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The neurobiological characterization of distinct cognitive subtypes in early-phase schizophrenia-spectrum disorders

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ABSTRACT

Introduction: Cognitive deficits are present in some, but not all patients with schizophrenia-spectrum disorders (SSD). We and others have demonstrated three cognitive clusters: cognitively intact patients, patients with deficits in a few domains and those with global cognitive deficits. This study aimed to identify cognitive subtypes of early-phase SSD with matched controls as a reference group, and evaluated cognitive subgroups regarding clinical and brain volumetric measures.

Methods: Eighty-six early-phase SSD patients were included. Hierarchical cluster analysis was conducted using global performance on the Brief Assessment of Cognition in Schizophrenia (BACS). Cognitive subgroups were subsequently related to clinical and brain volumetric measures (cortical, subcortical and cortical thickness) using ANCOVA.

Results: Three distinct cognitive clusters emerged: relative to controls we found one cluster of patients with preserved cognition (n = 25), one moderately impaired cluster (n = 38) and one severely impaired cluster (n = 23). Cognitive subgroups were characterized by differences in volume of the left postcentral gyrus, left middle caudal frontal gyrus and left insula, while differences in cortical thickness were predominantly found in fronto-parietal regions. No differences were demonstrated in subcortical brain volume.

Discussion: Current results replicate the existence of three distinct cognitive subgroups including one relatively large group with preserved cognitive function. Cognitive subgroups were characterized by differences in cortical regional brain volume and cortical thickness, suggesting associations with cortical, but not subcortical development and cognitive functioning such as attention, executive functions and speed of processing.

1. Introduction

Schizophrenia-spectrum disorders (SSD) have been characterized as highly heterogeneous in both symptom characteristics and outcome (Ahmed et al., 2018; Salagre et al., 2020). This prevailing heterogeneity is hampering progress in research and clinical practice as it is poorly understood which illness characteristics require a personalized approach for treatment and care. A promising direction towards personalized treatment is the application of data-driven clustering techniques that classify individuals with shared illness characteristics into more homogeneous subgroups, enabling a better prediction of their needs for care. Over the last two decades, cognitive impairment has received considerable attention because of its presence early in the course of illness and remarkable stability over time with similar deficits observed during the first episode of psychosis and throughout the further course of the disorder (Jiménez-López et al., 2019; Sauvé et al., 2018). Clustering on cognitive performance may therefore lead to stable subtypes of SSD with different disease outcomes and different needs for care.

Previous findings suggest that poor cognitive performance may be associated with alterations in brain morphology. Ventricular enlargement and reduced gray matter volume are among the best established neurobiological findings in SSD (Van Erp et al., 2016; van Erp et al., 2018). Studies have further demonstrated reduced volume and cortical thickness in regions as the anterior cingulate, middle frontal gyrus, insula and middle and superior temporal regions (Haijma et al., 2013;

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Shepherd et al., 2012a; Van Erp et al., 2016; van Erp et al., 2018; Van Haren et al., 2011). These regions are involved in a wide variety of cognitive functions, suggesting that abnormalities in these regions may account for cognitive impairments seen in SSD (Karantonis et al., 2021a). Patients with SSD have significantly greater structural variability relative to healthy controls (Brugger and Howes, 2017; Kuo and Pogue-Geile, 2019) which indicates the existence of significant neurobiological heterogeneity. Distinct cognitive subtypes may reflect differences in underlying neurobiological processes. Indeed, previous studies examining neuroanatomical structures across cognitive subtypes have generally demonstrated decreased volumes of regional structures in more severely impaired cognitive subtypes compared to preserved cognitive subtypes (Czepielewski et al., 2017; Geisler et al., 2015; Ho et al., 2020; Rüsch et al., 2007; Shepherd et al., 2015; Van Rheenen et al., 2018; Vaskinn et al., 2015; Weinberg et al., 2016; Woodward and Heckers, 2015; Yasuda et al., 2020). Furthermore, a similar pattern seems to exist regarding cortical thinning, with more pronounced cortical thinning in severely impaired cognition compared to preserved cognition (Cobia et al., 2011). Studies primarily investigated chronic patient samples, whereas it may be valuable to understand cluster membership at disease onset. Moreover, given that longer duration of illness and treatment with antipsychotic medication have been associated with increased reductions in gray matter (Haijma et al., 2013), it is essential to extend findings to early-phase SSD. Identifying distinct cognitive subtypes and related neuronal markers of early-phase SSD could ultimately enhance prognostic accuracy and serve as a first step towards personalized treatment. However, studies investigating neuroanatomical patterns in distinct cognitive subtypes in early onset samples are scarce. Furthermore, previous studies were limited to specific regions of interest or specific domains of cognition and were not able to provide a comprehensive examination of the neurobiological correlates of cognitive clusters.

Therefore, this study aimed to identify cognitive subtypes of early-phase SSD and their relation with clinical, demographic and brain volumetric measures. Emergent cognitive subgroups were compared to matched controls to assess the level of cognitive impairment. Clusters were then related to clinical and demographic variables, and volumetric brain correlates of the clusters were examined using a large set of brain regions. The current study focused on cortical and subcortical volume and cortical thickness based on a recent meta-analysis indicating that replicated findings were predominantly related to volume and cortical thickness (Karantonis et al., 2021a). Based on a recent systematic review regarding cognitive subgrouping studies in SSD, we expected to find three distinct cognitive subtypes; a relatively intact cognitive subgroup, an intermediate cognitive subgroup and a severely impaired subgroup (Carruthers et al., 2019). We further hypothesized that the emergent cognitive subtypes showing more severe impaired cognition, have decreased volume and cortical thickness compared to the group with intact cognition.

2. Material and methods

2.1. Participants

Baseline data was used from the Simvastatin study (Begemann et al., 2015; Sommer et al., 2021) performed at the University Medical Center Utrecht (UMCU), the Netherlands. Written informed consent was obtained prior to study participation. Participants consisted of 86 patients with a DSM-IV diagnosis of schizophrenia (n = 32), schizoaffective (n = 6) or schizophreniform disorder (n = 1) or psychotic disorder 'not otherwise specified' (n = 47). The Comprehensive Assessment of Symptoms and History (CASH; Andreasen et al., 1992) was administered to confirm the inclusion diagnosis, which was provided by the treating clinician. In addition, prior psychiatric diagnoses were assessed with this instrument. Eligible patients were aged between 18 and 50 years and the onset of their first psychosis was no longer than three years before inclusion. Symptom severity was assessed using the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987) and general functioning was evaluated using the Global Assessment of Functioning scale (GAF; Jones et al., 1995). Information about antipsychotic medication use at time of assessment was obtained from patient report. Dose of antipsychotic medication intake (mg/day) was converted into a chlorpromazine equivalent (CPZE) for each patient using the method of Gardner et al. (Gardner et al., 2010). Educational attainment was provided in terms of years of education (YoE). This study has been performed according to the Declaration of Helsinki (October 2013). Ethical approval covering all participating sites was obtained from the research and ethics committee of the UMCU, the Netherlands, protocol number 13-249. The trial is registered in the ClinicalTrails.gov database (identifier NCT01999309) and the European Clinical Trials Database (EudraCT number 2013-000834-36).

Moreover, 40 healthy controls were included as reference group for cognitive functioning. Healthy controls were recruited via advertisements on notice boards and in newspapers. They did not have any history of psychiatric illness and were aged between 19 and 45 years (Trial registration: ABR NL50657.041.14).

2.2. Measures

2.2.1. Cognitive function

Cognitive function was assessed using the Dutch version of the Brief Assessment of Cognition in Schizophrenia (BACS; Keefe et al., 2004). The test consists of six subtests that assess different cognitive domains, including list learning (verbal memory), digit sequencing task (working memory), token motor task (motor speed), category instances and controlled oral word association test (verbal fluency), symbol coding (attention & information processing speed) and the tower of London (executive function). Performances of all participants on the subtests of the BACS were adjusted for gender and age using standardized norms of Keefe et al. (2004). Scores were then converted to individual z-scores and a composite z-score reflecting global cognitive function. As we selected participants with data on all subtests of the BACS, there was no missing data. To ensure data quality, raters were comprehensively trained. This training included the original training video from the BACS (Keefe) and regular meetings with the central team of raters during which interrater reliability and protocol adherence was checked. Furthermore, BACS assessments were always performed and rated by two researchers to increase interrater reliability.

2.2.2. Magnetic Resonance Imaging (MRI) — T1-weighted scans

MRI data was acquired at the UMCU using a 3 T Philips Ingenia CX and a 32-channel SENSE head-coil. Three-dimensional high-resolution T1-weighted structural scans were obtained with a 3-Dimensional T1-Weighted Turbo Field Echo sequence (repetition time = 10 ms, echo-time = 4.6 ms, flip angle = 8°, reconstructed voxel size = 0.75 × 0.75 × 0.8 mm^3, field of view = 240 mm × 240 mm × 160 mm). Processing of the images was done using FreeSurfer software, version 6.0.1 (http://surfer.nmr.mgh.harvard.edu/). Volumetric segmentation and cortical surface reconstruction were based upon the Destrieux atlas and the Desikan-Killiany atlas respectively (Desikan et al., 2006; Destrieux et al., 2010). Scans were visually checked for errors in segmentation. Thirty-four selected cortical regions of interest were located in the frontal, temporal and parietal lobe, supplemented with ten subcortical regions of interest. See supplementary Table S2–4 for a list of the selected ROIs.

2.3. Statistical analyses

Statistical analyses were performed using Statistical Package for Social Sciences (SPSS) version 25 (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.). Healthy controls and patients with SSD were compared on demographic variables such as gender, age, YOE and cognitive performance using

Pearson's Chi-Square (categorical variables) and One-way Analysis of Variance (ANOVA, continuous variables). All variables were tested for normal distribution. In case this was violated, median and interquartile range (IQR) were reported and a non-parametric Kruskal-Wallis test was used for group analyses. Next, to identify homogeneous subgroups of cognition, patients were clustered based on their general performances on the BACS (composite z-scores). A hierarchical clustering approach (HCA) was performed for the total sample of patients. Case similarity was computed using squared Euclidean Distance and Ward's Linkage was used as agglomeration procedure specification (Ward, 1963). After careful inspection of the dendrogram and meaningful jumps in the agglomeration schedule coefficients, the optimal number of clusters was defined, following Carruthers et al. (2019). For the dendrogram and agglomeration schedule coefficients, see Supplementary Figs. S1 and S2. Next, a k-means clustering technique was applied to optimize the retained clusters. The number of k clusters and initial partitions in the k-means solution were defined by results obtained from the hierarchical clustering procedure.

Emergent cognitive patient clusters were then compared to a group of controls regarding cognitive scores to verify the level of cognitive (under)performance. Furthermore, emergent clusters and healthy controls were compared on demographic and clinical variables using Pearson's Chi-Square (categorical variables) and One-way Analysis of Variance (ANOVA) or Kruskal-Wallis test (continuous variables). Post-hoc comparisons with Bonferroni correction for multiple testing were conducted for all significant ANOVA effects. Subsequently, emergent clusters were compared in three separate sets of analyses with intracranial volume entered as covariate 1) cortical brain volume; 2) subcortical brain volume; and 3) cortical thickness using analysis of covariance (ANCOVA). False positive results related to multiple comparisons were controlled using the Benjamini-Hochberg false discovery rate (FDR) method ($\alpha = 0.05$) (Benjamini and Hochberg, 1995).

3. Results

3.1. Demographics

A total of 86 patients with SSD and 40 healthy controls were

Table 1
Sample characteristics for healthy controls and cognitive patient clusters.

	Healthy controls (n = 40)	SSD patients (n = 86)			Test statistic H, F, χ^2	df	*p*-Value	Post hoc analysis[†]
		Preserved cognition (n = 25)	Moderately impaired cognition (n = 38)	Severely impaired cognition (n = 23)				
Male, n (%)	32 (80.0%)	18 (72.0%)	29 (76.3%)	18 (78.3%)	$\chi^2 = 0.59$	3	$p = 0.899$	–
Age (y), median (IQR)	23.00 (6.00)	25.00 (7.00)	26.00 (13.00)	26.00 (1.001)	H = 6.56	3	$p = 0.087$	–
Years of education, median (IQR)	15.00 (3.00)	15.00 (6.00)	14.00 (4.00)	11.00 (4.00)	H = 23.26	3	$p < 0.001$	b, c, e
Parental years of education, median (IQR)	14.50 (3.00)	13.50 (4.50)	13.50 (4.75)	13.50 (5.00)	H = 2.40	3	$p = 0.493$	–
Duration of illness (y), mean (SD)	N.A.	1.24 (1.13)	1.03 (1.03)	1.26 (0.92)	F = 0.50	2	$p = 0.606$	–
Chlorpromazine equivalent, median (IQR)	N.A.	300.00 (450.00)	300.00 (315.00)	320.00 (316.00)	H = 1.21	2	$p = 0.547$	–
Intracranial volume (mm^3), mean (SD)	1,601,564.96 (179,388.53)	1,512,400.58 (24,863.98)	1,528,495.97 (166,435.53)	1,489,599.72 (177,655.89)	F = 2.13	3	$p = 0.100$	–
BACS *Z*-score, mean (SD)								
Composite score	0.13 (1.15)	0.02 (0.67)	−1.40 (0.40)	−2.70 (0.40)	F = 83.82	3	$p < 0.001$	b, c, d, e, f
Verbal memory	0.43 (1.01)	0.37 (1.05)	−0.63 (0.96)	−1.49 (0.93)	F = 23.74	3	$p < 0.001$	b, c, d, e, f
Working memory	0.07 (1.05)	0.12 (0.91)	−0.76 (0.89)	−1.81 (1.07)	F = 22.54	3	$p < 0.001$	b, c, d, e, f
Motor speed	−0.15 (0.96)	−0.46 (1.11)	−1.15 (1.01)	−1.47 (1.01)	F = 11.16	3	$p < 0.001$	b, c, e
Verbal fluency	0.11 (1.05)	0.14 (0.82)	−0.86 (0.95)	−1.62 (0.97)	F = 21.17	3	$p < 0.001$	b, c, d, e, f
Attention & Processing speed	−0.23 (1.19)	−0.57 (0.93)	−1.22 (0.74)	−2.10 (0.55)	F = 22.50	3	$p < 0.001$	b, c, d, e, f
Executive function	0.24 (0.87)	0.47 (0.66)	−0.35 (0.97)	−1.05 (1.28)	F = 13.08	3	$p < 0.001$	b, c, d, e, f
PANSS, mean (SD)								
Total	N.A.	58.56 (17.22)	58.05 (12.24)	59.91 (13.03)	F = 0.13	2	$p = 0.882$	–
Positive	N.A.	13.60 (4.59)	13.03 (4.59)	13.91 (5.01)	F = 0.27	2	$p = 0.762$	–
Negative	N.A.	14.64 (5.60)	14.87 (5.57)	15.52 (4.94)	F = 0.17	2	$p = 0.842$	–
General	N.A.	30.32 (8.76)	30.16 (5.94)	30.48 (6.56)	F = 0.02	2	$p = 0.986$	–
GAF, mean (SD)	N.A.	54.96 (14.23)	52.59 (10.13)	52.73 (9.11)	F = 0.37	2	$p = 0.691$	–

SSD, schizophrenia-spectrum disorder; BACS, Brief Assessment of Cognition in Schizophrenia; PANSS, Positive and Negative Syndrome Scale; GAF, Global Assessment of Functioning.

[†] a HC significantly different from preserved cognitive cluster; b HC significantly different from moderately impaired cognitive cluster; c HC significantly different from severely impaired cognitive cluster; d preserved cognitive cluster significantly different from moderately impaired cognitive cluster; e preserved cognitive cluster significantly different from severely impaired cognitive cluster; f moderately impaired cognitive cluster significantly different from severely impaired cognitive cluster.

included. Sociodemographic and clinical characteristics are presented in supplementary Table S1.

3.2. Cognitive clusters

Hierarchical clustering (Ward's method) with k-means optimization using BACS composite scores for the total sample of patients resulted in three distinct cognitive clusters (see Table 1). Subgroups were subsequently compared to a group of healthy controls to assess the level of cognitive impairment. Compared to controls, the emergent clusters were characterized as follows: a relatively preserved cognitive cluster (n = 25), a moderately impaired cognitive cluster (n = 38) and a severely impaired cognitive cluster (n = 23), see Table 1 and Fig. 1. Clusters did not differ significantly regarding gender ($p = 0.899$) and showed trend-level effects for age ($p = 0.087$). The moderately impaired and severely impaired cognitive clusters had significantly fewer years of education compared to healthy controls ($p = 0.001$ and $p < 0.001$ respectively) and the severely impaired cognitive cluster had significantly fewer years of education compared to the relatively preserved cognitive cluster ($p = 0.002$). Clusters did not differ significantly regarding parental years of education ($p = 0.493$), duration of illness ($p = 0.606$) and chlorpromazine equivalents ($p = 0.547$). Furthermore, total intracranial volume was not significantly different between healthy controls and the three cognitive clusters ($p = 0.100$).

The relatively preserved cognitive cluster showed cognitive performances similar to healthy controls on composite BACS score and all cognitive subtests. The moderately impaired cluster showed intermediate cognitive performance, with significantly lower scores compared to healthy controls and the relatively preserved cluster on all cognitive subtests, but higher scores on all cognitive subtests compared to the severely impaired cluster except for motor speed. Most severe deficits were displayed on attention & processing speed, and motor speed. The severely impaired cluster showed impaired cognitive performance compared to all other groups on all cognitive subtests, except for motor speed. Performance on working memory and attention & processing speed were showing the most severe deficits (Fig. 1). No significant differences on PANSS and GAF scores were shown between cognitive clusters (Table 1).

3.3. Regional brain volume

Differences in brain volumetric measures of the selected ROIs between healthy controls and cognitive clusters were assessed in three separate sets of analyses (cortical, subcortical and cortical thickness) using ANCOVA. Additional sensitivity analyses were performed corrected for age and Euler number (a proxy of image quality). Results are shown in Figs. 2–3 and supplementary Tables S2–S4.

3.4. Cortical brain volume

Cortex volume, total gray matter and 68 cortical regions of interest were assessed. After FDR correction, univariate analyses showed significant differences between groups in the left postcentral area ($F(3) = 6.43$, $p < 0.001$), with larger volumes in the group with preserved cognition compared to healthy controls ($p = 0.027$) and both groups with moderately impaired and severely impaired cognition (both $p < 0.001$). Furthermore, in the left caudal middle frontal gyrus ($F(3) = 5.22$, $p = 0.002$), individuals with moderately impaired and severely impaired cognition showed smaller volumes compared to healthy controls ($p < 0.001$ and $p = 0.015$). Also, the group with moderately impaired cognition showed smaller volumes compared to preserved cognition ($p = 0.020$). Finally, in the left insula ($F(3) = 5.26$, $p = 0.002$), a similar pattern was shown with the moderately and severely impaired cognitive subgroups showing smaller volumes compared to healthy controls ($p = 0.001$ and $p = 0.006$ respectively) and individuals with moderately impaired cognition showed smaller volumes compared to those with preserved cognition ($p = 0.027$). See Fig. 2 and Table S2 for detailed statistics.

3.5. Subcortical brain volume

Total subcortical gray matter and 20 subcortical regions of interest were assessed. No significant differences between groups were shown for subcortical brain regions ($p > 0.05$, FDR corrected). See supplementary Table S3 for detailed statistics.

3.6. Cortical thickness

Cortical thickness was assessed in 68 regions of interest. After FDR correction, univariate analyses showed significant differences between groups in cortical thickness of the left banks of the superior temporal sulcus ($F(3) = 4.31$, $p = 0.006$), the left and right caudal middle frontal gyrus ($F(3) = 4.83$, $p = 0.003$ and $F(3) = 4.04$, $p = 0.009$ respectively), right fusiform ($F(3) = 5.21$, $p = 0.002$), right isthmus cingulate gyrus (F

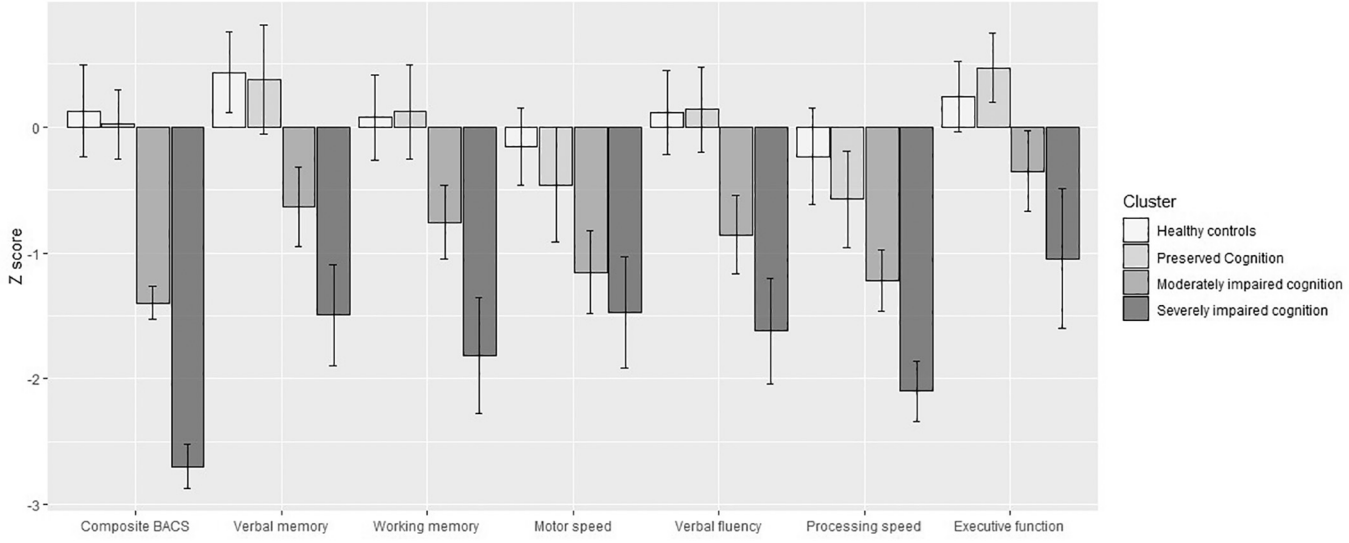

Fig. 1. Composite BACS and subdomain z-scores for healthy controls and cognitive clusters.
Error bars represent 95% confidence intervals. See Table 1 for detailed statistics. BACS = Brief Assessment of Cognition in Schizophrenia.

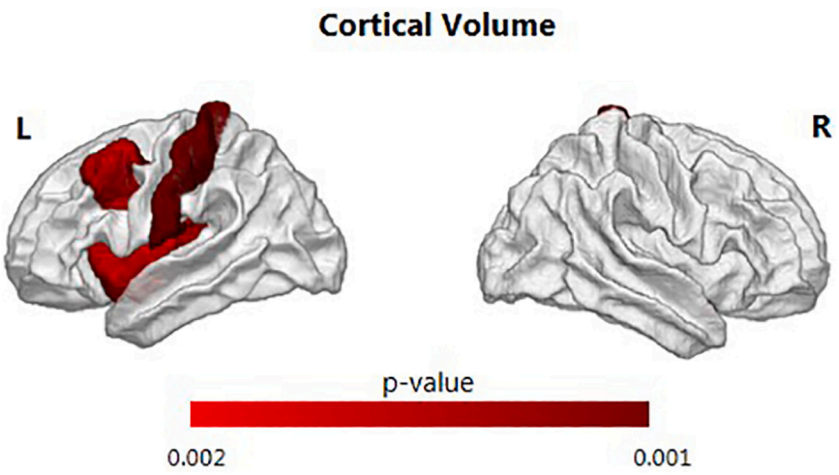

Fig. 2. Cortical brain regions showing significant volume differences between healthy controls and cognitive clusters.
Differences between groups were shown in the left postcentral gyrus, left middle caudal frontal gyrus and left insula. See supplementary Table S2 for detailed statistics. L = Left hemisphere; R = Right hemisphere.

(3) = 4.71, $p = 0.004$), right lateral orbitofrontal gyrus (F(3) = 4.12, $p = 0.008$), right medial orbitofrontal gyrus (F(3) = 5.15, $p = 0.002$), right paracentral (F(3) = 4.22, $p = 0.007$), right pars orbitalis (F(3) = 6.15, $p = 0.001$), right pars triangularis (F(3) = 4.38, $p = 0.006$), right posterior cingulate gyrus (F(3) = 5.43, $p = 0.002$), left and right precentral area (F(3) = 4.50, $p = 0.005$ and F(3) = 4.83, $p = 0.003$ respectively), left precuneus F(3) = 4.72, $p = 0.004$), right rostral middle frontal gyrus (F(3) = 3.94, $p = 0.010$), left and right superior frontal gyrus (F(3) = 3.84, $p = 0.011$ and F(3) = 5.40, $p = 0.002$ respectively) and left superior parietal gyrus (F(3) = 4.07, $p = 0.009$). See Fig. 3 and supplementary Table S4 for post-hoc results and detailed statistics.

4. Discussion

The current results confirmed the existence of three distinct cognitive subgroups in a sample of early-phase SSD, including a relatively large subgroup with preserved cognition (29.1%), a moderately impaired subgroup (44.2%) and a severely impaired subgroup (26.7%) relative to healthy controls. No significant differences between cognitive subgroups were demonstrated regarding clinical measures such as symptom severity (PANSS) and global functioning (GAF). Cognitive subgroups were characterized by differences in volume of the left postcentral gyrus, left middle caudal frontal gyrus and left insula, and differences in cortical thickness were predominantly found in fronto-parietal regions. No differences were demonstrated in subcortical brain volume.

4.1. Cognitive clusters

The results of the current study provide further evidence for the existence of three distinct cognitive subtypes in a population of early-phase SSD. This is in line with previous clustering studies reporting on three cognitive subgroups in patients with longer duration of illness (Carruthers et al., 2019; Gilbert et al., 2014; Menkes et al., 2019; Uren et al., 2017; Wells et al., 2015). Although cognitive impairment has long been recognized as a core feature of SSD, the current results show that a significant proportion of patients (29%) remains cognitively intact. This subgroup with relatively preserved cognition does not show any significant differences compared to healthy controls, on both global cognition or cognitive subtasks. The moderately impaired subgroup (44%) showed global cognitive impairment compared to the healthy controls on all cognitive domains. Findings regarding the intermediate cluster suggest global impairments of cognitive performance rather than domain specific deficits. The severely impaired subgroup (27%) showed pronounced cognitive impairments that were not restricted to specific domains, with more severe performance deficits compared to the other cognitive subgroups (except for motor speed) and healthy controls. The existence of a severely impaired cognitive subgroup in SSD has previously been demonstrated in older patients (Lewandowski et al., 2014; Uren et al., 2017; Van Rheenen et al., 2016; Wells et al., 2015) and more recently in another cohort of recent onset SSD by our group (Oomen et al. in press). However, the percentage of individuals showing severely impaired cognition in this study is lower than the 44% reported in a large recent systematic review (Carruthers et al., 2019). This difference is possibly attributable to the relatively young age and the recent onset of the disease.

Fewer years of education was demonstrated in the moderately and severely impaired cognitive clusters compared to healthy controls, and in the severely impaired cognitive cluster compared to individuals with preserved cognition. As years of education may be a reflection of premorbid functioning, this supports previous findings by Wenzel et al. (2021) and Weinberg et al. (2016), demonstrating higher premorbid functioning in both the preserved cognitive subgroup and healthy controls (Weinberg et al., 2016; Wenzel et al., 2021).

4.2. Clinical measures

Remarkably, no significant differences between cognitive subgroups were demonstrated on clinical measures such as symptom severity or global functioning. Previous clustering studies did show more severe symptomatology and lower global functioning in subgroups with poor cognitive performance compared to the relatively spared cognitive subgroups (Green et al., 2004; Lewandowski et al., 2014; Ortiz-Gil et al., 2011; Uren et al., 2017; Van Rheenen et al., 2018; Weinberg et al., 2016; Wells et al., 2015; Wenzel et al., 2021; Woodward and Heckers, 2015; Yasuda et al., 2020; Oomen et al., 2021). This may be explained by possible selection bias in the current sample, including relatively "mildly ill" patients who were able to participate in extensive testing as part of a randomized-controlled trial (RCT). This is supported by the average total PANSS score of our patient sample (58.71), which is considered 'mildly ill' according to Leucht et al. (2005). Moreover, we included patients with an average illness duration of only 1.15 years, whereas other studies included study populations with a notably longer mean duration of illness (Green et al., 2004; Lewandowski et al., 2014). This may have affected the extent to which clinical symptoms were displayed in our sample as duration of illness is associated with global functioning (Schennach-Wolff et al., 2009).

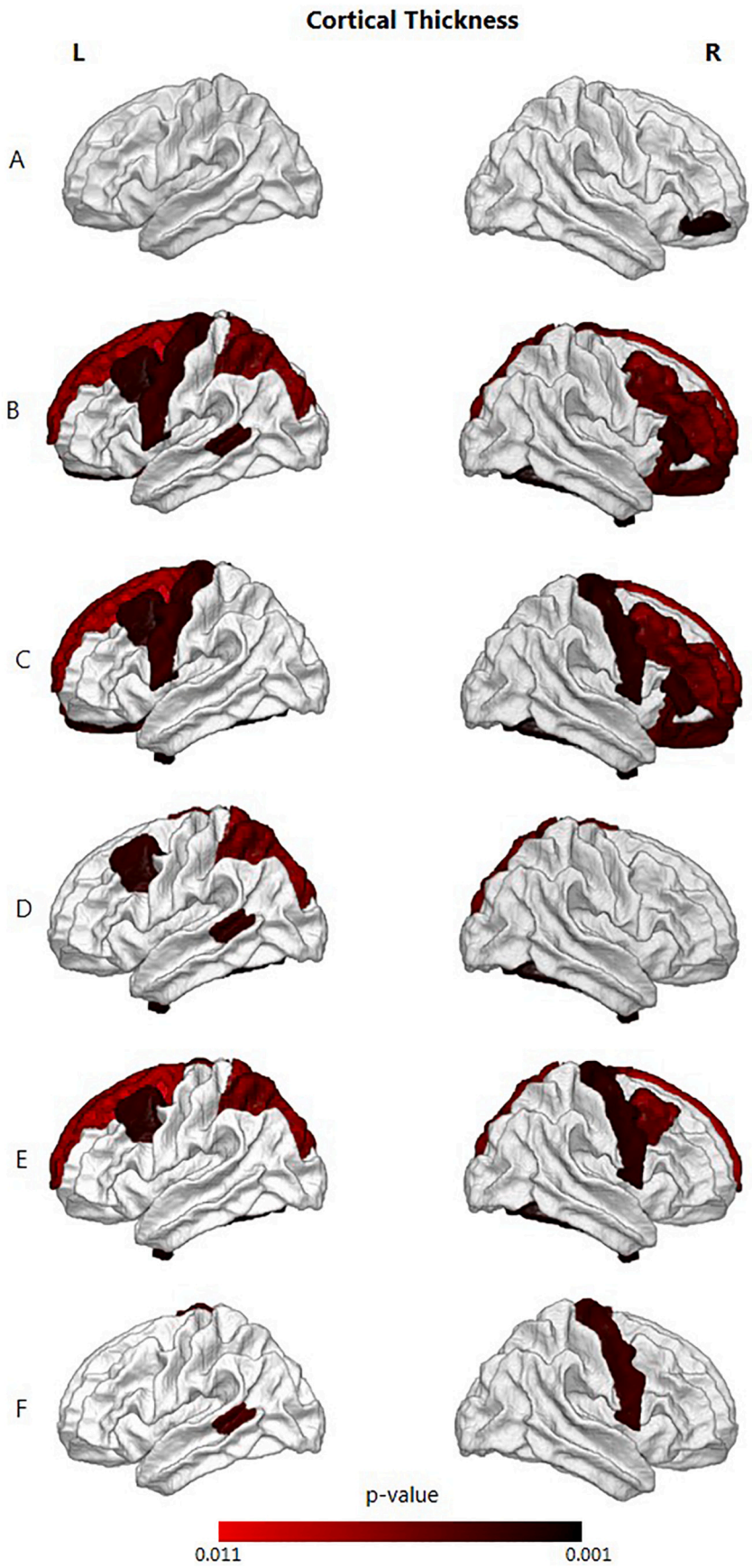

Fig. 3. Brain regions showing significant differences in cortical thickness between healthy controls and cognitive clusters. A) HC significantly different from preserved cognitive cluster; B) HC significantly different from moderately impaired cognitive cluster; C) HC significantly different from severely impaired cognitive cluster; D) preserved cognitive cluster significantly different from moderately impaired cognitive cluster; E) preserved cognitive cluster significantly different from severely impaired cognitive cluster; F) moderately impaired cognitive cluster significantly different from severely impaired cognitive cluster. See supplementary Table S4 for detailed statistics. L = left hemisphere; R = right hemisphere.

4.3. Brain volumetric measures

Groups were characterized by differences in the left postcentral gyrus, left caudal middle frontal gyrus and left insula. Volume reductions in SSD relative to healthy controls were previously reported for these regions in more chronic populations (Czepielewski et al., 2017; Ferro et al., 2015; Goodkind et al., 2015; Gupta et al., 2015; Haijma et al., 2013; Kuo and Pogue-Geile, 2019; Shepherd et al., 2012a, b; Weinberg et al., 2016; Wylie and Tregellas, 2010; Yasuda et al., 2020; Zhou et al., 2007). Volume of the left postcentral gyrus differentiated the preserved cognitive cluster from the moderately impaired and severely impaired clusters. The postcentral gyrus is located on the parietal lobe which is involved in sensory integration. Volume of this area positively correlates with cognitive functions as attention (Ferro et al., 2015; Salgado-Pineda et al., 2003; Shepherd et al., 2012a; Zhou et al., 2007) and may be associated with deficits in sensory integration and perception (i.e. one of the earliest and most prominent symptoms of schizophrenia) (Zhou et al., 2007). In addition, groups were characterized by differences in the caudal middle frontal gyrus, for which positive correlations with executive functions and speed of processing were reported (Bonilha et al., 2008; Knöchel et al., 2016). Van Rheenen et al. (2018) demonstrated differences in frontal and temporal areas including the middle frontal gyrus in all cognitive subgroups compared to healthy controls, with most prominent reductions shown in the severely impaired group which is in line with the current study (Van Rheenen et al., 2018). Finally, volume of the insula has been positively correlated to global cognitive function, intelligence and measures of verbal memory and executive function (Banaj et al., 2018; Caldiroli et al., 2018; Goodkind et al., 2015).

No significant differences were demonstrated between healthy controls and cognitive clusters in subcortical regions of interest. This is in contrast with several previous studies investigating subcortical brain volume in distinct cognitive subtypes of longer disease duration (Ho et al., 2020; Van Rheenen et al., 2018; Weinberg et al., 2016; Woodward and Heckers, 2015; Yasuda et al., 2020). Structures such as the hippocampus, amygdala, thalamus and cerebellum have been shown to be decreased in SSD compared to healthy controls (Fan et al., 2019; Haijma et al., 2013; Van Erp et al., 2016) and volumes of these regions have been associated with cognitive functions such as reasoning, problem solving and verbal learning and memory (Antoniades et al., 2018; Fan et al., 2019). A recent study by Fernández-Linsenbarth et al. (2021) demonstrated lower thalamus and hippocampus volume in a group with severely impaired cognition compared to a group with moderately impaired cognition and healthy controls. This severely impaired cognitive group was significantly older, included more chronically ill schizophrenia patients and had a longer duration of illness compared to the moderately impaired patient group (Fernández-Linsenbarth et al., 2021). The absence of such a relation in the current study could be a result of the relatively "mildly ill" and young patient sample with a short illness duration. Indeed, in early SSD, subcortical brain volumes are not frequently implicated in cognitive performance (Karantonis et al., 2021a) and suggests that subcortical volumes may not yet be related to cognitive performance in early SSD. However, given the relatively small sample size in the current study, we cannot rule out the possibility of insufficient statistical power to identify differences that were previously demonstrated.

We found widespread differences in cortical thickness in frontal, temporal and parietal regions in cognitive subgroups and healthy controls. Widespread reduced cortical thickness in similar regions has been reported before in SSD (Hanford et al., 2019; Karantonis et al., 2021b; van Erp et al., 2018; Van Haren et al., 2011; Van Rheenen et al., 2018). In general, more severely impaired individuals show more widespread cortical thinning (Fernández-Linsenbarth et al., 2021; Geisler et al., 2015; Guimond et al., 2016; Ho et al., 2020). These results indicate that patients who display more severe cognitive impairment also have thinner cortex in key regions associated with this cognitive domain. Indeed, earlier studies show an association between thinning of the frontal lobe and cognitive dysfunction in domains such as verbal learning and memory (Oertel-Knöchel et al., 2013; Zipparo et al., 2008).

In agreement with the current study, Yasuda et al. (2020) demonstrated larger volume differences between healthy controls and the severely impaired cognitive subgroup, than between healthy controls and the cognitively preserved subgroup (Yasuda et al., 2020). However, they also demonstrated differences in both patient groups compared to healthy controls suggesting that these alterations are not specific to cognitive impairment. Possibly, specific structural brain abnormalities in SSD are a function of the disorder rather than of the cognitive impairment associated with it (Vaskinn et al., 2015). This is supported by a study performed in healthy controls and cognitively-matched individuals with schizophrenia. Reduced cortical thickness was shown in patients versus controls, despite the matching level of cognitive performance (Hanford et al., 2019). This indicates that structural abnormalities in SSD cannot be explained solely by cognitive impairments.

The current study showed more widespread differences in cortical thickness compared to cortical volume. Literature has shown that cortical thickness and volume have different biological corollaries. Although each measure is highly heritable, cortical thickness and surface area (together volume) appear to be genetically independent and differently influenced by development (Panizzon et al., 2009; Wierenga et al., 2014). It is not yet clear which one contributes more to cognitive function and more research should be performed on both parameters in order to study the contribution of both cortical thickness and volume to cognitive performance.

It is often questioned whether cognitive subtypes derived from cluster analyses represent meaningful subtypes or whether they are depictions of a linear continuum of illness severity. Looking at cognitive performance across the cognitive subgroups derived from the present study, the clusters seem to represent a linear continuum of cognitive impairment. When looking at cortical volume, corresponding patterns are shown in areas significantly different between cognitive subgroups. Both the healthy controls and subgroup with preserved cognition show larger volumes compared to the moderately and severely impaired cognitive subgroups. A similar gradual decrease of cortical thickness is shown in most significantly different areas, i.e. the groups with moderately and severely impaired cognition show more thinning of the cortex compared to the preserved cognitive subgroup and healthy controls. These findings support the existence of a continuum, however, replication of our results in larger samples is needed to confirm the biological validity of a cognitive continuum in SSD.

4.4. Strengths and limitations

The strength of the current study is its extensive evaluation of cortical thickness and cortical and subcortical regions of interest in homogeneous cognitive subtypes of SSD. Furthermore, we studied early-phase SSD patients with an average illness duration of one year. This should minimize long-term influences of antipsychotic medication use and the illness itself on neuroanatomical structures. Therefore, our results may be more specific for cognitive impairment than studies including more chronic patient samples. We also note that our study comes with some limitations. First, the relatively small sample size may have led to insufficient statistical power to identify differences that were previously demonstrated. Second, although chlorpromazine equivalents were not significantly different between groups, we could not calculate cumulative dose of antipsychotic medication use in this study. Moreover, antipsychotic medication use was assessed by patient self-report, which may be less reliable as it often overestimates adherence (Jónsdóttir et al., 2010). Third, we included patients that were able to participate in extensive testing as part of a RCT, which may have led to selection bias and limited generalizability (because of relatively preserved cognition) to wider SSD populations within this study. Fourth, we could not take medical comorbidities into account in the present

analyses. Finally, we did not include a measure of pre-morbid cognitive functioning. Therefore, it should be noted that cognitive performance similar to that of healthy controls is not necessarily synonymous with cognitively unaffected.

4.5. Conclusions

The current results provide further support for cognitive heterogeneity within individuals with SSD and confirm the presence of three distinct subgroups defined by cognitive functioning. An indirect correlation between cognitive performance and structural brain abnormalities has been shown in the current study, as the moderately impaired and severely impaired cognitive patients groups showed specific volume and thickness reductions that were not seen in the preserved group and healthy controls. This was demonstrated in regions such as the post-central gyrus, middle temporal gyrus and insula, which have been associated with attention, executive functions and speed of processing. Yet, structural abnormalities in schizophrenia cannot be explained solely by cognitive impairment as some alterations were demonstrated in all patient groups compared to healthy controls.

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Data availability

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to them containing information that could compromise research participant privacy or consent.

CRediT authorship contribution statement

P.P. Oomen: Conceptualization, Methodology, Formal analysis, Writing – original draft, Validation. **S.S. Gangadin:** Methodology, Formal analysis, Writing – original draft. **M.J.H. Begemann:** Writing – review & editing, Validation. **E. Visser:** Data curation, Formal analysis, Writing – review & editing, Validation. **R.C.W. Mandl:** Methodology, Supervision, Writing – review & editing, Validation. **I.E.C. Sommer:** Supervision, Writing – review & editing, Funding acquisition, Validation.

Declaration of competing interest

Authors declare to have no competing interest related to this study.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2022.02.006.

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