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Alterations in the volume and shape of the basal ganglia and thalamus in schizophrenia with auditory hallucinations

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ABSTRACT

Different lines of evidence indicate that the structure and physiology of the basal ganglia and the thalamus is disturbed in schizophrenia. However, it is unknown whether the volume and shape of these subcortical structures are affected in schizophrenia with auditory hallucinations (AH), a core positive symptom of the disorder. We took structural MRI from 63 patients with schizophrenia, including 36 patients with AH and 27 patients who had never experienced AH (NAH), and 51 matched healthy controls. We extracted volumes for the left and right thalamus, globus pallidus, putamen, caudate and nucleus accumbens. Shape analysis was also carried out. When comparing to controls, the volume of the right globus pallidus, thalamus, and putamen, was only affected in AH patients. The volume of the left putamen was also increased in individuals with AH, whereas the left globus pallidus was affected in both groups of patients. The shapes of right and left putamen and thalamus were also affected in both groups. The shape of the left globus pallidus was only altered in patients lacking AH, both in comparison to controls and to cases with AH. Lastly, the general PANSS subscale was correlated with the volume of the right thalamus, and the right and left putamen, in patients with AH. We have found volume and shape alterations of many basal ganglia and thalamus in patients with and without AH, suggesting in some cases a possible relationship between this positive symptom and these morphometric alterations.

1. Introduction

Schizophrenia is a heterogeneous disorder that can present a wide range of symptoms, one of which is auditory hallucinations (AH). These are present in around 56%–70% of patients (Andreasen and Flaum, 1991), and may be persistent and distressing. Many theories of AH have been proposed but so far none has achieved wide acceptance (McCarthy, 2012). An important tool to investigate brain changes in schizophrenia is magnetic resonance imaging (MRI), and has been extensively employed in schizophrenia research for over 30 years. These studies have revealed volume reductions in widespread cortical regions and some subcortical structures such as the hippocampus, amygdala, and thalamus (Haijma et al., 2013; Perez-Rando et al., 2023; Perez et al., 2022; van Erp et al., 2018; van Erp et al., 2016).

The basal ganglia are a set of cerebral regions with diverse functions and several studies have described alterations in their physiology and structure in patients with schizophrenia. They include the caudate nucleus, putamen, globus pallidus and nucleus accumbens; the dorsal regions of the first three of these have predominantly motor functions (Graybiel, 1995), whereas the nucleus accumbens and adjacent ventral or 'limbic' regions of the striatum are involved in reward processing (Zahm, 1999). Another subcortical structure is the thalamus, whose

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function entails not only the relay of information to the neocortex, but also the integration of this information (Giraldo and Woodward, 2017). Alterations in the structure and function of these subcortical regions and their connectivity have been proposed to explain the onset of schizophrenia (Robison et al., 2020; Simpson et al., 2010), and to be associated with positive symptoms, including AH (Ikuta et al., 2015; Percie et al., 2023; Perez et al., 2022; Wei et al., 2020). One study also found that intrinsic striatal activity was increased during acute psychosis and was associated with presence of delusions and hallucinations (Sorg et al., 2013), suggesting that alterations in the basal ganglia may contribute to positive symptomatology.

Volumetric studies of the basal ganglia and thalamus in patients with schizophrenia have produced heterogenous findings, both in macro-analysis of the ENIGMA consortium (van Erp et al., 2016) and in smaller patient cohorts. Regarding the latter, in the nucleus accumbens most studies on patients have not found volumetric changes (see for example Ballmaier et al., 2008; Glenthoj et al., 2007; Gunduz et al., 2002). However, a few studies have found decreases in the volume of this structure, particularly in specific subtypes or treatment resistant patients (see for example De Rossi et al., 2016; Liu et al., 2022). Regarding the globus pallidus, most reports have described increases in its volume in patients with schizophrenia (see for example Okada et al., 2016; Tu et al., 2022; van Erp et al., 2016), or no alterations (Ohi et al., 2022). Findings with respect to the volume of the caudate nucleus are diverse and contradictory. Many studies have not found differences (for example, (Takahashi et al., 2022; van Erp et al., 2016), whereas other reports on chronic and first episode patients have described increases (Cuesta et al., 2021; Koshiyama et al., 2018a) and decreases (Ebdrup et al., 2010; Haijma et al., 2013). In the case of the putamen, most reports have found increased volumes (Koshiyama et al., 2018a; van Erp et al., 2016). The volume of the thalamus is also strongly affected in schizophrenia, and this has been reported in big meta-analyses (Okada et al., 2016; van Erp et al., 2016), and in individual studies. In fact, its reduction has been described both in chronic and first episode patients (Fan et al., 2019; Koshiyama et al., 2018a; Okada et al., 2016). However, it has to be noted that there are also some studies with negative results (Cahn et al., 2002; Mamah et al., 2016).

Examination of the shape of subcortical structures could provide additional information concerning structural alterations in schizophrenia. This type of analysis detects alterations that otherwise would be overlooked and gives morphometric information on their location. In the case of the nucleus accumbens, a number of studies have failed to observe changes (Mamah et al., 2016; Mamah et al., 2007; Wang et al., 2008). By contrast, the shape of the globus pallidus was found to be altered in two studies (Jamea et al., 2019; Mamah et al., 2007) but not in another (Alden et al., 2022). A similar pattern has been found with respect to the caudate nucleus: several reports have described morphological changes (Jamea et al., 2019; Mamah et al., 2007; McClure et al., 2013), whereas others have failed to detect differences (Ballmaier et al., 2008; Mamah et al., 2016). In the case of the putamen, a number of studies have found shape alterations in patients with schizophrenia compared to healthy controls or unaffected siblings (Jamea et al., 2019; Mamah et al., 2008; Mamah et al., 2007). Finally, there are also several reports indicating the presence of shape alterations in the whole thalamus and specific thalamic nuclei (Danivas et al., 2013; Jamea et al., 2019; Wang et al., 2008).

Despite this evidence that the structure of the thalamus and basal ganglia may be impacted by schizophrenia, little is known about whether and to what extent any such changes might be related to the symptoms of the disorder. With respect to AH, a previous report has shown alterations in these patients in the surface area of the left precentral gyrus, caudal middle frontal gyrus and insula; as well as bilateral reductions of the hippocampal volume (Sone et al., 2022). Furthermore, in previous studies from our laboratory on patients with persistent AH, we found no volume alterations of the hippocampus, significant volumetric alterations of the left amygdala (Perez-Rando et al., 2023) and alterations of its gray matter density (García-Martí et al., 2008). However, to date there are only scarce reports studying volume alterations of the thalamus and basal ganglia in this type of patients. A small number of studies have reported volume decreases in the caudate nucleus and the thalamus comparing drug naïve first episode patients with AH and healthy controls (Huang et al., 2015) and between patients with and without AH in the putamen (van Tol et al., 2014). On the other hand, one study found increases in the volume of the gray matter of the striatum when comparing patients with schizophrenia and AH to controls (Zhuo et al., 2020). To our knowledge there are no reports on shape alterations in patients with AH.

In this study we hypothesized that the volume and shape of basal ganglia and the thalamus will be affected in patients of schizophrenia, particularly those with persistent AH, and that these alterations will be correlated with symptom severity.

To test our hypothesis, we examined volumetric and shape alterations of subcortical structures in a cohort of chronic patients with schizophrenia presenting persistent AH, chronic patients lacking AH, and matched healthy controls. In addition, we correlated the affected volumes of these structures with the general, negative, and positive PANSS subscales, uncovering interesting differential associations in patients with and without AH.

2. Methods

2.1. Study participants

The healthy subjects and patients suffering from schizophrenia were recruited from two centers of the Network of Biomedical Research Centers in Mental Health (CIBERSAM): the Health Research Institute of Valencia (INCLIVA) and the Santa Creu i Sant Pau Hospital in Barcelona. All the patients met DSM-IV criteria for schizophrenia and all of them were able to understand and give informed consent. None of them were hospitalized at the time of evaluation, and all of them were legally competent. All the procedures were approved by the local Ethics Committee. The total sample consisted of 114 individuals made of schizophrenia patients ($n = 63$) experiencing persistent AH ($n = 36$), schizophrenia patients lacking AH ($n = 27$) and matched healthy controls ($n = 51$) (see Table 1 for a description of the demographic characteristics). In detail:

2.2. Patients with schizophrenia and persistent auditory hallucinations

A group of 36 patients diagnosed with schizophrenia in a chronic

Table 1
Demographics (± SD; *chlorpromazine equivalents).

	Matched healthy controls ($N = 51$)	Patients with schizophrenia with AH ($N = 36$)	Patients with schizophrenia without AH ($N = 27$)
Sex, F(%)/M(%)	18(35%)/33 (65%)	13(36%)/23(64%)	8(30%)/19(70%)
Age (range)	36.9 (23–68)	39.4 (17–68)	35.7 (18–57)
Age when first diagnosed (range)		21.17 ± 6.25 years (8–33)	31.15 ± 9.65 years (18–50)
Duration of illness (range)		13.54 ± 8.68 (1–29)	7.50 ± 5.60 years (1−20)
Pharmacological treatment* (range)		709.71 ± 618.07 mg/d (50–1950 mg/d)	314.60 ± 182.19 mg/d (100–800 mg/d)
Duration of the pharmacological treatment		14.3 ± 6.9 years	UNK
PANSS positive		18.12 ± 5.48	15.00 ± 5.19
PANSS negative		19.16 ± 6.53	17.38 ± 5.66
PANSS general		34.80 ± 7.33	32.77 ± 7.52
PANSS total		72.48 ± 14.55	64.77 ± 15.62

stage experiencing persistent AH was included in the present study. These patients were diagnosed with persistent AH by their psychiatrist following the clinical assessment used in previous studies (Martí-Bonmatí et al., 2007; Sanjuan et al., 2007). The sample consisted of participants of both sexes (F/M: 36%/64%). The demographic characteristics of all the participants are summarized in Table 1.

All patients who participated in the study met the following inclusion criteria for persistent AH:

a) Voices had been present at least once a day during the last year.
b) At least two antipsychotics had been tested on the patient at doses equivalent to 600 mg/day of chlorpromazine.
c) Voices had not been modified by pharmacological treatment.
d) Patients freely accepted participating in the study.

In addition, we also followed these exclusion criteria:

a) Patients meeting criteria of Intellectual disability.
b) Presenting neurological lesions or cranioencephalic trauma.
c) Patients who were not able to understand the nature, consequences of the trial and the procedures they were asked to follow.
d) Patients with absolute or relative contraindications to MR examination (claustrophobia or severe hearing loss).

2.3. Patients with schizophrenia without auditory hallucinations

A group of 27 patients diagnosed with schizophrenia without AH was also considered in this study. These patients were diagnosed by their psychiatrist as those in the AH group. The sample consisted of participants of both sexes (F/M: 30%/70%). We followed the same exclusion criteria that was applied in the group of patients with schizophrenia and AH. The demographic characteristics of all the participants are summarized in Table 1.

2.4. Healthy control subjects

Using a pool of 89 healthy control subjects, we selected 51 for the comparison with patients with schizophrenia and AH and patients with schizophrenia without AH. These healthy controls were matched to the patients with schizophrenia for age, sex, and intracranial volume (eTIV). The healthy participant sample was composed of both males and females (Table 1).

2.5. Structural MRI acquisition

T1 images were acquired for all participants on a 3-Tesla scanner (Achieva, Philips Medical Systems, Best, The Netherlands) in both research centers. A 3D spoiled gradient-echo sequence was used (TE = 7.38 ms; TR = 13.18 ms; flip angle = 8°, NEX = 1, 160 contiguous slices with no interslice gap, acquisition matrix = 256 × 256, FOV = 240 mm, and voxel size = 0.90 × 0.90 × 1 mm).

2.6. Image processing

Prior to image processing, we performed a visual quality check of all T1-weighted images. Then, we performed volumetric and vertex analyses:

2.7. Volumetric analysis

Then, two different methods were used to analyze the volume and shape of subcortical structures. Regarding the former, we processed T1 images using FreeSurfer v7.2 (Fischl, 2012) (https://surfer.nmr.mgh.harvard.edu/) by default settings and used the automatic parcellation of different subcortical structures (Fischl et al., 2002), which includes the volumetric estimation of the entire thalamus, caudate, putamen, globus pallidus, and nucleus accumbens.

2.8. Vertex analysis

Shape analysis was performed by means of a vertex analysis of these subcortical regions. To do so, we processed the same T1 images using FSL v6.0 (https://fsl.fmrib.ox.ac.uk/) (Smith et al., 2004) and its module FIRST (Patenaude et al., 2011). This tool uses a Bayesian appearance model (BAM) to use anatomical points and intensity information to create a surface mesh of subcortical structures, providing an automatic segmentation of basal ganglia and the thalamus, in the MNI152 template space. FIRST also outputs 3D vertex information of these structures for each subject, allowing to locate alterations in their shape though the comparison between experimental groups. This results in scalar values that represent the distance of divergence from the MNI152 standard for each vertex, and that can be statistically studied to compare between experimental groups, finally giving coordinates of shape differences with associated *p*-values.

We checked whether the subcortical segmentation was being performed correctly at every step, and ultimately performed the vertex analysis to investigate if the shape of these structures was affected in patients with and without AH, as well as healthy controls.

2.9. Statistical analyses

In the volumetric analysis, we compared the volumes of the different regions among our 3 cohorts of subjects: patients with schizophrenia and AH, patients with schizophrenia without AH, and matched healthy controls. We used a multiple analysis of covariance (MANCOVA) to study the three groups, including as covariate the eTIV (see supplementary methods and supplementary results). Each structure was evaluated separately in two independent contrasts (per hemisphere), resulting in two comparisons of 5 volumes. The significance level was adjusted using the False Discovery Rate (FDR) method of Benjamini and Hochberg (Benjamini and Hochberg, 1995a, 1995b). For the regions above the significance threshold, we also performed pairwise comparisons between patients with schizophrenia with and without AH, and healthy control subjects. Again, these pairwise comparisons were corrected using the FDR correction.

In addition, we also performed bilateral correlations between the affected volumes, and the PANSS positive, negative, general psychopathology subscales, and total PANSS score. These were performed using Spearman's ρ, and again corrected for multiple comparisons using the FDR correction.

For the shape analysis, we used the randomize module of FSL performing 5000 permutations (Winkler et al., 2014). Results were again corrected using the FDR method. For more information, see the Supplementary Methods.

3. Results and statistical analyses

3.1. Volumetric analysis of the subcortical structures in patients with schizophrenia with and without auditory hallucinations

Once we determined there were no differences in the demographic traits among the three cohorts of patients, and the covariates that needed to be used (eTIV) (see supplementary results), we proceeded with the ANCOVAs. These revealed a significant difference in the volume of the right thalamus ($F_{2,111} = 5.249$, $p = 0.007$), and follow-up analysis showed that patients with AH had smaller volumes of this structure ($p = 0.003$) than the healthy controls. Likewise, we found significant bilateral alterations in the putamen (RH: $F_{2,111} = 7.214$, $p = 0.001$; LH: $F_{2,111} = 5.436$, $p = 0.006$), and this difference was due to increases in the volume of this nucleus only in patients with AH when compared to controls, both in the right ($p = 2.42 \cdot 10^{-4}$) and left ($p = 0.001$) hemispheres. Lastly, the globus pallidus was significantly altered bilaterally (RH: $F_{2,111} = 4.453$, $p = 0.014$; LH: $F_{2,111} = 8.590$, $p = 3.42{\cdot}10^{-4}$). The difference in the right hemisphere was due to increases in its volume in patients with AH ($p = 0.004$) when compared to the healthy controls; on the left, the volume of left globus pallidus was increased both in patients with AH ($p = 9.50{\cdot}10^{-5}$) and patients with schizophrenia without AH ($p = 0.021$) compared to the healthy controls. These findings are summarized in Fig. 1 and Table 2.

Furthermore, we also performed a correlation analysis between the duration of the illness or the antipsychotic treatment (chlorpromazine equivalents), and the volume of subcortical structures, and found no significant association (supplementary Fig. 1).

3.2. Vertex analysis of subcortical structures

In line with our volumetric results, we then analyzed vertices of basal ganglia and the thalamus of every subject, to later compare the shape of these structures between experimental groups. This resulted in coordinates of shape alterations, with associated *p*-values.

The right and left thalami displayed alterations in its whole structure in patients with AH when comparing to healthy controls (RH: Fig. 2B, $p = 0.003$; LH: Fig. 2C, $p = 0.009$). The shape of the right thalamus was also altered in patients without AH compared to healthy controls, in its temporal part at the coordinates of the geniculate nuclei (RH: Fig. 2D, $p = 0.026$). The left thalamus also showed shape alterations in this cohort of patients in comparison with healthy controls, in its medio-occipital region (LH: Fig. 2E, $p = 0.036$). The shape of right and left putamen was affected in its medio-temporal part when comparing patients with AH to healthy controls (RH: Fig. 2F, $p = 0.002$; LH: Fig. 2G, $p = 0.001$). Similarly, the shape of the right and left putamen was also altered prominently in its medio-temporal part in patients without AH when compared to healthy controls (RH: Fig. 2H, $p = 0.001$; LH: Fig. 2I, $p = 0.004$). Likewise, the left globus pallidus showed shape alterations, more prominently in its middle-parietal part, in patients without AH when compared to controls (LH: Fig. 2J, $p = 0.001$). Lastly, when comparing patients with AH to patients lacking AH, we also found shape disturbances around the whole structure (LH: Fig. 2K, $p = 0.002$). These results are summarized in Fig. 2.

3.3. Correlation of volumes with clinical scores

To understand how closely related were the volumes of the affected structures to clinical features, we performed bilateral correlations between the affected volumes in each cohort of patients, and the PANSS negative, positive, and general subscales, as well as the total score. In patients with AH (Fig. 3), neither the positive nor negative PANSS subscales were significantly correlated. However, we found a significant correlation between the general subscale of PANSS and the volume of the right thalamus ($\rho = -0.477$, $p = 0.016$), as well as with the right and

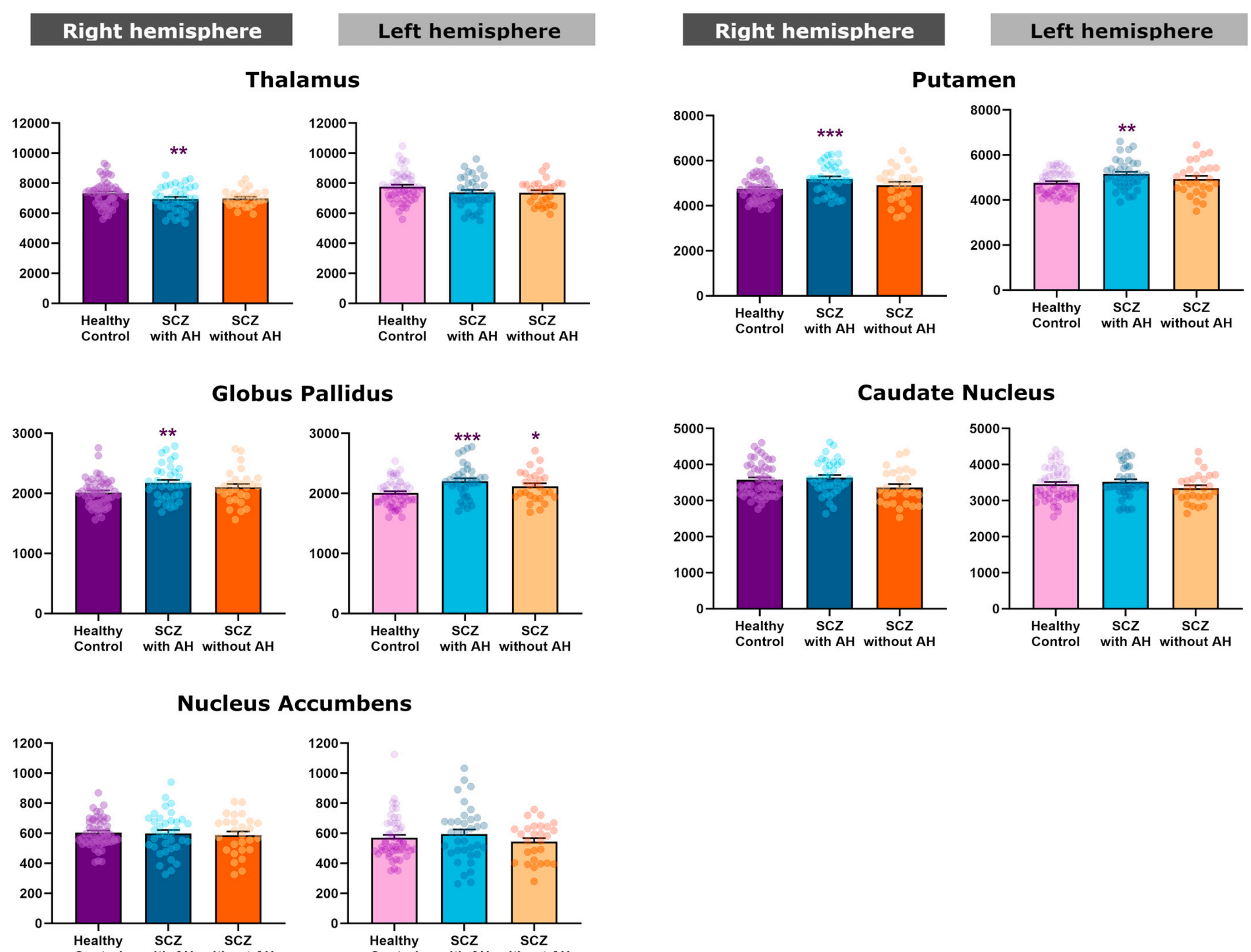

Fig. 1. Volumetric alterations of basal ganglia and the thalamus in patients of schizophrenia with and without persistent auditory hallucinations. Significance as follows: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Table 2
Volumetric results (mm^3).

							p-values from pairwise comparisons		
		HC	AH	NAH	F (from general contrast)	DF	HC vs SCZ with AH	HC vs SCZ without AH	SCZ with AH vs SCZ without AH
Thalamus	R	7337.47 ± 845.89	6957.59 ± 853.53	6998.83 ± 550.2	5.249	2, 111	0.003	ns	ns
	L	7769.76 ± 979.84	7386.26 ± 1032.82	7377.74 ± 809.7	3.619	2, 111	ns	ns	ns
Caudate nucleus	R	3579.99 ± 461.85	3633.43 ± 470.99	3365.41 ± 474.45	2.957	2, 111	ns	ns	ns
	L	3457.59 ± 441.14	3517.39 ± 448.48	3349.32 ± 408.91	1.058	2, 111	ns	ns	ns
Putamen	R	4749.52 ± 513.28	5195.43 ± 643.9	4919.7 ± 755.55	7.214	2, 111	$2.42 \cdot 10^{-4}$	ns	ns
	L	4765.65 ± 488.41	5152.47 ± 642.12	4936.1 ± 729.66	5.436	2, 111	0.001	ns	ns
Globus Pallidus	R	2014.41 ± 236.7	2176.55 ± 289.51	2101.39 ± 286.9	4.453	2, 111	0.004	ns	ns
	L	2006.08 ± 213.94	2204.62 ± 274.72	2119.56 ± 252.85	8.590	2, 111	$9.5 \cdot 10^{-5}$	0.021	ns
Nucleus Accumbens	R	604.45 ± 97.67	599.62 ± 139.23	587.24 ± 129.53	0.165	2, 111	ns	ns	ns
	L	569.59 ± 142.65	595.06 ± 184.23	543.33 ± 126.8	0.775	2, 111	ns	ns	ns

left putamen (RH: $\rho = -0.469$, $p = 0.019$; LH: $\rho = -0.439$, $p = 0.028$). In patients lacking AH, we only studied the correlations between the left globus pallidus and these PANSS scores. However, we did not find any significant correlation with the general, positive, negative PANSS or its total score (supplementary Fig. 2).

4. Discussion

This study found alterations in the volume and shape of subcortical structures in chronic patients of schizophrenia with AH. In addition, we have correlated the affected volumes to different PANSS subscales, showing a clear association between these traits and the general subscale in patients with persistent AH.

In the nucleus accumbens we have not found differences between the different analyzed groups. This agrees with most of the volumetric studies of this nucleus in chronic patients with schizophrenia (Mamah et al., 2016; Mamah et al., 2007; Tu et al., 2022; van Erp et al., 2016). However, it has to be noted that some studies have found volumetric reductions in the nucleus accumbens in chronic patients (Koshiyama et al., 2018b; Okada et al., 2016). There are also 3 reports, with low numbers of samples, describing increases in the volume of this nucleus or its gray matter (Forns et al., 2017; Lauer et al., 2001; Massana et al., 2005). Although we have failed to find volumetric differences in patients with AH, there is a report in first episode patients that has correlated positive symptoms with the volume of this nucleus (Fan et al., 2019), and increases in striatal gray matter have been described in first episode schizophrenia patients with AH (Zhuo et al., 2020).

Our results show bilateral increases in the volume of the globus pallidus. We have described a significant increase in the left hemisphere in patients with and without AH when compared to controls. However, it should be noted that the increase in its right volume was only present in patients with AH. These results are in agreement with the vast majority of studies evaluating volumetric changes in the globus pallidus in schizophrenia (Goldman et al., 2008; Hokama et al., 1995; Ito et al., 2022; Mamah et al., 2016; Rozycki et al., 2018; van Erp et al., 2016). Some studies have also found that the increase in volume correlates positively with the illness duration (Hashimoto et al., 2018; van Erp et al., 2016) or the severity of symptoms (Ito et al., 2022). Nevertheless, there are also some reports that have failed to find changes in this subcortical structure in chronic (Ohi et al., 2022; Spoletini et al., 2011; Takahashi et al., 2022; Tu et al., 2022) and, specially, in first episode patients (Fan et al., 2019; Liu et al., 2019; Xu et al., 2021). Regarding AH, there is only a study of the globus pallidus in individuals of the normal population experiencing these hallucinations, but no changes were described (Schoorl et al., 2021). Unfortunately, there are no previous reports describing volumetric alterations in this structure in schizophrenia with AH. Our results describing alterations in its shape are in agreement with previous studies in patients with schizophrenia, which described changes in the right globus pallidus (Jamea et al., 2019; Mamah et al., 2007) and suggested a putative involvement of AH in these morphometric anomalies.

We have not found significant changes in the volume or shape of the caudate nucleus. This agrees with several reports describing similar negative findings, both in chronic and first episode patients (see for example (Ballmaier et al., 2008; Fan et al., 2019; Mamah et al., 2016; Tu et al., 2022). However, a few reports have found alterations in the volume and shape of this subcortical nucleus (Ebdrup et al., 2010; Hokama et al., 1995; Mamah et al., 2008).

Interestingly, our study only found a volumetric increase in the putamen of patients with AH, which suggests a relationship with this positive symptom. In agreement with this, a previous report found that schizophrenia patients with AH have increased gray matter volumes of the striatum (Zhuo et al., 2020). Moreover, a previous report has shown functional hyperconnectivity between the putamen and the prefrontal cortex in patients of first-episode schizophrenia with AH (Cui et al., 2016). However, there are also studies describing volumetric decreases in putamen when comparing patients with AH to those lacking them (van Tol et al., 2014). Furthermore, many studies describe bilateral volume increases (Goldman et al., 2008; Koshiyama et al., 2018a; van Erp et al., 2016; van Erp et al., 2014) or reductions in patients with schizophrenia (see for example (Ballmaier et al., 2008; Mamah et al., 2016). Some other studies, particularly some recent ones in chronic patients (Ohi et al., 2022; Takahashi et al., 2022; Tu et al., 2022) and previous ones in first episode patients (Ebdrup et al., 2011; Emsley et al., 2015; Gunduz et al., 2002) did not find significant volumetric differences. Our results regarding the change in putamen shape, both in AH and NAH patients, are also in agreement with previous reports (Ballmaier et al., 2008; Jamea et al., 2019; Mamah et al., 2008; Mamah et al., 2007).

In the case of the thalamus, the present results also agree with most of the previous literature on chronic patients. There is a decrease in its volume, which in many cases seems specific to the right hemisphere (Ellison et al., 2008; Jamea et al., 2019; Okada et al., 2016; Takahashi et al., 2022). Similar results have been reported frequently for first

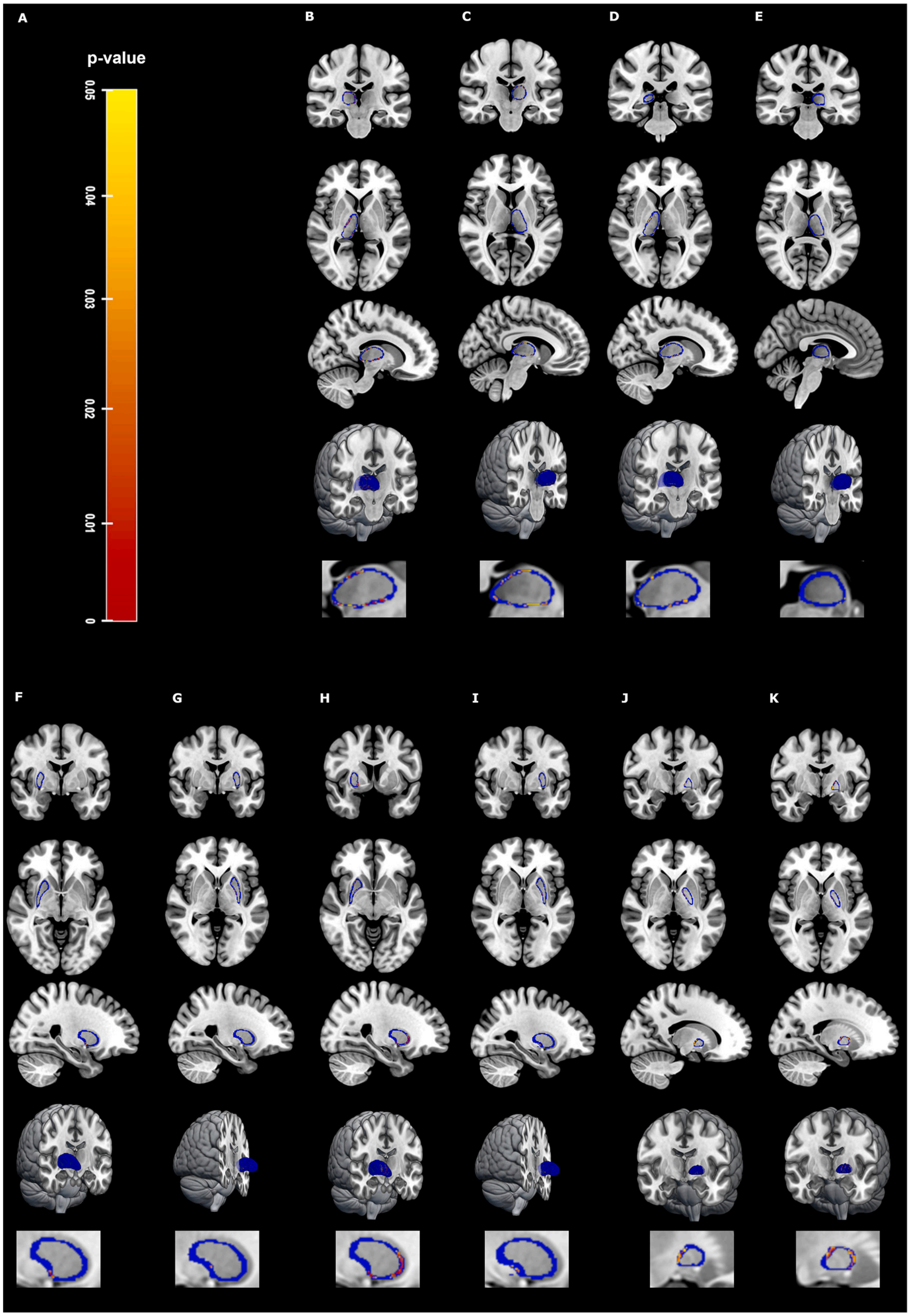

Fig. 2. Significant alterations of the shape of basal ganglia and the thalamus in patients of schizophrenia with and without persistent auditory hallucinations. Basal ganglia and thalamus are drawn in blue, while the *p*-value of shape differences follows a color scale depicted in (A): This graph shows the color scale for *p*-values ranging from yellow ($p = 0.05$) to red ($p = 0$). (B) Right thalamus differences between AH patients and controls. (C) Left thalamus differences between AH patients and controls. (D) Right thalamus differences between NAH patients and controls. (E) Left thalamus differences between NAH patients and controls. (F) Right putamen differences between AH patients and controls. (G) Left putamen differences between AH patients and controls. (H) Right putamen differences between NAH patients and controls. (I) Left putamen differences between NAH patients and controls. (J) Left globus pallidus differences between NAH patients and controls. (K) Left globus pallidus differences between patients experiencing and lacking AH. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

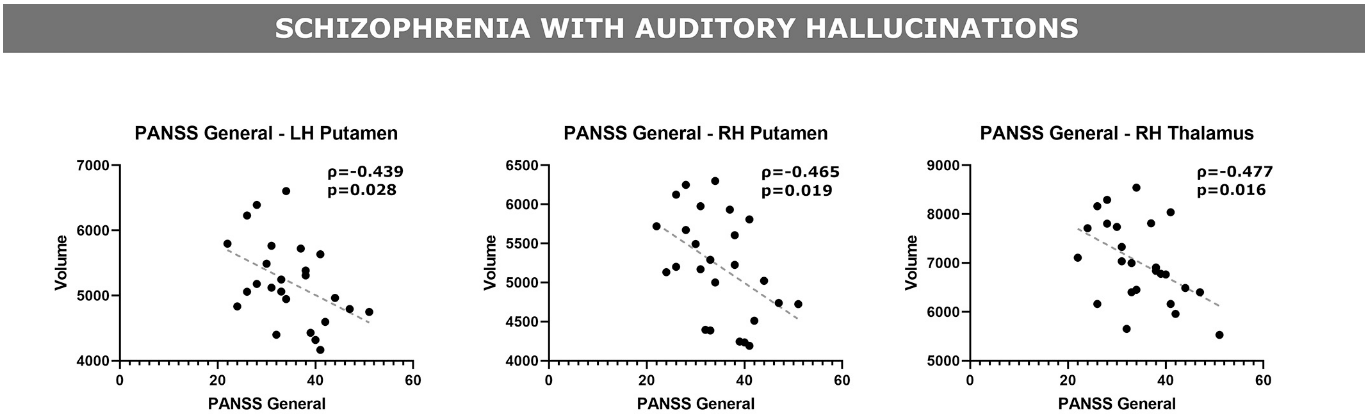

Fig. 3. Significant bilateral correlations (Spearman's ρ) between general PANSS subscore, and affected volumes, in patients with schizophrenia and persistent auditory hallucinations. Significant correlations display its ρ, p-value, and have drawn the estimated correlative line.

episode patients (Coscia et al., 2009; Ellison et al., 2008; Fan et al., 2019; Huang et al., 2015). However, we only found this difference when comparing patients with AH to controls, suggesting an involvement of this positive symptom on the volumetric alterations. Another study on first episode patients also found volume reductions in the thalamus when comparing patients with AH to controls (Huang et al., 2015). Interestingly, our current results totally agree with a previous article from our laboratory showing volumetric alterations in several thalamic nuclei also in chronic schizophrenia patients with persistent AH (Perez et al., 2022). Nevertheless, it should be noted that there are also some reports that have not found volumetric alterations in the thalamus in patients with schizophrenia (see for example (Cahn et al., 2002; Goldman et al., 2008; Mamah et al., 2016). We have also described bilateral shape alterations in the thalamus of both AH and NAH patients, which is in agreement with several previous reports (Coscia et al., 2009; Csernansky et al., 2004; Jamea et al., 2019; Kang et al., 2008; Mamah et al., 2016). Our results in the thalamus are interesting because there are previous articles describing hypoactivity and abnormal glucose metabolism in certain thalamic nuclei associated to AH (Kanemoto et al., 2020; Kumari et al., 2010). In fact, the thalamus is involved in the cerebello-thalamo-cortical circuit, which might be associated with AH (Cao et al., 2018; Pinheiro et al., 2020).

On the other hand, we provide for the first-time significant correlations between different PANSS subscales, and the affected volumes of basal ganglia and thalamus in patients with AH. This scale is used to evaluate the severity of positive, negative, and general psychopathic symptomatology in schizophrenia. Since its description in 1987 (Kay et al., 1987), it has become not only widely used in schizophrenia research, but is also considered a gold standard to evaluate efficacy of antipsychotic treatment in clinical trials (Opler et al., 2017). In our study, we have shown significant correlations between the volumes of the right and left putamen, and right thalamus with the PANSS clinical scale. Interestingly, patients with persistent AH did not present significant correlations with the positive subscale, but with the general psychopathology subscale of the PANSS, which may imply a higher sensitivity of this subscale to predict volumetric alterations in this cohort.

Some limitations might be overshadowing our results, albeit these are intrinsic of this type of analysis using human subjects. First and foremost, schizophrenia is a highly heterogeneous disorder that includes many endophenotypes, increasing the variability that can be found among and within studies. Patients with and without AH in our study have different disease severities, as can be seen in the scores of the PANSS positive, negative, and general subscales. Disease severity measured through these scales has been correlated before with structural alterations. It is inversely correlated with the thickness of several neocortical regions in first episode patients (Xiao et al., 2015). Likewise, brain volume changes have been inversely correlated with disorganization scores in schizophrenia (Collin et al., 2012). Therefore, the different PANSS subscores of patients with and without AH, might be associated to volumetric and shape alterations of basal ganglia and the thalamus in our study. However, we can never conclude that these alterations are indeed due to the existence of persistent AH, since other symptoms can be present and linked to these hallucinations. However, we also show significant correlations between the affected volumes and the PANSS subscales, clearing the understanding of how different dimensions of the patients positive, negative, and general symptomatology might indeed be affecting subcortical volumes. On the other hand, the patients from this study were exposed to chronic antipsychotic treatment for an average of 14 years. Since it is known that antipsychotic exposure affects the volume of subcortical structures (Ebdrup et al., 2011; Hashimoto et al., 2018; Li et al., 2012), our reported volume and shape alterations might also be influenced by these treatments. In line with this consideration, the illness duration of the patients used in this study is strongly variable and this might also be influencing differentially morphometric traits. Nevertheless, to address these two latter concerns, we also performed bilateral correlations between the antipsychotic treatment (chlorpromazine equivalents) or the illness duration, and the different subcortical volumes, finding no significant association between parameters.

Altogether we have presented alterations in the volume and shape of different subcortical structures in patients with schizophrenia with and without AH, important cohorts that allow us to infer alterations that are due to the presence of these hallucinations. We have also correlated these results with clinical scales, uncovering different relationships for the first time.

5. Conclusion

We have found volume decreases in the right thalamus, as well as bilateral increases in the putamen, in schizophrenia patients with persistent AH. The volume of the right globus pallidus was increased only in patients with AH, whereas its left counterpart was also enlarged in patients lacking AH. Vertex analysis revealed further morphometric alterations, proving more sensitive than volume studies. Here we show additional shape alterations in the left thalamus in patients with AH, while the left putamen is affected in patients with and without AH, and the left globus pallidus is affected when comparing patients with AH to those patients lacking them. We have also shown associations between the general PANSS score and the volume of the right thalamus and putamen from both hemispheres.

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CRediT authorship contribution statement

Marta Perez-Rando: Writing – review & editing, Writing – original draft, Validation, Methodology, Investigation, Formal analysis, Data curation. **Gracián García-Martí:** Validation, Methodology, Investigation. **Maria J. Escarti:** Methodology, Investigation, Formal analysis. **Pilar Salgado-Pineda:** Writing – original draft, Methodology. **Peter J. McKenna:** Writing – original draft, Methodology. **Edith Pomarol-Clotet:** Writing – original draft, Methodology. **Eva Grasa:** Writing – original draft, Methodology. **Alba Postiguillo:** Writing – original draft, Methodology, Data curation. **Iluminada Corripio:** Writing – original draft, Methodology. **Juan Nacher:** Writing – review & editing, Writing – original draft, Validation, Supervision, Methodology, Investigation, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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