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Cognitive deficits among people with schizophrenia and prediabetes or diabetes

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Abstract

Introduction: Both type 2 diabetes mellitus (T2DM) and schizophrenia are known to be associated with cognitive deficits. The impact of the comorbidities of T2DM or prediabetes (PD) on cognition among people with schizophrenia has been poorly researched. We evaluated the cognitive functioning of patients with schizophrenia and PD or T2DM and compared them to patients with schizophrenia with normal blood sugar.

Methods: We retrospectively collated data on cognition, fasting blood glucose (FBG), lipids and other selected demographic and clinical variables of 171 patients with schizophrenia and 16 patients with schizoaffective disorder who were admitted to an inpatient rehabilitation facility in Western Australia from 2011 to 2018. The Brief Assessment of Cognition in Schizophrenia (BACS) was used to evaluate cognitive functioning. Parametric and non-parametric analyses were used to examine the study's aims.

Results: Sixty-six percent of the patients had normal blood sugar, 25% had PD and 9% had T2DM. The BACS composite score revealed an increasing gradient of cognitive deficits, ranging from mild to severe, between the normal, PD and T2DM groups, respectively. The T2DM group had a significantly lower composite score compared with the PD ($p = 0.026$) and normal groups ($p < 0.001$). On the BACS subtests, the scores of T2DM and PD patients were similar except for the token motor task, in which the T2DM group had significantly lower scores ($p < 0.001$). The T2DM group also had lower scores on the subtests of BACS, except memory tests, compared with those with normal blood sugar. There was no significant difference in the composite and subtest cognitive scores between the PD and normal groups.

Conclusions: Our study revealed more pronounced cognitive deficits among patients with schizophrenia and dysglycaemia, particularly those with T2DM, compared with those with schizophrenia with normal blood sugar.

KEYWORDS

cognitive deficits, diabetes, prediabetes, schizophrenia

1 | INTRODUCTION

Type 2 diabetes mellitus (T2DM) is common among people with schizophrenia, with meta-analyses suggesting a prevalence rate of around 11%.[1,2] Similarly, pre-diabetes (PD), defined as having impaired fasting glucose and/or impaired glucose tolerance, is prevalent among people with schizophrenia, with more than a quarter of the patients meeting the diagnostic criteria for this condition.[3,4] Both T2DM and schizophrenia are associated with a range of cognitive deficits, affecting the person's functioning and illness management abilities. Cognitive deficits ranging from mild to severe intensity affecting multiple domains, such as verbal and visual learning, processing speed, reasoning and problem-solving, working memory and visuospatial skills, are present in most people with schizophrenia, both in the early and chronic stages.[5–8] Similarly, cognitive dysfunctions varying in intensity from subtle cognitive decrements in domains such as verbal and visual memory, attention and concentration, processing speed, executive function and motor control to severe cognitive impairment meeting the criteria for mild cognitive disorder or dementia have been reported in people with T2DM.[9–11] While dementia is uncommon among people with DM under the age of 65,[12,13] subtle cognitive decrements, on average, one-third to one-half the standard deviation lower than in those without diabetes, are common among people with T2DM under the age of 60.[9–13] Low-quality evidence for increased risk of dementia and neurodegeneration has also been observed among patients with PD based on a small number of studies.[14] Although schizophrenia and T2DM are chronic illnesses associated with significant cognitive problems, awareness and evaluation of cognitive issues have often lagged behind other symptom domains in these conditions.[6,7,15,16]

The longitudinal course of cognitive deficits in schizophrenia is still unsettled and debated. While the proponents of the neurodevelopmental theory of schizophrenia postulate that the cognitive deficits in this condition are manifest by the first episode and are stable from then onwards others have suggested that a significant subset of people with schizophrenia experience further worsening of cognitive deficits after the first episode.[7,17] In addition to other factors such as inflammatory processes, chronic psychotic symptoms, a deprived environment and other psychosocial factors, metabolic syndrome and diabetes have been proposed as linked to this further deterioration.[7,17,18] Impairment of cognitive functions has significant implications, with cognitive function being a robust predictor of real-world functioning in people with schizophrenia. It can affect illness management skills such as monitoring symptoms effectively, following

Significant outcomes

- Patients with comorbid schizophrenia and type 2 diabetes mellitus exhibited significantly more global cognition impairment compared with those with schizophrenia alone.
- Similarly, those with the two comorbidities did poorly on various subdomains of cognition except the memory tests, verbal memory and learning and working memory.
- Among patients with schizophrenia, there was an increasing gradient of cognitive deficits, ranging from mild to severe, between the normal, prediabetes and type 2 diabetes groups. However, there was no significant difference in cognitive function between those with prediabetes and those with normal blood sugar.

Limitations

- The study was cross sectional in nature and did not take into account the duration of diabetes and prediabetes on cognition.
- The study was done at a medium length of stay public inpatient rehabilitation facility with a high proportion of people with treatment-resistant schizophrenia being treated with clozapine, and generalisability to other settings should be cautiously done.
- Functional capacity and everyday functioning were not assessed in this study, and the impact of the excess cognitive deficits on community functioning and illness management skills among patients with comorbidities of diabetes and schizophrenia was not evaluated.

complicated medication regimens and tests, implementing diet and exercise plans, participating in rehabilitation programmes, and planning and organising medical and other appointments.[19,20] Hence, if there are additional cognitive deficits in people with schizophrenia and comorbid T2DM, these are likely to further affect illness management abilities and successful community functioning in this population.

Despite the clinical relevance of this area, there has been only modest interest in researching the cognitive functions of people with comorbid schizophrenia and T2DM. Two recent meta-analyses identified only 6 and 8 published studies in this area, with the research being predominantly carried out in China and the United States.[18,21] Hagi et al.[21] analysing eight studies

($n = 2976$) and Bora et al.[18] evaluating six studies, observed that global cognition was significantly more impaired in patients with schizophrenia with comorbid T2DM compared with patients with schizophrenia without diabetes. However, the effect size for the differences between the two groups was small. Similarly, various sub-domains of cognition such as attention/vigilance, reasoning/problem-solving, processing speed and verbal and visual learning were more affected in those with comorbid schizophrenia and diabetes. However, there was no significant difference in working memory between people with schizophrenia with and without diabetes.[21] Of note, the findings among the individual studies included in these meta-analyses on global cognition and subdomains of cognition were discrepant, with no difference, worse performance and better performance reported in those with comorbid schizophrenia and T2DM compared with those with schizophrenia alone.[22–30] Furthermore, the evaluation of cognitive function among people with schizophrenia and PD has received little attention, with one study finding a decrement in emotional intelligence but not on other cognitive tests,[31] while another observed a positive effect of hyperglycaemia on verbal memory.[23] Given the minimal number of published studies on the cognitive function of patients with PD and schizophrenia and the discrepant findings reported on cognitive function among those with T2DM and schizophrenia in various studies, we evaluated the cognitive functioning of patients with schizophrenia who had PD and T2DM, comparing them to patients with schizophrenia with normal blood sugar levels.

2 | MATERIALS AND METHODS

2.1 | Participants

This retrospective research was conducted over 7 years at a 12-bed, medium-length-of-stay, inpatient psychiatric rehabilitation ward at a public hospital in Perth, Western Australia. After obtaining permission from the Human Research Ethics Committee of the South Metropolitan Health Service, Western Australia, we retrospectively collated from the medical records relevant demographic, clinical, cognitive and metabolic information of patients with an ICD-10 diagnosis of schizophrenia and schizoaffective disorder who were admitted to the facility between September 2011 and December 2018. Diagnosis was made using the International Classification of Diseases 10th Revision (ICD-10; World Health Organisation, 1992) criteria by a senior consultant psychiatrist who was the clinical lead of this ward's multidisciplinary mental health team.

2.2 | Measures

As part of usual clinical practice, in addition to other clinical assessments, the cognitive function of patients was evaluated using a standardised instrument within 2 weeks of admission to the rehabilitation facility. Fasting blood glucose (FBG), lipid profile and other haematological investigations were carried out by phlebotomy on admission to the unit at the accredited hospital laboratory. The Brief Assessment of Cognition in Schizophrenia (BACS) was used to evaluate the cognitive functioning of patients.[32,33] The BACS takes approximately 35 min to administer and has demonstrated robust reliability and concurrent validity against lengthy neuropsychological tests.[33] The BACS includes six subtests: list learning (verbal memory), digit sequencing (working memory), token motor task (motor speed), semantic fluency (verbal fluency), symbol coding (attention and speed of information processing) and Tower of London (executive function-reasoning and problem-solving). Normative scores were established by the developers of the BACS by administering the instrument to 404 healthy controls and were organised in a way that allows the calculation of standardised scores (z-scores) adjusted for age and sex for the six subtests and a composite cognitive score, which is the unweighted average of the scores on the subtests.[32] The BACS testing was done by clinical psychologists or a senior nurse working in the rehabilitation unit after building good rapport with the patients.

Sociodemographic details, such as age and gender, and clinical information, such as length of admission, principal diagnosis, comorbidities, current substance abuse, duration of psychosis and whether the patient met the criteria for a clinical diagnosis of treatment-resistant schizophrenia[34] and was treated with clozapine were collated. In addition, the raw and z-scores of the BACS subtests and composite score, as well as the results of the FBG and lipids (total cholesterol, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol and triglycerides) conducted at the time of admission to the facility, were obtained from the medical records. We divided the patients into three groups based on their FBG; those with levels lower than 5.6 mmol/L were considered to have normal blood sugar, those between 5.6 and 6.9 mmol/L as having PD (impaired fasting glucose) and 7.0 mmol/L or above as having T2DM (Diabetes Tests. Centres for Disease Control and Prevention. Accessed May 16, 2023. https://www.cdc.gov/diabetes/basics/getting-tested.html). None of the patients received a diagnosis of type 1 diabetes. If patients were prescribed anti-diabetic medications, they were classified as having diabetes, irrespective of the results of their FBG.

2.3 | Statistical analyses

The BACS subtests and composite scores used were z-scores standardised by age and gender. Initially, we used bivariate correlations to assess the relationships between the various variables collected for this study and to determine covariates that would be controlled for in the main analyses. As we assessed a large number of demographic and clinical variables, we did not have the statistical power to conduct between-group analyses on each variable. Therefore, we used the variables with significant associations with one or more BACS tests to inform our choice of control variables for the remaining analyses. Each variable that had a significant association with one or more BACS tests, including other metabolic variables (total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides), was controlled for in our parametric testing. These measures were done to allow for the assessment of between FBG group differences in the BACS tests while minimising confounding variables.

Next, we used a multivariate analysis of covariance (MANCOVA) to examine if there were statistically significant differences with regards to each of the seven BACS variables between (a) patients who had normal blood glucose, (b) patients who had PD and (c) patients who had T2DM, after controlling for other metabolic variables (total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides) and any other clinical or demographic variable that was significantly associated with one or more of the BACS components. The alpha value for significance was set at the standard 0.05 for all analyses. However, in line with recommendations for best practice[35] Bonferroni-adjusted p-values (as provided through IBM SPSS version 28) were used for the planned pairwise comparisons from the MANCOVA between the three groups on the BACS variables. Analyses were conducted using IBM SPSS version 28.

3 | RESULTS

Two hundred ninety-two patients diagnosed with schizophrenia or schizoaffective disorder were admitted to the ward during the study period. Of these, 187 patients had the complete set of relevant demographics, clinical, cognitive and metabolic data collated for the study.

3.1 | Demographic and clinical data of the sample

The mean age of the sample was 32.63 years (SD = 10.29), and the age ranged between 18 and 69 years. Sixty-nine and a half percent (n = 130) were males, and the mean duration of psychosis was 8.67 years (SD = 7.52). Among the participants, 91.4% (n = 171) were diagnosed with schizophrenia and 8.6% (n = 16) with schizoaffective disorder. Treatment refractoriness was common, with 86.55% (n = 148) of participants being classified as having treatment-resistant (TRS), and 61.5% (n = 115) were treated with clozapine. Seventy-seven percent of the sample had at least one psychiatric comorbidity, and 38.00% (n = 71) were diagnosed with comorbid alcohol abuse, 28.3% (n = 52) with stimulant abuse, 44.40% (n = 83) with cannabis abuse and 23.9% (n = 26) with other substance abuse.

3.2 | Cognitive and metabolic descriptive statistics

The BACS composite score revealed that the patients experienced significant cognitive deficits (mean − 1.88, SD = 1.45). All subtests were affected, with symbol coding and verbal memory showing the greatest deficits. The mean z-scores of the patients on the BACS subtest were as follows: verbal memory and learning = −1.60 (SD = 1.36), digit sequencing = −1.23 (SD = 1.19), token motor test = −0.755 (SD = 1.25), verbal fluency = −0.893 (SD = 1.22), symbol coding = −1.88 (1.45) and Tower of London = −0.313 (1.35). The means of total cholesterol for the patients were 4.79 (SD = 1.11), LDL cholesterol 2.87 (SD = 0.946), HDL cholesterol 1.11 (SD 0.345) and triglycerides 1.80 (SD 0.862).

One hundred twenty-three (65.8%) patients were classified as having normal FBG (mean FBG = 4.93, SD = 0.390, range = 3.6–5.5), 47 (25.1%) as having PD (mean FBG = 6.00, SD = 0.378, range = 5.6–6.8) and 17 (9.1%) as having T2DM (mean FBG = 7.31, SD = 2.03, range = 4.5–13.2). The demographic and clinical characteristics of the three groups are shown in Table 1.

3.3 | Cognitive measures based on fasting blood sugar categories

The bivariate correlations between all variables are shown in Table 2. Of note, the grouping of patients based on FBG to normal, PD and T2DM was significantly negatively associated with six out of the seven BACS tests, with digit sequencing (working memory) the only BACS test not to be significantly associated with this grouping. Other variables significantly associated with one or more BACS tests were gender, treatment-resistant schizophrenia, duration of psychosis, clozapine use, total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides. Each of these

TABLE 1 Clinical and demographic characteristics of the three groups of patients with schizophrenia with normal blood sugar, prediabetes and diabetes.

	Normal (Mean [SD], or count [%]) (N = 123)	Prediabetic (Mean [SD], or count) (N = 47)	Type2 Diabetes (Mean [SD], or count) (N = 17)
Age	31.51 (SD = 10.40)	34.43 (SD = 9.66)	35.71 (SD = 10.42)
Gender (Males)	90 (73.2%)	30 (63.8%)	10 (58.8%)
Duration of Psychosis (years)	7.70 (SD = 7.30)	10.34 (SD = 7.83)	11.09 (SD = 7.35)
Diagnosis			
Schizophrenia	113 (91.9%)	42 (89.4%)	16 (94.1%)
Schizoaffective	10 (8.1%)	5 (10.6%)	1 (5.9%)
TRS	92 (74.8%)	40 (85.1%)	16 (94.1%)
Comorbidity (Yes)	95 (77.2%)	36 (76.6%)	13 (76.5%)
Clozapine	73 (59.3%)	30 (63.8%)	12 (70.6%)
Alcohol	44 (35.8%)	23 (48.9%)	4 (23.5%)
Stimulants	38 (30.9%)	13 (27.7%)	2 (11.8%)
THC	55 (44.7%)	22 (46.8%)	6 (35.3%)
Other Substances	18 (14.6%)	6 (12.8%)	2 (11.8%)
Cholesterol (mmol/L)	4.78 (SD = 1.10)	4.84 (SD = 1.18)	4.71 (SD = 0.997)
LDL (mmol/L)	2.89 (SD = 0.955)	2.88 (SD = 0.955)	2.66 (SD = 0.880)
HDL (mmol/L)	1.13 (SD = 0.277)	1.10 (SD = 0.494)	1.02 (SD = 0.290)
Triglycerides (mmol/L)	1.64 (SD = 0.814)	2.03 (SD = 0.907)	2.24 (SD = 0.668)

Abbreviations: Chol., Cholesterol; HDL, High-density lipoprotein; LDL, Low-density lipoprotein; THC, Tetrahydrocannabinol use (Yes, No); TRS, Treatment resistant schizophrenia.

variables was controlled for in the subsequent MANCOVA and related pairwise comparisons.

The results of the MANCOVA analyses indicated a significant main effect of the FBG grouping on performance on the BACS, $F(14, 342) = 0.198$, $p > 0.001$, partial eta$^2 = 0.099$. The analysis of the dependent variables separately showed that there was a significant, independent, main effect of FBG groups on each of the seven BACS tests (VML, $F(2, 176) = 3.14$, $p = 0.046$, partial eta$^2 = 0.034$; DS, $F(2, 176) = 3.17$, $p = 0.045$, partial eta$^2 = 0.035$; TMT, $F(2, 176) = 9.74$, $p > 0.001$, partial eta$^2 = 1.00$, VF, $F(2, 176) = 3.20$, $p = 0.043$, partial eta$^2 = 0.035$; SC, $F(2, 176) = 4.15$, $p = 0.017$, partial eta$^2 = 0.045$; TL, $F(2, 176) = 3.23$, $p = 0.042$, partial eta$^2 = 0.035$; CS, $F(2, 176) = 7.69$, $p < 0.001$, partial eta$^2 = 0.080$). Table 3 presents the estimated marginal means of the BACS tests after accounting for the covariates. The BACS z scores for all three groups were impaired. The mean z score on global cognition and all subtests showed a gradient of impairment, with the T2DM group being most impaired, followed by those with PD and the patients with normal blood sugar being the least impaired.

Finally, we conducted pairwise comparisons to assess differences between the normal, PD and T2DM groups on the BACS tests while accounting for the covariates.

Table 4 presents the results of the pairwise comparisons with Bonferroni-adjusted p-values for the multiple comparisons. For the BACS composite score ($p < 0.001$) and all subtests, except the memory tasks (digital sequencing and verbal memory and learning) the patients with T2DM had significantly worse scores than those with normal blood sugar. Furthermore, those with T2DM had significantly more deficits on the BACS composite compared with those with PD ($p = 0.026$). However, the only subtest that revealed a significant difference between PD and T2DM was the token motor task ($p < 0.001$), with those with T2DM having more pronounced deficits on this task. There was no significant difference in the BACS composite score and the subtest scores between those with normal blood sugar and PD.

4 | DISCUSSION

This study examined cognitive function in patients with schizophrenia and schizoaffective disorder who had PD and T2DM and compared them against patients with schizophrenia without either of these comorbidities. The prevalence of T2DM (9.1%) and PD (25.1%) among our sample is similar to the rates reported in literature.[1–4] The relative risk of developing T2DM in people with

TABLE 2 Correlation matrix between the variables ($n = 187$).

	Age	Gend	Diagn.	TRS	Comor	DoP	CLZ	ALC	STIM	THC	Other	VML	DS	TMT	VF	SC	TL	CS	FBG-G	Chol.	LDL	HDL	TGC
Age	1	0.192**	0.097	0.027	−0.214**	0.582**	0.132	−0.275**	−0.331**	−0.361**	−0.144	−0.118	−0.048	0.024	−0.065	−0.037	−0.092	−0.045	0.151*	0.188*	0.171*	0.132	−0.005
Gend	0.192**	1	0.047	0.054	−0.107	0.076	0.046	−0.207**	−0.184*	−0.217**	−0.165*	−0.171*	0.081	0.040	0.041	−0.043	−0.077	0.018	0.112	0.087	0.040	0.083	0.042
Diagn.	0.097	0.047	1	−0.125	−0.105	0.061	−0.072	−0.121	−0.108	−0.119	−0.068	0.051	0.033	0.019	0.058	−0.032	0.028	0.046	0.002	0.082	0.059	0.061	0.024
TRS	0.027	0.054	−0.125	1	0.126	0.226**	0.622**	0.049	0.031	0.035	0.016	−0.201**	−0.168*	−0.168*	−0.024	−0.056	−0.123	−0.165*	0.159*	0.040	0.020	−0.050	0.139
Comor	−0.214**	−0.107	−0.105	0.126	1	−0.136	0.116	0.428**	0.344**	0.488**	0.220**	−0.045	−0.087	−0.018	0.066	0.053	−0.060	−0.038	−0.007	−0.036	−0.046	0.002	0.037
DoP	0.582**	0.076	0.061	0.226**	−0.136	1	0.265**	−0.145*	−0.231**	−0.192**	−0.100	−0.152*	−0.023	−0.080	−0.100	−0.025	−0.059	−0.075	0.175*	−0.033	−0.023	−0.046	−0.039
CLZ	0.132	0.046	−0.072	0.622**	0.116	0.265**	1	0.008	−0.039	−0.001	−0.063	−0.195**	−0.166*	−0.114	0.060	−0.047	−0.137	−0.130	0.070	0.025	−0.012	−0.034	0.152*
ALC	−0.275**	−0.207**	−0.121	0.049	0.428**	−0.145*	0.008	1	0.486**	0.587**	0.291**	0.010	−0.004	0.074	−0.046	−0.007	−0.001	−0.003	0.004	−0.047	−0.028	−0.052	0.059
STIM	−0.331**	−0.184*	−0.108	0.031	0.344**	−0.231**	−0.039	0.486**	1	0.656**	0.399**	0.018	0.014	0.086	0.112	0.066	0.079	0.068	−0.108	−0.121	−0.066	0.077	−0.145*
THC	−0.361**	−0.217**	−0.119	0.035	0.488**	−0.192**	−0.001	0.587**	0.656**	1	0.388**	0.085	−0.039	0.110	0.049	0.103	0.074	0.076	−0.032	−0.058	−0.009	0.001	−0.071
Other	−0.144	−0.165*	−0.068	0.016	0.220**	−0.100	−0.063	0.291**	0.399**	0.388**	1	0.026	−0.009	0.066	0.062	0.109	0.052	0.052	−0.030	−0.010	−0.002	−0.002	−0.051
VML	−0.118	−0.171*	0.051	−0.201**	−0.045	−0.152*	−0.195**	0.010	0.018	0.085	0.026	1	0.534**	0.320**	0.378**	0.421**	0.456**	0.723**	−0.224**	0.079	0.102	0.016	−0.023
DS	−0.048	0.081	0.033	−0.168*	−0.087	−0.023	−0.166*	−0.004	0.014	−0.039	−0.009	0.534**	1	0.406**	0.432**	0.447**	0.426**	0.754**	−0.119	0.162*	0.066	0.048	0.229**
TMT	0.024	0.040	0.019	−0.168*	−0.018	−0.080	−0.114	0.074	0.086	0.110	0.066	0.320**	0.406**	1	0.244**	0.378**	0.314**	0.642**	−0.199**	0.176*	0.150*	0.118	0.032
VF	−0.065	0.041	0.058	−0.024	0.066	−0.100	0.060	−0.046	0.112	0.049	0.062	0.378**	0.432**	0.244**	1	0.519**	0.380**	0.676**	−0.154*	0.063	0.027	0.145*	0.074
SC	−0.037	−0.043	−0.032	−0.056	0.053	−0.025	−0.047	−0.007	0.066	0.103	0.109	0.421**	0.447**	0.378**	0.519**	1	0.534**	0.746**	−0.173*	0.185*	0.119	0.074	0.156*
TL	−0.092	−0.077	0.028	−0.123	−0.060	−0.059	−0.137	−0.001	0.079	0.074	0.052	0.456**	0.426**	0.314**	0.380**	0.534**	1	0.719**	−0.189**	0.055	0.027	0.129	0.021
CS	−0.045	0.018	0.046	−0.165*	−0.038	−0.075	−0.130	−0.003	0.068	0.076	0.052	0.723**	0.754**	0.642**	0.676**	0.746**	0.719**	1	−0.251**	0.161*	0.110	0.124	0.106
FBG-G	0.151*	0.112	0.002	0.159*	−0.007	0.175*	0.070	0.004	−0.108	−0.032	−0.030	−0.224**	−0.119	−0.199**	−0.154*	−0.173*	−0.189**	−0.251**	1	−0.003	−0.057	−0.094	0.249**
Chol.	0.188*	0.087	0.082	0.040	−0.036	−0.033	0.025	−0.047	−0.121	−0.058	−0.010	0.079	0.162*	0.176*	0.063	0.185*	0.055	0.161*	−0.003	1	0.933**	0.011	0.426**
LDL	0.171*	0.040	0.059	0.020	−0.046	−0.023	−0.012	−0.028	−0.066	−0.009	−0.002	0.102	0.066	0.150*	0.027	0.119	0.027	0.110	−0.057	0.933**	1	−0.037	0.181*
HDL	0.132	0.083	0.061	−0.050	0.002	−0.046	−0.034	−0.052	0.077	0.001	−0.002	0.016	0.048	0.118	0.145*	0.074	0.129	0.124	−0.094	0.011	−0.037	1	−0.326**
TGC	−0.005	0.042	0.024	0.139	0.037	−0.039	0.152*	0.059	−0.145*	−0.071	−0.051	−0.023	0.229**	0.032	0.074	0.156*	0.021	0.106	0.249**	0.426**	0.181*	−0.326**	1

Legend:
≥0.75
≥0.50
≥0.25
≥0.10
= 0.00
≤−0.10
≤−0.25

Note: ** Correlation is significant at the 0.01 level (2-tailed). * Correlation is significant at the 0.05 level (2-tailed).

Abbreviations: ALC, Alcohol use (Yes, No); Chol., Cholesterol; CLZ, Clozapine (Yes, No); Comor, Comorbidity (Yes, No); CS, Composite score; Diagn., diagnosis (Schizophrenia or schizoaffective); DoP, Duration of psychosis; DS, Digit sequencing; FBG, Fasting blood glucose; FBG-G, fasting blood glucose group; Gend, Gender; HDL, High-density lipoprotein; LDL, Low-density lipoprotein; Other, Other drug use; SC, Symbol coding; STIM, Stimulant use (Yes, No); TGC, Triglycerides; THC, Tetrahydrocannabinol use (Yes, No); TL, Tower of London; TMT, Token motor test; TRS, Treatment resistant schizophrenia; VF, Verbal fluency; VML, Verbal memory and learning.

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TABLE 3 Estimated marginal means of the BACS tests for three group of patients with schizophrenia.

Dependent Variable	Group	Mean[a]	Standard Error	95% Confidence Interval		
				Standard Deviation	Lower Bound	Upper Bound
VML	Normal	−1.413	0.121	1.34	−1.653	−1.174
	Prediabetes	−1.912	0.197	1.35	−2.301	−1.522
	Diabetic	−2.070	0.328	1.35	−2.717	−1.423
DS	Normal	−1.081	0.103	1.14	−1.285	−0.878
	Prediabetes	−1.456	0.168	1.15	−1.787	−1.125
	Diabetic	−1.717	0.278	1.15	−2.266	−1.168
TMT	Normal	−0.696	0.109	1.21	−0.911	−0.481
	Prediabetes	−0.479	0.177	1.21	−0.829	−0.130
	Diabetic	−1.940	0.294	1.21	−2.520	−1.360
VF	Normal	−0.787	0.111	1.23	−1.006	−0.569
	Prediabetes	−0.913	0.180	1.23	−1.267	−0.558
	Diabetic	−1.605	0.299	1.23	−2.195	−1.016
SC	Normal	−1.909	0.089	0.987	−2.084	−1.734
	Prediabetes	−2.102	0.144	0.987	−2.386	−1.817
	Diabetic	−2.648	0.239	0.985	−3.121	−2.176
TL	Normal	−0.152	0.123	1.36	−0.395	0.091
	Prediabetes	−0.479	0.200	1.37	−0.874	−0.084
	Diabetic	−1.024	0.332	1.37	−1.680	−0.368
CS	Normal	−1.649	0.127	1.41	−1.899	−1.398
	Prediabetes	−2.045	0.206	1.41	−2.452	−1.637
	Diabetic	−3.086	0.343	1.41	−3.762	−2.409

Abbreviations: CS, Composite score; DS, Digit sequencing; SC, Symbol coding; TL, Tower of London; TMT = Token motor test; VF, Verbal fluency; VML, Verbal memory and learning.

Note: a = Covariates appearing in the model are evaluated at the following values: gender = 1.30, duration of psychosis = 8.67, clozapine = 0.61, cholesterol = 4.79, triglycerides = 1.80, HDL = 1.11, LDL = 2.87, treatment resistant schizophrenia = 0.79.

schizophrenia is estimated to be around two times that of the general population.[1,2] The mechanisms for the increased prevalence of T2DM in patients with schizophrenia are multifactorial and complex, involving shared environmental, genetic and biological factors such as sedentary lifestyle, poor diet, low socioeconomic status, chronic stress, common vulnerability genes, chronic inflammation, oxidative stress and HPA axis dysfunction.[35,36] The findings of significant global cognitive deficits in our sample of people with schizophrenia as a whole (BACS composite mean score of −1.88) and symbol coding and verbal memory being the most severely affected subdomains are consistent with the reports from previous literature on this area.[5–7]

4.1 | Cognitive deficits in people with schizophrenia and T2DM

Our finding of more severe global cognition impairment in patients with schizophrenia with comorbid T2DM compared with patients with schizophrenia without diabetes is concordant with the results of the two meta-analyses on this subject.[18,21] However, individual studies included in the meta-analyses have reported inconsistent findings, with a significant increase[25–29] and no difference in cognitive deficits[22] reported among those with schizophrenia and comorbid diabetes compared with patients without the comorbidities. Interestingly, Li et al.[24] observed that patients with schizophrenia and comorbid diabetes scored better on delayed memory than those with schizophrenia alone. Similarly, Goughari et al.[23] noticed that patients with schizophrenia and hyperglycaemia performed significantly better on verbal memory and verbal fluency than those without hyperglycaemia. Hagi et al.[21] observed that on the composite cognitive score and on all subtests except memory tasks, patients with schizophrenia and comorbid T2DM performed more poorly than those with schizophrenia without diabetes. These observations and our finding that there was no significant difference in verbal memory and

TABLE 4 Pairwise comparisons between the normal, prediabetes and diabetes groups on the BACS subtests and composite score.

Dependent Variable	(I) FBG-G	(J) FBG-G	Mean Difference (I-J)	Standard Error	Sig.[b]	Hedges g	95% Confidence Interval for Difference[b] Lower Bound	Upper Bound
VML	Normal	Prediabetes	0.499	0.237	0.111	0.371	−0.075	1.07
		Diabetes	0.657	0.355	0.199	0.490	−0.202	1.52
	Prediabetes	Diabetes	0.158	0.375	1.00	0.117	−0.747	1.06
DS	Normal	Prediabetes	0.375	0.201	0.194	0.328	−0.112	0.862
		Diabetes	0.636	0.302	0.109	0.557	−0.093	1.37
	Prediabetes	Diabetes	0.261	0.318	1.00	0.227	−0.508	1.03
TMT	Normal	Prediabetes	−0.217	0.213	0.928	0.179	−0.731	0.297
		Diabetes	1.24*	0.319	<0.001	1.028	0.473	2.01
	Prediabetes	Diabetes	1.46[a]	0.336	<0.001	1.207	0.648	2.27
VF	Normal	Prediabetes	0.125	0.216	1.00	0.102	−0.397	0.648
		Diabetes	0.818[a]	0.324	0.037	0.665	0.036	1.60
	Prediabetes	Diabetes	0.693	0.341	0.132	0.665	−0.132	1.52
SC	Normal	Prediabetes	0.193	0.173	0.803	0.196	−0.226	0.611
		Diabetes	0.740[a]	0.259	0.015	0.749	0.113	1.37
	Prediabetes	Diabetes	0.547	0.273	0.141	0.553	−0.114	1.21
TL	Normal	Prediabetes	0.327	0.241	0.527	0.240	−0.254	0.909
		Diabetes	0.872[a]	0.360	0.050	0.641	0.001	1.74
	Prediabetes	Diabetes	0.545	0.380	0.460	0.398	−0.373	1.46
CS	Normal	Prediabetes	0.396	0.380	0.337	0.281	−0.204	0.996
		Diabetes	1.44[a]	0.372	<0.001	1.02	0.539	2.34
	Prediabetes	Diabetes	1.04[a]	0.392	0.026	0.738	0.094	1.99

Note: Covariates appearing in the model are: gender, duration of psychosis, clozapine, cholesterol, triglycerides, HDL, LDL, treatment resistant schizophrenia. Based on estimated marginal means. [a] = The mean difference is significant at the 0.05 level. [b] = Adjustment for multiple comparisons: Bonferroni.

Abbreviations: CS, Composite score; DS, Digit sequencing; SC, Symbol coding; TL, Tower of London; TMT, Token motor test; VF, Verbal fluency; VML, Verbal memory and learning.

working memory between those with comorbid schizophrenia and T2DM compared with those with schizophrenia raise the question of whether the pathways and substrates for learning and memory are differentially affected among those with schizophrenia and T2DM compared to those relevant for other cognitive functions. However, there is no evidence of either verbal or visual memory or learning being spared in people with T2DM.[9–12] Furthermore, verbal memory and learning is one of the domains of cognition that are significantly impaired in people with schizophrenia.[5,7] The reasons for memory tasks being selectively spared from further deterioration in people with schizophrenia and T2DM are unclear and need to be further explored.

In our sample, the mean composite cognitive score was in the severely impaired range for those patients with schizophrenia with T2DM, moderately impaired among those with PD and mildly impaired in those with normal blood sugar levels. The effect size of the difference in global cognition between patients with and without diabetes in our study is much larger (Hedges $g = 1.02$) than the small effect sizes reported in the previous meta-analyses on this subject.[18,21] Sampling variations, such as the chronicity and severity of diabetes and schizophrenia, and methodological differences in assessing cognitive function and haematological parameters for diagnosis could partially account for some of the discrepant findings. The mechanism through which T2DM causes cognitive deficits and excess cognitive deficits in those with schizophrenia is not clearly known and is likely to be multifactorial. Microvascular dysfunctions leading to ischaemia, haemorrhage, altered neuronal function and cell death, hyperglycaemia and insulin resistance generating oxidative stress, excess free radicals, angiogenesis,

inflammatory changes and advanced glycation end products, and an increased risk of metabolic syndrome, depression and hypoglycaemia are all likely to contribute to cognitive deficits in people with diabetes.[12,13] Many of these risk factors are also common among people with schizophrenia and thus can contribute to the additional cognitive deficits.[17,37] It could also be argued that people with schizophrenia with more severe cognitive deficits could lead a more unhealthy life style, such as excess alcohol or substance abuse, an unhealthy diet and a lack of exercise, and have suboptimal access to health care and adherence to treatment, leading to an increased chance of developing T2DM. The metabolic, inflammatory and vascular changes in diabetes can lead to substantial grey and white matter and regional brain atrophy in people with diabetes.[38] Similarly, schizophrenia can be associated with asymmetric brain atrophy and progressive grey matter volume loss in structural MRI.[39] However, brain imaging studies comparing people with schizophrenia with and without diabetes, which could assist with a greater understanding of the excess cognitive deficits in this group of patients, are currently lacking.

The additional cognitive deficits in people with schizophrenia with comorbid T2DM have clinical implications. Both schizophrenia and T2DM are chronic medical conditions requiring considerable long-term illness management. Skills such as monitoring symptoms effectively, following often-complicated medication regimens and tests, implementing diet and exercise plans, participating in rehabilitation programmes and planning and organising appointments can be more affected by the excess cognitive deficits in people with comorbidities of both conditions.[19,20] These excess cognitive deficits in those with comorbid T2DM and schizophrenia can potentially lead to more complications, hospitalisation, burden for carers and mortality.[40,41] Furthermore, an association between dysglycaemia and greater severity of negative and poorer functioning has been reported in people with schizophrenia.[42] Unfortunately, cognitive dysfunction in both T2DM and schizophrenia is not adequately addressed and evaluated by healthcare providers.[15,17] Interventions such as cognitive remediations[43] and structured aerobic exercise[44] have proven to be effective in ameliorating cognitive deficits in people with schizophrenia and should be evaluated among those with the comorbidities of schizophrenia and T2DM.

4.2 | Cognitive deficits in people with schizophrenia and PD

We found no significant difference in the composite score or individual subtest scores of the cognitive function of patients with schizophrenia and PD compared with those with normal blood sugar levels. Similarly, Chen et al.[31] evaluating 175 first-episode patients with schizophrenia, observed that those with PD differed from patients with normal blood sugar only on the emotional intelligence test and not on other cognitive functions tested. We did not test the emotional intelligence of our subjects. Goughari et al.[23] observed in a small sample of patients with schizophrenia that those with hyperglycaemia (FBG >5.5) but not in the diabetic range performed significantly better on verbal memory and verbal fluency than those without hyperglycaemia. However, our observation of a gradient of severity of cognitive deficits in patients with schizophrenia from those with normal blood sugar, PD and T2DM and no significant difference in the BACS subdomains between PD and T2DM, except token motor tasks, points towards the need for monitoring cognition and providing appropriate interventions among those with schizophrenia and impaired glucose regulation at early stages. All previous studies on this subject and ours were cross-sectional, and the point at which additional cognitive deficits in people with schizophrenia and dysglycaemia start accumulating is not known. Longitudinal studies on the effect of dysglycaemia in schizophrenia and its effect on cognition are lacking. Two studies that explored the relationship between cognitive deficits and duration and age of onset of diabetes found a significant relationship between cognitive deficits and more prolonged duration and younger onset of diabetes.[25,28] Further longitudinal studies of the long-term effect of sustained elevated blood sugar on cognitive function among people with schizophrenia are warranted.

4.3 | Limitations

Our study had a number of methodological advantages, such as carrying out the research in an everyday clinical practice setting, trained hospital nursing staff ensuring that patients were fasting before phlebotomy and administering the standardised cognitive test by clinical psychologists or a trained senior nurse working in the unit after building sufficient rapport with the patient. In the analyses, we accounted for metabolic and other collected clinical and demographic variables that affected the cognitive function test results. However, the assessment of blood sugar and cognition was done only once, and the duration of diabetes/hyperglycaemia was not assessed in this study. Measures of sustained glucose imbalance, such as levels of glycosylated haemoglobin were not available and its relationship as a continuous variable with BACS scores could not be assessed. This could be a more robust variable than categorising patients based

on fasting blood glucose to ascertain the relationship between dysglycaemia and cognition in people with schizophrenia and should be explored in future research. Our sample size was modest, particularly those who were classified as having T2DM. The study was cross-sectional, and we did not account for the effects of antipsychotics and illness severity on cognitive function. Furthermore, we are unable to collect details of psychopathology such as the severity of positive, negative and mood symptoms in the three groups, and the impact of these symptoms on cognitive function and blood sugar categories was not assessed in this study. Sixteen patients (8.6%) of the study sample were diagnosed with schizoaffective disorder rather than schizophrenia. However, the inclusion of participants with schizoaffective disorder is unlikely to have significant implications for the results, as evidenced by our correlation analysis finding no significant relationship between diagnosis and any of the BACS test scores or blood glucose categories. Additionally, there were differences in the sample size of each fasting blood glucose group (normal = 123, impaired = 47, T2DM = 17). However, equal sample sizes between groups are not an assumption of the main analysis used (i.e., MANCOVA), and further, visual inspection of histograms and QQ plots revealed that the BACS test scores were approximately normally distributed within each group, further supporting the use of these analyses. Therefore, there is a limited potential impact of unequal sample sizes on the results. As we drew the sample from a tertiary care treatment and rehabilitation unit, our sample had a high proportion of patients with treatment-resistant schizophrenia (>85%) and those treated with clozapine (>60%), and hence generalisability of the results to other settings and patients with treatment-responsive schizophrenia should be done cautiously. Also, in this study, we did not evaluate whether the additional cognitive deficits in people with comorbid schizophrenia and T2DM translated to more severe functional impairments in this group.

To conclude, In summary, we found that presence of T2DM among people with schizophrenia had a significant additional negative impact on their global cognition and subdomains except memory tasks. There was a gradient of greater cognitive impairment from those with normal blood sugar, PD and T2DM among patients with schizophrenia though the differences between the PD and normal groups on cognitive deficits were not significant. Many people with schizophrenia have significant cognitive deficits and the further worsening of cognition with dysglycaemia and T2DM among those with these comorbidities are likely to have significant impact on their illness management skills and everyday functioning. Cognitive deficits among people with schizophrenia and dysglycaemia and its impact on functioning should be routinely evaluated in clinical practice, and appropriate pharmacological, psychosocial and environmental interventions to mitigate the impairments should be more vigorously implemented in at clinical settings.

CONFLICT OF INTEREST STATEMENT
The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available for reasonable request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICS STATEMENT
The protocol for this research was reviewed by the Human Research Ethics Committee, South Metropolitan Health Service, Western Australia.

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