Alterations in the volume of thalamic nuclei in patients with schizophrenia and persistent auditory hallucinations

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ABSTRACT

The thalamus is a subcortical structure formed by different nuclei that relay information to the neocortex. Several reports have already described alterations of this structure in patients of schizophrenia that experience auditory hallucinations. However, to date no study has addressed whether the volumes of specific thalamic nuclei are altered in chronic patients experiencing persistent auditory hallucinations. We have processed structural MRI images using Freesurfer, and have segmented them into 25 nuclei using the probabilistic atlas developed by Iglesias and collaborators (Iglesias et al., 2018). To homogenize the sample, we have matched patients of schizophrenia, with and without persistent auditory hallucinations, with control subjects, considering sex, age and their estimated intracranial volume. This rendered a group number of 41 patients experiencing persistent auditory hallucinations, 35 patients without auditory hallucinations, and 55 healthy controls. In addition, we have also correlated the volume of the altered thalamic nuclei with the total score of the PSYRATS, a clinical scale used to evaluate the positive symptoms of this disorder. We have found alterations in the volume of 8 thalamic nuclei in both cohorts of patients with schizophrenia: The medial and lateral geniculate nuclei, the anterior, inferior, and lateral pulvinar nuclei, the lateral complex and the lateral and medial mediodorsal nuclei. We have also found some significant correlations between the volume of these nuclei in patients experiencing auditory hallucinations, and the total score of the PSYRATS scale. Altogether our results indicate that volumetric alterations of thalamic nuclei involved in audition may be related to persistent auditory hallucinations in chronic schizophrenia patients, whereas alterations in nuclei related to association cortices are evident in all patients. Future studies should explore whether the structural alterations are cause or consequence of these positive symptoms and whether they are already present in first episodes of psychosis.

1. Introduction

One of the most common positive symptom of schizophrenia is the presence of auditory hallucinations (AH), which occur in 75% of patients of this disease (Waters and Fernyhough, 2017). Disturbingly, while some patients who experience AH may benefit from pharmacological treatment, in others these hallucinations are resistant to pharmacological therapy and tend to become chronic (MacKay et al., 2018;

Nicolson et al., 2006). Several MRI studies performed on patients experiencing AH suggest that this psychosis might be due to an aberrant interaction between linguistic, auditory and mnemic/limbic networks (Allen et al., 2012; Ćurčić-Blake et al., 2017). In fact, different neocortical regions related to auditory processing, such as the superior and middle temporal gyri, and the transverse temporal gyrus (Heschl's gyrus), display morphological and functional alterations in patients with schizophrenia (Chen et al., 2015; Cui et al., 2018; Oertel-Knochel et al., 2013; van Swam et al., 2012). However, to date, the study of the implication of subcortical structures in AH has remained more elusive. Among these structures, the thalamus has already gathered interest for its implication in sensory processing (Byne et al., 2009; Pergola et al., 2015).

The thalamus is a diencephalic structure composed of a heterogeneous group of nuclei that have distinct synaptic inputs and cortical connections (Giraldo-Chica and Woodward, 2017). Its main function consists in relaying sensory information, such as early visual or auditory stimuli, and help the integration of cognitive processes, which includes attention and executive functions, as well as memory and language (Halassa and Kastner, 2017; Wolff and Vann, 2019). Among these thalamic nuclei, several prove interesting to understand the positive symptoms in patients with schizophrenia, particularly those related to AH, because of their relationship with audition or language. The medial geniculate nucleus (MGN) is the most related to audition since it receives information from the brachium of the inferior colliculus and relays the auditory information to the primary auditory cortex (Vasquez-Lopez et al., 2017). Additionally, other thalamic nuclei, such as the pulvinar complex (Pu) and the mediodorsal complex (MD), are associated with language processing, because of their connections with cortical regions and neuronal networks involved in this task (Barbas et al., 2013; Crosson, 2013).

Previous reports have shown decreases in the volume of the whole thalamus in first episode schizophrenia patients (FEP) (Gilbert et al., 2001) and when comparing twins with and without the disorder (Ettinger et al., 2007). However, only one, analyzing FEP, has specifically shown these reductions in patients experiencing AH (Huang et al., 2015). Furthermore, there is scarce information on how the individual thalamic nuclei might be affected by this disease. Different neuroimaging reports have consistently indicated volumetric decreases in Pu and MD in patients with schizophrenia when compared to their healthy counterparts (Huang et al., 2020; Kemether et al., 2003; Shimizu et al., 2008). In these nuclei, some postmortem studies have also found lower neuronal numbers and decreases in neuronal sizes (Byne et al., 2009). In addition, there are reductions of the MD connectivity in patients with schizophrenia (Parnaudeau et al., 2013). Similarly, a couple of studies found reductions in the volume of the MGN in 22q11.2 deletion syndrome patients, a genetic disorder, which confers high risk for schizophrenia and frequently courses with AH (Cantonas et al., 2021; Mancini et al., 2020).

Interestingly, previous reports from our laboratory have already established negative correlations between the Psychotic Symptom Rating Scale (PSYRATS) scale, a reliable tool to evaluate different traits of hallucinations and delusions (Haddock et al., 1999), and changes in grey matter concentration in patients suffering AH. Concretely, PSYRATS score is negatively correlated with the gray matter concentration in the superior and middle temporal gyri (García-Martí et al., 2012), and the left inferior frontal and right postcentral gyri (García-Martí et al., 2008). Moreover, using spectroscopic measures, we found that patients with schizophrenia had significantly lower bilateral NAA/Cho ratios in the thalamus when compared with healthy subjects. There was also a significantly lower NAA/Cho ratio in the right thalamus in patients with AH compared to patients without AH and control subjects, which could suggest increased membrane turnover or demyelinating processes (Martínez-Granados et al., 2008). However, as far as we know, there is no information yet on how the score on hallucination scales, as well as its total value, might be related to morphometric changes of different thalamic nuclei.

Despite the cumulative research performed in the last few decades, the common neural mechanisms underlying hallucinations remain extensively unknown (Zhuo et al., 2020). Hence, in this study we aimed to understand how the volumes of the different thalamic nuclei are affected in patients experiencing persistent AH. To do so we have segmented two cohorts of patients of schizophrenia with and without AH, and matched healthy control subjects. We have used a novel probabilistic segmentation technique for thalamic nuclei parcellation (Iglesias et al., 2018). In addition, we have also studied whether the different alterations we reported in these nuclei could also explain the PSYRATS scored by patients with schizophrenia and AH.

2. Material and methods

2.1. Study participants

All the samples from both healthy subjects and patients suffering from schizophrenia come from two centers of the network of biomedical research centers in mental health (CIBERSAM): the Institute of research of the Clinic Hospital from Valencia (INCLIVA) and the Sant Pau Hospital from Barcelona. All the patients meet DSM-IV criteria for schizophrenia and all of them were able to read, understand and give an informed consent. None of them was hospitalized at the moment of evaluation, and all of them were legally competent. All the procedures were approved by the local Ethics Committee.

2.1.1. Patients with schizophrenia and persistent auditory hallucinations

A group of 41 patients diagnosed with schizophrenia in a chronic 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 (González et al., 2006; Martí-Bonmatí et al., 2007). The sample consisted of participants of both sexes (F/M: 39%/61%). The demographic characteristics of all the participants are summarized in Table 1.

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:

Table 1
Demographic and clinical data of patients with schizophrenia and AH and their matched controls (*Clozapine equivalents).

	Matched healthy controls	Patients with schizophrenia with AH	Patients with schizophrenia without AH
Sex, F(%)/M(%)	16(41%)/25(59%)	16(39%)/25(61%)	14(40%)/21(60%)
Age (range)	37.43 ± 10.61 (23–68)	40.02 ± 12.54 years (17–68)	36.15 ± 9.96 years (18–57)
Age when first diagnosed (range)		21.17 ± 6.04 years (8–32)	30.88 ± 9.29 years (16–52)
Duration of illness (range)		15.60 ± 11.78 (2–54)	6.26 ± 5.87 years (1–20)
Pharmacological treatment* (range)		503.40 ± 448.74 mg/d (66–1850 mg/d)	153.56 ± 89.79 mg/d (25–400 mg/d)
Duration of the pharmacological treatment		14.3 ± 6.9 years	6.26 ± 5.87 years (1–20)

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).

All patients were being treated with stable doses of antipsychotic medication.

Patients began experiencing AH at a mean age of 21.17 ± 6.04 years and the average duration of their illness was 15.60 ± 11.78 years. All patients were being treated with antipsychotic drugs at the time of evaluation, with an average duration of treatment of 14.3 ± 6.9 years. In addition, 24 h prior to image acquisition, **26** of these patients were also assessed with the PSYRATS scales to gain insight into the severity of their AH.

2.1.2. Patients with schizophrenia without auditory hallucinations

A group of 35 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: 40%/60%). These patients were first diagnosed at a mean age of 30.88 ± 9.29 years and the average duration of the illness was 6.26 ± 5.87. In addition, 20 of these patients were also evaluated using the PSYRATS scales prior to image acquisition.

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.

2.1.3. Healthy control subjects

Using a pool of 89 healthy control subjects, we selected 55 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).

2.2. Structural MRI acquisition

T1 images were acquired for all participants on 3-Tesla magnets (Achieva, Philips Medical Systems, Best, The Netherlands). 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).

2.3. Image processing

T1-weighted images were processed for automatic segmentation using the latest version of FreeSurfer v7.1.1 (Fischl, 2012) (FS7.1. https://surfer.nmr.mgh.harvard.edu) by default settings. Next, to quantify the volume of thalamic nuclei, we implemented an automatic parcellation of 25 nuclei using the module designed for this purpose (Iglesias et al., 2018), which has been built based on a manual delineation combining in vivo and ex vivo data. A visual inspection was then carried out to check whether this automatic segmentation and labeling was conducted properly. This led to the exclusion of the following nuclei: paratenial, limitans suprageniculate, ventromedial, parafasciculate, paracentral and central lateral nuclei. Because the latter three nuclei were part of the intralaminar anatomic group, we finally discarded the whole intralaminar complex. In addition, we combined nuclei from the ventral (VPL, VLa, VAmc, VA, VLp and VM) and lateral (LD and LP) anatomic complexes to simplify their analysis. Therefore, we finally calculated 12 volumetric measurements per hemisphere, as well as the intracranial volume (eTIV) for each subject. All the thalamic nuclei included in the analysis can be found in Table 2.

Table 2
Thalamic nuclei analyzed (*nuclei or anatomic groups analyzed).

Anatomic group	Nucleus	Abbreviation
Anterior	Anteroventral*	AV
Lateral*	Laterodorsal	LD
	Lateral posterior	LP
Ventral*	Ventral anteior	VA
	Ventral anterior magnocellular	Vamc
	Ventral lateral anterior	Vla
	Ventral lateral posterior	VLp
	Ventral posterolateral	VPL
Medial	Reuniens (medial ventral)*	MV-re
	Mediodorsal medial*	MDm
	Mediodorsal lateral*	MDl
Posterior	Lateral geniculate*	LGN
	Medial geniculate*	MGN
Pulvinar	Pulvinar anterior*	PuA
	Pulvinar medial*	PuM
	Pulvinar lateral*	PuL
	Pulvinar inferior*	PuI

2.4. Statistical analyses

All statistical analyses were performed using R version 4.0.5 and the Statistical Package for the Social Sciences (SPSS) version 26.0. We analyzed whether there were any significant differences in the variables age, sex, and eTIV between the group of patients suffering from schizophrenia and that of matched participants. The statistical analyses of the structural volumetric data consisted of two blocks. First, to determine which variables needed to be used as covariates, we performed multiple linear regression models. Here we included sex, age and eTIV to determine their contribution to the total thalamic volume (TTV). In the second block of analyses, we compared the volumes of the different nuclei among our 3 cohorts of subjects: patients with schizophrenia and AH, patients with schizophrenia without AH, and matched healthy controls. We used then a multiple analysis of covariance (MANCOVA) to study the three groups, including as covariates the variables that showed significant effects in the previous analysis step, namely eTIV. Each nucleus was evaluated separately in two independent contrasts per hemisphere, resulting in two comparisons of 12 volumes (nuclei and anatomic groups). The significance level was adjusted using the False Discovery Rate (FDR) method of Benjamini and Hochberg (Benjamini and Hochberg, 1995) to prevent increases in the false discovery rate in the general comparisons. Therefore, for the 12 nuclei tested the significance level resulted in 0.019 for the left hemisphere and 0.023 for the right hemisphere. For the nuclei that surpassed the significance threshold, we performed again the FDR correction to perform pairwise comparisons among patients with schizophrenia with and without AH, and healthy control subjects. The FDR significance thresholds for the left hemisphere were 0.033 (LGN, PuI, MDm and MDl) and 0.017 (PuA). For the right hemisphere these were 0.033 (MGN, PuA, MDm and MDl) and 0.017 (PuL and the lateral complex). The effect sizes were always calculated for all the significant pairwise comparisons (either in relation to the matched controls or to the group of patients with schizophrenia lacking AH) using Cohen's d.

To study the relationship between the volume of the affected thalamic nuclei in patients with schizophrenia and the total PSYRATS score, we performed bilateral correlations using the Spearman rank-order correlation coefficient (ρ). This could only be performed in those patients that also had the clinical assessment available (26 patients with AH, and 26 patients lacking AH). We then used again the FDR method of Benjamini and Hochberg to prevent increases in the false discovery rate, rendering correlations with p-values below 0.014 as significant.

3. Results

3.1. Demographics

No significant differences were found in age (t = 0.315, p = 0.75) or intracranial volume (t = 0.13, p = 0.88) between schizophrenia patients with AH and their matched control subjects. Likewise, no significant differences in age (t = 0.036, p = 0.97) and eTIV (t = 0.409, p = 0.68) were found between patients with schizophrenia without AH and their matched controls.

3.2. Determination of covariates for structural volumetric analysis.

Associations between TTV, sex, age or eTIV were studied using a stepwise multiple regression model. This model explained 50% of the variance of TTV ($R^2 = 0.51$; p = 0.001) with eTIV (p = $5.4 \cdot 10^{-4}$) and sex (p = $2.3 \cdot 10^{-4}$) as significant factors.

3.3. Volumetric variation in thalamic nuclei of patients with schizophrenia and auditory hallucinations

Among the 12 nuclei considered in the exploratory analysis,
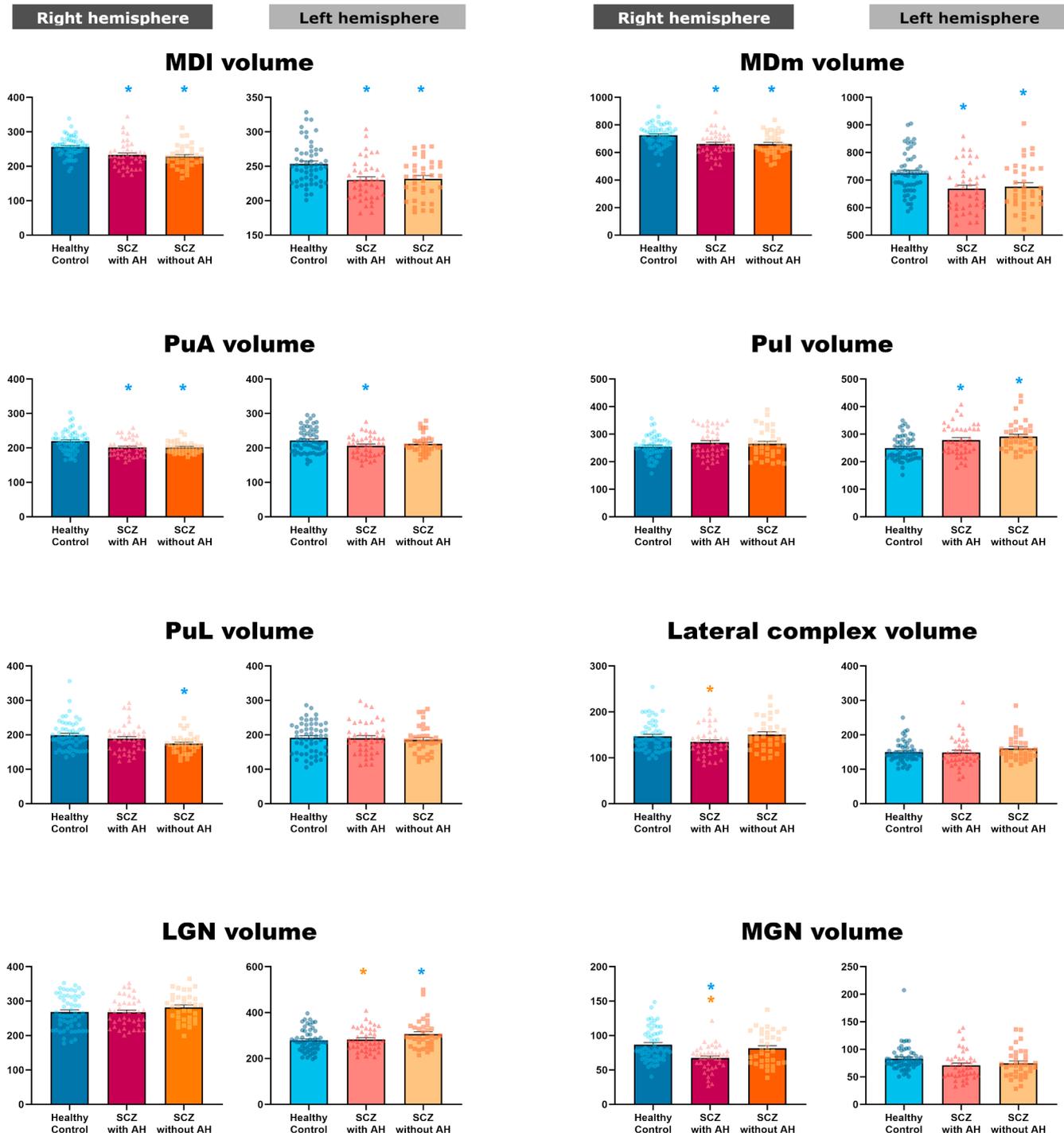
Fig. 1. Volumes of thalamic nuclei and anatomic groups that were affected in patients of schizophrenia with and without AH when compared with matched healthy subjects.

significant differences were only detected in 5 volumes belonging to the pulvinar, mediodorsal and posterior groups, in which we found volume reductions in patients with schizophrenia and AH. Inter-group volumetric differences that were significant are summarized in Figs. 1 and 2, and Table 3. We found significant bilateral volumetric reductions in two nuclei of the dorsomedial complex. Concretely, the MDm from both right and left hemispheres were reduced (RH: p = 1.62·10^{-4}; LH: p = 1.78·10^{-4}), with associated medium effect sizes (RH: d = -0.740; LH: d = -0.679). Likewise, we also found strong reductions bilaterally on the MDl (RH: p = 2.40·10^{-4}; LH: p = 1.05·10^{-5}) with also medium effect sizes on both hemispheres (RH: d = -0.683; LH: d = -0.748). There were also significant volumetric reductions in several nuclei from the pulvinar complex. The PuA nucleus was reduced bilaterally (RH: p = 2.69·10^{-4}, d = -0.668; LH: p = 0.003, d = -0.461), while the PuI was only affected in the left hemisphere (LH: p = 0.005, d = 0.551). The volume of the right lateral group was also decreased in patients with schizophrenia with AH when compared to those patients lacking AH (RH: p = 0.006, d = -0.551). In the geniculate group, patients with persistent AH showed a smaller left LGN in relation to patients lacking AH (LH: p = 0.011, d = -0.443), with no differences when compared to healthy controls.). Last of all, the volume of the MGN from the right hemisphere was also reduced when compared to healthy control subjects (RH: p = 2.34·10^{-6}) showing a large effect size (RH: d = -0.820), and to those patients with schizophrenia without AH (RH: p = 2.44·10^{-4}, d = -0.590).

3.4. Volumetric variation in thalamic nuclei of patients of schizophrenia without auditory hallucinations

To clarify which results were due to AH, we also considered in the analysis 35 patients with schizophrenia lacking AH. These results are summarized in Figs. 1 and 2, and Table 3. We found differences in the pulvinar and mediodorsal groups when compared to healthy controls. The PuA and PuL from the right hemisphere were significantly decreased (RH: PuA p = 0.003, d = -0.677; PuL p = 0.007, d = -0.296),

while the volume of the PuI was only reduced in the left hemisphere (LH: p = 9.74·10^{-6}, d = 0.551). Bilateral reductions could also be found in the MDm (RH: p = 4.92·10^{-4}; LH: p = 0.011), with associated medium effect sizes (RH: d = -0.740; LH: d = -0.679. Likewise, the volume of the MDl was also decreased (RH: p = 2.48·10^{-4}; LH: p = 0.001) and the effect sizes were moderate (RH: d = -0.683; LH: d = -0.748).

In addition, we also found increases in the volume of the LGN from the left hemisphere in this cohort of patients when comparing to healthy control subjects (LH: p = 0.005, d = 0.497), while no differences could be found in the MGN from both hemispheres.

3.5. Correlation with clinical scores

Next, we aimed to study the relationship between the volumes of the affected nuclei and clinical assessments. Therefore, we performed bilateral correlations between the volumes of affected thalamic nuclei in those patients in which the PSYRATS scores were available (26 patients with AH, and 26 patients lacking AH), and the total PSYRATS score in both cohorts of schizophrenia patients. We found that, indeed, the PSYRATS score was correlated to the volume of the MDl from the left hemisphere (LH: ρ = -0.4893, p = 0.0096; Fig. 3) and the MDm from both hemispheres (RH: ρ = -0.5006, p = 0.0078; LH: ρ = -0.5794, p = 0.0015; Fig. 3) in patients with schizophrenia and AH. Interestingly, no significant correlations could be found between the thalamic nuclei affected and the total PSYRATS score in schizophrenia patients without AH.

4. Discussion

In this study we have found volumetric reductions in different thalamic nuclei in patients of schizophrenia with and without persistent AH. Furthermore, we have described correlations between these changes and scores of PSYRATS, a clinical scale frequently used to evaluate the severity and frequency of hallucinations and delusions,
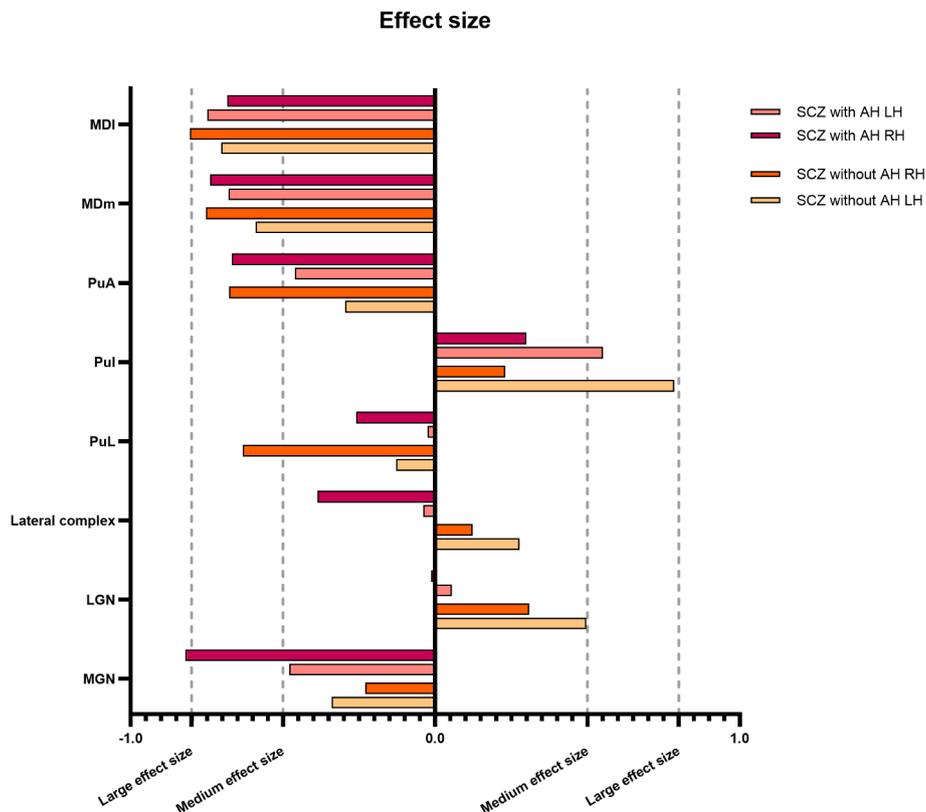
Effect size

Fig. 2. Effect size in relation to matched healthy controls (Cohen's d).

Table 3

Significant results from the comparison between matched healthy controls vs patients with schizophrenia with and without AH. We proceeded with pairwise comparisons when the significance in the nuclei was below 0.019 for the left hemi-sphere and 0.023 for the right hemisphere.

Anatomic group			HC	SCZ with AH	SCZ without AH	F (from general contrast)	df	p-values from pairwise comparisons		
								HC vs SCZ with AH	HC vs SCZ without AH	SCZ with AH vs SCZ without AH
Medial	MDm	R	725.699 ± 76.899	661.819 ± 86.218	660.672 ± 80.59	9.990	2, 128	$1.62 \cdot 10^{-4}$	$4.92 \cdot 10^*$	NS
		L	725.682 ± 75.385	668.363 ± 82.849	675.903 ± 85.766	8.105	2, 128	$1.78 \cdot 10^{-4}$	0.011	NS
	MDl	R	256.591 ± 28.896	232.712 ± 37.574	228.417 ± 32.382	10.178	2, 128	$2.40 \cdot 10^{-4}$	$2.48 \cdot 10^{-4}$	NS
		L	253.642 ± 29.983	230.253 ± 29.234	231.669 ± 28.624	11.734	2, 128	$1.05 \cdot 10^{-5}$	0.001	NS
Pulvinar	PuA	R	219.669 ± 30.297	201.623 ± 25.339	201.382 ± 16.336	8.463	2, 128	$2.69 \cdot 10^{-4}$	0.003	NS
		L	221.555 ± 36.157	206.464 ± 30.125	211.861 ± 28.014	4.616	2, 128	0.003	NS	NS
	PuI	R	254.856 ± 39.152	268.925 ± 50.73	265.662 ± 52.648	1.339	2, 128	NS	NS	NS
		L	249.715 ± 43.877	278.933 ± 55.606	291.347 ± 53.116	11.195	2, 128	0.005	$9.74 \cdot 10^{-6}$	NS
	PuL	R	199.274 ± 41.95	189.04 ± 40.995	174.383 ± 27.624	3.955	2, 128	NS	0.007	NS
		L	191.594 ± 44.64	190.473 ± 47.141	185.973 ± 39.844	0.143	2, 128	NS	NS	NS
Posterior	LGN	R	268.099 ± 49.442	267.541 ± 41.409	281.976 ± 40.566	2.429	2, 128	NS	NS	NS
		L	279.637 ± 49.02	282.604 ± 49.728	306.665 ± 63.744	4.723	2, 128	NS	0.005	0.011
	MGN	R	86.639 ± 24.015	67.195 ± 18.106	81.191 ± 24.083	13.268	2, 128	$2.34 \cdot 10^{-6}$	NS	$2.44 \cdot 10^{-4}$
		L	83.003 ± 23.481	70.986 ± 25.267	74.447 ± 25.98	3.242	2, 128	NS	NS	NS
Lateral		R	146.985 ± 32.201	134.516 ± 30.095	150.962 ± 32.883	4.202	2, 128	NS	NS	0.006
		L	150.286 ± 29.285	148.905 ± 41.551	160.031 ± 35.465	1.891	2, 128	NS	NS	NS
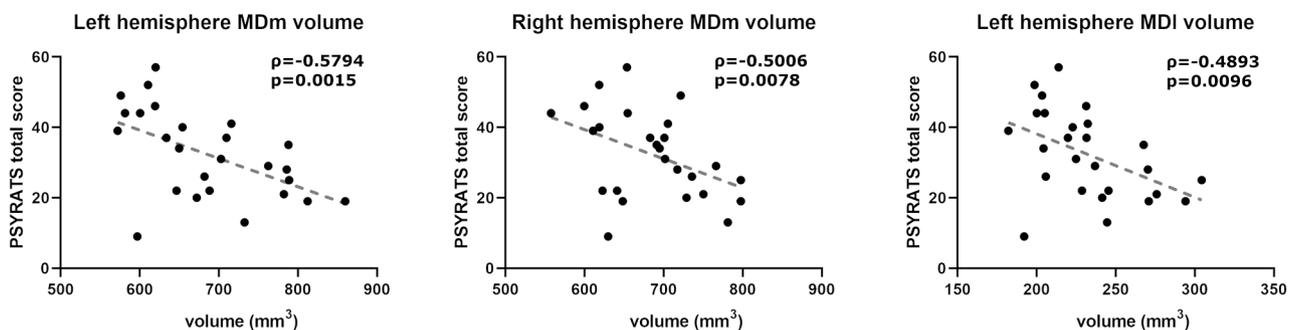
Fig. 3. Significant correlations between the total PSYRATS score and the volumes of those thalamic nuclei that were affected in patients with schizophrenia. Significance below 0.014.

especially for the group of patients with schizophrenia and AH.

Several studies, including postmortem and different neuroimaging analyses, have examined the volume of the whole thalamus in schizophrenia (see Byne et al., 2009 for review). Most of these studies have found reductions in patients with schizophrenia, which is consistent with our present results in the specific nuclei. Also, in line with our results, restricted to chronic schizophrenia patients with AH, one of these studies found a correlation between the reduction of gray matter volume in the left thalamus and AH (Neckelmann et al., 2006).

Among the relationships of the reductions in the volumes of thalamic nuclei with the AH, the most straightforward to explain might be that observed in the MGN, since this nucleus relays auditory information to the auditory cortex (Dorph-Petersen and Lewis, 2017). In concordance with our results, a recent report has found reductions in the volume of

the MGN in 22q11.2 deletion syndrome patients, a genetic disorder, which confers high risk for schizophrenia and frequently courses with AH (Mancini et al., 2020). In addition, patients with AH show a thinner thickness of the Heschl's gyrus (Mørch-Johnsen et al., 2017), which contains the primary auditory cortex. These type of patients also have altered tonotopy maps in primary auditory regions, including the Heschl's gyrus (Doucet et al., 2019), which depend on the ordered output arising from the MGN. Furthermore, patients with schizophrenia have consistently showed decreased prepulse inhibition of the startle reflex (Braff et al., 1992; Grillon et al., 1992; Kumari et al., 2000), a test of sensorimotor gating that includes information arising from the cochlear nucleus (Fendt et al., 2001; Swerdlow et al., 2001). These changes have also been broadly reported in animal models of the disease (Brody et al., 2004; Geyer et al., 2001; Powell et al., 2009). Moreover,

also in line with our volumetric findings in the MGN, a genetic mouse model of 22q11.2 deletion syndrome displays a decreased auditory input from this thalamic nucleus to the auditory cortex (Chun et al., 2014). On the other hand, we have found increases in the volume of the LGN only in schizophrenia patients without AH compared with controls. These interesting results seem to agree with a previous report showing slight increases in this nucleus in patients of this disorder, regardless of the presence of AH (Dorph-Petersen et al., 2009). However, no further information exists on how AH might influence the effect of the disease on this nucleus. Further research should address why these increases seem to be limited to patients lacking AH.

We have also reported reductions on the volumes of Pu, MDl and MDm nuclei in schizophrenia patients with and without AH. These nuclei establish sparse connections with the auditory cortex, as shown by tracer studies performed in primates (de la Mothe et al., 2012; Scott et al., 2017), and they receive inputs from Broca's area, indicating an involvement in language processing (Goldman-Rakic and Porrino, 1985). Furthermore, their lesion leads to subcortical aphasia (Crosson, 2013). This connectivity of the Pu and MD nuclei also links directly our results to the alterations in the auditory cortex found in patients with schizophrenia (Doucet et al., 2019; Mørch-Johnsen et al., 2017). Similarly, the Pu, MDl and MDm nuclei send their main synaptic output to the PFC. This region has extensively been shown to be smaller (Fornito et al., 2009; Kawada et al., 2009; Rimol et al., 2010) and less activated while performing a task (Barch et al., 2001) in schizophrenia patients, independently of the presence of AH. In addition, previous reports have also described that patients suffering from psychotic disorders display smaller volumes of Pu and MD nuclei (Byne et al., 2009; Huang et al., 2020), and the connectivity between the MD and the PFC is reduced in these patients (Giraldo-Chica et al., 2018). Altogether these results are in accordance with the reduced volume we report in Pu and MD. However, there are also significant differences between the studies. In the MD and Pu complexes (the only regions that could be compared between the studies), our effect sizes were much bigger than those from Huang et al. (2020). In addition, they also included bipolar patients in the study, only tested for cognitive impairment and the positive score in PANSS was relatively low (16.8/49). To our knowledge the influence of AH has not been evaluated in these reports.

The reduction in volume observed in our study can be due to different factors affecting the neurons and glial cells or their microenvironment. These changes may be the result of the progression of the disease during many years or may be already present, at similar or lower levels in FEP. These factors include reductions in the density of neurons, which have already been described in the Pu and MD (Byne et al., 2007; Highley et al., 2003), or in their dendritic arborization. Changes in the density of different synaptic inputs to these thalamic nuclei may also contribute to the volumetric reductions. Although there are no specific studies in postmortem brains, some neuroimaging studies analyzing connectivity have found alterations in these nuclei (Giraldo-Chica et al., 2018). Alterations in the density or structure of astrocytes, microglial cells, oligodendrocytes or polydendrocytes may have also contributed to the volume reductions. Future studies should analyze in detail these glial cells in postmortem brains.

We have found significant negative correlations between PSYRATS total scores and the volumes of the MD nuclei of patients of schizophrenia with AH. Interestingly, the PSYRATS score has also been negatively correlated with the density of gray matter of different brain regions in chronic schizophrenia patients with AH (García-Martí et al., 2012, 2008). In a similar way, the severity of AH has been significantly correlated with reductions in the volume of the PFC and the superior temporal gyrus, where most of the cortical auditory regions are located (Barta et al., 1990; Gaser et al., 2004; Levitan et al., 1999; Oertel-Knochel et al., 2013). We have found that PSYRATS have good predictive capability in regard to the volumes of the mediodorsal nuclei in patients with schizophrenia and AH. Interestingly, we have not been able to detect similar correlations when studying patients without AH.

This can be due to the smaller participant number of this cohort, or simply because patients without AH lack values in most of PYRATS items. In fact, it has to be noted that PSYRATS measure delusions as well as hallucinations (Haddock et al., 1999), symptoms that have more predictive validity in patients that also experience AH.

We should consider some limitations that might overcast our results. First and most important, the patients we have considered had been treated with antipsychotic drugs for an average of 14 years, to control their hallucinations and, consequently, this might have also influenced the volumetric changes we report. Despite this being a valid concern, given the widespread distribution of the receptors affected by these drugs, one would expect a general effect on most thalamic nuclei, and not only a limited effect in a few ones. Although there is no clear evidence of structural effects of antipsychotics, even in longitudinal MRI studies, some studies in patients and animal models suggest that chronic exposure to antipsychotics can induce volume loss (Byne et al., 2009; Goff et al., 2017; Roiz-Santiañez et al., 2015). Secondly, it is not clear from our design if the effect size we report in patients with schizophrenia and AH is secondary to chronic psychosis or specific to AH. We must consider that these patients have lived for years with the disease and, consequently, have had vital trajectories and/or non-pharmacological treatments that might have influenced their neural plasticity and might have contributed to the volumetric changes that we observe. Our analyses indicate that the duration of illness does not influence thalamic volume, but the severity of the disease may have also fluctuated over the years and influenced thalamic structure. Unfortunately, we do not have data on the illness progression in our patients. Although there are no studies on the volume of the different thalamic nuclei on FEP patients, reports analyzing the thalamus as a whole have found that its volume is already reduced (Huang et al., 2015). Moreover, a recent longitudinal study has found that the volume of the thalamus decreases during the 3 years after the FEP (Akudjedu et al., 2020). Although in one study the reduction of thalamic volume in FEP was correlated with delusions (Huang et al., 2017), it is not known yet whether these structural changes also correlate with hallucinations. Therefore, future studies comparing psychotic patients with and without AH, as well as in FEP patients, are granted to analyze volumetric alterations in specific thalamic nuclei.

Schizophrenia is an impairing disorder that leads to dysfunctional attention processing, working memory and executive functions (Gold et al., 2018; Kamal et al., 2016; Mihaljević-Peleš et al., 2019; Orellana and Slachevsky, 2013). However, problems in the early processing of sensory information often escape the scope of clinical evaluation (Butler et al., 2001; Rissling et al., 2012; Saccuzzo and Braff, 1981; Thomas et al., 2017). Among them, those arising from the malfunctional coding and transmission of auditory stimuli are increasingly important as they appear to contribute directly to the overall psychosocial disability and cognitive dysfunctions reported in these patients (Cantonas et al., 2019; Javitt and Sweet, 2015). Furthermore, interventions tackling early processing of auditory information have been proposed to improve cognition in these patients (Medalia et al., 2019; Moschopoulos et al., 2021).

Altogether our results show reductions in the volume of thalamic nuclei related to information integration in patients of schizophrenia with and without AH. In addition, for those patients experiencing AH the data also shows alterations mainly in thalamic nuclei related to auditory experience. In this line, future research should address whether the connectivity between thalamic nuclei and auditory regions is affected in these patients, especially that with the primary auditory cortex, and with cortical regions related to language processing. In addition, our results also highlight the relationship between these volumetric alterations and the clinical outcome, suggesting a relationship between structural changes in thalamic regions relevant for information processing and the presence of persistent AH.

CRediT authorship contribution statement

Marta Perez-Rando: Formal analysis, Investigation, Writing – original draft, Writing – review & editing. **Uriel K.A. Elvira:** Formal analysis, Investigation, Writing – original draft. **Gracian García-Martí:** Formal analysis. **Marien Gadea:** Formal analysis. **Eduardo J Aguilar:** Writing – review & editing. **Maria J Escarti:** Writing – review & editing. **Mónica Alba Ahulló-Fuster:** Writing – review & editing. **Eva Grasa:** Investigation. **Iluminada Corripio:** Investigation, Writing – review & editing. **Julio Sanjuan:** Writing – review & editing, Funding acquisition. **Juan Nacher:** Supervision, Writing – original draft, Writing – review & editing, Project administration, 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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