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SUPPLEMENT ARTICLE

Paracingulate Sulcus Length and Cortical Thickness in Schizophrenia Patients With and Without a Lifetime History of Auditory Hallucinations

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Background: **It has been theorized that hallucinations, a common symptom of schizophrenia, are caused by failures in reality monitoring. The paracingulate sulcus (PCS) has been implicated as a brain structure supporting reality monitoring with the absence or shorter length of PCS associated with an occurrence of hallucinations in schizophrenia. The absence or shorter length of PCS has been associated with an occurrence of hallucinations. There are inconsistent findings in the literature regarding the role of the asymmetry of this structure for hallucinations. Here, we investigated the length of the PCS and cortical thickness of surrounding structures in patients with a lifetime history of auditory verbal hallucinations (AVH).** ***Design:*** **Seventy-seven patients and twenty-eight healthy controls (HC) underwent an anatomical MRI scan. PCS length and cortical thickness were estimated using Mango brain visualization and FreeSurfer, respectively. Patients with AVH ($n = 45$) and patients without AVH were compared ($n = 32$) to the controls.** ***Results:*** **PCS length significantly differed between HC and patient groups ($F(2,102) = 3.57$, $P = .032$) in the left but not in the right sulcus. We found significantly longer PCS between HC and AVH group but no difference between patient groups. Similarly, we found significant thinning of cortical structures including structures surrounding anterior parts of PCS between HC and patients either in general or per group, but no significant differences were observed between patient groups.** ***Conclusions:*** **PCS length in the left hemisphere is shorter in schizophrenia patients with hallucinations as compared to HC subjects. The patient group without hallucinations was in between those 2 groups. Cortical thickness of neighboring areas of PCS is diminished in patient groups relative to the healthy comparison subjects. The role of lateralization and functional involvement of the PCS region in processes underlying hallucinations, such as reality monitoring, needs further clarification.**

Keywords: auditory verbal hallucinations/paracingulate sulcus/schizophrenia

Introduction

Hallucinations are a common symptom of psychotic disorders, but can also occur in other psychiatric and neurologic conditions. Commonly defined as perceptions without corresponding external stimuli, auditory hallucinations in the form of hearing voices can be a distressing and debilitating symptom of schizophrenia. Over the past decades, several hypotheses have been advanced regarding the cognitive underpinnings of hallucinations in schizophrenia, the most influential of which have invoked perceptual expectations[1,2] and reality monitoring.[3,4] With regard to their neural basis, a distributed network has been implied of cortical and subcortical regions.[5] As a key region, involvement of the superior temporal lobe, including the temporoparietal junction (speech perception area) has been consistently found, which may correspond to the perceptual aspect.[6] More recently, evidence

is mounting for a role of the paracingulate sulcus (PCS), which has been reported to be involved in reality monitoring processing.[7]

Reality monitoring refers to the ability to discriminate between real and imagined information. It has been shown to be impaired in patients with schizophrenia and hallucinations.[8] Buda et al[9] reported, in healthy individuals, that bilateral absence of the PCS was associated with reductions in reality monitoring performance. Several studies have subsequently reported reduced PCS length to be associated with hallucinations in patients with schizophrenia.[10] A recent functional study[11] also found that the PCS was implicated in controlling hallucinatory episodes, suggesting a role for the PCS in auditory verbal hallucinations (AVH) episode on- and offsets.

In the present study, we attempted to replicate and extend the PCS findings in patients with AVH. The replication of previous findings regards measurement of PCS length. The extension, with respect to prior results, concerns our inclusion of cortical thickness measurements. To this end, we analyzed available data from patients that were previously scanned at the Cognitive Neuroscience Center in Groningen. We hypothesized reduced PCS length and reduced cortical thickness of the PCS in patients with AVH as compared to patients without AVH and healthy control (HC) subjects. Note, we will use the term "hallucinations" if the hallucinatory modality is not specified or could be multiple, and the term "auditory verbal hallucinations (AVH)" if the modality that was investigated is clearly "auditory verbal."

Materials and Methods

Participants

For this study, structural T1 MR images of 77 patients and 28 HC were pooled from 5 studies performed at our center, investigating schizophrenia and related psychotic disorders. Four of these studies were also pooled together in a previous study of neuro-metabolites related to AVH in schizophrenia.[12] The first study was a randomized controlled trial with rTMS for the treatment of negative symptoms of schizophrenia (Dutch Trial Registry: NTR1261[13]). The second study was a trial that compared the effects of aripiprazole vs risperidone on negative symptoms of schizophrenia and related psychotic disorders (EUDRA-CT: 2007-002748-79[14]). The third study was a trial to investigate the effects of a cognitive-emotional intervention to improve insight in patients with schizophrenia (Dutch Trial Registry: NTR1799[15]). The fourth study investigated the neural basis of cognitive-emotional processing in individuals with an at-risk mental state (Current Controlled Trials: ISRCTN21353122). In the fifth study, the NEMO study, both participants and schizophrenia patients performed the metrical stress evaluation task to investigate emotional memory in patient population.[16,17]

For this study, we selected only right-handed participants because lateralization is not consistent for left-handed people,[18] while AVH are related to the language network, which is in turn lateralized to the left hemisphere in the majority of right-handed people.[19] Most patients fulfilled the DSM IV criteria of schizophrenia, whereas others fulfilled the criteria of related disorders such as schizophreniform or psychosis not otherwise specified (for an overview of diagnoses, see table 1). Schizophrenia diagnosis was established by a clinician according to DSM V criteria. Subsequently, in patients the diagnosis was confirmed either by the Mini-International Neuropsychiatric Interview (M.I.N.I.[20]) or the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) interview.[21] The majority of the patients had a diagnosis of schizophrenia, although several patients with other psychotic disorders were also included (table 1). The severity of current symptoms was assessed in all patients using the positive and negative syndrome scale (PANSS[22]). Note that 4 out of 5 studies had the exact same scanning parameters, while NEMO study[17] had different parameters. We carefully examined the effect of the study to the PCS length and to the cortical thickness measures (see below following 3 sections). Therefore, the participants from the NEMO study were included for the PCS length but not in the measures of cortical thickness. In addition, special attention was paid to whether patients had ever experienced AVH (AVH group; n = 46 and 45, for the PCS length investigation and the cortical thickness, respectively) or had never experienced them (NoAVH group; n = 32 and 22, for the PCS length and the cortical thickness investigations, respectively). This was done by careful examination of interview recordings, interview notes and M.I.N.I. item M6a where applicable. Patients were only included in the study if it could be confirmed whether or not they had ever experienced AVH. Some patients in the NoAVH group had experienced tactile or olfactory hallucinations.

The control participants were recruited through local advertisements and through word-of-mouth, and reported to be healthy. The absence of psychiatric disorders was confirmed using screening questions of the SCAN interview.[21] They experienced no hallucinations.

Education was scored according to the Verhage system, with a scale ranging from 1 = primary school to 7 = university. Supplementary table S1 summarizes antipsychotic medication taken by the participants. Antipsychotic medication was converted to haloperidol equivalent using primarily the conversion rules by Andreasen et al.[23] Levels of haloperidone, flupentixol, and primozide were first converted to olanzepine by the method of Gardner et al[24] and subsequently converted to haloperidol.[23]

Exclusion criteria for all participants were having any comorbid neurological disorder, insufficient mastery of the Dutch language, and standard MRI exclusion criteria (such as claustrophobia and metal implants). In addition,

Table 1. Demographic Data of Subjects

	Mean (SD)			Significance		
	Healthy	Schizophrenia Patients NoAVH	Schizophrenia Patients AVH	Three Groups	HC vs Sczhi	NoAVH vs AVH
	(*n* = 28)	(*n* = 32)	(*n* = 45)		*P*	
Age in years	27.3 (10.9)	33.1 (7.8)	31.0 (10.7)	$F(2,102) = 2.6$ (0.08)	.037	n.s.
Sex males	21/9	18/4	34/11	$\chi(2,102) = 2.1$ (0.47)	n.s.	n.s.
Education	5.5 (0.7)	5.1 (1.5)	4.7 (1.6)	$F(2,102) = 3.2$ (0.04)	.026	n.s.
Diagnosis						
Schizophrenia	—	21	39			
Schizophreniform disorder	—	0	1			
Psychosis not otherwise specified	—	1	2			
Substance-induced psychosis	—	0	1			
Delusional disorder	—	0	1			
PANSS pos.	—	12.9 (4.6)	14.6 (4.2)			$U = 520$ (0.09)
PANSS neg.	—	16.2 (5.9)	15.6 (5.1)			$U = 687$ (0.90)
PANSS gen.	—	29.4 (7.4)	30.8 (6.5)			$U = 577$ (0.29)
PANSS tot.	—	58.2 (14.3)	61.0 (12.2)			$U = 756.5$ (0.4)
P3		1.8 (1.3)	3.0 (1.5)			$U = 1001$ (<0.001)
P4		1.3 (0.5)	1.7 (0.9)			$U = 797$ (0.059)
Duration of illness in years	—	7.8 (8.2)	8.3 (8.1)			$T(2.71) = -0.23$ (0.8)
Medication [mg] haloperidol equivalent	—	9.6 (14.4)	6.6 (6.9)			$U = 585$ (0.16)
Nonmedicated	—	3	7			

The left column lists the demographic variables. The second to fourth columns from the left show average values of the variables across the group; the SDs are in brackets. Education level was rated according to a 6-point scale defined by Verhage, which ranges from primary school (1) to university level (6). Nonparametric tests were used to test the group differences for PANSS and Medication equivalent (Mann-Whitney test), and gender (chi-square). *Note*: AVH, auditory verbal hallucinations; HC, healthy controls; P3, hallucination item of PANSS; P4, delusion neighboring areas item of PANSS; PANSS, positive and negative syndrome scale; PANSS gen., general symptoms subscale of PANSS; PANSS neg., negative symptoms subscale of PANSS; PANSS pos., positive symptoms subscale of PANSS.

substance dependency within the previous 6 months was an exclusion criterion for 3 of the studies[13,14,25] and all HC.

Informed Consent and Ethics Committee Approval

The participants provided written informed consent before the scanning session, after the procedure had been fully explained. All study protocols were fully approved by the medical ethical board of the University Medical Center Groningen (METC; UMCG), with exception of the study on at-risk mental state that was approved by the Mental Healthcare Research Ethics Committee (METiGG). All procedures were carried out according to the declaration of Helsinki.

MRI Acquisition

The MR images were acquired using a 3T Philips Intera MRI scanner (Philips, Best). The standard 8-channel SENSE head coil was used to acquire whole T1-weighted anatomical images. For the first 4 studies, T1-weighted images were acquired with the following parameters: 160 slices; isotropic voxels of 1 mm; TR = 9 ms; TE 3.5 ms; flip angle 30°; field of view (FOV) 256 × 232 × 170 mm^3, matrix 256 × 256, resulting in the voxel size 1 × 0.90625 × 1 mm^3, covering the whole brain. For the NEMO study T1-weighted images were acquired with the following parameters: 3D/FFE/CLEAR (TR = 25 ms, TE = 2.5 ms, flip angle = 30°, FOV = 204 × 256 × 160 mm^3, matrix 256 × 256, slice thickness 1.0 mm, resulting in the voxel size of 0.796875 × 1 × 1 mm^3.

PCS Length

All files were converted from PAR and REC file formats to NIfTI format by using the MRIcron software (Version v1.0.20190902; https://www.nitrc.org/projects/mricron). The images were then reoriented such that the line with anterior (AP) and posterior (PC) commissure axis was horizontal and the origin set to AP, following procedure described by Ashburner[26] and using SPM12 software (https://www.fil.ion.ucl.ac.uk/spm/software/spm12/).

The individual scans were then imported into Mango brain visualization software (Version 4.1;

http://ric.uthscsa.edu/mango/) and inspected for integrity. The length of the PCS for each hemisphere was measured using the procedure described by Garrison et al.[27] In short, after navigating 4 slices to the left (or to the right for the right hemisphere) of the medial fissure and plain ($x = 0$) the cingulate sulcus (CS) was identified. Using CS as a landmark the PCS was identified running parallel above CS (according to z direction) and visible for minimum of 3 sagittal slices measured from the medial plane. To confirm the identity of the PCS, the images were also inspected using MRIcron software. Subsequently, the "trace line" function in Mango was used to measure the length of the PCS (see example in figure 1). The investigator performing this procedure, AdV, was blinded to the group status of participants.

Using ANOVA with PCS length as a variable and the study (site) as a fixed variable we compared the effect of the study on the left and the right PCS length. In addition, post hoc *t* tests were used to compare the PCS lengths from 4 individual studies vs the NEMO study. We found no effect of the study, nor significant difference between the NEMO study and the other studies specifically. Therefore, all participants were included in the measurements of PCS length.

Cortical Thickness

The cortical thickness measures were calculated using FreeSurfer software package (Version 7.1.1; https://surfer.nmr.mgh.harvard.edu/fswiki/DownloadAndInstal).[28,29] The preprocessing steps included removal of nonbrain tissue; transformation to the Talairach reference space; segmentation into gray and white matter; correction of topological defects and intensity normalization. After these steps, the cortical surface was inflated and the surface was then registered to the spherical atlas based on the folding patterns and cortical thickness was calculated as the shortest distance between the 2 surfaces.[28–30] The images were then smoothed using a 10-mm, full-width, half-maximum Gaussian kernel.[31]

Statistical Analysis

Statistical analysis of PCS length was performed with SPSS 26 (IBM Corp. Released 2019. IBM SPSS Statistics for Windows, Version 26.0.0.0. Armonk, NY: IBM Corp.). Demographic data between groups were compared either with ANOVA, or *t* tests, when appropriate. As demographic and clinical data were not normally distributed, nonparametric tests were applied to test for group differences. Demographic differences between the 3 groups were compared using Kruskal-Wallis tests and subsequent post hoc Mann-Whitney *U* tests in case of significant differences. Chi-square tests were applied to test for differences in group distributions of gender. Clinical differences between the 2 patient groups were evaluated with the Mann-Whitney *U* tests.

Group differences in PCS length were tested using univariate ANOVA, with planned Simple comparison in which the first variable is compared with the following variables separately and Helmert comparisons in which the levels of 1 variable are compared with the mean of the subsequent levels of the variable. Thus, the PCS length of the HC group was tested against the PCS length of the total patient group (AVH and NoAVH groups together), and then the PCS length of the HC was tested against each patient group. Subsequently, the AVH group was tested against the NoAVH group. Next, univariate ANCOVA was performed to calculate group differences in PCS length with significant covariates (age and education level), with planned comparisons similar to those used in the previous test. Spearman correlations were calculated to investigate possible correlations between hallucination severity and positive symptoms (measured with Hallucinations item P3 and Delusions item P4 of the PANSS and Positive symptoms subscale of the PANSS) with PCS length.

For the statistical analysis of the cortical thickness maps, the images were first grouped together using FreeSurfer Group Descriptor, then nonparametric *t* tests were performed for the HC vs patients, HC vs AVH, HC vs NoAVH, and AVH vs NoAVH comparisons. The results were thresholded for statistical significance at $P = .05$ using cluster thresholding correction for whole brain surface multiple comparisons (comparable to FWE correction for the whole brain analysis). Because age differed between HC and patient group, as well as between HC and NoAVH group, we repeated these 2 comparisons adding age as a covariate.

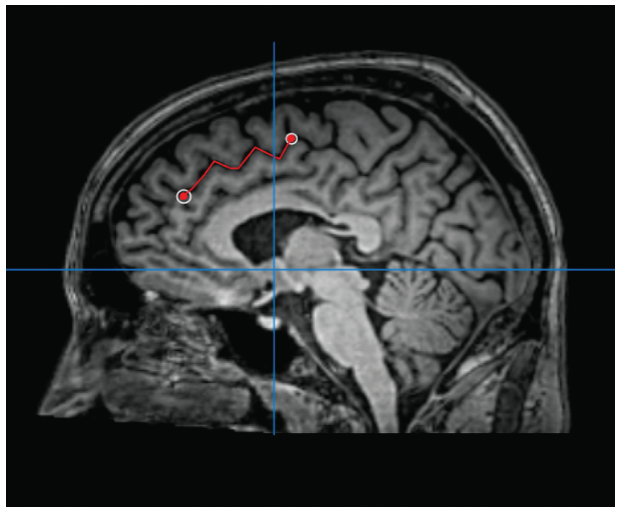

Fig. 1. Illustration of the calculation of the left PCS length. Grey line connecting two dots—estimated PCS trajectory. *Note*: PCS, paracingulate sulcus.

Results

Demographic Details

The 3 groups (control participants, AVH, and NoAVH) did not significantly differ in gender (details in table 1). The 2 patient groups did not differ in medication (haloperidol equivalents), negative symptoms or general psychopathology (subscales of PANSS) (table 1). In total, 10 patients were not using antipsychotics ($n = 3$ in NoAVH group and $n = 7$ in AVH group). There was a significant difference in education and a trend toward significance in age among groups, with the HC group having lower age and higher education then the combined patient groups. The age differed between HC and patient group ($P = .037$) as well as HC and NoAVH group ($P = .020$), but not between HC and AVH ($P = .147$). Therefore, we included age and education as covariates in the analysis of PCS length (ANCOVA).

In line with patient selection, out of all positive items of the PANSS questionnaire, only the P3 (hallucinations) was significantly different between the 2 groups of patients ($U = 1001$ $P < .001$; with higher score in the AVH group).

PCS Length

ANOVA analysis of PCS length revealed a significant effect of the group ($F(2,102) = 3.57$, $P = .032$, $\eta^2 = 0.065$) for the left but not for the right PCS. Planned comparisons showed that the total patient group had significantly shorter left PCS than the control participants group ($P = .023$, $\eta^2 = 0.049$). However, within the total patient group, we observed a small effect size of the AVH group having shorter length of left PCS levels than the NoAVH group but not significant ($P = .157$, $\eta^2 = 0.026$). In line with Garrison et al,[27] the length of left PCS differed significantly between the AVH group and control participants (table 2). The PCS lengths are shown in figure 2.

The main effect of the group remained significant after adding the significant covariates age and education ($F(4,100) = 3.2$, $P = .045$, $\eta^2 = 0.06$), for the left PS length. The difference between control participants and the patient group remained significant ($P = .04$, $\eta^2 = 0.04$). The length of the left PCS remained significantly lower in the AVH group compared to the HC group ($P = .015$). In addition, comparison of PCS length between AVH and NoAVH group, including only patients with the schizophrenia diagnosis, did not change the results (supplementary table S5).

We found no significant difference in the length of the left or right PCS between medicated and nonmedicated patients, and the results for the comparison of PCS length between the 2 patient groups did not change after adding medication as a covariate, meaning they were not significant.

When patient groups were divided according to P3, thus not specifically for the presence of AVH specifically (as P3 does not distinguish hallucination modality) nor history of AVH but including other types of hallucinatory experiences there was no significant difference between patients groups (see supplementary materials) in the length of PCS.

We found no evidence for an association between the severity of either hallucinations (P3), delusions (P4), nor for positive symptoms with PCS length of the left ($\rho = -0.093$, $P = .43$; $\rho = 0.152$, $P = .19$; $\rho = 0.144$, $P = .22$, respectively) or right hemisphere ($\rho = 0.176$, $P = .13$; $\rho = 0.025$, $P = .83$; $\rho = 0.166$, $P = .15$, respectively).

Repeated measures ANOVA was conducted with side (left or right) and group (HC, AVH, and NoAVH) to investigate difference between left and right PCS length (see supplementary table S3). We found significant effect of side ($F(1,102) = 85$, $P < .001$, $\eta^2 = 0.46$), which remained after adding covariates ($F(1,100) = 5.6$, $P = .02$, $\eta^2 = 0.053$), and marginally significant interaction (side × group; $F(2,102) = 2.6$, $P = .075$, $\eta^2 = 0.049$) which remained after adding covariates (side × group; $F(2,100) = 2.9$ $P = .057$, $\eta^2 = 0.056$). Comparison of left and right PCS lengths showed that there was significant difference in length across groups ($t(2,105) = 8,821$, $P < .001$) (see supplementary table S4).

Table 2. The Differences of the Left and the Right PCS Length Among Groups

	Mean (SD) [mm]							
	HC	NoAVH	AVH	ANOVA	HC vs Patients	NoAVH vs AVH	HC vs AVH	HC vs NoAVH
PCS L	47.9 (23.5)	41.3 (18.5)	35.0 (19.4)	$F(2,102) = 3.57$ (0.032)	**0.023**	n.s.	**0.009**	n.s.
PCS R	23.4 (16.2)	20.5 (18.2)	21.7 (15.7)	$F(2,102) = 0.2$ (0.8)	n.s.	n.s.	n.s.	n.s.
PCS L[a]				$F(4,100) = 3.2$ (0.045)	**0.04**	n.s.	**0.015**	n.s.
PCS R[a]				$F(4,100) = 0.05$ (0.95)	n.s.	n.s.	n.s.	n.s.

Columns 2–4, the mean PCS length and the SD per group. Column 5, results of ANOVA, *F* value, and *P* value (within brackets). Columns 6–9, *P* values of corresponding post hoc analysis. *Note*: AVH, auditory verbal hallucinations; HC, healthy controls; PCS, paracingulate sulcus.

[a]The length of the PCS after adding covariates (age and education).

Bold values indicate statistical significance.

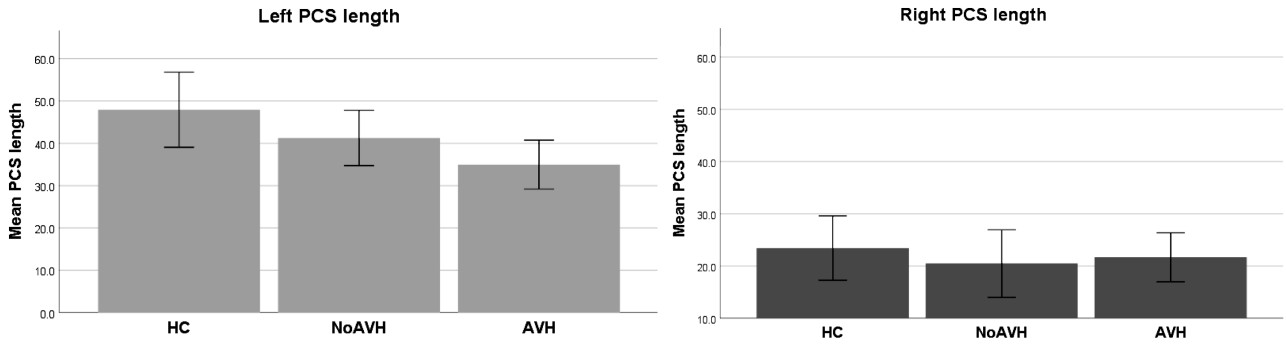

Fig. 2. Bar plots of the length of the left and the right PCS per group. *Note*: PCS, paracingulate sulcus.

Cortical Thickness

Analysis of cortical thickness data showed significant differences between HC and patients after correction for multiple comparisons (cluster correction). Nonparametric analysis showed that the cortical thickness was decreased in both patient groups when compared to the HC group. This was found in the left precentral cortex, middle frontal cortex (MFC), and anterior cingulate cortex (ACC), right postcentral cortex (PostCC), and superior frontal cortex and in bilateral inferior parietal lobe (IPL) and in the precuneus. The findings remained significant after correction for age.

The AVH group had decreased cortical thickness as compared to the HC group in the left MFC, supramarginal cortex, precentral cortex, superior parietal cortex, and rostral ACC, right PostCC and in the precuneus. When the HC group was compared with the NoAVH group, the HC group showed increased thickness in the left IPL, middle temporal cortex, ACC, and lateral orbitofrontal cortex, right superior frontal cortex, insula, and middle temporal cortex. Again, this difference remained significant after correction for age. No significant difference was observed between the 2 patient groups.

Correlation Between Cortical Thickness and PCS Length

Further we investigate the correlation between cortical thickness in the left hemisphere with the length of the left PCS, and the correlation between cortical thickness in the right hemisphere with the length of the right PCS. We found significant correlations after correction for multiple comparisons in the left hemisphere between PCS length and surrounding gyri (figure 3d). Namely the medial superior frontal gyrus was significantly correlated with the PCS length after correction for multiple comparisons. When we investigated using more lenient threshold ($P < .001$, uncorrected) we found a blob in ACC that was correlated with PCS length. There were no significant correlations in the right hemisphere.

Discussion

The aim of this study was to investigate the association of AVH in schizophrenia patients with the length of the PCS and its cortical thickness. We replicated the pattern reported in previous studies by Garrison et al in which a gradient was found with the shortest PCS length in patients with hallucinations, and the longest in healthy comparison subjects. The patient group without hallucinations was in between those 2 groups. The most pronounced difference that we found, in line with Garrison et al,[27] was seen in left PCS length when patients with lifetime AVH were compared to control participants. It has been suggested that a reduction in PCS length could be due to genetic factors that influence the neurodevelopmental process of cortical folding (the PCS is formed around 36 weeks of gestation), or alternatively may be a consequence of a nongenetic factors affecting primary sulcal development, or represent extremes of normal statistical variation in the development of primary and secondary sulci.[27]

Our study goes beyond previous studies by contrasting patients with and without a lifetime history of hallucinations (enabling the investigation of a trait effect) and by also investigating cortical thickness of the PCS region in relation to hallucinations. We found significant thinning of cortical regions including areas surrounding anterior parts of the PCS between HC and patients. The cortical thickness of areas surrounding the left PCS was correlated with the length of the left PCS. These were more apparent for patients in the AVH group (relative to HC) than for patients without AVH. However, no significant differences were observed in a direct comparison of the 2 patient groups. Two suggestions can be made, based on this complex pattern of results: (1) PCS length may be more strongly associated with AVH than cortical thickness of bordering regions, (2) with a larger power and more extensive characterization of hallucination status and history, the possibility remains that cortical thickness could still yield relevant findings (as we saw more differences in cortical thickness between AVH patients compared to control group than between non-AVH patients and the control group, see figure 3).

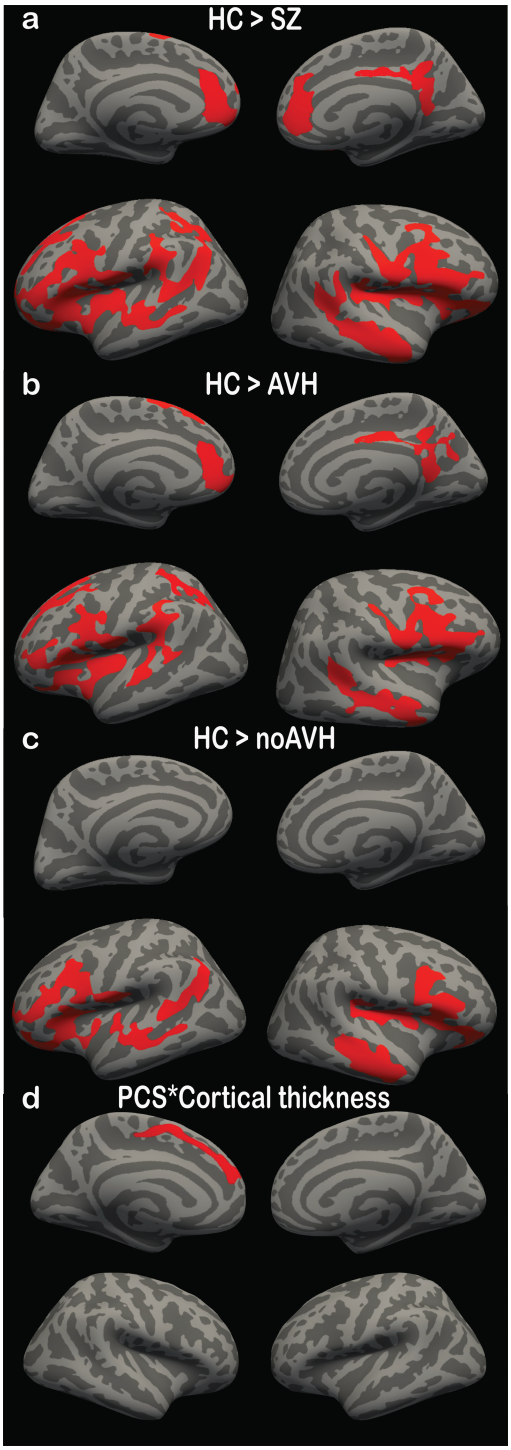

Fig. 3. Cortical thickness differences. The results are presented on the blown up cortical surface. The red blobs illustrate the area where cortical thickness differed significantly thresholded at a cluster corrected $P < .05$. (a) Difference between HC and patients. (b) Difference between HC and AVH group. (c) Difference between HC and NoAVH group. (d) Correlation between cortical thickness in the left hemisphere and the left PCS length, at a threshold corrected for multiple comparison (above) and by looking at a more lenient threshold ($P < .001$, uncorrected). *Note*: AVH, auditory verbal hallucinations; HC, healthy controls; PCS, paracingulate sulcus.

Our results are consistent with earlier studies that reported reduced PCS length in patients with AVH.[27,32] This has been shown based on data from at least 3 different countries (the United Kingdom, United States, and the Netherlands). The current data are from a different Dutch sample (measured in Groningen, the Netherlands). We found, in line with Garrison et al[27] specifically the left PCS to be significantly shorter in patients with AVH. Garrison et al[27] found that people with shorter left PCS have 19.9% chance to experience AVH. Powers et al,[32] however, reported the right but not left PCS to be shorter in voice hearers regardless of diagnosis or clinical status. The lack of significant difference in the left PCS could be due to the relatively low statistical power of the study (15 participants per group). Notably, we included exclusively right-handed people, as it has been shown that lateralization may not be consistent in non-right-handed people.[18] Unfortunately, none of the above studies controlled or gathered information for handedness, and discrepancies in findings may be associated with possible differences in handedness between samples.

The PCS, as with any sulcus, is just a fold—thus, the functional implications of the PCS findings probably are related to the gyri making up the upper and lower banks of the PCS, ie, the inferior bank of the superior frontal gyrus, and the superior bank of the cingulate gyrus. One could therefore relate the morphological findings regarding the PCS to the functions associated with the inferior frontal gyrus and cingulate gyrus. A possible functional explanation is differential connectivity between the ACC region and sensory regions that might explain the hallucination association. The PCS has been reported to be of relevance for reality monitoring,[9] the ability to distinguish between the source of information used in cognitive and perceptual processing: specifically whether such information was internally generated or externally presented. Reality monitoring has been shown to be associated with hallucinations in patients with schizophrenia. In healthy participants, Buda et al[9] reported absence of PCS (bilaterally) to be associated with significantly reduced reality monitoring performance. Perret et al[33] investigated PCS length and reality monitoring in patients with schizophrenia and AVH and found a reduced PCS length (in the right hemisphere) to be associated with reduced reality monitoring performance. This study did not include a control group, however (neither a patient group without AVH nor a healthy comparison group). Using fMRI measurements during a reality monitoring task, Garrison et al[34] showed reduced activation of left medial anterior prefrontal cortex (in the vicinity of the PCS) in patients with schizophrenia. Thus, there is some support for the relevance of PCS for reality monitoring processes and for involvement in schizophrenia and hallucinations, but more research is needed, to corroborate initial findings and to clarify issues of laterality.

In our sample, we found that the right PCS length was approximately half the length of the left PCS for all groups. While previous studies observed differences between left and right PCS[10,27] the difference observed in previous studies was smaller. For example, Rollins et al[10] found that asymmetry between length of right and left PCS was more pronounced in HC and groups without hallucinations. They observed ~20 mm difference between those groups. Upon careful inspection of our data we observed that this somewhat drastic asymmetry is caused by a large number of absent (nonobservable) PCS in the right hemisphere. Namely, 25 subjects (across groups) had no measurable right PCS while 8 had no measurable left PCS. In this case, the PCS length is modeled as 0 mm, in accordance to previous literature[27] decreasing the average length of the right PCS.

Further, previous studies found high individual variability in the PCS length.[35,36] Some studies found reduced hemispheric asymmetry in patients compared to HC[37–39] while other failed to find the lack of asymmetry in patients groups.[40,41] Thus, possibly other factor influence the degree of asymmetry, such as age, sex, handedness, and hallucination status. An important distinction between the current study and those undertaken previously is that we included only right-handed individuals which influences the anatomical lateralization toward left hemisphere. Indeed, previous studies demonstrated the difference brain lateralization between left- and right-handed people for language[18,19] or motor tasks.[42,43]

Wei et al[44] reported higher proportion of right-handed males with prominent PCS than in females, and Yücel et al[45] found females more likely to exhibit symmetrical folding pattern across the hemispheres. In addition to right handedness, our sample is predominantly male. Variability on these metrics between the different samples might explain the increased asymmetry observed in this sample.

Treatment approaches may investigate neurofeedback methods, in which a patient learns to change brain activity based on direct feedback of activation of certain brain regions. Recently, Garrison et al[46] investigated this for the paracingulate/mPFC and source monitoring performance in 39 healthy subjects randomized to an active or sham group with 3 sessions in 1 scanning run. They found increased mPFC activation for the active vs sham group and a trend toward better source monitoring performance. It remains to be tested, though, whether more than 3 practice sessions could induce a stronger change.

Several limitations of our study should be noted. First, the assessment of hallucinations could have been more comprehensive, eg, to distinguish between AVH and other types of hallucinations. It should be noted, though, that we did repeat the analysis using the P3 item of the PANSS, that includes more than only AVH, which did not alter our results. A second limitation is the sample size. Though not too small, with 77 patients and 28 HC, the group analyses contained smaller numbers (with $N = 22$ in the non-AVH patient group being the smallest). This limited statistical power, though the fact that we replicated earlier findings is reassuring. A final limitation concerns the use of different MR protocols, which was the case for a subset of the data. However, we checked whether this could explain differences, and did not find evidence of an effect on our findings.

Conclusion

PCS length in the left hemisphere is shorter in schizophrenia patients with AVH as compared to healthy comparison subjects. The patient group without AVH was in between those 2 groups. Cortical thickness of neighboring areas is diminished in patient groups relative to the healthy comparison subjects. Studies that investigated PCS length in relation to hallucinations report conflicting results regarding laterality: most imply the left PCS, some both sides, and there are also reports finding the right PCS to be involved. This deserves further investigation. Finally, functional involvement of the PCS region in processes underlying hallucinations (eg, reality monitoring) needs further clarification.

Supplementary Material

Supplementary material is available at *Schizophrenia Bulletin* online.

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Authors' Contribution

B.Ć.-B. made substantial contributions to the design of the work, the acquisition, analysis, interpretation of data and have drafted the work and substantively revised. A.A. made substantial contributions to the conception of the work, data interpretation, have drafted the work and substantively revised the manuscript. A.V. made substantial contributions to the data analysis and interpretation. R.J.R and J.B.C.M. made substantial contributions to the data analysis, interpretation, and revised the manuscript. J.G. and K.H. made substantial contribution to the interpretation of the data, and revised the manuscript. All authors approved the submitted version of the manuscript

and have agreed both to be personally accountable for the author's own contributions and the accuracy and integrity of presented work.

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