight gain and end-point working memory performance.

Effects of substance use on baseline BMI, weight change and working memory performance

Substance use was associated with poorer working memory scores at end-point ($p = 0.01$), with a significant improvement in performance from baseline to end-point only evident for non-users ($p = 0.02$). In addition, the majority ($n = 11$; 78%) of patients who lost weight ($n = 14$), which was itself associated with lower end-point working memory scores ($p = 0.04$), tested positive for substance use over the course of the study. Moreover, a significant increase in BMI over the course of the study was evident for non-users ($p < 0.01$) but not substance users ($p > 0.05$). Baseline BMI was also significantly lower in substance users compared to non-users ($p = 0.03$). Lastly, low baseline BMI ($\beta = -0.86$, $p = 0.01$) predicted better end-point

Table 3 Linear regression models incorporating clinical, metabolic and treatment-related factors as predictors of MCCB composite score and the working memory domain at end-point

MCCB composite end-point score							
					Predictors		
	R-squared	Model df	*F*-statistic	*P* value	Beta-coefficient	*T*-value	*P* value
	0.58	8,41	9.53	<0.01			
BMI change score					1.17	2.38	0.02**
Age					0.25	1.06	0.30
Sex					−3.00	−1.04	0.31
Modal antipsychotic dose					−0.04	−0.10	0.92
Treatment weeks					−0.03	−0.19	0.85
Substance use					1.27	0.41	0.69
Baseline MCCB composite score					0.70	6.75	<0.01**
Baseline BMI					−0.58	−1.67	0.10
MCCB working memory end-point score							
					Predictors		
	R-squared	Model df	*F*-statistic	*P* value	Beta-coefficient	*T*-value	*P* value
	0.49	7,47	8,37	<0.01			
BMI change score					0.89	2.40	0.02**
Age					−0.03	−0.15	0.88
Sex					0.04	0.02	0.99
Modal antipsychotic dose					0.45	1.31	0.20
Treatment weeks					0.05	0.32	0.75
Baseline MMCCB working memory					0.57	6.46	<0.01**
Baseline BMI					−0.43	−1.49	0.14

BMI Body mass index, *MCCB* MATRICS Consensus Cognitive Battery, ** statistically significant

working memory performance in non-users, adjusting for age, sex, modal antipsychotic dose, treatment duration and baseline cognitive score ($R^2 = .55$, $F(6,25) = 7.35$ $p < 0.01$). In contrast, low baseline BMI predicted poorer working memory at end-point in substance users ($\beta = 1.22$, $p = 0.04$) adjusting for the same covariates ($R^2 = .55$, $F(6,17) = 4.66$, $p < 0.01$).

Discussion

The main finding from this study was that increased BMI over 12 months of treatment predicted better overall cognition and working memory performance in antipsychotic-naïve or minimally treated first episode schizophrenia spectrum disorder patients, independent of the degree of antipsychotic exposure. In contrast, substance use and weight loss were both associated with lower end-point working memory scores. Our findings are in agreement with those from previous studies demonstrating an association between weight gain and symptomatic improvement in schizophrenia (Raben et al. 2018). In addition, they expand on previous research by suggesting that an increase in BMI over the course of antipsychotic treatment is associated with favorable overall cognitive outcome and better working memory performance.

There are several possible explanations for the association between weight gain and better cognitive performance at end-point evident from our study. Firstly, changes in serotonin signaling may be involved, with 5HT receptor blockade being implicated in antipsychotic-induced weight gain (Panariello et al. 2011) and improvement in cognitive performance (Schmitt et al. 2006). In contrast, aberrant 5HT transmission has been implicated in poor cognitive functioning in animal and human studies (Strac et al. 2016) with 5HT receptor agonists known to not only impair working memory performance (Luciana et al. 1998), but also decrease appetite and promote weight loss (Halford et al. 2011). In this context, flupenthixol is known to exhibit 5HT receptor blockade (Wiesbeck et al. 2003) which may underscore its effects on both weight gain (Chiliza et al. 2015) and cognitive improvement (Olivier et al. 2015) previously demonstrated in our larger study cohort. Secondly, glucose metabolism and altered insulin signaling have been proposed as common mechanisms underscoring the effects of weight gain on symptomatic improvement in schizophrenia (Girgis et al. 2008). Weight gain is known to increase levels of insulin, the acute administration of which has been shown to improve cognitive performance (Shemesh et al. 2012). Similarly, acute administration of glucose improves memory in schizophrenia patients (Newcomer et al. 1999). Indeed, insulin plays a key role in modulating the level and activity of neurotransmitters including serotonin in brain regions such as the hippocampus and hypothalamus (Umbriaco et al. 1995; Orosco et al. 2000; Dickinson and Harvey 2009). Important metabolic changes considered deleterious in chronic schizophrenia may therefore be considered favorable in antipsychotic-naïve patients in the acute stage of treatment.

In the present study, weight loss and substance use were both associated with poorer working memory at end-point, with the majority of patients who lost weight testing positive for substance over the course of treatment. It remains unclear whether weight loss is associated with worsening of psychopathology symptoms in schizophrenia (Chukhin et al. 2016), and most studies have shown that weight loss has a beneficial effect on cognition in obese individuals (Smith et al. 2010). Therefore, the influence of weight loss evident in our study may rather reflect the effects of substance use on working memory performance. Interestingly, multiple studies have shown that cannabis use in particular is associated with better working memory performance in first-episode psychosis patients, as demonstrated in a meta-analysis by Yücel et al. (2012). However, a meta-analysis by Sanchez-Gutierrez and colleagues (Sanchez-Gutierrez et al. 2018) concluded that ongoing cannabis use in first-episode psychosis may exert deleterious effects on cognition. In accordance with our study, findings from a recent meta-analysis of 14 studies by Bogaty et al. (2018) further suggest that comorbid cannabis use is indeed associated with poorer working memory performance in early-onset psychosis.

We further demonstrated the favorable effects of low baseline BMI as a predictor of better working memory in substance non-users, who showed a significant increase in BMI over the course of our study, as well as a significant improvement in working memory from baseline to end-point. Low baseline BMI may represent a favorable prognostic indicator in antipsychotic-naïve, substance non-using patients, who are also at greater risk for weight gain (Basson et al. 2001; Kinon et al. 2005; Raben et al. 2018). The favorable effects of a low baseline BMI in the context of weight gain is further evidenced by its association with symptomatic remission and recovery in schizophrenia (Novick et al. 2007, 2009; Stauffer et al. 2011). In contrast, baseline BMI showed the opposite effect in substance users, consistent with the observation that cannabis users did not gain significant weight over the course of treatment in our larger sample (Scheffler et al. 2018). Weight loss or failure to gain weight may therefore represent a poor prognostic marker in substance users with schizophrenia.

The present study had several important limitations, including a short study duration and relatively small sample size, which limited our ability to explore the putative moderating effect of substance use on the relationship between BMI and working memory performance. Moreover, our sample generally had a low baseline BMI, which may conceivably have influenced our results. Furthermore, our study did not include

the assessment of waist circumference as an indicator of central obesity, and dietary habits and physical activity as determinants of cardio-metabolic risk in schizophrenia spectrum disorder patients treated with antipsychotics were not examined. Also, our findings are not necessarily generalizable to other patient populations which may differ in terms of clinical profile, treatment approach and metabolic risk profile. However, the strength of the present study lies in the evaluation of a well-characterized sample of first-episode patients, with regular laboratory assessments, a mode of antipsychotic delivery that was standardized, and assured adherence.

Conclusions

In conclusion, our study demonstrated that weight gain over 12 months of treatment is associated with better overall cognition as well as working memory in first-episode schizophrenia spectrum disorder patients, independent of age, sex, and the degree of antipsychotic exposure. In addition, our findings suggest that substance use disrupts the relationship between baseline BMI, weight gain and working memory in first-episode schizophrenia spectrum disorders. Our study supports the role of weight gain as a predictor of better cognitive performance in schizophrenia. In contrast, failure to gain weight may represent an unfavorable marker for poor working memory performance in substance users.

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Compliance with ethical standards

Conflicts of interest Bonginkosi Chiliza has received honoraria from Lundbeck, Mylan and Sandoz for speaking at educational meetings. Robin Emsley has participated in speakers/advisory boards and received honoraria from Janssen, Lundbeck, Servier and Otsuka. Hilmar Luckhoff, Lebogang Phahladira, Freda Scheffler, Stefan du Plessis, Laila Asmal, Riaan Oosthuizen, and Sanja Kilian declare that they have no conflicts of interest.

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