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Do the generalised cognitive deficits observed in schizophrenia indicate a rapidly-ageing brain?

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ABSTRACT – Background and Objectives: The nature and pattern of cognitive deficits (CD) in schizophrenia and whether the deficits are generalised or domain specific continues to be debated vigorously. We ascertained the pattern of CD in schizophrenia using a novel statistical approach by comparing the similarity of cognitive profiles of patients and healthy individuals.

Methods: In a consecutive sample of 78 patients with schizophrenia, performance on six cognitive domains (verbal memory, working memory, motor speed, processing speed, verbal fluency and executive functions) was measured using the Brief Assessment of Cognition in Schizophrenia (BACS). The similarity of cognitive profile between patients and two groups of healthy controls (age-matched and older adults who were in the age group of 70-79) was evaluated using a special purpose-built macro.

Results: Cognitive performance profiles in various domains of patients with schizophrenia and age-matched controls were markedly similar in shape, but differed in the overall performance, with patients performing significantly below the healthy controls. However, when the cognitive profiles of patients with schizophrenia were compared to those of older adult controls, the profiles remained similar whilst the overall difference in performance vanished.

Conclusions: Cognitive deficit in schizophrenia appears to be generalised. Resemblance of cognitive profiles between patients with schizophrenia and older adult controls provides some support for the accelerated ageing hypothesis of schizophrenia.

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Introduction

Schizophrenia is a neurobiological disorder characterised by positive, negative, mood and motor symptoms, prominent neurocognitive and social cognitive deficits, and significantly impaired functioning in many realms^{1,2,3}. Consistent evidence through research carried out in the past few decades supports the universality of cognitive deficits in schizophrenia and cognitive changes are considered as fundamental features of this condition^{4,5,6}. The relevance of cognitive deficits in schizophrenia is further enhanced by the findings that they are robust predictors of patients' community functioning and their treatment outcomes, thus contributing further to the overall burden of the disorder^{7,8}. Despite these, cognitive impairments in schizophrenia continue to be conceptualised as a secondary phenomenon and diagnostically uninformative, and recent exhortations to incorporate them into the Diagnostic and Statistical Manual volume 5 (DSM-V) diagnostic apparatus were not successful⁹⁻¹¹.

Even though the core clinical characteristics and the heterogeneity of cognitive deficits in schizophrenia have been widely scrutinized over the last few decades¹²⁻¹⁴, final agreement on the true nature of cognitive deficits in schizophrenia is still missing. In this area of research two contrasting views have crystallised over the last few decades: a) generalised deficit of cognition, whereby patients perform poorly on a range of cognitive tests^{6,12,15}, and b) specific or differential deficits, whereby patients perform poorly on some but not on all cognitive tests^{7,16-19}. Others have conceptualised cognitive deficits as a cardinal feature of a sub-group of schizophrenia patients^{13, 20}, evoking the old concept of dementia praecox²¹. Both generalised and domain specific views have depended for support on differing cognitive assessment

tools, the heterogeneity of schizophrenia samples, comorbidity issues, treatment outcomes, and other less well defined facets of cognition such as emotional and/or social intelligence. The way data are analysed and/or interpreted also determines the conceptual framework: using a cognitive battery and traditional analysis of variance approach, followed by numerous unplanned post-hoc comparisons²², the emphasis on single task differences (i.e., differential deficit) may prevent researchers from seeing the elephant in the room, i.e., the fact that patients exhibit consistent deterioration of performance across the remaining cognitive domains.

In the present study we adopt a novel analytical approach to the old question of generalised versus specific cognitive deficit. In particular, we focus on the examination of similarities in cognitive performance between schizophrenia patients and healthy controls, rather than on fluctuation of performance within the study groups. Specifically, we evaluated the *parallelism* of cognitive profiles of schizophrenia patients and two cohorts of healthy controls, age matched and older adult controls.

Methods

We collated from the medical records to retrospectively cognitive function data of a consecutive sample of 78 patients with schizophrenia admitted during the period from August 2010 to October 2014 to a medium length of stay, tertiary care treatment and rehabilitation unit located at Bentley Health Service, Western Australia. Diagnoses were generated after detailed clinical interview and observation utilising ICD-10 Criteria by a senior psychiatrist who was the clinical lead of the unit and was quite familiar with the patients. Cognitive function was measured using

the Brief Assessment of Cognition in Schizophrenia (BACS)^{23,24}. The study was approved by the local institutional ethics committee. In most cases evaluation of cognitive function assessments were carried out within a week of the patient's admission to the unit.

BACS is a brief pencil and paper cognitive assessment instrument, taking approximately 35 minutes to administer, and measuring four of the seven neurocognitive domains recognised as relevant for measurement in schizophrenia by the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) consortium^{2,25,26}: reasoning and problem solving, processing speed, verbal memory, and working memory. The BACS was designed for ease of administration and scoring, and has higher acceptance by patients and demonstrated robust reliability and concurrent validity when compared against lengthy standard batteries of neuropsychological tests^{23,24}. The six sub-tests include List learning (LL; verbal memory), Digit sequencing (DS; working memory), Token motor task (TMT; motor speed), Verbal fluency (VF; processing speed), Digit symbol coding (DSC; attention and processing speed) and Tower of London (ToL; reasoning and problem solving). Norms are organised in a manner that will allow the calculation of standardised scores adjusted for age and sex for each test, and for overall composite scores. The mean score of healthy controls was set as 0 and the standard deviation (SD) to 1. Cognitive profiles of the control subjects were adopted from a large normative study²⁴ which ascertained subjects randomly from the general community using a rigorous survey sampling procedure. Control subjects were screened using the Structured Clinical Interview for DSM-IV Axis I disorders and were excluded if lifetime and past month history of alcohol or illicit substance use was observed. An additional inclusion criterion was to have English

as primary language. Demographically, this sample was representative of the U.S. population, as in the 2005 U.S. census data, providing thus a "realistic comparison to clinical samples, especially patients with schizophrenia"²⁴ (p. 110).

Conventional data analyses were conducted using IBM SPSS Statistics 22. Profile analysis was conducted using a special purpose macro developed by one of the authors of this study. This macro is available free of charge and can be downloaded from [<http://www.stanef.in.rs>]. Profile distances were examined by calculating Euclidean (raw) and Mahalanobis' (standardised) distances²⁷, while the similarity of cognitive profiles was estimated by calculating intraclass coefficients of correlations²⁸ (ICC).

Results

Profile analyses

There were 94 admissions to the unit between the ages of 18 and 65 with the ICD-10 diagnosis of schizophrenia during the period from August 2010 to September 2014. BACS evaluation was not conducted or completed for 16 patients due reasons such as non-fluency with English, refusal to undergo the test, or test administration deemed not appropriate due to clinical reasons. The demographic and clinical information about sample used in this study are presented in Table 1.

The overall differences of cognitive profiles between patients and controls were evaluated. First, we compared cognitive profiles of schizophrenia patients and age matched (20-59 years) healthy controls, and then compared cognitive profiles between patients and older adult healthy controls (age range 70-79)²⁴. Comparison of cognitive profiles between schizophrenia patients and age-matched con-

Table 1
Basic demographics of schizophrenia patients and healthy controls

Variables	Schizophrenia patients <i>n</i> = 78	Controls <i>n</i> = 303	Elderly controls <i>n</i> = 50
Sex – % Males	70.5	48.5	45.5
Age – Mean (range)	31 (18-52)	43 (20-59)	74 (70-79)
Length of illness – M(SD)	8.2 (6.8)	–	–
Length of stay (days) – M (SD)	145 (80.4)	–	–
Comorbidities*	51 (65.4%)	–	–
No of pts on clozapine	52 (66.7%)	–	–
Unemployed	65 (83.3%)	–	–

* Alcohol/substance abuse, *n* = 34; anxiety disorder, *n* = 7; intellectual disability, *n* = 3; Pervasive developmental disorder, *n* = 4; personality disorder, *n* = 6; depressive disorder, *n* = 5.

trols demonstrated significantly lower scores on the set of BACS measures for schizophrenia patients. In contrast, the overall difference among groups was not significant when the cognitive profile of schizophrenia patients was compared to that of the older adult controls (age range 70-79 years). Raw and standardised distance estimates are presented in Table 2.

Similarity of cognitive profiles between schizophrenia patients and healthy controls (age-matched and older adult controls) was investigated by calculating Intraclass coefficients of correlation. This statistical procedure can also be interpreted as the test of parallelism of profiles, i.e. whether groups of study participant exhibit similar patterns of highs and lows on the set of commensurate measures. There was a significant resemblance between the cognitive profiles of schiz-

ophrenia patients and healthy controls (20-59 years), ICC = 0.947, 95%CI (0.76-0.99), $p < 0.001$). Similarity of cognitive profiles was even stronger between schizophrenia patients and older adult controls, ICC = 0.963, 95%CI (0.83-0.99), $p < 0.0001$. Figure 1 demonstrates cognitive profile jointly presented for all groups using the mean raw scores.

Exploratory factor analysis

Principal component axis factoring based on eigenvalues greater than 1 was used to investigate the underlying structure of cognitive domains. First, we examined if data were suitable for factor analysis. Both tests, the Kaiser-Meyer-Olkin measure of sampling adequacy (KMO = 0.818), and the Bartlett's test of sphericity (Chi-square = 167.1, $p < 0.001$)

Table 2
Distances between cognitive profiles of schizophrenia patients and healthy controls

Controls	Schizophrenia patients (<i>n</i> = 78)			
	Euclidean	Euclidean ²	Mahalanobis	<i>P</i> -value
20-59 years	27.52	757.06	2.08	<0.05
70-79 years	10.02	100.20	1.08	ns

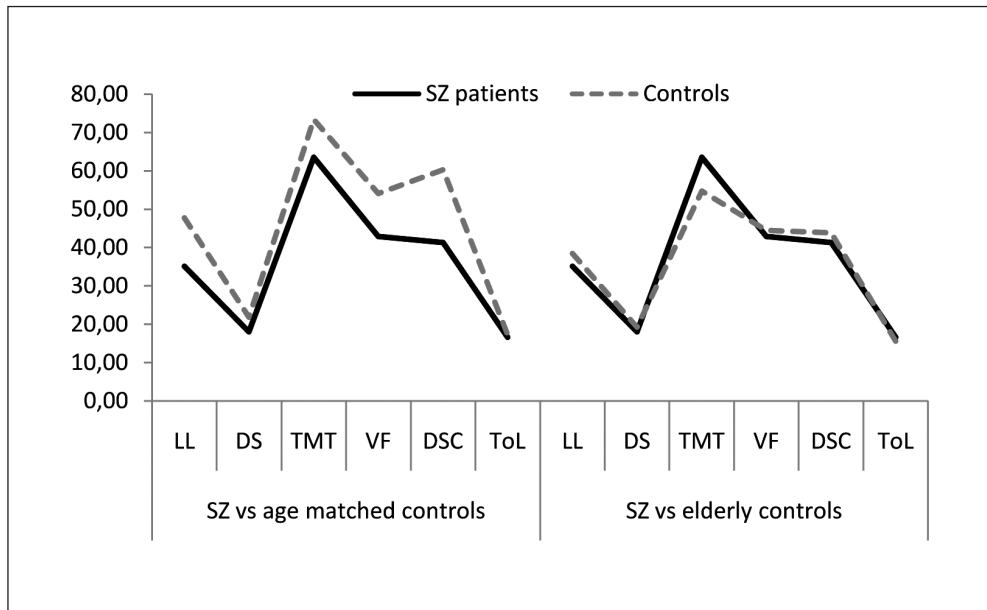


Figure 1. Cognitive profiles of schizophrenia patients and two groups of healthy controls.

indicated that data were highly suitable for factor analysis. A single principal component (the only one with eigenvalue exceeding 1) accounting 55.9% of the variance was identified as underlying six cognitive domains (Table 3). Individual sub-tests had similar loadings for the single principal component.

Table 3
Single factor structure of the six BACS cognitive domains

Cognitive Domain	Loadings
Processing Speed	0.829
Executive Functions	0.788
Working Memory	0.780
Verbal Memory	0.715
Verbal Fluency	0.715
Motor Speed	0.645

Discussion

Results obtained in the present study, using a variety of statistical procedures, all indicate that cognitive deficit in our sample of schizophrenia patients is generalised. First, conventional exploratory factor analysis confirms that performance on various cognitive tests was mediated through a single underlying cognitive dimension. The estimated factor loadings had similar magnitude, implying that each sub-test has almost equally contributed to the general cognitive factor. Factor analytic results are therefore supportive of the generalised deficit hypothesis^{6,12,15,29,30}. Second, we provide converging evidence that cognitive profiles between schizophrenia patients and healthy controls are strikingly similar, even though they differ significantly in the overall performance¹².

Patients occasionally show some fluctuation of performance relative to healthy controls, but this does not dispute a clear parallelism of the cognitive profiles. For example, performance of patients on the Tower of London task (executive control) reveals that patients performed fairly similar to age-matched healthy controls (Figure 1). This unexpected similarity however, can be a result of a psychometric artefact or inability of this particular task to discriminate successfully performance of patients and controls (ceiling effect), i.e., the mean scores of both groups were close to the maximum raw score of 22 for this sub-test. Availability of the age stratified normative data for the BACS²⁴ has added further impetus to the understanding of cognitive profile of schizophrenia patients relative to healthy controls.

There are some limitations to this study. The BACS evaluates only four out of seven cognitive domains incorporated in the MATRICS battery and in particular social cognitive deficits are not measured^{25,26}. Also, the sample size in the present study is not as large as recommended by rule-of-thumb metrics. For example, Tabachnick and Fidell (2007) suggest³¹ 300 cases, while others³² maintain that sample to variable ratio can be as low as 6:1. We are confident that our sample is large enough to fulfil the requirements for conducting factor analysis. Importantly, identified latent structures in both samples are reasonably similar. We also acknowledge that we compared cognitive profiles using two samples from geographically distinct populations. However, as both populations are from similar socioeconomic and cultural backgrounds, we believe sampling did not confound our results. As in many research fields, the best protection of the type II error is an independent replication of the present study, which we encourage.

Of particular interest in the present study is the resemblance of cognitive profiles between schizophrenia patients and older adult controls (70-79 years old) despite substantial age differences. The closeness of cognitive profiles is consistent with the concept of schizophrenia as a disorder of accelerated cognitive and functional decline²¹. In modern terms, the old concept of dementia praecox brings to mind the premature ageing hypothesis in schizophrenia³³. In brief, this hypothesis postulates that in people affected with schizophrenia, some physiological changes occur earlier. These include metabolic abnormalities³⁴, cardiovascular problems³⁵, brain abnormalities³⁶, cerebral white matter changes³⁷, and shorter telomeres compared to healthy subjects³⁸, leading to a lifespan 20-25 years shorter than the general population. However, pathophysiology of cognitive deficits in schizophrenia might be distinct from pathophysiology that underpins cognitive decline in normal subjects, e.g., powerful life style factors such as substance abuse (illicit and licit drugs), diet, and sedentary life style and social withdrawal.

Due to absence of our own control sample, in this study we were dependent on the normative data for healthy controls from other studies. This fact somewhat limits the generalisability of our results. However, we believe our choice of the normative control sample is reasonable: to our best knowledge, Keefe *et al* (2008)²⁴ provided the only normative data for the BACS which are age stratified, and which are representative of the general population. Second, we are aware that our sample of schizophrenia patients ($n = 78$) and, especially older adult control ($n = 50$) are rather small than large for this type of analysis. Hence, we strongly encourage replication of this study. The analytical tool (SPSS macro) is freely available and, with minor modifications, should be used in similar studies.

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