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Parahippocampal area three gray matter is reduced in first-episode schizophrenia spectrum: Discovery and replication samples

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Abstract

Early course schizophrenia is associated with reduced gray matter. The specific structures affected first and how deficits impact symptoms and cognition remain unresolved. We used the Human Connectome Project multimodal parcellation (HCP-MMP) to precisely identify cortical areas and investigate thickness abnormalities in discovery and replication samples of first-episode schizophrenia spectrum individuals (FESz). In the discovery sample, T1w scans were acquired from 31 FESz and 31 matched healthy controls (HC). Thickness was calculated for 360 regions in Freesurfer. In the replication sample, high-resolution T1w, T2w, and BOLD-rest scans were acquired from 23 FESz and 32 HC and processed with HCP protocols. Thickness was calculated for regions significant in the discovery sample. After FDR correction (q < .05), left and right parahippocampal area 3 (PHA3) were significantly thinner in FESz. In the replication sample, bilateral PHA3 were again thinner in FESz (q < .05). Exploratory correlation analyses revealed left PHA3 was positively associated with hallucinations and right PHA3 was positively associated with processing speed, working memory, and verbal learning. The novel use of the HCP-MMP in two independent FESz samples revealed thinner bilateral PHA3, suggesting this byway between cortical and limbic processing is a critical site of pathology near the emergence of psychosis.

KEYWORDS

first-episode psychosis, gray matter thickness, parahippocampal area 3, parahippocampal gyrus, schizophrenia spectrum disorder

1 | INTRODUCTION

Schizophrenia spectrum disorder is associated with widespread reductions in cortical and subcortical gray matter. The most commonly reported cortical volume reductions in chronic schizophrenia spectrum are in the prefrontal, parietal, temporal, and parahippocampal cortices, while subcortical volume loss is frequently detected in the amygdala, hippocampus, and thalamus (Birur, Kraguljac, Shelton, & Lahti, 2017; Cropley et al., 2017; Goldman et al., 2009; Haijma et al., 2013; Rimol et al., 2010; Shenton, Dickey, Frumin, & McCarley, 2001; van Erp et al., 2016). Widespread cortical thinning is also present in chronic schizophrenia with the most pronounced thinning observed

in the frontal and temporal lobes (Rimol et al., 2010; Rimol et al., 2012; van Erp et al., 2018; van Haren et al., 2011). Specific regional gray matter differences emerge early in the disorder. In first-episode schizophrenia spectrum disorder (FESz), meta-analyses report reduced volumes in the hippocampus, insula, and anterior cingulate (Ellison-Wright, Glahn, Laird, Thelen, & Bullmore, 2008; Vita, De Peri, Silenzi, & Dieci, 2006). Gray matter volume deficits are also often reported in temporal and prefrontal cortical areas at the first episode (Hirayasu et al., 2000; Hirayasu et al., 2001; Kasai et al., 2003; Keshavan et al., 1998; Lee et al., 2002), though some studies report nonsignificant changes in these areas (Cahn et al., 2002; Molina, Sanz, Sarramea, Benito, & Palomo, 2004). Frontal and temporal cortices are most consistently thinner in FESz, while thickness differences in other cortical regions (i.e., parietal, anterior cingulate, and medial temporal cortices) are less consistently reported (Narr et al., 2005; Schultz et al., 2010; Sprooten et al., 2013; van Haren et al., 2011). In the first few years of the disorder, there is widespread progressive gray matter volume decline in the bilateral frontal, parietal, cingulate, and superior temporal cortex (Asami et al., 2012; Kasai et al., 2003). Similarly, the cortex experiences widespread thinning, most substantially in frontal and temporal lobes (van Haren et al., 2011). Thus, gray matter deficits are present at the first episode of schizophrenia spectrum, and there is a progressive decline throughout the disorder.

Gray matter differences are reported as early as the prodrome for psychosis. Compared with non-converters, individuals at clinical high-risk for psychosis (CHR) who later convert to psychosis have less gray matter volume in lateral and medial temporal, frontal, cingulate, and bilateral insular cortices (Mechelli et al., 2011; Pantelis et al., 2003; Takahashi et al., 2009). Further, CHR converters experience a progressive decrease of gray matter volumes in frontal, insular, fusiform, and parahippocampal cortices (Pantelis et al., 2003; Takahashi et al., 2009). It remains inconclusive if there are cortical thickness deficits in CHR who later convert to psychosis at baseline (Cannon et al., 2015; Chung et al., 2019; Tognin et al., 2014), however, those who later convert experience a progressive thinning in right frontal cortical regions (Cannon et al., 2015). While there is accumulating evidence of progressive gray matter deficits in schizophrenia spectrum disorder that are present in the prodrome and continue throughout the disorder, the evidence is limited to relatively large cortical regions, such as entire anatomical gyri, and thus it remains unresolved which specific functional subregions are impacted early in the disorder.

As schizophrenia is associated with early course progressive gray matter loss, it is particularly important to study this population as early as possible in the disease course to capture which areas are impacted when initial pathology is emerging. While many FESz studies report on individuals within 1 year (or more) of their first hospitalization (DeLisi et al., 1997; Hirayasu, McCarley, et al., 2000; Lee et al., 2002), the individuals in this study were at their first clinical contact for psychosis, with less than 2 months of lifetime antipsychotic medication exposure. This project is thus uniquely situated to investigate differences very early after the onset of full psychosis and has the marked advantage of utilizing a discovery and a replication sample for statistical control.

The uncertainty regarding which specific cortical regions are affected early in the disorder may also reflect methodological limitations. Previous studies investigating gray matter differences performed voxel-based morphometry (VBM) or region of interest (ROI) analyses, either manually-edited or automated. VBM makes comparisons at each of the thousands of voxels in the MRI brain reconstruction, resulting in inflated type-2 error due to multiple comparisons and a lack of sensitivity to small effect sizes, which may be expected in the early course of schizophrenia. By dividing the cortex into a limited number of regions, ROI analyses have greater statistical power than voxel-wise analyses. The gold standard for gray matter ROI analyses is manual tracing of regions of interest, but this technique is limited by reliance on anatomical information (i.e., sulcal-gyral boundaries). Manual tracing is unable to delineate purely functional regions, such as primary sensory cortices or functional subregions. For example, Heschl's gyrus can be traced manually, but the gyrus includes primary auditory cortex and portions of surrounding auditory belt regions (Sweet, Dorph-Petersen, & Lewis, 2005), which cannot be identified with standard structural MRI. Further, manually traced ROIs are time-consuming to create and therefore less practical for whole brain analyses and larger data sets. Automated or semi-automated cortical parcellations are ideal for larger data sets and whole brain ROI analyses but are similarly restricted to defining regions based on structural information alone, which results in the division of cortex into coarse ROIs and an inability to parcellate smaller functional areas. It is not possible with these traditional methods to parcellate cortical areas that can only be defined by both structure and function (i.e., primary sensory areas). We used a multimodal atlas developed by the Human Connectome Project (HCP), which used structural and functional information to parcellate the cortex into 360 areas (Glasser et al., 2016). The HCP multimodal parcellation (HCP-MMP) provides the most precise and functionally relevant regions of interest to investigate gray matter deficits in FESz (or, for that matter, any disorder).

Likely in concert with the early gray matter changes, symptoms, particularly auditory perceptual abnormalities among the attenuated positive symptoms, and cognitive deficits begin to emerge prior to full psychosis. Auditory verbal hallucinations (AVH) are a common and debilitating symptom of schizophrenia present in >70% of FESz (Salisbury, Kohler, Shenton, & McCarley, 2019). AVH likely involve a number of areas that are also engaged in language, memory, and auditory processing, such as the striatum, Broca's area, Wernicke's area, anterior cingulate, medial temporal lobe, and superior temporal gyrus (Ćurčić-Blake et al., 2017; Dierks et al., 1999; Hoffman, 1986; Jardri, Pouchet, Pins, & Thomas, 2011; Raij et al., 2009), and gray matter deficits within the superior temporal gyrus are related to hallucinations in chronic schizophrenia (Asami et al., 2012; Barta, Pearlson, Powers, Richards, & Tune, 1990; Shenton et al., 2001). Similarly, delusions and thought disorder involve the anterior cingulate and medial temporal lobe (Epstein, Stern, & Silberswieg, 1999; Lahti et al., 2006; Prasad, Rohm, & Keshavan, 2004; Shenton et al., 1992), and gray matter deficits in the STG, anterior cingulate, and medial temporal lobe are related the severity of delusions and thought disorder in chronic schizophrenia (Asami et al., 2012;

Shenton et al., 1992). Cognitive deficits are also a core feature of schizophrenia (Green & Nuechterlein, 1999; McCleery et al., 2015; Seidman et al., 2010). Gray matter in temporal and frontal lobes are related to cognitive performance, such as working memory, verbal recall, and semantic fluency in chronic schizophrenia and in first-episode psychosis (schizophrenia-spectrum and affective psychoses) (Baare et al., 1999; Nestor et al., 1993; Radua et al., 2012; Shenton et al., 2001). While it is evident that gray matter is related to symptoms and cognitive performance in chronic schizophrenia (Shenton et al., 2001; van Erp et al., 2018), these relationships are not commonly found or reported in the first episode schizophrenia spectrum (Crespo-Facorro et al., 2011; Hirayasu et al., 2001; Hirayasu, McCarley, et al., 2000; Lee et al., 2002). For this reason, we were interested in performing exploratory correlations with symptoms, with a focus on hallucinations, delusions, and thought disorder, and cognitive domains typically impaired in schizophrenia spectrum disorder.

The aim of this study was to determine which specific brain structures show gray matter deficits very early in schizophrenia spectrum disorder and how such gray matter deficits relate to cognition and symptoms. To examine differences early in the disease course, this study investigated two different first episode schizophrenia spectrum (FESz) samples. In the discovery sample, the HCP-MMP atlas was used to estimate gray matter thickness in 180 bilateral cortical ROIs. Differences in gray matter thickness were examined between FESz and matched healthy controls (HC). To investigate whether these reductions were replicated in an independent sample of FESz, cortical regions that were thinner in FESz in the discovery sample were used

as ROIs in a replication sample. High-resolution MRI scans were acquired, and gray matter differences in these ROIs were again examined between FESz and matched HC. Finally, we examined exploratory associations with symptoms measured with the Positive and Negative Syndrome Scale (PANSS) and cognitive measures from the MATRICS consensus cognitive battery (MCCB).

2 | DISCOVERY SAMPLE

2.1 | Methods

2.1.1 | Participants

All participants were recruited from Western Psychiatric Hospital (WPH) inpatient and outpatient services. Participants included 31 FESz individuals (paranoid: $n = 8$; undifferentiated: $n = 5$; residual: $n = 1$; schizoaffective: $n = 5$; schizophreniform: $n = 5$; psychotic disorder NOS: $n = 7$) within their first episode of psychosis with less than 2 months of lifetime antipsychotic medication exposure, and 31 healthy controls (HC). None of the participants had a history of concussion or head injury with sequelae, history of alcohol or drug addiction or detox in the last 5 years, or neurological comorbidity. Groups were matched for age, gender, parental social economic status, and premorbid IQ, measured by the vocabulary component of the Wechsler Abbreviated Scale of Intelligence (WASI) (Table 1). The work described was carried out in accordance with The Code of Ethics of the World Medical

TABLE 1 Sample 1 demographic and clinical information

	Mean ± SD			
	HC (n = 31)	FESz (n = 31)	p	X²
Sociodemographic data				
Age (years)	21.2 ± 3.1	21.5 ± 4.4	.83	
Sex (M/F)	20/11	20/11	1.0	1.0
SES	33.3 ± 13.5	27.0 ± 12.0	.06	
Parental SES	49.2 ± 12.6	44.3 ± 11.5	.11	
Neuopsychological tests				
WASI vocab (t-score)	50.8 ± 8.1	53.7 ± 8.6	.18	
MCCB-total	48.9 ± 6.5	39.4 ± 14.0	.001[a]	
Symptoms				
PANSS-total		70.6 ± 11.8		
PANSS-positive		18.3 ± 4.9		
PANSS-negative		16.0 ± 4.1		
PANSS-general		36.3 ± 6.6		
Medication data				
Medicated/unmedicated		17/14		
Cpz. Equivalent dose (mg)		223 ± 147		
Duration (days)		20.3 ± 16.8		

Note: Descriptive and inferential statistics for healthy controls (HC) and first-episode schizophrenia spectrum (FESz).
[a]Denotes significance ($p < .05$).

Association (Declaration of Helsinki) for experiments involving humans. All participants provided informed consent and were paid for participation.

Socioeconomic status (SES) for all participants and their parents was measured with the 4-factor Hollingshead Scale. FESz participants' diagnoses were based on the Structured Clinical Interview for DSM-IV (SCID-P) (First, Spitzer, Gibbon, & Williams, 1998) and were confirmed 6 months after initial clinical assessment (5 were lost to follow up). Symptoms were rated using the PANSS for 25 of the 31 FESz (Table 1) (Kay, Fiszbein, & Opler, 1987). Cognitive ability was assessed with the MCCB (Nuechterlein et al., 2008). MCCB was collected for all participants (HC and FESz) except one FESz, who was unable to complete testing. All tests were conducted by an expert diagnostician.

Just over half of the FESz participants were medicated (17/31, 54.8%) (range = 1–56 days, median = 16.0 days). Gray matter thickness was not different between medicated (n = 19) and unmedicated (n = 14) FESz, and gray matter thickness did not correlate with CPZ equivalent dose or duration of medication use (p values>.1). These analyses suggest gray matter was unaffected by medication, which will not be discussed further.

2.1.2 | Data acquisition and processing

MRI data were acquired with a Siemens Tim Trio using a 32-channel phase array head coil. Sagittal T1-weighted anatomical MR images were obtained with a multi-echo 3D MPRAGE sequence (TR/TE/TI = 2530/1.74, 3.6, 5.46, 7.32/1260 ms, flip angle = 7°, field of view [FOV] = 220 × 220 mm, 1 mm isotropic voxel size, 176 slices, GRAPPA acceleration factor = 2). FreeSurfer (stable v6.0) was used for MRI processing (Dale, Fischl, & Sereno, 1999; Fischl & Dale, 2000; Fischl, Sereno, & Dale, 1999). Briefly, processing involved registration to MNI space, intensity normalization, skull stripping, segmentation of white matter, and the generation of white and pial surfaces.

Cortical thickness was estimated for 180 bilateral ROIs using the HCP-MMP atlas (Glasser et al., 2016). Using the HCP workbench, the HCP-MMP cortical parcellation was resampled to fsaverage space. In Freesurfer, the parcellation was applied to individual data (see HCP Users FAQ [https://wiki.humanconnectome.org/display/PublicData/HCP+Users+FAQ#HCPUsersFAQ-9.HowdoImapdatabetween FreeSurferandHCP?]). Cortical thickness was calculated as the average distance from each point of the WM surface within each ROI to the closest point on the pial surface.

TABLE 2 Sample 1 gray matter thickness reductions in FESz

Brain area	Mean ± SD HC (n = 31)	FESz (n = 31)	t	p	Cohen's d
Left hemisphere					
1. AVI	2.86 ± 0.16	2.77 ± 0.19	2.06	.044	0.51
2. 6r	2.83 ± 0.15	2.72 ± 0.17	2.66	.010	0.69
3. FOP1	3.06 ± 0.18	2.95 ± 0.23	2.02	.048	0.53
4. Area 25	3.10 ± 0.32	2.95 ± 0.22	2.07	.043	0.55
5. 24dd	2.77 ± 0.15	2.69 ± 0.17	2.07	.042	0.50
6. TGv	3.48 ± 0.19	3.37 ± 0.19	2.48	.016	0.58
7. ProS	2.25 ± 0.27	2.12 ± 0.19	2.02	.047	0.56
8. PHA2	2.51 ± 0.17	2.38 ± 0.19	2.85	.006	0.78
9. PHA3	2.75 ± 0.14	2.59 ± 0.16	4.33	<.001[a]	1.06
Right hemisphere					
10. OP2-3	2.64 ± 0.19	2.53 ± 0.24	2.10	.040	0.51
11. 9a	2.63 ± 0.13	2.54 ± 0.16	2.55	.013	0.62
12. 9 m	2.85 ± 0.14	2.77 ± 0.17	2.04	.046	0.51
13. Area 25	3.16 ± 0.35	2.98 ± 0.30	2.23	.029	0.55
14. ProS	2.42 ± 0.27	2.27 ± 0.23	2.30	.025	0.60
15. PHA1	3.02 ± 0.24	2.88 ± 0.29	2.10	.040	0.53
16. PHA2	2.46 ± 0.21	2.33 ± 0.17	2.90	.005	0.68
17. PHA3	2.68 ± 0.17	2.51 ± 0.16	4.01	<.001[a]	1.03
18. VVC	2.90 ± 0.15	2.80 ± 0.20	2.25	.028	0.57

Note: Gray matter thickness in mm (mean ± SD) differences between HC and FESz with at least moderate effect sizes (Cohen's d ≥ 0.5).

Abbreviations: 24dd, dorsal midcingulate cortex area 24d; 6r, rostral premotor area 6; 9a, dorsolateral prefrontal area 9 anterior; 9m, dorsolateral prefrontal area 9 medial; Area 25, subgeneal area 25; AVI, anterior ventral insula; FOP1, frontal opercular area 1; OP2-3, posterior opercular area 2–3; PHA1, parahippocampal area 1; PHA2, parahippocampal area 2; PHA3, parahippocampal area 3; ProS, prostriate area; TGv, temporal gyrus ventral; VVC, ventral visual complex.

[a]Denotes comparisons that survived FDR correction (q < .05).

2.1.3 | Analysis

Group demographics were compared using independent samples *t* test and chi-square tests where appropriate. Gray matter thickness compared between groups using independent samples *t* tests. To minimize type II error, we first performed an exploratory analysis by identifying regions with significant gray matter thickness differences of at least medium effect size (Cohen's *d* > 0.5). Benjamini-Hochberg False Discovery Rate (FDR) correction was applied to correct for multiple comparisons (360 comparisons).

2.2 | Results

2.2.1 | Uncorrected cortical thickness

Eighteen cortical regions were thinner in FESz compared with HC with at least medium effect size (*p* < .05, Cohen's *d* > 0.5). Thinner gray matter in FESz was identified bilaterally in the parahippocampal gyrus (PHA2, PHA3), subgenual anterior cingulate cortex (area 25), and prostriate cortex (ProS). In the left hemisphere, FESz had thinner gray matter in the rostral premotor area (6r), left frontal operculum
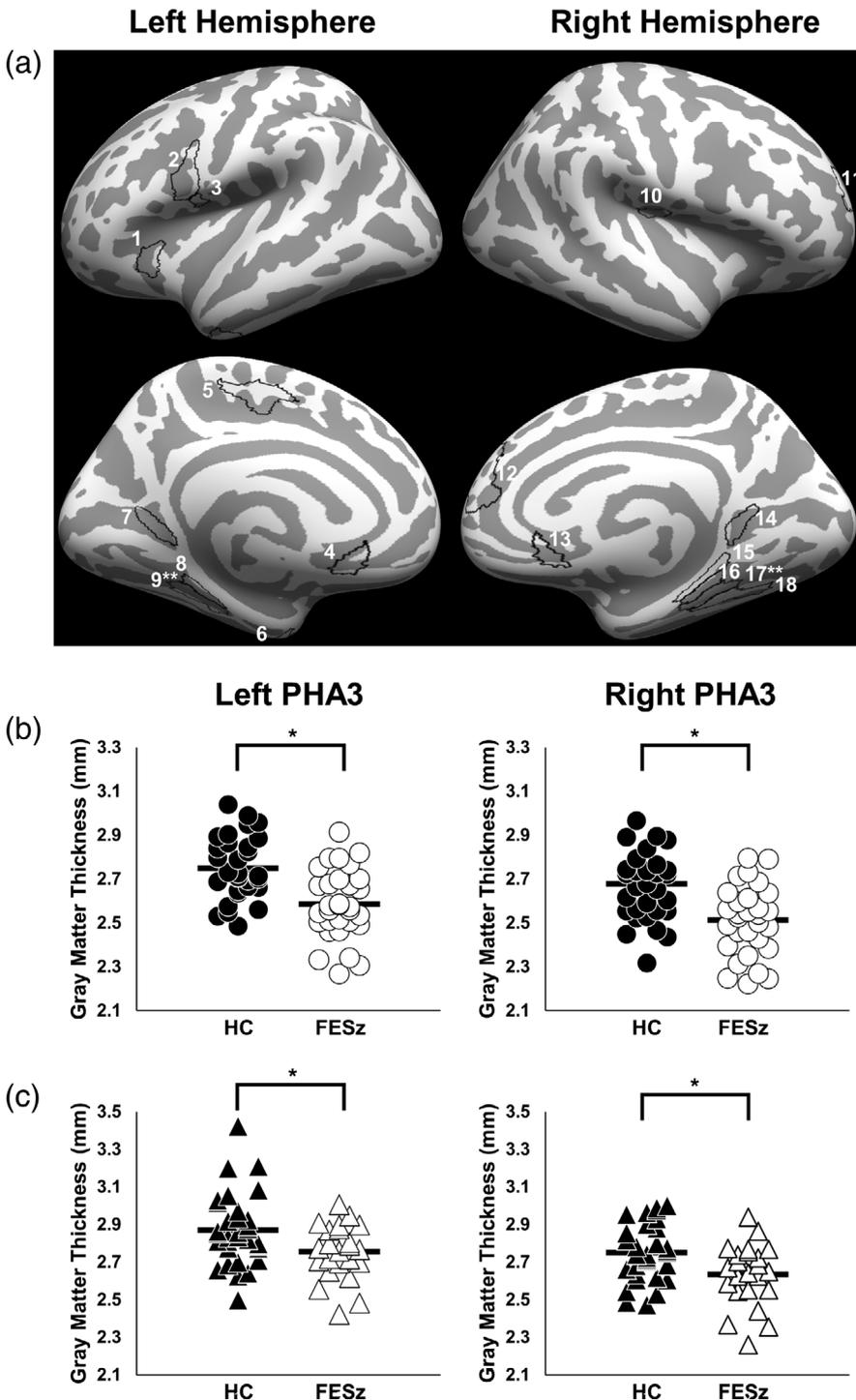

FIGURE 1 Gray matter thickness differences. (a) Outlines of the areas that were thinner in FESz with a moderate effect size (Cohen's *d* ≥ 0.5) in the discovery sample. Bilateral PHA3 is outlined in blue. Refer to Table 2 for region names associated with the numerical indices. (b) After FDR correction for multiple comparisons (*q* < .05), the left and right parahippocampal area 3 (PHA3) were significantly thinner in FESz. (c) After FDR correction in the replication sample, left and right PHA3 were significantly thinner in FESz. **Denotes *q* < .05. *Denotes *p* < .05

TABLE 3 Sample 2 demographic and clinical information

	Mean ± SD			
	HC (n = 32)	FESz (n = 23)	p	X^2
Sociodemographic data				
Age (years)	25.4 ± 5.6	24.0 ± 5.0	.35	
Sex (M/F)	21/11	17/6	.52	.51
SES	42.0 ± 14.4	32.2 ± 16.1	.03[a]	
Parental SES	48.8 ± 10.0	43.4 ± 15.1	.13	
Neuopsychological tests				
WASI vocab T-score	52.5 ± 6.8	49.2 ± 100.5	.17	
MCCB-total	47.7 ± 6.5	29.7 ± 14.4	<.001[a]	
Symptoms				
PANSS-total		82.8 ± 15.0		
PANSS-positive		21.5 ± 5.3		
PANSS-negative		19.4 ± 4.9		
PANSS-general		42.2 ± 8.0		
Medication data				
Medicated/unmedicated		19/4		
Cpz. Equivalent dose (mg)		253 ± 140		
Duration (days)		22.2 ± 17.6		

Note: Descriptive and inferential statistics for healthy controls (HC) and first-episode schizophrenia spectrum (FESz).
[a]Denotes significance ($p < .05$).

TABLE 4 Sample 2 gray matter thickness reductions in FESz

	Mean ± SD				
Brain area	HC (n = 32)	FESz (n = 23)	t	p	Cohen's d
Left hemisphere					
1. AVI	3.04 ± 0.21	2.96 ± 0.17	1.57	.062	0.42
2. 6r	2.80 ± 0.13	2.80 ± 0.16	−0.20	.577	0.04
3. FOP1	2.98 ± 0.19	2.98 ± 0.24	−0.06	.525	0.02
4. Area 25	3.21 ± 0.26	3.12 ± 0.22	1.41	.082	0.37
5. 24dd	2.86 ± 0.17	2.77 ± 0.16	2.00	.025	0.55
6. TGv	3.29 ± 0.16	3.23 ± 0.27	0.98	.166	0.27
7. ProS	2.20 ± 0.20	2.16 ± 0.25	0.70	.243	0.18
8. PHA2	2.54 ± 0.25	2.31 ± 0.22	3.44	<.001[a]	0.98
9. PHA3	2.87 ± 0.19	2.75 ± 0.15	2.48	.008[a]	0.70
Right hemisphere					
10. OP2-3	2.61 ± 0.17	2.61 ± 0.23	0.03	.489	0.00
11. 9a	2.66 ± 0.19	2.69 ± 0.19	-0.67	.748	0.16
12. 9m	3.04 ± 0.19	3.09 ± 0.19	−0.96	.831	0.26
13. Area 25	3.24 ± 0.22	3.16 ± 0.35	0.98	.166	0.27
14. ProS	2.35 ± 0.26	2.24 ± 0.25	1.44	.078	0.43
15. PHA1	2.86 ± 0.31	2.80 ± 0.28	0.79	.216	0.20
16. PHA2	2.38 ± 0.21	2.20 ± 0.18	3.39	<.001[a]	0.92
17. PHA3	2.75 ± 0.15	2.63 ± 0.16	2.75	.004[a]	0.77
18. VVC	3.00 ± 0.16	2.96 ± 0.15	0.95	.173	0.26

Note: Gray matter thickness in mm (mean ± SD) differences between HC and FESz from the ROIs that were reduced Sample 1. One-tailed hypotheses (HC > FESz) were used.
Abbreviations: 24dd, dorsal midcingulate cortex area 24d; 6r, rostral premotor area 6; 9m, dorsolateral prefrontal area 9 medial; 9a, dorsolateral prefrontal area 9 anterior; Area 25, subgeneal area 25; AVI, anterior ventral insula; FOP1, frontal opercular area 1; OP2-3, posterior opercular area 2–3; PHA1, parahippocampal area 1; PHA2, parahippocampal area 2; PHA3, parahippocampal area 3; ProS, prostriate area; TGv, temporal gyrus ventral; VVC, ventral visual complex.
[a]Denotes comparisons that survived FDR correction ($q < .05$).

(FOP1), temporal pole (TGv), cingulate motor cortex (24dd), and anterior ventral insula (AVI). In the right hemisphere, FESz had thinner gray matter in the right Brodmann area 9 in prefrontal cortex (9a, 9m), parahippocampal area 1 (PHA1), posterior operculum (OP2-3), and ventral visual complex (VVC) (Table 2, Figure 1).

2.2.2 | FDR-corrected cortical thickness

After using FDR to correct for multiple comparisons, two regions remained significantly reduced relative to HC. The left parahippocampal area 3 (PHA3) was significantly thinner ($p < .001$, $q < .05$), as was the right PHA3 ($p < .001$, $q < .05$) (Table 2, Figure 1).

3 | INDEPENDENT REPLICATION SAMPLE

3.1 | Methods

All methods and procedures were identical to Sample 1 with the following differences.

3.1.1 | Participants

Participants included 23 FESz individuals (paranoid: $n = 10$; undifferentiated: $n = 9$; schizophreniform: $n = 2$; psychotic disorder NOS: $n = 2$) and 32 matched healthy controls (HC). Symptoms were rated using the PANSS for 22 of the 23 FESz. Cognitive ability was assessed with the MCCB and was collected for all participants (Table 3).

3.1.2 | Data acquisition and processing

High-resolution MRI data were acquired on a Siemens 3T MAGNETOM Prisma scanner using a 32-channel phase array head coil. Sagittal T1-weighted anatomical MR images were obtained with a 3D MPRAGE sequence (TR/TE/TI = 2400/2.22/1000 ms, flip angle = 7°, field of view (FOV) = 256 × 240 mm, 0.8 mm isotropic voxel size, 208 slices, GRAPPA acceleration factor = 2). T2-weighted T2-SPACE images were obtained (TR = 3,200 ms TE = 563 ms, FOV = 256 × 240, 0.8 mm isotropic voxel size, 208 slices). A standard fieldmap (TR = 731 ms, TE = 4.92/7.38, FOV = 208x180, 2.0 mm voxel size, 72 slices) was collected for correcting readout distortion in the T1w and T2w images. Ten minutes of eyes-open (passive crosshair viewing) resting state BOLD fMRI data were acquired using a multiband pulse sequence (TR =800 ms, TE =37 ms, multiband factor = 8, flip angle = 52°, FOV = 208 × 208 mm, voxel size = 2.0 mm^3, 72 slices). A single-band reference image with no slice acceleration was acquired at the beginning of each run to improve registrations. Finally, two spin echo EPI images (TR = 8,000 ms, TE = 66 ms, flip angle = 90, FOV = 208 × 208 mm, 2.0 mm voxel size, 72 slices) with reversed phase encoding directions were acquired.

The publicly available HCP-pipelines (https://github.com/Washington-University/HCPpipelines) were used for MRI processing (detailed in Glasser et al., 2013). The structural images were corrected for gradient nonlinearity, readout, and bias field, followed by AC-PC alignment. Myelin maps were created by dividing the T1w image by the T2w image. Native space images were used to generate white and pial surfaces with Freesurfer software (Dale et al., 1999;

TABLE 5 Exploratory correlations with symptoms and cognitive ability in FESz

Brain area	ρ	p
Left PHA3		
PANSS		
Total	0.11	.451
Positive	0.13	.379
Delusions (P1)	0.23	.127
Hallucinations (P3)	0.32	.026[a]
Unusual thought content (G9)	0.22	.146
Negative	0.01	.968
General	0.09	.529
MCCB		
MCCB composite	0.07	.620
Speed of processing	0.09	.545
Attention/vigilance	0.03	.821
Working memory	0.09	.631
Verbal learning	0.11	.429
Visual learning	−0.01	.920
Reasoning and problem solving	0.08	.579
Social cognition	−0.05	.725
Right PHA3		
PANSS		
Total	−0.10	.486
Positive	−0.01	.976
Delusions (P1)	−0.03	.828
Hallucinations (P3)	0.22	.132
Unusual thought content (G9)	0.05	.731
Negative	−0.12	.431
General	−0.08	.603
MCCB		
Composite	0.26	.061
Speed of processing	0.27	.049[a]
Attention/vigilance	0.17	.232
Working memory	0.29	.038[a]
Verbal learning	0.31	.024[a]
Visual learning	0.05	.752
Reasoning and problem solving	0.13	.357
Social cognition	0.03	.820

Note: Relationships between PHA3 gray matter and both PANSS and MCCB gender- and age-normalized t-scores.
[a]Denotes significance ($p < .05$).

Fischl et al., 1999; Fischl & Dale, 2000). Surfaces were refined using T2w data, which improves pial and white surface reconstructions, ultimately improving cortical thickness measurements (Glasser et al., 2013; Glasser, Goyal, Preuss, Raichle, & Van Essen, 2014). Thickness was calculated in FreeSurfer using the improved white and pial surfaces. Then, the individual's native-mesh surfaces were registered with a multimodal surface matching (MSM) algorithm with MSMsulc to the Conte69 folding-based template (Robinson et al., 2014; Van Essen, Glasser, Dierker, Harwell, & Coalson, 2012).

The functional resting-state data were first corrected for gradient-nonlinearity. A 6 DOF FLIRT registration of each frame to the single-band reference image was used to correct for motion. The reverse phase spin-echo images were used to correct functional distortion. The single band reference image was registered to the T1w image with FreeSurfer's BBRegister (Greve & Fischl, 2009). All the transforms and distortion correction were applied in a single resampling step. The data were brain masked and intensity normalized to a 4D whole brain mean of 10,000. Then, a voxel to surface mapping was performed to sample the volumetric fMRI data to the individual's native surfaces, which were subsequently resampled to a standard 32 k fs_LR surface. The ICA + FIX pipeline was used to remove artifactual noise (Griffanti et al., 2014; Salimi-Khorshidi et al., 2014). Finally, individual subjects were registered to a group average atlas surface using a two-stage process based on the MSM algorithm

(Robinson et al., 2014). The first stage was driven by cortical folding patterns, and the second stage utilized cortical areal features (myelin, resting-state network maps, and topographic maps) (Glasser et al., 2016). The group average HCP-MMP was applied to individuals' MRI data and mapped to individuals' native space where thicknesses were computed.

3.1.3 | Analysis

The 18 regions that were reduced (uncorrected) in the discovery sample were used as ROIs for the analysis in the replication sample. Differences in gray matter thickness between groups were compared using one-tailed independent samples t tests. Benjamini-Hochberg false discovery rate (FDR) correction was then applied to correct for multiple comparisons (18 comparisons).

3.2 | Results

3.2.1 | Gray matter thickness

After FDR correction for multiple comparisons ($q < .05$), four regions remained significantly thinner in FESz. The left and right PHA2 and
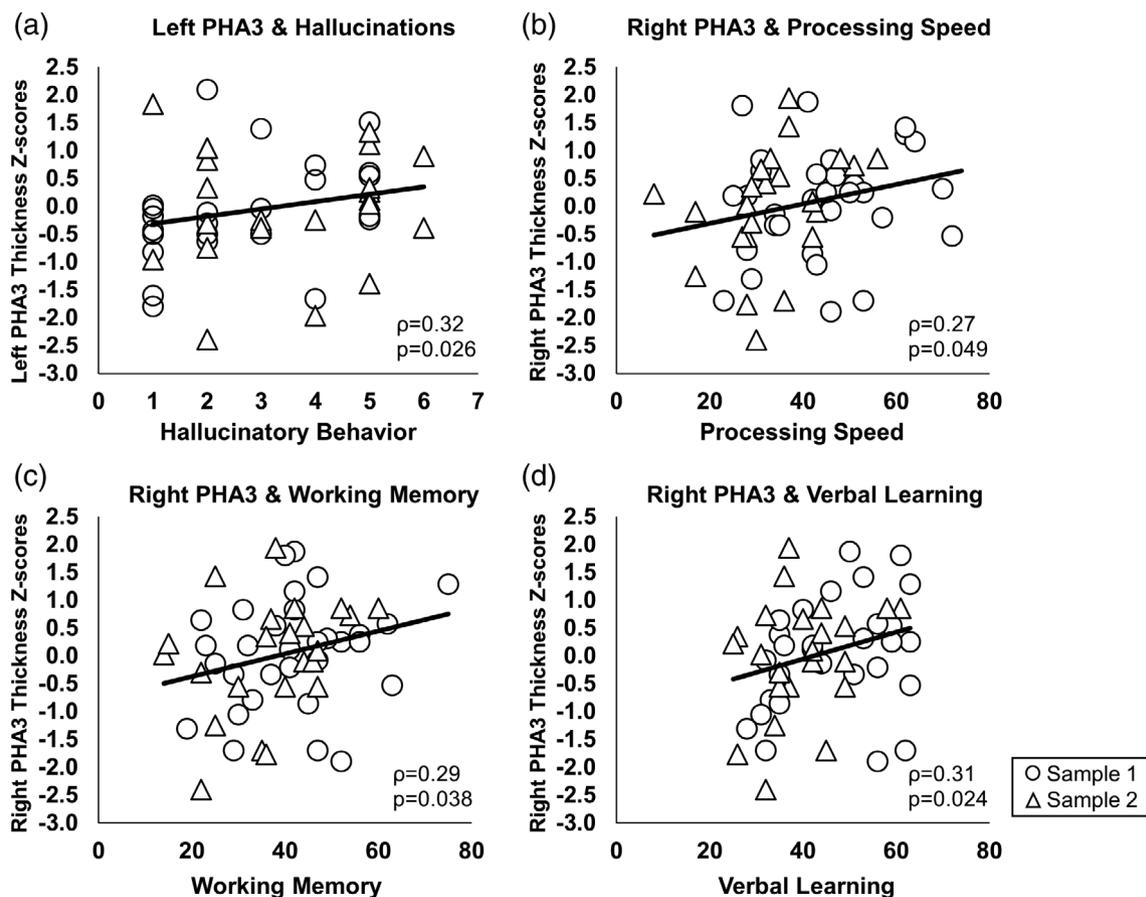

FIGURE 2 Exploratory Correlations. (a) Thinner left PHA3 was related to lower hallucinatory behavior scores in FESz. (b) Thinner right PHA3 was related to deficits in processing speed, working memory (c), and verbal learning (d) Spearman's correlations were used. $p < .05$

the left and right PHA3 were significantly thinner in FESz (p's < .01, q < .05) (Table 4, Figure 1).

4 | EXPLORATORY CORRELATIONS WITH SYMPTOMS AND COGNITION

4.1 | Methods

To investigate relationships among replicated gray matter thickness reductions, symptoms, and cognition, thickness data from each data set were normalized using z-scores was calculated separately for each sample. Spearman's correlations were used to examine relationships between gray matter thickness, PANSS scores, and MCCB gender- and age-normalized t-scores. We report uncorrected exploratory correlations (p < .05).

4.2 | Results

In FESz, left PHA3 was significantly positively associated with hallucinatory behavior (p < .05). In FESz, right PHA3 was significantly positively related to processing speed, working memory, and verbal learning (p < .05). There were no other significant correlations with any other PANSS or MCCB scores in FESz or HC (p's > .05) (Table 5, Figure 2).

5 | CONCLUSION

This study was the first to utilize the HCP-MMP atlas to investigate cortical gray matter thickness abnormalities in FESz. The HCP-MMP improves upon traditional, strictly anatomical parcellations as it divides cortex into functionally relevant ROIs. Using this more precise parcellation in a discovery sample, we were able to identify several specific cortical areas that were thinner in FESz. A specific subregion of the parahippocampal gyrus (PHA3) was robustly thinner bilaterally in FESz, surviving conservative correction for multiple comparisons. This finding was replicated in the independent replication sample, as the regions to survive correction for multiple comparisons were bilateral parahippocampal area 2 (PHA2) and PHA3. While many previous studies of first-episode patients report on individuals within the first year following first hospitalization (DeLisi et al., 1997; Hirayasu, McCarley, et al., 2000; Lee et al., 2002), the individuals in this study were within their first-episode of psychosis, but their symptoms had not necessarily progressed to the severity of needing hospitalization, and participants had less than 2 months of lifetime antipsychotic medication exposure. This allowed us to probe gray matter deficits very early in the disorder. Thus, the findings indicate these specific parahippocampal subregions are particularly impacted very early in the disease course and thus may play a critical role in the etiology of schizophrenia spectrum disorder.

Parahippocampal gray matter has previously been shown to be reduced in chronic and first-episode schizophrenia and in individuals at high risk for psychosis (Borgwardt et al., 2007; Jung et al., 2011; Mechelli et al., 2011; Meisenzahl et al., 2008; Shenton et al., 2001; Tognin et al., 2014; van Erp et al., 2018; van Haren et al., 2011). However, parahippocampal gyrus gray matter deficits are not consistently observed in schizophrenia spectrum disorder or to the extent observed in this study (Sprooten et al., 2013; van Erp et al., 2018). The large multisite ENIGMA metanalysis reported a small effect size for the parahippocampal gyrus reduction in schizophrenia (van Erp et al., 2018). The current study had several differences that likely contributed to the ability to detect a much larger effect size in the parahippocampal areas. An advantage was the ability to maintain precision without the need to average across heterogenous samples with varying scan quality. In addition, we had the advantage of high-resolution MRI scans, particularly in the replication sample, and improved surface reconstructions with the HCP pipelines improving cortical thickness measurements. Finally, the novel use of the HCP-MMP divides the parahippocampal gyrus into three functional subregions, instead of averaging across a large area that includes all parahippocampal subregions and additional cortex. Thus, it allows a more precise detection of thickness within each specific subregion.

The current study did not find thickness differences in other temporal or frontal regions that are commonly reported in FESz (Narr et al., 2005; Schultz et al., 2010; Sprooten et al., 2013; van Haren et al., 2011). This may in part be explained by methodological differences. Previous studies have used either structural based regions of interest or all cortical vertices, while this study used new regions parcellated by both structure and function. Further, the participants were very early in the disease course and may not show significant gray matter deficits in other subregions until later. Future longitudinal analyses can investigate this directly.

As less gray matter in schizophrenia is likely due to neuropil loss, rather than neuronal loss (Selemon & Goldman-Rakic, 1999), parahippocampal cortex may undergo an abnormal dendro-toxicity that manifests as thinner gray matter. Early imaging studies have revealed hippocampal reductions in FESz (Hirayasu, Shenton, Salisbury, & McCarley, 2000), and medial temporal lobe regions undergo significant neuroanatomical changes as high-risk patients transition to psychosis (Wood et al., 2008). In fact, hippocampal damage has long been suspected as one etiology of schizophrenia (Lipska, Jaskiw, & Weinberger, 1993; Lipska & Weinberger, 2002). Postnatal ventral hippocampal lesions in rats have been associated with EEG-derived oscillatory auditory abnormalities similar to those observed in schizophrenia (Vohs et al., 2009; Vohs et al., 2010). As the parahippocampal gyrus has bidirectional connections with hippocampus and other limbic structures and provides a major hub of bidirectional communication between polymodal cortical areas, including auditory association cortex, it likely serves a key role in cortical–subcortical communication in service of contextual memory (Aminoff, Kveraga, & Bar, 2013). The current data provide strong support for parahippocampal gyrus as a key early anatomical site of pathology proximal to the emergence of psychosis.

PHA3 is a subregion of the parahippocampal gyrus, primarily within the collateral sulcus (Baker et al., 2018). It has functional

connections to inferior frontal, temporal, and parietal areas and is involved in spatial and contextual information processing (Baker et al., 2018). In this study, exploratory analyses suggest right PHA3 thickness may be associated with processing speed, working memory, and verbal learning. This would be consistent with known cognitive functions of the parahippocampal cortex (i.e., spatial memory and verbal fluency) (Frith, Friston, Liddle, & Frackowiak, 1991; Squire, Stark, & Clark, 2004). While the left medial temporal lobe is commonly associated with verbal memory and the right medial temporal lobe with spatial memory, right medial temporal lobe structures appear to have a role in verbal tasks, specifically verbal retrieval (Persson & Soderlund, 2015). In individuals with schizophrenia, right medial temporal lobe structures appear to be related to both verbal and working memory performance (Antoniades et al., 2018; Ehrlich et al., 2012; Hurlemann et al., 2008). Further, patients with lower verbal memory ability have less bilateral parahippocampal thickness (Guimond, Chakravarty, Bergeron-Gagnon, Patel, & Lepage, 2016). Our data support that right PHA3 in particular may be related to some cognitive deficits in early schizophrenia, though this should be interpreted with caution, as the correlations were exploratory in nature and need replication.

In the context of schizophrenia, the parahippocampal gyrus is associated with positive symptoms, such as thought disorder, delusions, and hallucinations (Prasad et al., 2004; Shenton et al., 1992). In this study, we did not find significant associations between PHA3 thickness and delusions or thought disorder, but instead, we found a potential relationship with hallucinations. The parahippocampal gyrus has a role in hallucinations as it appears to deactivate before auditory verbal hallucinations and activate during hallucinations (Diederen et al., 2010; Escartí et al., 2010; van Lutterveld et al., 2014). While this study suggests that left PHA3 thickness may be positively related to hallucinations, the nature of this relationship is not entirely clear. We speculate that within the context of overall reduced PHA3 in FESz, the more intact PHA3 contributes dysfunctional activity to the language circuit (e.g., imprecise information content and dysfunctional information transfer), contributing to hallucinations. Future studies will be able to support or refute our initial speculation regarding this somewhat paradoxical and exploratory finding.

This study was not without limitations. The sample size is relatively small compared with larger multisite studies; thus, replication of these findings is needed in larger samples. This newer HCP parcellation is restricted to cortex, yet many subcortical volume deficits (e.g., *hippocampus*) have been implicated in schizophrenia, which we were unable to identify here. Future studies can use traditional volumetric approaches to examine subcortical area deficits in FESz. In addition, although this study suggests that this area of parahippocampal cortex is particularly impacted in early schizophrenia, it is unclear if this area is specific to schizophrenia or if it is common to other disorders of psychosis. Finally, it is unclear if this difference is related to the transition to psychosis. This study was a cross-sectional design, and future studies investigating clinical high-risk patients can use this HCP-MMP to investigate the longitudinal trajectories of these deficits.

In summary, using the HCP multimodal parcellation we identified robust gray matter deficits in specific subregions of the parahippocampal gyrus in early schizophrenia. These deficits may be related to hallucinations and cognitive deficits, though future work is needed to replicate these relationships and explore possible mechanisms. This study provides insight to the initial pathology near the onset of schizophrenia and suggests the parahippocampal area 3 may be a specific subregion particularly critical to the emergence of psychosis.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author.

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