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Patterns of Impaired Neurocognitive Performance on the Global Neuropsychological Assessment, and Their Brain Structural Correlates in Recent-onset and Chronic Schizophrenia

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Objective: Schizophrenia is associated with impairment in multiple cognitive domains. There is a paucity of research on the effect of prolonged illness duration (≥ 15 years) on cognitive performance along multiple domains. In this pilot study, we used the Global Neuropsychological Assessment (GNA), a brief cognitive battery, to explore the patterns of cognitive impairment in recent-onset (≤ 2 years) compared to chronic schizophrenia (≥ 15 years), and correlate cognitive performance with brain morphometry in patients and healthy adults.
Methods: We assessed cognitive performance in patients with recent-onset (n = 17, illness duration ≤ 2 years) and chronic schizophrenia (n = 14, duration ≥ 15 years), and healthy adults (n = 16) using the GNA and examined correlations between cognitive scores and gray matter volumes computed from T1-weighted magnetic resonance imaging images.
Results: We observed cognitive deficits affecting multiple domains in the schizophrenia samples. Selectively greater impairment of perceptual comparison speed was found in adults with chronic schizophrenia (p = 0.009, $\eta^2_{partial}$ = 0.25). In the full sample (n = 47), perceptual comparison speed correlated significantly with gray matter volumes in the anterior and medial temporal lobes (TFCE, FWE p < 0.01).
Conclusion: Along with generalized deficit across multiple cognitive domains, selectively greater impairment of perceptual comparison speed appears to characterize chronic schizophrenia. This pattern might indicate an accelerated or premature cognitive aging. Anterior-medial temporal gray matter volumes especially of the left hemisphere might underlie the impairment noted in this domain in schizophrenia.

KEY WORDS: Schizophrenia; Neuropsychological tests; Cognitive dysfunction; Temporal lobe; Cognitive aging; Magnetic resonance imaging.

INTRODUCTION

Cognitive impairment is a consistent feature of schizophrenia as conclusively proven by numerous original research studies and meta-analyses [1-4]. Cognitive deficits are seen not only in patients diagnosed as having schizophrenia [5], but also in the at-risk state/prodrome [6,7], and even in the unaffected first degree relatives of index

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patients with schizophrenia [8,9]; thus, they are considered endophenotypes of the disorder [10].

Cross-sectional studies of patients with neuroleptic-naïve, recent-onset and chronic schizophrenia have shown comparable magnitude of diffuse cognitive impairment affecting multiple domains across the different phases of the illness [11,12]. However, there is evidence to suggest that the effect of illness chronicity on cognition may be different across various domains. Certain domains like working memory, executive functioning, and processing speed may show differentially severe impairment in patients with chronic schizophrenia [7,13-15]. A majority of the cross-sectional and longitudinal studies have examined the effect of chronicity over a period of 10 years or less [16]. The few longitudinal studies in adult-onset schizophrenia that have examined the effect of prolonged duration of illness (15 years or more) on cognitive functioning have shown discrepant results. Bonner-Jackson *et al.* [17] reported that processing speed and general knowledge test performance in patients remained stable at 20 years from baseline; Andreasen *et al.* [18] reported progressive decline in regional gray and white matter volumes that significantly correlated with the performance in learning, working memory, and problem solving tests at 18 years follow-up; Albus *et al.* [1] reported an overall stable cognitive performance in multiple domains with significant improvement in verbal intelligence over 15 years, although a subset of patients showed significant deterioration in visuomotor processing speed; Fett *et al.* [19] reported significant decline in all the cognitive domains except verbal fluency and verbal knowledge between assessments done 18 years apart.

Most of the comprehensive neuropsychological batteries used in schizophrenia like the MATRICS Consensus Cognitive Battery (MCCB), the Cambridge Neuropsychological Test Automated Battery, or the Clinical Antipsychotic Trials of Intervention Effectiveness project neurocognitive battery take at least 1−2 hours to complete [20-23]. Even the brief batteries like the Repeatable Battery for the Assessment of Neuropsychological Status or the Brief Assessment of Cognition in Schizophrenia take around 40 minutes to complete [24]. A common problem with long neuropsychological batteries is fatigue which can affect test performance. A general psychomotor slowness may be seen in patients with schizophrenia due to medication effects, sleep impairment, primary negative symptoms etc. that could make patients more prone to get fatigued [25]. Hence a brief battery that can cover the relevant cognitive domains would be beneficial to study the profile of cognitive impairment in schizophrenia, which would in turn allow us to make more definitive conclusions regarding the effect of chronicity on cognitive performance in cross-sectional and longitudinal studies.

The Global Neuropsychological Assessment (GNA) is a brief neuropsychological battery developed as part of the initiative to develop global norms for cognitive tests by a public non-profit organization [26]. It is available in five alternate forms. The GNA consists of seven main tests—Immediate Story Memory Trial 1 and 2, Perceptual Comparison, Digit Span Forward and Backward, Delayed Story Memory, Verbal Fluency and Category Switching, Spatial Span Forward and Backward, and Patient Health Questionnaire-4. These tests are adaptations or modifications of extensively studied and validated cognitive tests, and the battery is currently under the process of validation worldwide. The GNA can be administered in less than 25 (healthy adults) to 30 minutes (patients) in most cases. Preliminary validation and test-retest reliability of this battery in mild cognitive impairment and Alzheimer's disease were recently reported [27], as were analyses of GNA interform differences and the effects of repeated administration [28]. The utility of this battery for detecting neurocognitive impairment in schizophrenia has not been examined so far.

In this pilot study, we used the GNA for detecting neurocognitive abnormalities in schizophrenia, determine whether these impairments are differentially present in adults with chronic schizophrenia of prolonged illness duration (≥ 15 years) compared to recent-onset schizophrenia (≤ 2 years) and healthy adults, and explore the relationship between the various GNA cognitive domains and brain morphometry.

METHODS

Participants

This cross-sectional study was conducted on patients with recent-onset schizophrenia (ROSZ) with duration of illness 2 years or less (n = 17), chronic schizophrenia (CHSZ) with duration of illness 15 years or more (up to 25 years) (n = 14), and healthy comparison subjects (HCS)

(n = 16). Patients who met the criteria as per the Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-5) [29] for schizophrenia based on the Structured Clinical Interview for DSM-5 Disorders-Clinician version (SCID-5-CV) [30] were recruited from the outpatient and inpatient sections of the Department of Psychiatry, National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore, India, during the period from May 2019－February 2020. Healthy subjects were recruited by word of mouth from hospital staff and students at NIMHANS, during the same period. The study was approved by the NIMHANS Institutional Ethics Committee (No. NIMH/DO/IEC (BEH.Sc.DIV)/2019, dated 25th May 2019), and research participants were recruited after obtaining their written informed consent, in accordance with the principles laid out in the Helsinki declaration of 1975, amended in 2013 [31]. Healthy subjects were screened to rule out psychiatric or other medical disorders, substance use disorders, and first-degree family history of psychiatric disorders, using a study-specific checklist. Patients with comorbid psychiatric disorders including substance use disorders (except tobacco use disorder), and other medical/neurological disorders were excluded from the study. Patients who have had electroconvulsive therapy within the previous 6 months, or who had been on regular dose of benzodiazepines over the previous 2 weeks or having received a single dose of benzodiazepine on ‘as-required’ basis within the previous 48 hours were also excluded. Handedness was assessed using Edinburgh Handedness Inventory [32] and only right-handed subjects were recruited. All the participants underwent the clinical and neurocognitive assessments as well as magnetic resonance (MR) imaging either on the same day or within 1－2 days of each other.

Socio-demographic and Clinical Details of the Study Samples

The socio-demographic details of the study participants are summarized in Table 1. Clinical symptom ratings were done for all the patients using the Psychotic Symptom Rating Scales (PSYRATS) [33], the Scale for the Assessment of Negative Symptoms (SANS) [34], and the Scale for the Assessment of Positive Symptoms (SAPS) [35]. Medication associated abnormal movements were measured using the Abnormal Involuntary Movement Scale [36], the Simpson-Angus Scale [37], and the Barnes Akathisia Rating Scale [38] (Table 2). The socio-demographic details of the study participants are summarized in Table 1.

The risperidone equivalents of antipsychotics were calculated based on the defined daily doses by the World Health Organization (WHO) Collaborating Centre for Drug Statistics Methodology (https://www.whocc.no/atc_ddd_index/) implemented in an excel conversion sheet by Leucht *et al.* (http://www.cfdm.de/indexab2e.html?option=com_ content&task= view&id=15&Itemid=29) [39, 40]. See the Supplementary Tables 1 and 2 (available online) for the medication details of patients.

Global Neuropsychological Assessment

The GNA covers most of the cognitive domains that have been reported in the literature to be impaired in schizophrenia [3], namely, attention, verbal and visuospatial working memory, perceptual comparison/process-

Table 1. Socio-demographic details of the study samples

Variable	HCS (n = 16)	ROSZ (n = 17)	CHSZ (n = 14)	Statistics
Age (yr)	31.2 ± 6.1 31.7 (27.2, 34.7)	24.5 ± 3.0 24.7 (22.9, 26.7)	40.7 ± 6.3 40.0 (37.2, 46.4)	$F(2, 44) = 36.4$ $p < 0.001$[a]
Sex (male/female)	12/4	10/7	8/6	$\chi^2(2, n = 47) = 1.3$ $p = 0.52$
Education (yr)	15.8 ± 3.4 17.0 (14.8, 19.0)	15.2 ± 1.8 16.0 (15.0, 16.0)	12.6 ± 4.1 13.0 (12.0, 15.8)	$F(2, 44) = 4.3$ $p = 0.02$[b]
Body mass index (kg/m^2)	24.4 ± 4.5 24.0 (23.2, 26.9)	23.5 ± 3.3 23.8 (21.5, 25.7)	25.8 ± 4.1 25.0 (23.1, 28.2)	$F(2, 44) = 1.3$ $p = 0.28$

Values of the continuous variables are presented as mean ± standard deviation or median (Q1, Q3).
HCS, healthy comparison subjects; CHSZ, chronic schizophrenia; ROSZ, recent-onset schizophrenia.
[a]HCS-ROSZ, CHSZ-ROSZ, and CHSZ-HCS pairwise comparisons were significantly different in the *post-hoc* Tukey HSD test; [b]HCS-CHSZ pairwise comparison was significantly different in the *post-hoc* Tukey HSD test.

Table 2. Clinical details of the schizophrenia samples

Variable	ROSZ (n = 17)	CHSZ (n = 14)	Welch's t test t(df), p value
Age at onset	22.8 ± 3.3	21.8 ± 6.0	$t(19.2) = 0.58$, $p = 0.57$
PSYRATS	30.8 ± 18.9	18.3 ± 17.0	$t(28.7) = 1.93$, $p = 0.06$
SANS	35.6 ± 17.4	33.9 ± 21.4	$t(25.0) = 0.24$, $p = 0.81$
SAPS	28.4 ± 16.3	18.5 ± 18.3	$t(26.4) = 1.58$, $p = 0.12$
AIMS	0.5 ± 1.6	0.5 ± 1.0	$t(27.5) = 0.06$, $p = 0.95$
SAS	1.8 ± 2.1	1.9 ± 0.9	$t(27.5) = -0.18$, $p = 0.86$
BARS	0.3 ± 0.9	0.4 ± 0.8	$t(28.9) = -0.23$, $p = 0.86$

Values are presented as mean ± standard deviation.
CHSZ, chronic schizophrenia; ROSZ, recent-onset schizophrenia; PSYRATS, Psychotic Symptom Rating Scales; SANS, Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms; AIMS, Abnormal Involuntary Movements Scale; SAS, Simpson Angus Scale; BARS, Barnes Akathisia Rating Scale.

Table 3. Tests in the GNA and the cognitive domains assessed

Test items in the GNA	Cognitive domain
1. Immediate story memory – Trial 1	Verbal declarative memory
Total correct	
Immediate story memory – Trial 2	
Total correct	
2. Delayed story memory	
Total correct	
3. Perceptual comparison	Perceptual comparison/processing speed
Total items correct	
4. Digit span forward	Simple attention
Highest item correct	
Total correct	
5. Digit span backward	Verbal working memory
Highest item correct	
Total correct	
6. Category fluency (animal naming)	Verbal fluency/executive functioning
Total animals named	
Category switching (body parts/foods)	
Total category switches	
Total words	
7. Spatial span forward	Visuospatial working memory
Total items correct	
Spatial span backward	
Total items correct	

GNA, Global Neuropsychological Assessment.
There were seven main tests with 13 scorable items (shown in italics) in the GNA. The Immediate and Delayed story memory tests were grouped into the 'Verbal declarative memory' domain as these tests measured the immediate and delayed recall performance of the same story.

ing speed, verbal declarative memory (immediate and delayed story recall), and verbal fluency (category fluency and switching). There are seven main tests in the GNA: 1) Immediate story memory, 2) Delayed story memory, 3) Perceptual comparison, 4) Digit span forward, 5) Digit span backward, 6) Verbal fluency (category switching and animal naming), and 7) Spatial span forward and backward. Of these, Immediate and Delayed story memory test scores were grouped together into 'Verbal declarative memory', as both these tests measured the immediate and delayed recall performance of the same story (Table 3).

English, Hindi, and Malayalam versions of the GNA were administered according to the language preferences of the study participants. Bi-/multi-lingual mental health professional volunteers under the supervision of AL, VM, and JPJ ensured equivalence of the content of items and their intended meaning in the Hindi and Malayalam translations with those of the original English version (semantic

and content equivalence).

The GNA battery was administered in single session, by a psychiatrist (VM). The tests were administered in the same sequence and as per the standard instructions for administration of the GNA. All the participants completed the full battery including all the tests. The average durations of the GNA sessions were 21.2 ± 1.2 minutes in the healthy subjects and 25.8 ± 2.3 minutes in the schizophrenia sample. The individual test items were scored and entered in a spreadsheet and visually double-checked for data entry errors before the analysis.

We converted the raw individual test scores to *z*-scores using the overall mean and pooled standard deviation of the three groups, and grouped the *z*-scores into the six cognitive domains (Table 3) by averaging the *z*-scores of the tests under each domain, so that all of them would be in the same scale for better interpretability of scores across the various cognitive domains. This approach is often followed in neuropsychological studies where the ranges of different test scores vary to make it convenient to interpret and compare the shape or pattern of cognitive profiles of groups [41,42]. Thus, the GNA test battery which had seven cognitive tests with 13 scorable items was reduced into six meaningful and comparable domains, which were then analyzed using R, version 4.0.5 (R Studio 1.3.1073) [43].

Magnetic Resonance Imaging (MRI) Acquisition and Preprocessing

The MR images were acquired on a 3 Tesla Philips Ingenia CX scanner (Philips Healthcare, Best, Netherlands) using a 32-channel head coil (TR 6.5 ms, TE 2.9 ms, flip angle 9°, 192 slices in sagittal orientation, voxel size 1mm isotropic). The T1-weighted images were checked for MR artefacts, motion, and structural abnormalities using a systematic quality check pipeline [44]. The scans were also reviewed independently by a neuroradiologist to rule out any gross morphological abnormality. After quality assurance, we set the origin of T1-weighted images approximately at the anterior commissure using acpcdetect v2.0 [45-47] (https://www.nitrc.org/projects/art). The T1-weighted images were then segmented into gray matter, white matter and, cerebrospinal fluid tissue classes using the Computational Anatomy Toolbox [48] (CAT12, version 1727, https://neuro-jena.github.io/cat/) with SPM12 (version 7771, https://www.fil.ion.ucl.ac.uk/spm/) running in the background on MATLAB R2016a (MathWorks; https://www.mathworks.com). We used the modulated normalized gray matter images smoothed by a Gaussian kernel of 6 mm full width at half maximum for voxel-level correlation of gray matter with cognitive scores.

Analysis of the Neuropsychological Data

We calculated the Pearson's correlations between cognitive domains, and visualized the distribution of *z*-scores in each group using violin plots. To examine the cognitive profiles of each group, we plotted the mean *z*-scores and their standard errors for each domain. Additionally, we calculated the effect size (Hedge's *g*) for each cognitive domain in ROSZ and CHSZ (with respect to HCS group) assuming unequal variance in scores between groups, using the package 'effectsize' in R [49,50]. Hedge's *g* [51] corrects for the bias in Cohen's *d* [52], given the small sample sizes in the present study [53].

We analyzed the distribution of cognitive scores using Mardia's test for multivariate normality [54] and calculated the Mahalanobis distances to check for multivariate outliers. We performed a multivariate general linear model (GLM-MANCOVA) analysis with the six cognitive domain scores as dependent variables and group (factor with three levels–HCS, ROSZ, and CHSZ), age, education, and group-by-age interaction as independent variables. We additionally did *post-hoc* univariate GLM (ANCOVA) analyses, to explore the cognitive domains that contributed the most to the group difference.

Analysis of the Neuroimaging Data

To examine the association of cognitive scores with gray matter volumes, we performed a voxel-level correlation with cognitive scores in the overall sample (n = 47) and included the total intracranial volume (TIV) and age as covariates of no interest in a general linear model framework, as implemented in CAT12. We employed non-parametric statistical inference using the Threshold Free Cluster Enhancement (TFCE) algorithm [55] implemented in the TFCE toolbox (version 210, http://www.neuro.uni-jena.de/tfce/). We used the default settings (Smith method; 5000 permutations, cluster size weighting of $E = 0.5$) and examined the results at a stringent family-wise error (FWE) rate threshold of FWER < 0.0083, to account for probable false positives due to six correlational analyses (Bonferroni corrected $\alpha = 0.05/6 = 0.0083$).

RESULTS

The skewness (44.95, $p = 0.86$) and kurtosis (-1.05, $p = 0.29$) values were in acceptable limits, as tested using Mardia's test. We tested the Mahalanobis distances for chi-squared distribution with 6 degrees of freedom, and none of the values turned as outliers based on a cut-off of $p = 0.001$ [56]. The largest Mahalanobis distance observed was 11.36 ($p = 0.08$). All the six cognitive domains showed significant correlations with each other, surviving Bonferroni correction ($\alpha = 0.05/15 = 0.0033$) (Supplementary Fig. 1; available online). The mean and median cognitive performance *z*-scores showed a pattern of HCS > ROSZ > CHSZ in all the domains (Figs. 1, 2).

In ROSZ group, the largest effect size of difference from healthy adults was observed for verbal fluency and perceptual comparison speed ($g = -1.49$). Perceptual comparison speed in the CHSZ sample ($g = -2.39$) had the largest effect overall (Fig. 2)

Multivariate Effects of Group on Cognitive Performance, in the Overall Sample (n = 47)

Multivariate GLM (MANCOVA) revealed significant main effect of group (Pillai's trace = 0.69, $F(12, 72) = 3.15$, $p = 0.001$) on the six cognitive domain scores taken as dependent variables, after adjusting for mean-centered age, education, and group-by-age interaction (added to account for the possible differential effects of aging, as the three groups differed significantly in age distribution; Table 1 and Supplementary Fig. 2 [available online]). We also observed a significant effect of age on GNA performance (Pillai's trace = 0.30, $F(6, 35) = 2.47$, $p = 0.042$) (Table 4).

In *post-hoc* univariate analysis (ANCOVA), all the cognitive domains showed significant main effect of group, at an uncorrected threshold of $\alpha = 0.05$. Perceptual comparison speed, verbal fluency, verbal working memory and verbal declarative memory survived Bonferroni correction for six univariate tests. Perceptual comparison speed had the largest effect size ($F(2, 40) = 13.92$, $p < 0.001$, $\eta^2_{partial} = 0.41$) in univariate tests (Table 5).

Multivariate Analysis of Neurocognitive Performance between Healthy (n = 16) and Schizophrenia Samples (n = 31)

In multivariate analysis, there was a significant differ-

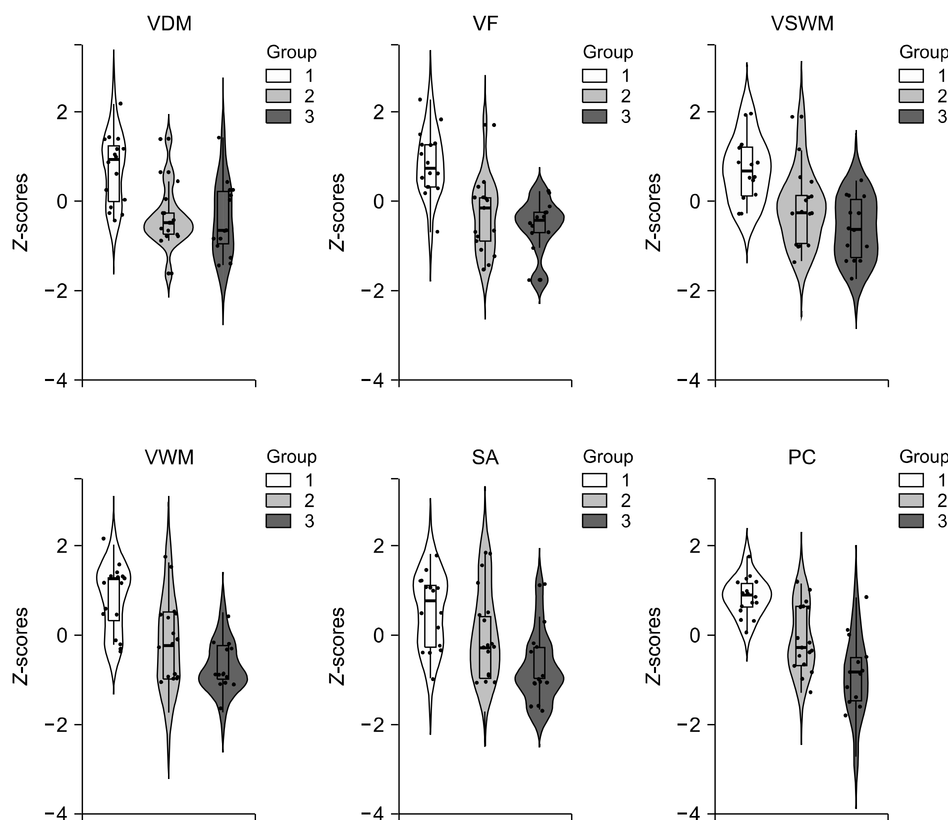

Fig. 1. Violin plots depicting the domain-wise cognitive *z*-score distribution in the three groups. As the violin plots are based on kernel density estimates, they extend beyond the range of actual scores in the sample depicted by the jittered dots. The solid horizontal lines within the boxplots represent the median *z*-score. Group 1: Healthy control subjects (HCS); Group 2: Recent-onset schizophrenia (ROSZ); Group 3: Chronic schizophrenia (CHSZ).
VDM, verbal declarative memory; PC, perceptual comparison; SA, simple attention; VWM, verbal working memory; VF, verbal fluency; VSWM, visuospatial working memory.

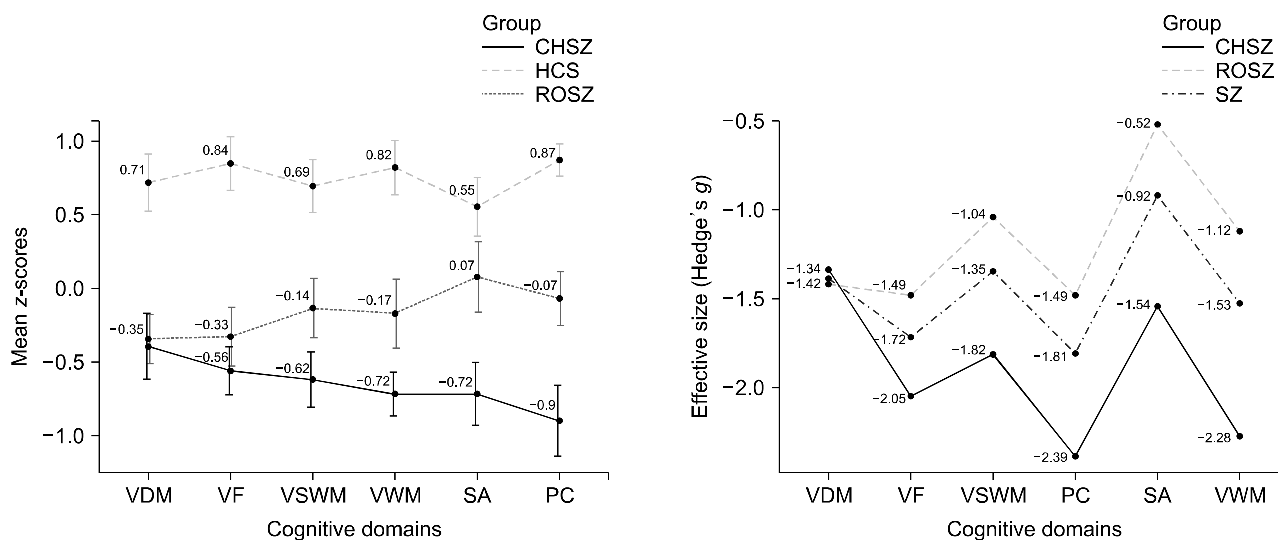

Fig. 2. Mean *z*-scores with standard error bars across cognitive domains in HCS, ROSZ and CHSZ (upper panel), and their effect sizes (Hedge's *g*) of difference from HCS in ROSZ and CHSZ (lower panel). The domains are arranged in the ascending order of the magnitudes of difference between ROSZ and CHSZ groups. The dashed line in the lower panel is the effect size plotted for both the patient groups combined. See Supplementary Tables 3 and 4 (available online) for all effect size estimates with their 95% confidence intervals.
HCS, healthy comparison subjects; CHSZ, chronic schizophrenia; ROSZ, recent-onset schizophrenia; VDM, verbal declarative memory; PC, perceptual comparison; SA, simple attention; VWM, verbal working memory; VF, verbal fluency; VSWM, visuospatial working memory.

Table 4. Multivariate GLM (MANCOVA) results (n = 47)

Variable	Pillai's trace	*F*-statistic, *p* value	$\eta^2_{partial}$
Group[a]	0.69	$F(12, 72) = 3.15$, $p = 0.001$	0.34
Age	0.30	$F(6, 35) = 2.47$, $p = 0.042$	0.29
Education	0.24	$F(6, 35) = 1.86$, $p = 0.116$	0.24
Group × Age	0.27	$F(12, 72) = 0.95$, $p = 0.507$	0.14

GLM, general linear model; HCS, healthy comparison subjects; CHSZ, chronic schizophrenia; ROSZ, recent-onset schizophrenia.
[a]Group factor with three levels, 1 = CHSZ, 2 = ROSZ, and 3 = HCS.

Table 5. Univariate main effects[a] of group on cognitive domains (*post-hoc*)

Cognitive domain	$F(2, 40)$, *p* value	Bonferroni corrected *p* value	$\eta^2_{partial}$
Perceptual comparison	13.92, $p < 0.001$*	< 0.001	0.41
Verbal fluency	12.18, $p < 0.001$*	< 0.001	0.38
Verbal working memory	7.63, $p = 0.002$*	0.009	0.28
Verbal declarative memory	7.32, $p = 0.002$*	0.012	0.27
Simple attention	5.04, $p = 0.011$	0.067	0.20
Visuo-spatial working memory	4.72, $p = 0.014$	0.087	0.19

GLM, general linear model.
[a]Univariate GLM (ANCOVA) adjusted for age, education, and group × age; *Significant at Bonferroni corrected threshold of $\alpha = 0.05/6 = 0.0083$; the cognitive domains are listed in the decreasing order of effect size.

ence between healthy and schizophrenia samples in neurocognitive performance scores (Pillai's trace = 0.59, $F(6, 37) = 8.92$, $p < 0.001$), after adjusting for mean-centered age, education, and group-by-age interaction (Table 6). Additionally, we observed a significant main effect of age on cognitive scores, although the effect was smaller than the main effect of group ($F(6, 37) = 2.45$, $p = 0.043$, $\eta^2_{partial} = 0.28$).

In *post-hoc* univariate analysis, all the six domains were significantly different between healthy and schizophrenia groups ($p < 0.001$). All the domains except for simple attention survived Bonferroni correction for six tests (Table 7).

Table 6. Multivariate GLM (MANCOVA) in healthy and schizophrenia samples

Variable	Pillai's trace	$F(6, 37)$, p value	$\eta^2_{partial}$
Group[a]	0.59	8.92, $p < 0.001$	0.59
Age	0.28	2.45, $p = 0.043$	0.28
Education	0.19	1.49, $p = 0.209$	0.19
Group × Age	0.04	0.27, $p = 0.945$	0.04

GLM, general linear model; HCS, healthy comparison subjects; CHSZ, chronic schizophrenia; ROSZ, recent-onset schizophrenia.
[a]Group factor with level 1 = HCS (n = 16), level 2 = ROSZ + CHSZ (n = 31).

Table 7. Univariate main effects[a] (*post-hoc*) in healthy and schizophrenia samples

Cognitive domain	$F(1, 42)$, Bonferroni corrected p value	$\eta^2_{partial}$
Perceptual comparison	29.35, $p < 0.001$*	0.41
Verbal fluency	29.11, $p < 0.001$*	0.41
Verbal working memory	21.21, $p < 0.001$*	0.34
Verbal declarative memory	16.40, $p = 0.001$*	0.28
Visuo-spatial working memory	16.38, $p = 0.001$*	0.28
Simple attention	6.88, $p = 0.072$	0.14

GLM, general linear model.
[a]Univariate GLM (ANCOVA) adjusted for age, education, and group × age; *Significant at Bonferroni corrected threshold of $\alpha = 0.05/6 = 0.0083$ the cognitive domains are listed in the decreasing order of effect size.

Comparative Analysis of Neurocognitive Performance between Recent-onset (n = 17) and Chronic Schizophrenia (n = 14) Samples

In the overall schizophrenia sample (recent-onset and chronic combined), we performed a multivariate GLM (MANCOVA) to evaluate the main effect of patient group on the cognitive scores (Table 8). To avoid multicollinearity, age was not included in the model as there were significant between-group differences in age (Table 1 and Supplementary Fig. 2 [available online]). In such a situation where the covariate substantially differs between groups, estimation of covariate adjusted means would not be meaningful [57]. Age at onset of symptoms was added as a covariate in view of its link to cognitive impairment [58,59] and also to account for the potential bias of patients with earlier age at onset being overrepresented in the chronic schizophrenia group. The cumulative dose-years of antipsychotic exposure were substantially different between ROSZ and CHSZ; therefore, we included the average daily dose of antipsychotics (cumulative antipsychotic exposure divided by the total duration of treatment) as a covariate, to avoid multicollinearity. Our schizophrenia samples consisted of patients predominantly exposed to second generation antipsychotics (Supplementary Tables 1, 2; available online). Anticholinergic (trihexyphenidyl) dose was not added in the model due to the negligible difference between ROSZ and CHSZ (Supplementary Table 1; available online).

Analysis of multivariate differences between ROSZ and CHSZ did not reveal significant group effect at $p < 0.05$ threshold, after adjusting for the covariates ($F(6, 19) = 2.28$, $p = 0.079$).

Post-hoc univariate analyses were done to explore the pattern of univariate group effects, keeping in mind the possibility that multivariate main effect of group could have been subtle, and hence not detected in our small sample (Table 9).

Table 8. Results of Multivariate GLM (MANCOVA)[a] analysis of neurocognitive performance between recent-onset and chronic schizophrenia samples, controlling for demographic and clinical variables

Variable	Pillai's trace	$F(6, 19)$, p value	$\eta^2_{partial}$
Group[a]	0.42	2.28, $p = 0.079$	0.42
Age at onset	0.36	1.79, $p = 0.155$	0.36
Education	0.35	1.70, $p = 0.176$	0.35
SANS	0.38	1.97, $p = 0.121$	0.38
SAPS	0.59	4.63, $p = 0.005$	0.59
ADD[b]	0.26	1.09, $p = 0.404$	0.26

GLM, general linear model; SANS, Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms; CHSZ, chronic schizophrenia; ROSZ, recent-onset schizophrenia.
[a]Group factor (level 1 = CHSZ and level 2 = ROSZ); [b]Average daily dose (ADD) of antipsychotic exposure in risperidone-equivalents.

In univariate analyses, group effects were significant for the perceptual comparison ($F(1, 24) = 8.04$, $p = 0.009$, $\eta^2_{partial} = 0.25$), and visuospatial working memory ($F(1, 24) = 4.70$, $p = 0.04$, $\eta^2_{partial} = 0.16$) domains, although neither survived Bonferroni correction for six univariate tests. Thus, the overall difference between ROSZ and CHSZ was subtle, with a trend for disproportionately greater impairment in perceptual comparison domain, which possibly could have been more evident in a larger sample.

Gray Matter Correlates of the Cognitive Scores

In the overall sample (n = 47) we found significant positive correlation between perceptual comparison speed and gray matter volume of the left anterior-medial temporal lobe and adjacent regions, after adjusting for TIV and age (TFCE, $p < 0.0083$, FWE corrected). Right anterior

medial temporal lobe regions also showed significant positive correlation, albeit to a lesser extent and magnitude (Fig. 3 and Table 10).

Verbal working memory (digit span backward) scores showed significant positive correlation with the right precentral gyrus, the left inferior frontal gyrus, and the left anterior lateral temporal lobe volumes (Fig. 4 and Table 11). Other cognitive domains did not show statistically significant correlation with the gray matter volumes after correction for multiple comparisons.

Table 9. Univariate GLM (ANCOVA) analysis[a] of cognitive domain scores between recent-onset and chronic schizophrenia samples (*post-hoc*)

Cognitive domain	$F(1, 24)$, uncorrected p value	Bonferroni corrected p value	$\eta^2_{partial}$
Perceptual comparison	8.04, $p = 0.009$	0.054	0.25
Visuo-spatial working memory	4.70, $p = 0.040$	0.240	0.16
Simple attention	3.95, $p = 0.058$	0.348	0.14
Verbal fluency	2.14, $p = 0.156$	0.936	0.08
Verbal working memory	1.55, $p = 0.224$	1.000	0.06
Verbal declarative memory	< 0.00, $p = 0.974$	1.000	< 0.00

GLM, general linear model; SANS, Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms.

[a]Univariate GLM (ANCOVA) adjusted for age at onset, education, SANS, SAPS, and average daily dose (ADD) of antipsychotics.

DISCUSSION

In this pilot study using GNA, we examined the patterns of neurocognitive impairment in recent onset and chronic schizophrenia, and studied the relationship between these deficits and brain morphometry to explore the link, if any, between the various cognitive domains and brain morphometry.

Pattern of Neurocognitive Deficits in Schizophrenia—Generalized, Selective or Both?

Using the GNA, we found an overall pattern of cognitive impairment affecting multiple domains that is consistent with previous reports of generalized cognitive impairment in the schizophrenia literature [60]. All the cognitive domains showed large effect size ($|g| > 0.8$) of difference from the healthy comparison sample, except simple attention in ROSZ group that had a medium effect

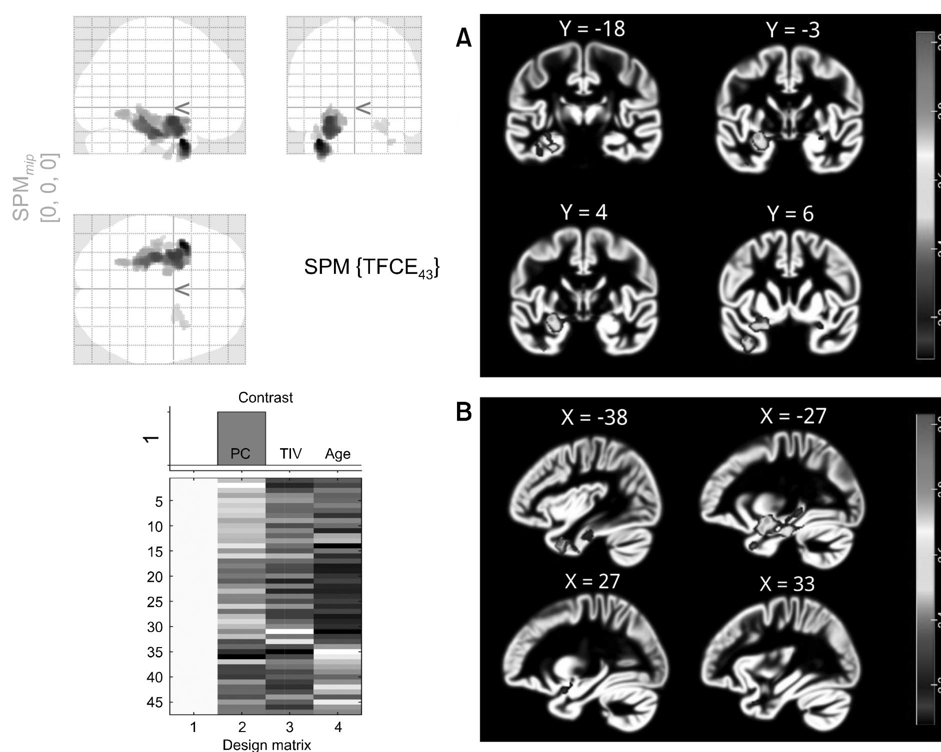

Fig. 3. Voxel-wise correlational analysis results showing gray matter clusters with statistically significant positive correlation (TFCE, FWE $p < 0.0083$) with perceptual comparison (PC) speed scores, adjusted for total intracranial volume (TIV) and age (n = 47). Coronal (A) and sagittal (B) slices are displayed in neurological convention (left side corresponds to the left hemisphere) and show significant clusters in bilateral anterior and medial temporal lobe regions, predominantly in the left hemisphere. The slices were chosen based on the MNI coordinates of the peak voxel in each cluster. The gradient of the colormap is based on negative logarithm of p values with a minimum threshold at 2.0792 ($p = 0.0083$). TFCE, Threshold Free Cluster Enhancement; FWE, family-wise error.

Table 10. The gray matter clusters that showed significant correlation with PC scores

Cluster size	Local maxima (MNI coordinates)	TFCE statistic	p value (TFCE, FWE)	Anatomical location (Hammers atlas)
674 voxels	−38, 6, −33	2,466.09	0.001	Left anterior medial temporal lobe (85%)
2834 voxels	−27, −3, −14	2,272.81	0.002	Left ambient and parahippocampal gyri (19%), left amygdala (16%), left hippocampus (14%), left anterior medial temporal lobe (11%), left posterior temporal lobe (11%)
201 voxels	−38, −18, −30	1,871.35	0.006	Left fusiform gyrus (77%), left inferior middle temporal gyri (23%)
38 voxels	33, 6, −33	1,796.28	0.007	Right anterior medial temporal lobe (100%)
160 voxels	27, 4 , −22	1,771.74	0.008	Right amygdala (46%), right anterior medial temporal lobe (32%)

MNI, montreal neurological institute; TFCE, Threshold Free Cluster Enhancement; FWE, family-wise error.
The contrast tested was positive slope of perceptual comparison (PC) test scores, with total intracranial volume (TIV) and age as covariates. The atlas regions covering 10% or lesser of each cluster are not listed for brevity (see Supplementary Table 5 [available online] for the complete table).

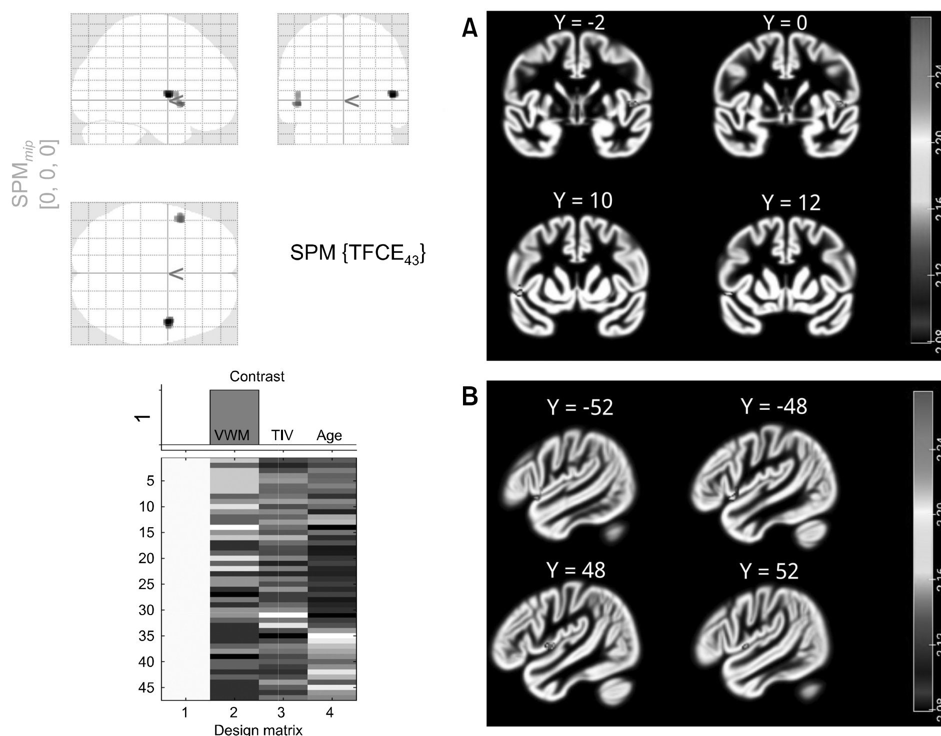

Fig. 4. Voxel-wise correlational analysis results showing gray matter clusters with statistically significant positive correlation (TFCE, FWE $p < 0.01$) with verbal working memory (VWM) scores, adjusted for total intracranial volume (TIV) and age (n = 47). The coronal (panel A) and sagittal (panel B) slices displayed in the neurological convention (left hand side corresponding to the left hemisphere) show significant clusters covering adjacent regions in the precentral gyrus on the right hemisphere (upper row in A and lower row in B), and the inferior frontal gyrus, the anterior lateral temporal lobe, and the precentral gyrus on the left hemisphere (lower row in A and upper row in B). The slices were chosen based on the MNI coordinates of the peak voxel in each cluster. The gradient of the colormap is based on negative logarithm of p values with a minimum threshold at 2.0792 ($p = 0.0083$).
TFCE, Threshold Free Cluster Enhancement; FWE, family-wise error.

($|g| \approx 0.5$). This exploratory study also revealed differential impairments across these domains. While perceptual comparison (PC) and verbal fluency (VF) showed the largest effect size ($g = -1.49$) in our sample of recent-onset patients, PC showed an even larger effect size in our chronic schizophrenia sample ($g = -2.39$) (Fig. 2). The

Table 11. The gray matter clusters that showed significant correlation with VWM scores

Cluster size	Local maxima (MNI coordinates)	TFCE statistic	p value (TFCE, FWE)	Anatomical location (Hammers atlas)
92 voxels	48, −2, 3	1,825.36	0.005	Right precentral gyrus (92%)
91 voxels	−48, 12, −6	1,768.57	0.006	Left inferior frontal gyrus (56%), left anterior lateral temporal lobe (29%)

MNI, montreal neurological institute; TFCE, Threshold Free Cluster Enhancement; FWE, family-wise error.
The contrast tested was positive slope of verbal working memory (VWM) scores, with total intracranial volume (TIV) and age as covariates. The atlas regions covering 10% or lesser of each cluster are not listed for brevity (see Supplementary Table 6 [available online] for the complete table).

GNA PC test is a measure of processing speed [27]. Impaired processing speed and verbal memory have been hypothesized to be central deficits that mediate the more generalized cognitive dysfunction in schizophrenia [61, 62], because of the disproportionate deficits reported in these domains [4,5,63].

Impairment in semantic verbal fluency is considered a key neurocognitive feature of schizophrenia, showing large effect sizes in neuropsychological and functional neuroimaging studies [64-66]. In our ROSZ sample, VF and PC had the largest effect sizes ($g = -1.49$). Category VF test performance relies on semantic word generation as well as executive functioning and processing speed [67]. As the verbal fluency and processing speed tests were both time-limited, VF and PC scores showed a strong correlation with each other in our full sample ($r(45) = 0.67$, $p < 0.001$; Supplementary Fig. 1 [available online]). Our samples had an age range of 18−50 years, a period during which the general intelligence and verbal abilities have been shown to have a trajectory of improvement as part of normal aging, before the age-related decline sets in [68]. The magnitude of difference in the effect sizes of PC (0.90) was substantially larger than that of VF (0.56) between ROSZ and CHSZ groups (Fig. 2). This disparity, despite a strong correlation between these two domains, may be because the CHSZ subjects were on an average, older (≈ 41 years) than ROSZ (≈ 24 years) and healthy (≈ 31 years) subjects, and aging might have had a moderating effect through the improvement in lexical semantic knowledge [68,69].

Neurocognitive Differences between Recent-onset and Chronic Schizophrenia

In our study, perceptual comparison speed was the chief domain that differed significantly between recent-onset and chronic schizophrenia samples (Table 9). Processing speed is a crucial cognitive function affected by normal aging that declines approximately linearly at about 0.02 standard deviation (with reference to young adult norms) per year from the peak at third decade of life until around 80 years of age [69-71]. Our three-group multivariate analysis showed significant effect of age, though with a smaller effect size than group (Table 4). It is unlikely that older age alone accounts for the slow processing speed shown by patients with chronic schizophrenia because patients with recent-onset schizophrenia also showed the largest decrement in this domain, and they were younger than the healthy controls. Also, the median age of CHSZ sample was ≈ 40 years, which is too early to observe substantial age-associated cognitive deterioration. Finally, our univariate analysis of PC speed revealed a significant difference between HCS and CHSZ groups after adjusting for age, education, and group-by-age interaction ($F(1, 25) = 17.53$, $p = 0.0003$, $\eta^2_{partial} = 0.41$). In short, this study provides evidence of disproportionate impairment of perceptual comparison/processing speed in chronic schizophrenia compared to recent-onset schizophrenia.

Longitudinal neuroimaging and neuropsychological studies have found evidence of progression in brain structural changes and cognitive dysfunction in schizophrenia [18,72,73]. The few studies that followed up patients for 15−20 years report overall stability of cognitive deficits over time until around 50 years of age, with probable accelerated decline in executive functions in later life compared to healthy controls, albeit of small effect size [1,13, 17,25].

There is emerging evidence from neurocognitive, neuroimaging, and metabolic studies for 'accelerated aging' in schizophrenia [74,75]. The neuropsychological premise of this hypothesis is that the cognitive profile of patients with schizophrenia is similar to that of older healthy

adults, with verbal memory, executive functions, and processing speed as the main affected domains [60]. The profile of impairment observed in the overall schizophrenia sample of our study also agrees with this pattern (Table 7). It may be noted that other than verbal declarative memory (VDM), all the five domains showed substantial differences between the ROSZ and CHSZ groups, with effect sizes ranging from 0.56 for VF to 1.16 for verbal working memory (VWM) (Fig. 2). However, after adjusting for the effects of symptoms, age at onset, education and daily antipsychotic dose, PC showed the largest difference between ROSZ and CHSZ ($\eta^2_{partial}$ = 0.25), while VWM ($\eta^2_{partial}$ = 0.06) and VDM ($\eta^2_{partial} \approx 0.00$) showed small to negligible differences (Table 9). This is consistent with previous longitudinal studies that have reported more pronounced age-related decline in processing speed compared to verbal memory [76]. In normal aging, processing speed starts declining early in the middle age [69,77,78], whereas verbal declarative memory tends to begin declining after about age 60 [79]. Around age of ≈ 40 years (median age of our CHSZ sample), one would not expect a marked decline in verbal declarative memory as part of normal aging [80]. It is also pertinent to note that early cognitive changes in classical neurodegenerative disorders like Alzheimer's Disease are characterized by significant deficits in verbal learning/memory and processing speed domains that are comparable in magnitude [81-84]. Thus, the picture of a disproportionate deficit in processing speed and negligible deficit in verbal declarative memory in our CHSZ sample could indicate a pattern of accelerated or premature cognitive aging, unlike the pattern seen in classical neurodegeneration. Nevertheless, we did not observe a significant group × age interaction effect in our three-group multivariate analysis. This might be because aging has been shown to have a non-linear effect as well [85] which will not be evident in a linear regression analysis. Moreover, our samples included participants in the age group 18－50 years, wherein the normal aging effect might be less apparent [69]. Additionally, interaction effects may require a larger sample than what is required to estimate main effects [86,87].

The Neuroanatomical Correlates of Cognitive Deficits in Schizophrenia

In our voxel-wise correlational analysis, Perceptual Comparison (PC) test performance correlated positively with gray matter volume in anterior and medial temporal lobe regions, predominantly of left hemisphere (Fig. 3 and Table 10). The GNA PC test requires one to make 'same/different' judgments about as many pairs of simple geometric shapes as possible in 45 seconds (Supplementary Fig. 3; available online). This requires speeded visual scanning, processing of geometric shapes, and oral responses that minimize motor system demands imposed by commonly used paper-and-pencil tests of processing speed, such as the Trail Making Test and Digit Symbol Substitution Test.

The anterior and medial temporal lobe aberrations have been consistently reported in schizophrenia [88-90]. The anterior temporal lobe (ATL) is considered a 'transmodal hub' (the 'hub-and-spoke' hypothesis of semantic memory) involved in processing semantic aspects of stimuli across sensory modalities [91]. There is increasing evidence that the anterior and ventromedial ATL regions are more specialized for complex visual processing than the posterior and dorsolateral regions [92,93]. Low frequency repetitive transcranial magnetic stimulation to the left ATL can significantly slow the reaction times in visual semantic processing tasks that also involve speech production, like picture naming [94,95]. Recent evidence supports the key role of medial temporal lobe (MTL) and adjacent structures—the hippocampus, entorhinal cortex, perirhinal cortex and parahippocampal cortex in visual perceptual processing [96]. There is also considerable evidence for the involvement of hippocampus and perirhinal cortex in visual discrimination tasks when there are similarities between the simultaneously presented stimuli [97-99]. As the GNA PC test entails comparing pairs of geometric shapes presented simultaneously, it does not require visual memory. Given the evidence supporting the role of anterior and medial temporal lobes in visual perceptual comparison, it is reasonable to conclude from our findings that subtle deficits in these regions may underlie the impairment in perceptual comparison speed seen in schizophrenia. If replicated in larger studies, these brain regions could be potential targets for transcranial neuromodulation intervention to improve processing speed in schizophrenia.

We found small clusters in the right precentral gyrus, left inferior frontal gyrus, left anterolateral temporal lobe, and left precentral gyrus showing significant positive correlation with verbal working memory scores (Fig. 4). The left inferior frontal gyrus is considered a key area for sub-

vocal rehearsal in Baddeley's phonological loop model [100]. The left perisylvian areas have been closely linked to backward digit repetition [101-103]. The inferior precentral gyrus has been shown to be important for short term retention of auditory stimuli before further processing and motor transformation [104,105]. Structural and functional aberrations in the perisylvian cortical regions like the precentral gyrus, the inferior frontal gyrus, and the superior temporal gyrus are widely implicated in the auditory processing dysfunction that may underlie auditory hallucinations in schizophrenia [106-108]. Overall, our findings are in line with the existing literature on neural correlates of phonological working memory; however, these preliminary results with modest effect sizes need replication in larger samples.

The Effects of Symptoms and Medications on Cognitive Performance

There is considerable evidence that negative symptoms have direct association with cognitive dysfunction [109, 110], while positive symptoms have a distracting effect on cognitive task performance [111]. Additionally, greater degree of positive symptoms warrants higher dose of medications like antipsychotics, anticholinergics, benzodiazepines etc. which can impede cognitive performance through anticholinergic effects [112,113], sedation, and psychomotor slowing due to extrapyramidal effects [114, 115]. In our study, we excluded patients who were on benzodiazepines. The ROSZ group had higher positive and negative symptom scores than CHSZ, and the difference was statistically significant for PSYRATS scores (Table 2). SAPS scores significantly contributed to reduction in cognitive scores in our schizophrenia sample (Table 8). Our sample consisted of patients who were cooperative and motivated for assessments and MR imaging, and therefore did not include patients with prominent negative symptoms. This unavoidable selection bias, along with the small sample size, might explain why we did not find significant effects of SANS ratings on cognitive performance.

The ongoing daily antipsychotic dose was significantly higher in the CHSZ group (Table 2); a similar trend has been noted in previous studies as well [116]. However, the daily anticholinergic doses and extrapyramidal side effects were not significantly different between the groups (Table 2 and Supplementary Table 1 [available online]). Even with substantially greater cumulative medication exposure, the Body Mass Index of CHSZ sample was not significantly higher than ROSZ sample (Table 1). Therefore, the differential cognitive deficits observed in our ROSZ and CHSZ samples are less likely to be due to anticholinergic dose differences or the extrapyramidal and metabolic side effects of antipsychotics.

The Utility of GNA as a Brief Cognitive Assessment Battery in Schizophrenia

This is the first study to demonstrate the usefulness of the GNA to detect both generalized and differential cognitive impairments in adults with recent-onset or chronic schizophrenia. The brevity of GNA confers the advantage of limiting the effect of fatigue on cognitive performance, which is especially important in research on patients with schizophrenia [25]. There is only minimal influence of language and culture on the test items, and literacy is not a pre-requisite. GNA covers most of the cognitive domains affected in schizophrenia that are included in the MCCB [117], except for reasoning/problem solving and social cognition. The process of validation and developing norms of GNA are currently undergoing worldwide (https://gninc.org/home/about/). An internationally accepted, culture- and language-neutral, brief neuropsychological battery could prove to be immensely useful in the clinical and research settings to study a widely prevalent illness like schizophrenia.

Strengths and Limitations

We studied the cognitive deficits in chronic schizophrenia of considerably long duration ($\geq$ 15 years) in comparison with recent-onset schizophrenia and healthy participants. Studies that examined such prolonged duration of illness are sparse [16]. Only four longitudinal studies have followed up the cognitive course of adult-onset schizophrenia beyond 15 years duration [1,17-19]. Furthermore, as our participants were all under 50 years of age, the cognitive effects due to illness chronicity may be less confounded with the effects of aging. Thus, the findings of this study hold substantial value in understanding the effect of chronicity in schizophrenia.

Having the cumulative antipsychotic exposure considered while studying the effect of chronicity is a strength of this study. In our analysis within schizophrenia samples, we controlled for the 'average daily dose of antipsychot-

ics' during the treated period, which could additionally be an indirect measure of the overall clinical course severity. However, there is the inevitable limitation that measures of cumulative medication dose and duration would be approximate at best due to missing old treatment documents and human errors in recall in cases of long illness duration.

Our ROSZ and CHSZ samples had comparable symptom scores and none of the patients had been chronically institutionalized. Thus, our study is free from the potential bias that could arise due to more symptomatic and institutionalized patients selected into the chronic schizophrenia group [118,119]. However, tertiary care hospital-based study samples like ours suffer from the unavoidable bias of representing a more relapse-prone disease than community-based samples [120]. An additional strength of this study was the comparable ages at onset in the ROSZ and CHSZ groups. We controlled for age at onset in our two-group analysis as well, thus minimizing the potential effect of this variable on cognitive performance [59,121].

The small sample size in the individual groups is a limitation, which was because the COVID-19 pandemic interrupted the recruitment of participants. All the subjects were recruited before March 2020 when the pandemic related lockdown and restrictions were announced in India, thus minimizing any psychosocial impact of the pandemic in our study subjects. The estimation of group effect in the comparison between ROSZ and CHSZ might have suffered greater Type II error due to limited sample size than the estimation of global effect in the three-group analysis because the expected effect size of difference between ROSZ and CHSZ would be smaller than between HCS and patients. Additionally, the effect of age was not controlled in the ROSZ-CHSZ comparison because of multicollinearity between group and age, as the two patient groups had minimal age overlap. Thus, the trend-level effect observed in this analysis ($p < 0.079$) should be interpreted with caution. However, this is an inherent problem in cross-sectional studies of the effect of illness duration, which will be inextricably linked with aging. An advantage of the HCS group having significantly higher average age than ROSZ was that any significant reduction in cognitive scores in ROSZ can be inferred to be primarily due to group effect.

The findings from this cross-sectional exploratory study provide support to the applicability of the GNA in detecting cognitive deficits of schizophrenia, which should be validated in larger samples. An ideal assessment of the effect of chronicity requires a longitudinal study design accounting for the variables that can contribute to the changes in cognitive performance over decades, including practice effects due to repeated assessments. The selective greater impairment of perceptual comparison speed in chronic schizophrenia underlines the need of such longitudinal studies of sufficiently long duration tailored to detect the possible accelerated decline in selected cognitive domains.

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■ Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

■ Author Contributions

Data curation: Vineeth Mohan, Pravesh Parekh. Methodology: Vineeth Mohan. Investigation: Vineeth Mohan, Pravesh Parekh, Ammu Lukose. Formal analysis: Vineeth Mohan. Software: Pravesh Parekh. Visualization: Pravesh Parekh. Fund acquisition: Sydney Moirangthem, Jitender Saini, John P. John. Development of the GNA: David J. Schretlen. Conceptualization: John P. John. Resources: John P. John. Writing-original draft prepara-

tion: Vineeth Mohan. Writing-review and editing: Pravesh Parekh, Ammu Lukose, Sydney Moirangthem, Jitender Saini, David J. Schretlen, John P. John. Supervision: Sydney Moirangthem, Jitender Saini, John P. John.

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