Hearing voices in the head: Two *meta*-analyses on structural correlates of auditory hallucinations in schizophrenia

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ABSTRACT

Past voxel-based morphometry (VBM) studies demonstrate reduced grey matter volume (GMV) in schizophrenia (SZ) patients' brains in various cortical and subcortical regions. Probably due to SZ symptoms' heterogeneity, these results are often inconsistent and difficult to integrate. We hypothesized that focusing on auditory verbal hallucinations (AVH) – one of the most common SZ symptoms – would allow reducing heterogeneity and discovering further compelling evidence of SZ neural correlates. We carried out two voxel-based *meta*-analyses of past studies that investigated the structural correlates of AVH in SZ. The review of whole-brain VBM studies published until June 2022 in PubMed and PsychInfo databases yielded (a) 13 studies on correlations between GMV and AVH severity in SZ patients (n = 472; 86 foci), and (b) 11 studies involving comparisons between hallucinating SZ patients (n = 504) and healthy controls (n = 524; 74 foci). Data were analyzed using the Activation Likelihood Estimation method. AVH severity was associated with decreased GMV in patients' left superior temporal gyrus (STG) and left posterior insula. Compared with healthy controls, hallucinating SZ patients showed reduced GMV on the left anterior insula and left inferior frontal gyrus (IFG). Our findings revealed important structural dysfunctions in a left lateralized cluster of brain regions, including the insula and temporo-frontal regions, that significantly contribute to the severity and persistence of AVH. Structural atrophy found in circuits involved in generating and perceiving speech, as well as in auditory signal processing, might reasonably be considered a biological marker of AVH in SZ.

1. Introduction

Schizophrenia (SZ) is perhaps the most challenging condition among all psychiatric diseases because it affects young adults (Abel, Drake, & Goldstein, 2010; Eranti, MacCabe, Bundy, & Murray, 2013), has various symptoms that result in a highly heterogeneous amount of clinical syndromes (American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 2013), and it is not associated with clear brain deficits or clear etiopathogenetic mechanisms underlying it (Andreasen, 1997; Goldstein et al., 1999; Lawrie & Abukmeil, 1998; McCarley et al., 1999; Seidman et al., 2003; Shenton, Dickey, Frumin, & Mccarley, 2010; Wright et al., 2000). In addition, SZ affects about 20 million individuals worldwide (Charlson et al., 2018; Jablensky et al., 1992; James et al., 2018), with a lifetime prevalence of about 0.3–0.7 % (American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 2013), notwithstanding that SZ patients usually reveal decreased fertility and have a reduced tendency to marry and

have children (i.e., the SZ paradox [Huxley, Mayr, & Osmond, 1964]).

Previous studies on SZ patients provided multiple findings that showed structural abnormalities in various brain areas, distributed in both the left and the right hemispheres. In particular, alterations were found at the cortical level, including the superior temporal gyrus, dorsolateral prefrontal and orbitofrontal cortex, but also the insula, thalamus, cingulate gyrus, hippocampus, cerebellum and ventricles were involved (Goldstein et al., 1999; Lawrie & Abukmeil, 1998; McCarley et al., 1999; Seidman et al., 2003; Shenton et al., 2010; Wright et al., 2000). A possible explanation for the lack of specificity and measurable biological markers for SZ depends on this disease's heterogeneous characteristic, considering that the various symptoms that characterize numerous syndromes are often associated with the same diagnostic classification. In this perspective, the focus on specific subgroups of patients who share common clinical symptoms and signs – rather than the same diagnostic classification, for example, paranoid SZ – could be a promising approach to study SZ endophenotypes. Among all

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the symptoms, auditory verbal hallucinations (AVH) – subjective experiences of "hearing voices" in the absence of corresponding external auditory stimulation (American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 2013) – are primary symptoms.

Focusing on AVH, previous studies showed that the severity of symptoms associated with grey matter volume (GMV) reductions in the left superior temporal gyrus (STG/Heschl's gyri) (Gaser, Nenadic, Volz, Büchel, & Sauer, 2004; Modinos et al., 2013), but also in the right STG (Palaniyappan, Balain, Radua, & Liddle, 2012), the middle/inferior right prefrontal gyri (Gaser et al., 2004), the bilateral insula (Chan, Di, McAlonan, & Gong, 2011; Palaniyappan et al., 2012; Shapleske et al., 2002) and the thalamus (Huang et al., 2015; Neckelmann et al., 2006). Notwithstanding the various brain regions altered, SZ patients commonly show decreased GMV compared to healthy controls (García-Martí et al., 2008; Gur, Turetsky, Bilker, & Gur, 1999), and this reduction appears to be significantly correlated with the severity of AVH, as the greater the GMV loss, the greater the symptom severity (e.g., Modinos et al., 2013; Palaniyappan et al., 2012). In addition, these findings showed significant GMV atrophy within the neural regions devoted to linguistic processing, suggesting that this network represents a core hub that characterizes SZ patients with AVH. At the same time, evidence exists of significant aberrations in other sensory as well as nonsensory regions (including, for example, anterior and posterior cingulate cortices), but also in limbic neural circuits (e.g., parahippocampal gyrus and amygdala) and cerebellum (Allen et al., 2012). Past reviews suggest that the complex and heterogenous symptomology in SZ makes investigating a specific clinical manifestation (i.e., hallucinations) particularly challenging. However, despite some divergence among studies, the most replicated finding has been abnormalities in the auditory cortex and language-related brain regions, which is consistent with evidence from functional neuroimaging studies in AVH (Allen et al., 2012; Gaser et al., 2004; Jardri, Pouchet, Pins, & Thomas, 2011; Modinos et al., 2013; Palaniyappan et al., 2012).

In the present research, we conducted two *meta*-analyses considering all structural MRI studies published before the end of June 2022, examining from different perspectives the brain structure alterations in auditory verbal hallucinating schizophrenia (henceforth AVH-SZ) patients. The first *meta*-analysis included results only from correlational analyses showing brain atrophy (or hypertrophy) that significantly associated with AVH severity in SZ patients, whereas the second *meta*-analysis considered aberrant GMV regions in AVH-SZ patients compared with healthy controls. To the best of our knowledge, this is among the very few research that systematically focusses on structural GMV atrophy associated with AVH in SZ patients based on both the correlational approach with symptom severity and the group differences with respect to healthy adults. Thus, the present *meta*-analysis study contributes to the existing literature by providing a fine-grained picture – updated to June 2022 – of structural abnormalities associated with hallucinatory phenomena, including a larger number of SZ and AVH-SZ patients (472 and 504, respectively) compared to the last *meta*-analysis on the same topic, using an Activation Likelihood Estimation (ALE) approach.

2. Methods

2.1. Studies selection

We conducted a systematic search on both PubMed and PsychInfo databases to identify all available studies on the whole-brain structural substrates of hallucinations in SZ. The following keywords were used for the literature search: 1) (schizophrenia) AND (hallucination) AND (grey matter), 2) (schizophrenia) AND (hallucination) AND (gray matter), and 3) (schizophrenia) AND (hallucination) AND (voxel-based morphometry). At the time of access (30 June 2022), this procedure returned 388 studies, 270 of which were duplicates. Therefore, we screened 118 studies for inclusion. In addition, we carefully inspected the reference lists of the most recent *meta*-analyses (Modinos et al., 2013;

Palaniyappan et al., 2012). We applied the following inclusion criteria for selecting the final pool of works:

1) studies published in peer-reviewed journals in English;
2) studies reporting brain activation foci from whole-brain analysis (we excluded studies that employed small volume correction [SVM] or region of interest [ROI] analyses);
3) studies reporting coordinate information on standard stereotactic space (MNI or Talairach);
4) studies including SZ patients;
5) studies that performed VBM analysis for investigating: i) the correlation between grey matter volume and severity of AVH symptoms (first *meta*-analysis), or ii) potential differences in grey matter volumes between patients with AVH and healthy controls (second *meta*-analysis).

Notably, we excluded studies considering visual or multisensory hallucination phenomena, as well as when these symptoms appeared together with AVH, considering the present *meta*-analyses focused on AVH-SZ patients only.

2.2. Data extraction

The studies selection is summarized in the PRISMA flow (see Fig. 1), following the PRISMA 2020 statement (Page et al., 2021). The resulting final number of studies eligible for inclusion in our first *meta*-analysis was 13, comprising 472 SZ patients and 86 foci associated to hallucination severity. Although it is unclear which brain areas could be responsible for hallucinatory experiences, ample evidence shows that this symptom is commonly associated with regional GMV atrophy (see, e.g., Hugdahl, Løberg, & Nygård, 2009; Hugdahl et al., 2008; Modinos et al., 2013; Palaniyappan et al., 2012). From our search, 12 studies reported negative correlations and only one reported a positive correlation emerged; we carried out the main analysis including all these studies, regardless of the direction (atrophy or hypertrophy) of GMV alterations in SZ patients. In addition, considering one study (Shapleske et al., 2002) found a significant correlation with hallucinations in a cluster that showed – in a preliminary whole brain VBM analysis – GMV atrophy in AVH-SZ versus nAVH-SZ patients, we decided to conduct a sensitivity analysis excluding this last article to test its contribution to the overall effect (see Fig. S1 and Table S1 in Supplementary material).[1]

Table 1 provides the list of the 13 studies included in this *meta*-analysis.

We then checked all the works that investigated whole-brain grey matter differences between SZ patients with AVH and healthy controls: 11 studies used VBM analysis for the groups' comparison and were all included in a secondary *meta*-analysis. In particular, we extracted data for 504 patients with SZ and hallucinations, 524 healthy controls and 74 foci (see Table 2). Notably, all these studies reported decreased grey matter in patients compared to controls, and only three studies (O'Daly, Frangou, Chitnis, & Shergill, 2007; Shapleske et al., 2002; Xie et al., 2021) further showed greater grey matter volume in patients compared to controls. We carried out the main analysis including all these studies, regardless of the direction (decreased or increased) GMV in AVH-SZ patients with respect to healthy controls.

2.3. Meta-analyses

Statistical analyses were carried out via GingerALE software version 3.0.2 (Eickhoff, Bzdok, Laird, Kurth, & Fox, 2012; Eickhoff et al., 2009). We performed a first Activation Likelihood Estimation (ALE) analysis to

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[1] Because the sensitivity analysis revealed no contribution of this study, and because past *meta*-analyses (Modinos et al., 2013; Palaniyappan et al., 2012) have included it, we decided to keep it too.
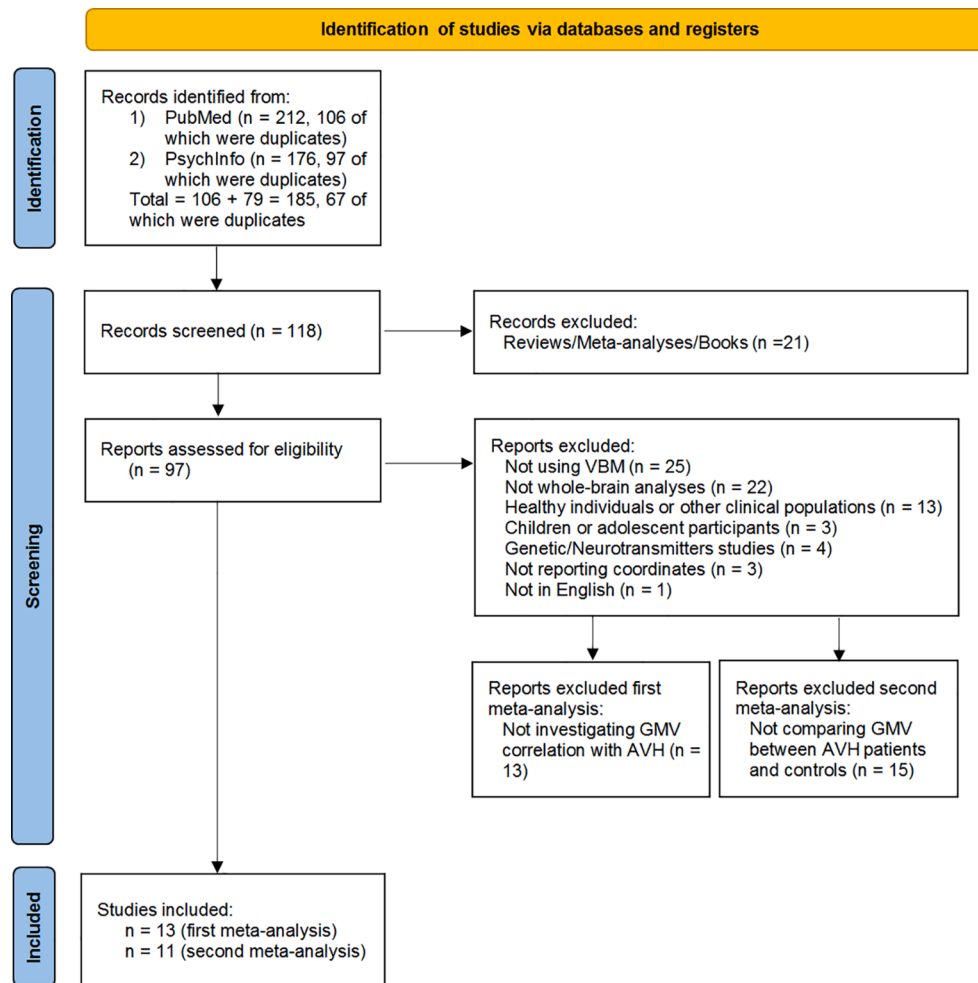
Fig. 1. Flow diagram of study inclusion following the PRISMA 2020 statement (adapted from Page et al., 2021). *VBM = voxel-based morphometry; GM = grey matter; AVH = auditory verbal hallucinations.*

emphasize the brain regions in which a decrease of GMV was associated with AVH-SZ patients. As a second step, we carried out a second analysis to compare the GMV in SZ patients with a history of AVH and healthy adults.

Before performing the two *meta*-analyses, Talairach coordinates were reported in MNI space using the convert foci option provided in the GingerALE interface. The ALE method determines the convergence of reported anatomical coordinates across studies using 3D foci Gaussian distributions with a full-width half-maximum (FWHM) empirically derived from the subject size (Eickhoff et al., 2012). The ALE map was assessed against a null distribution of random spatial association across experiments using a non-linear histogram integration algorithm (Eickhoff et al., 2009). We performed two separate ALE statistics (one for each data set) using a conservative mask size and applying a cluster-level FWE correction at $P < 0.05$ with a cluster-forming threshold of $P < 0.01$, with 5,000 permutations for multiple comparison correction (Duda & Sweet, 2020; Ioakeimidis, Haenschel, Yarrow, Kyriakopoulos, & Dima, 2020). In the second *meta*-analysis, considering each coordinate referred to the contrast between two groups (AVH-SZ patients vs healthy controls), the analysis relied on the *n* of the smaller of the two samples to yield a more conservative activation likelihood estimation (Kompus, Westerhausen, & Hugdahl, 2011; Ramsay, 2019).

3. Results

3.1. Patients' characteristics

All patients included in the selected studies (both the first and the second *meta*-analysis) were diagnosed as suffering from SZ. The mean age was about 32 years and the illness duration ranged between 6 and 224 months. The presence of AVH was assessed using standardized rating scales, such as the Positive and Negative Syndrome Scale (Kay, Fiszbein, & Opler, 1987), the Brief Psychiatric Rating Scale (Overall & Gorham, 1962), the Auditory Hallucinations Rating Scale (Hoffman et al., 2003), the Psychotic Symptom Rating Scales (Haddock, McCarron, Tarrier, & Faragher, 1999) and the Scale for the Assessment of Positive Symptoms (Andreasen & Olsen, 1982). During the course of illness, most patients were treated with antipsychotic medication. The healthy controls recruited in the comparison studies were similar to SZ patients regarding age and education level.

3.2. Grey matter volume changes in AVH

The *meta*-analysis of all studies investigating the link between decreased GMV and severity of AVH included 86 foci, totaling 472 schizophrenia patients. The minimum cluster size for considering a region statistically significant was 1,360 mm³. The results showed a region of convergence of 1,640 mm³ centered in the left insula/transverse temporal gyrus (MNI coordinates: X = −52.9, Y = −13.8, Z = 9.4,

Table 1
List of the 13 studies included in the first *meta*-analysis, focused on grey matter volume (GMV) loss associated with AVH severity (SZ patients only).

Study	Patients (n)	Gen-der	Medication	Hallucinationscale	Scan	Coordinate system	X	Y	Z
Shapleske, 2002	41	M	YES n.a.	SAPS	MRI 1.5 T	Talairach	−37	7	−4
Gaser, 2004	29	M/F	on stable neuroleptic medication	SAPS	MRI 1.5 T	Talairach	44	40	14
							−42	−16	10
							−44	−50	32
Neckelmann, 2006	12	n.a.	antipsychotic medication	BPRS	MRI 1.5 T	MNI	−15	−21	12
							−50	−16	14
O'Daly, 2007	28	25 M 3 F	antipsychotic medication (21 atypical; 5 typical; 2 unmedicated against medical advices)	BPRS	MRI 1.5 T	Talairach	47.4	−7.2	0.4
							47.5	−15	−22.4
							−31.8	−5.9	34.8
Garcia-Martì, 2008	18	M	typical and atypical antipsychotics	BPRS	MRI 1.5 T	MNI	−17	−14	−25
							70	−29	8
Modinos, 2009	26	13 M 13 F	CPZ equivalents	AHRS	MRI 3 T	MNI	−32	28	−24
Nenadic, 2010	99	57 M 42 F	antipsychotic medication	SAPS	MRI 1.5 T	MNI	−58	−11	9
							−57	3	−10
							64	−19	14
							55	−14	0
							51	−51	18
							−12	−38	75
							−14	−53	12
Garcia-Martì, 2012	22	M	wide range of first- and second-generation antipsychotics	PSYRATS	MRI 1.5 T	MNI	61	−50	5
							−56	−15	7
							−59	−52	15
Huang, 2015	18	10 M 8 F	drug-naïve first-episode	PANSS and HAHRS	MRI 3 T	MNI	4.5	−10.5	1.5
							−1.5	−19.5	1.5
Song, 2015	71	29 M 42 F	typical antipsychotics (7); atypical antipsychotics (71); lithium (2); anticonvulsant (6)	PANSS	MRI 3 T	Talairach	−14	3	70
							−47	48	−11
							−38	−36	46
							−56	−54	13
							−60	−19	−11
							17	53	34
							26	59	7
							57	−48	19
							65	−25	−20
Qiu, 2018	33	19 M 14 F	antipsychotic medication (converted into chlorpromazine equivalent dose)	PANSS	MRI 3 T	MNI	−24	−7	72
							−14	45	50
							−24	−10	72
							−4	−12	52
							−37	61	5
							−34	50	32
							−4	−54	10
							8	−52	8
							−3	44	13
							12	38	10
							−3	28	37
							6	27	34
							−10	−58	11
							4	−57	11
							−24	−19	−13
							24	−18	−16
							−18	−32	−12
							−5	−20	17
							7	−18	20

Table 1 (*continued*)

Study	Patients (n)	Gender	Medication	Hallucination scale	Scan	Coordinate system	X	Y	Z
							67	−40	22
							47	−4	6
							40	−13	13
							38	59	8
							41	39	30
							18	67	−11
							47	45	−13
Siddi, 2019	24	14 M 10 F	5 % Typical antipsychotics; 39 % Atypical antipsychotics	SAPS	MRI 1.5 T	MNI	9	70	13
Van Tol, 2013	51	44 M 7 F	41 antipsychotic medication (classical antipsychotic agents [n = 3]: haloperidol, perphenazine; atypical antipsychotic agents [n = 38]: risperidone, clozapine, olanzapine, quetiapine, and/or aripiprazol)	PANSS	MRI 3 T	MNI	30	5	−11
							30	5	4
							30	15	−2
							6	−60	1
							11	−55	−5
							−6	−12	−2
							9	−16	0
							3	−15	15
							29	−24	67
							41	−18	67
							−48	−10	−30
							−51	−3	−32
							−11	−85	37
							5	−79	33
							0	93	0
							−2	−88	−8
							−2	−93	10
							−33	−10	−9
							−29	2	−11
							−21	−1	−9
							−57	24	22
							8	−15	66
							8	−4	72
							38	−52	57
							−41	35	−2
							−42	32	−11

M = males; F = females; CPZ = chlorpromazine; SAPS = scale for the assessment of positive symptoms; BPRS = brief psychiatric rating scale; AHRS = auditory hallucinations rating scale; PSYRATS = psychotic symptoms rating scales; PsyRatS-AHS = psychotic symptoms rating scales – auditory hallucinations subscale; PANSS = positive and negative syndrome scale; HAHRS = Hoffman auditory hallucination rating scale.

Table 2

List of the 11 studies included in the second *meta*-analysis, focused on grey matter volume (GMV) loss (HC > AVH-SZ) and excess (HC < AVH-SZ) in hallucinating SZ patients with respect to healthy controls.

Study	Patients (n)	Gender	Medication	Controls (n)	Scan	Coordinate system	X	Y	Z
HC > AVH-SZ									
Shapleske, 2002	41	M	YES n.a.	32	MRI 1.5 T	Talairach	22	−1	−23
							6	0	−2
							−42	−7	9
							40	−8	6
							−4	−68	16
							5	−67	18
Neckelmann, 2006	12	n.a.	antipsychotic medication	12	MRI 1.5 T	MNI	−14	30	51
							10	−93	26
							−46	−20	18
O'Daly, 2007	28	25 M 3 F	antipsychotic medication (21 atypical; 5 typical; 2 unmedicated against medical advices)	32	MRI 1.5 T	Talairach	47.4	−7.2	0.4
							47.5	−15	−22.4
							31.8	−11.6	18.5
							30.9	12.9	1.6
							−33	8.4	5.9
							−31.8	−5.9	34.8
							−34.1	−71.2	0.1
Martí-Bonmatí, 2007	21	M	antipsychotic medication (16 s-generation, and 5 first and second-generation antipsychotic drugs)	10	MRI 1.5 T	Talairach	−42	16	−9
							13	−45	−2
							−60	−11	24
							12	−50	5
							47	15	−6
							10	59	−1
							−11	−52	1
							−62	−62	−3
Garcia-Martì, 2008	18	M	typical and atypical antipsychotics	19	MRI 1.5 T	MNI	−43	12	−10
							45	16	−9
							57	−35	8
							−23	4	−22
							−37	8	−18
Garcia-Martì, 2012	22	M	wide range of first- and second-generation antipsychotics	28	MRI 1.5 T	MNI	−42	10	−11
							59	−33	50
							−54	−19	4
							−5	42	14
							66	−16	3
							52	−48	36
							−61	−53	16
							19	−3	−13
							60	−42	4
							−20	1	−15
VanTol, 2013	31	(*)		51	MRI 3 T	MNI	21	6	−29
							−42	35	0
							−41	11	7
							−41	24	0
Huang, 2015	18	10 M 8 F	drug-naïve first-episode	18	MRI 3 T	MNI	−46.5	6	−4.5
							4.5	−10.5	1.5
							−1.5	−19.5	1.5
							−49.5	9	19.5
							42	−52.5	49.5
							46.5	−16.5	−30
							48	−9	32
							10.5	18	12
							3	48	−3
Song, 2015	71	29 M 42 F	typical antipsychotics (7); atypical antipsychotics (71); lithium (2); anticonvulsant (6)	35	MRI 3 T	Talairach	−29	−13	63
							−27	−28	52
							−33	11	−8
							−3	6	7
							53	0	51
							30	−1	1
							2	3	9
Escarti, 2009	93	58 M 35 F	antipsychotic medication	177	MRI 3 T	MNI	39	14	1
							41	20	24
							52	−4	4
							−9	38	−14
							11	50	6
							−37	−16	12
							−43	17	24
Xie, 2021	30	17 M 13 F	stable antipsychotic medication	33	MRI 3 T	MNI	−24	36	2
							−3	−38	15
							−17	−8	8

Table 2 (*continued*)

Study	Patients (n)	Gender	Medication	Controls (n)	Scan	Coordinate system	X	Y	Z
HC > AVH-SZ									
HC < AVH-SZ									
Shapleske, 2002	41	M	YES n.a.	32	MRI 1.5 T	Talairach	59	26	27
O'Daly, 2007	28	25 M 3 F	antipsychotic medication (21 atypical; 5 typical; 2 unmedicated against medical advices)	32	MRI 1.5 T	Talairach	47.5 14.1	−10 6.6	−17 6.8
Xie, 2021	30	17 M 13 F	stable antipsychotic medication	33	MRI 3 T	MNI	−48 35	−3 −14	−35 −41

(*) Gender and medications are referred for the whole SZ group, that included both hallucinating and non-hallucinating patients.
M = males; F = females.
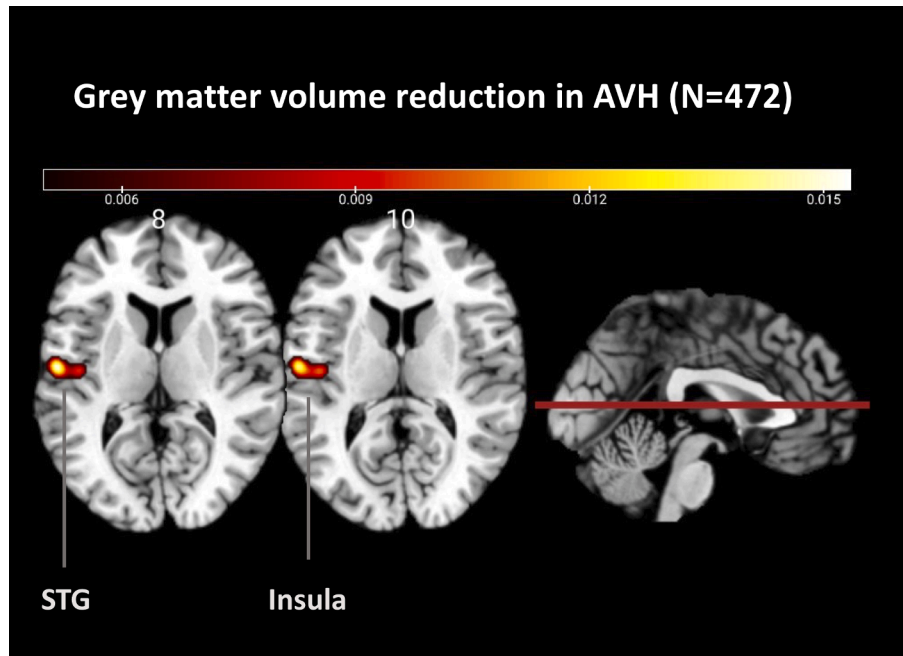
Fig. 2. Results obtained from the first *meta*-analysis, focused on grey matter volume (GMV) loss associated with AVH severity (SZ patients only).

Table 3

Summary of significant findings of structural atrophy in hallucinating SZ patients from our *meta*-analyses. Top: GMV loss correlated with AVH severity (SZ patients only). Bottom: GMV loss found in hallucinating SZ patients with respect to healthy controls.

First *meta*-analysis: GMV loss associated with AVH severity (SZ patients only)									
Cluster	Anatomical label	BA	MNI coordinates			Size (mm³)	ALE value	*p* value	Z score
			x	y	z				
1	Superior Temporal Gyrus (STG)	22	−58	−12	8	1,640	0.015341	0.0000098	4.267686
	Insula	13	−46	−14	10		0.010335	0.0002350	3.497229

Second *meta*-analysis: GMV loss in hallucinating SZ patients with respect to healthy controls									
Cluster	Anatomical label	BA	MNI coordinates			Size (mm³)	ALE value	*p* value	Z score
			x	y	z				
1	Insula	13	−42	12	−10	2,880	0.0175029	0.0000005	4.871925
	Inferior Frontal Gyrus (IFG)	13	−36	10	−16		0.0141302	0.0000120	4.223723

corresponding to BA 13/22), with two peak coordinates. The maximum ALE value (0.0153; p < 0.00001; z = 4.27) occurred in the left superior temporal gyrus (STG; MNI coordinates: X = −58, Y = −12, Z = 8, corresponding to BA 22). The second peak (ALE value 0.010; p = 0.0002; z = 3.50) was found in the left insula (MNI coordinates: X = −46, Y = −14, Z = 10, corresponding to BA 13). All peaks emerged in regions extended between the STG and the insula (see Fig. 2).

Notably, GingerALE software reports studies contributing to the significant cluster: the only one showing a positive correlation (i.e.,

hypertrophy associated) with AVH severity (Modinos et al., 2009) was not included. Overall, our findings suggest that reduced volumes of grey matter within the temporal regions and posterior insula are significantly associated to auditory hallucinations in SZ patients. Table 3 includes a summary of the significant results.

3.3. Grey matter comparison between SZ patients with AVH and controls

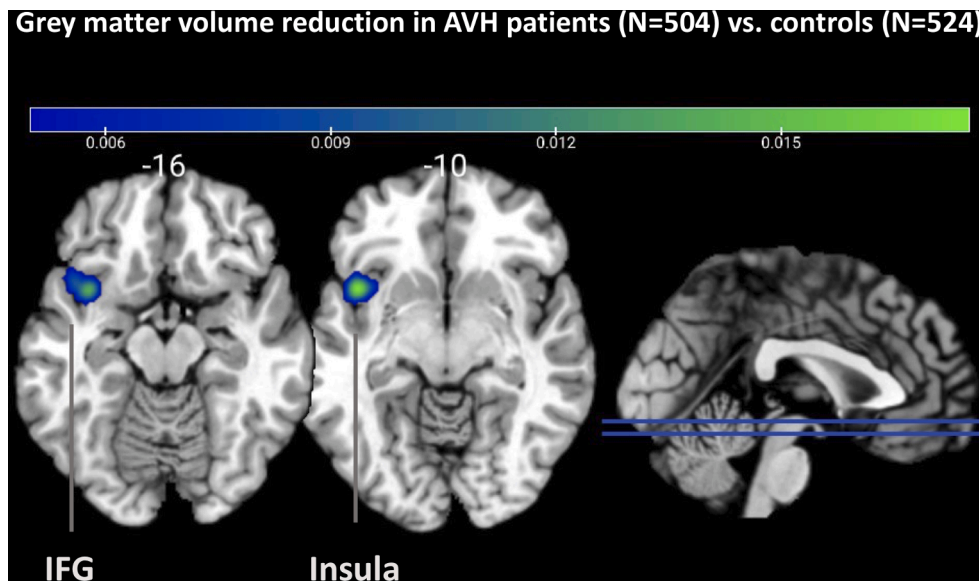We conducted the second *meta*-analysis on studies that compared

Fig. 3. Results obtained from the second *meta*-analysis, focused on grey matter volume (GMV) loss in AVH-SZ patients with respect to healthy controls.

GMV between AVH-SZ patients and healthy adults. In this analysis, which included 504 patients, 524 controls and 74 foci, the minimum size for a cluster to be considered statistically significant was 1,680 mm^3. Our results revealed a region of convergence of 2,880 mm^3 centered in the left insula (MNI coordinates: X = −41, Y = 10.9, Z = −11.9, corresponding to BA 13), with two peak coordinates. In particular, Fig. 3 shows that the significant cluster was lateralized in the left hemisphere and that it included the anterior insula and part of the inferior frontal gyrus (IFG).

The maximum ALE value (0.0175, p < 0.00001; z = 4.87) was found within the insula (MNI coordinates: X = −42, Y = 12, Z = −10, corresponding to BA 13). The second peak (ALE value 0.014; p = 0.00001; z = 4.22) was found in the left IFG (MNI coordinates: X = −36, Y = 10, Z = −16, corresponding to BA 13). Notably, the GingerALE report revealed that none of the three studies showing greater grey matter volume in patients compared to controls (O'Daly et al., 2007; Shapleske et al., 2002; Xie et al., 2021) contributed.

Given that all the experiments considered in the present analysis reported smaller GMV in the SZ patients group, our findings suggest that the GMV reduction in the left insula and IFG regions could be a characteristic marker of AVH patients. We provide a summary of the significant results in Table 3.

4. Discussion

The present study aimed at increasing knowledge of the anatomical correlates of the arguably most important and typical symptom of SZ, that is, AVH. Focusing on these SZ key symptoms is not a new approach; however, previous research on this topic considered a limited number of patients (García-Martí et al., 2008; Huang et al., 2015; Neckelmann et al., 2006) or chose either a correlational (Chan et al., 2011; Gaser et al., 2004; Huang et al., 2015; Modinos et al., 2013; Neckelmann et al., 2006; Palaniyappan et al., 2012; Shapleske et al., 2002) or a comparative approach only (García-Martí et al., 2008; Gur et al., 1999; Martí-Bonmatí et al., 2007). In the present study, we conducted two coordinate-based *meta*-analyses including – to our knowledge – the greatest number of SZ patients to investigate the correlation between grey matter volume and the severity of AVH symptoms (n = 472 patients, first *meta*-analysis) and the differences in grey matter volumes between AVH-SZ and healthy controls (n = 504 patients and 524 healthy controls, second *meta*-analysis). Therefore, agreeing with past literature, we systematically focused on structural GMV atrophy associated with

AVH in SZ patients not only based on the correlational approach with symptom severity but also considering group differences with respect to healthy adults. Thus, we have provided a more complete and fine-grained picture of structural abnormalities associated with hallucinatory phenomena.

We reviewed all articles published before June 2022 that investigated the whole-brain grey matter volume in patients experiencing auditory hallucinations. Although a limited number of studies has been conducted on this topic, the approach we adopted considers the whole brain voxels without *a priori* hypothesis on specific regions. Furthermore, our approach considers the number of subjects included in each experiment. Our results highlighted a cluster located in the left insula/STG: the smaller the GMV in this region, the higher the AVH severity. To examine further the hallucinatory phenomenon, we also ran a second *meta*-analysis for comparing the density of GMV in AVH-SZ patients and healthy controls. This analysis revealed a decreased volume of left insula and IFG in the SZ patients group. Notably, we found alterations in the insula grey matter both in the correlational and in the group comparison *meta*-analysis. We discuss the specific results that emerged from our study in the following sections, with particular emphasis on insula atrophy in patients with an SZ diagnosis and persistent auditory hallucinations.

4.1. The role of the insula

The insula is a key region located in a strategic brain site and connected with several brain areas involved in various cognitive processes (Türe, Yaşargil, Al-Mefty, & Yaşargil, 1999; Wylie & Tregellas, 2010). The insula's role in emotional responses has been widely established (Gasquoine, 2014). However, it also participates in language, speech, auditory, sensory-motor, decision-making, salience and attentional processing (Bamiou, Musiek, & Luxon, 2003; Oh, Duerden, & Pang, 2014; Uddin, Nomi, Hebert-Seropian, Ghaziri, & Boucher, 2017). Furthermore, due to a key role that allows integrating (external) sensory input with the emotional processing in the limbic system, the insula is integral to interoception – having awareness of the internal bodily state. This process is the basis of human's ability to perceive themselves as something different from the surrounding environment, allowing people to be aware of themselves, and finally to distinguish the image of "self" from "not oneself" (Damasio, 2003; Devue et al., 2007; Kircher et al., 2001). In detail, the anterior portion is involved in processing the emotional component of interoception awareness, mainly due to its

connection with limbic regions (Craig, 2003; Critchley, Melmed, Featherstone, Mathias, & Dolan, 2002). In contrast, the posterior portion engages in the inner processing of auditory, visual and somatosensory inputs (Lovero, Simmons, Aron, & Paulus, 2009; Olausson et al., 2002; Singer et al., 2004).

4.2. The role of the insula in schizophrenia and auditory hallucinations

Because of the role it plays, past studies investigated the correlation between structural anomalies in the insula and the presence of AVH. Indeed, according to some authors (Ford & Mathalon, 2004; Frith & Done, 1988), an inability to discriminate an internal sensory experience from an externally perceived one appears to mark the hallucinatory phenomenon. In this perspective, an insula dysfunction could result in a bias in attributing internally generated stimuli to external sources (Wylie & Tregellas, 2010). Structural insula abnormalities were consistently found in schizophrenia (Wylie & Tregellas, 2010), which in turn relate to hallucinations. However, whether this deficit is located in a particular portion of the insula (i.e., anterior vs posterior) or is lateralized in one hemisphere (left vs right) remains unclear (García-Martí et al., 2008; Shapleske et al., 2002). Our analysis revealed that the intensity of AVH was associated with grey matter loss in the left insula and superior temporal gyrus. This result is in line with two VBM *meta*-analyses that showed a negative correlation between the grey matter in a left cluster (including insula, STG, Heschl's gyri and IFG) and AVH severity (Modinos et al., 2013; Palaniyappan et al., 2012). However, Palaniyappan and colleagues found a correlation in a right hemisphere cluster, comprising insula and STG (Palaniyappan et al., 2012). In our analysis, alterations of the insula and STG were only observed within the left hemisphere (note that we included a larger number of studies compared to previous *meta*-analyses). Interestingly, when considering the correlation between GMV and AVH, the results showed the posterior insula's involvement. Nevertheless, the direct comparison between healthy and schizophrenia brains revealed decreased GMV in patients' anterior insula. Anatomically, the insula's anterior portion is connected with the limbic, visual, olfactory and thalamic systems, whereas the posterior part establishes connections with visual, somato-sensory and auditory areas (Flynn, Benson, & Ardila, 1999; Mesulam and Mufson, 1982; Wylie & Tregellas, 2010). As previously mentioned, the anterior insula plays an important role in evaluating emotional stimuli and in having self-awareness (Craig, 2009; Lovero et al., 2009), whereas the posterior insula is specialized for multimodal/somato-sensory processing (Olausson et al., 2002). Thus, it is not surprising that structural alterations in these regions relate to schizophrenia disorder and

hallucinations. The role of insula in processing sensory information suggests a possible relation with hallucinatory phenomenon. In particular, posterior insula is connected with the primary and secondary auditory cortex, the posterior superior temporal sulcus and the superior temporal gyrus (Wylie & Tregellas, 2010). Notably, we found decreased GMV also in the STG.

4.3. The role of temporo-frontal cortex in schizophrenia and auditory hallucinations

Evidence suggests that the left STG, which consists of primary and association auditory cortices, might be implicated in the genesis and/or the persistence of AVH in SZ (Allen, Larøi, McGuire, & Aleman, 2008). The left STG's involvement in phonological and semantic aspects of speech supports its role in auditory hallucinations (Modinos et al., 2013). According to the verbal self-monitoring hypothesis of AVH, decreased GMV in the left regions specialized in the auditory and speech perception might cause a deficit in the correct attribution of internal speech (Frith & Done, 1988). Moreover, abnormal functional activity in fronto-temporal areas was observed in patients experiencing AVH during scanning (Jardri et al., 2011). Crow's hypothesis, which proposes a common origin of functional psychoses (i.e., SZ or bipolar disorder) due to the failure of left hemisphere dominance for language (Crow, 1997; Crow, 2000), also supports the left hemisphere alterations in SZ, in particular at the level of the language areas.

Overall, our finding suggests that dysfunctions in a left lateralized cluster, including the insula and STG/transverse temporal gyrus, could relate to the intensity of auditory hallucinations. In our view, AVH symptomatology could result from structural abnormalities within regions that are critical for somato-sensory and auditory processing. Notably, these alterations could lead to confusion in distinguishing internal sensory information from an external source. Note that the insula (especially the posterior division) is strongly connected with auditory (temporal) areas. Furthermore, when we compared GMV between patients with AVH and healthy controls, the volume of a left cluster with two peaks in the insula (anterior part) and in the IFG reduced. Again, the insula emerged as an AVH marker in SZ. Previous studies observed abnormal grey matter volume in the insular, medial and inferior frontal and bilateral temporal regions when comparing patients with and without AVH (Escarti et al., 2019; Kubera et al., 2014). Interestingly, this pattern was not confirmed in the comparison between non-hallucinating patients and the controls, suggesting the presence of specific anatomical signatures in AVH (Kubera et al., 2014).
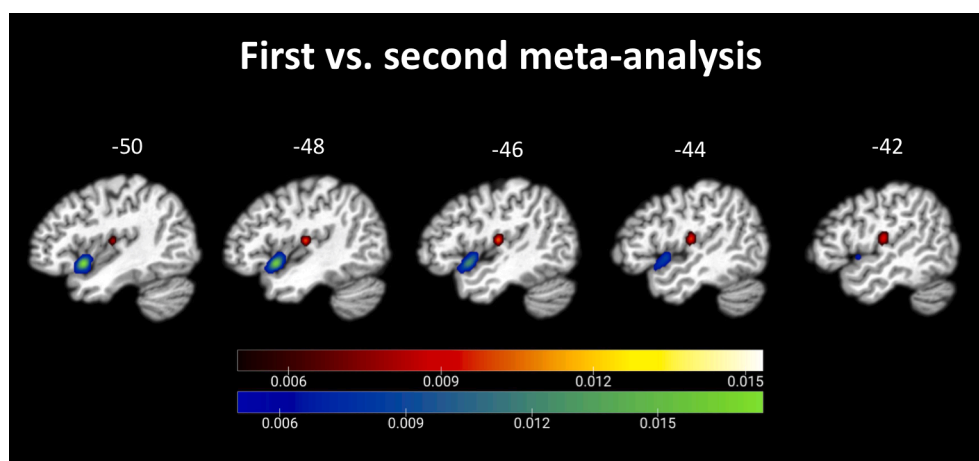

Fig. 4. Overview of the main results found in the present study, from the first and the second *meta*-analysis, in red and blue, respectively: a left lateralized cluster of brain regions, including the insula and temporo-frontal regions, that significantly contribute to the severity and persistence of AVH. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

4.4. Language network, schizophrenia and auditory hallucinations

The left IFG has been classically considered a critical hub within the language networks for its role in sentence comprehension (Just, Carpenter, Keller, Eddy, & Thulborn, 1996). In this perspective, past research on language and aphasic patients identified two main centers in a healthy brain: an anterior dominant network, related to organizing all linguistic processing and to the components of speech production, and a more posterior network, related to the comprehension constituents of language (Spironelli & Angrilli, 2015). Each network arises from the close interconnection of several critical areas within the left hemisphere, including Broca's area, IFG and the insula for the anterior hub; and Wernicke's area, inferior and middle temporal gyri, fusiform and lingual gyri for the posterior center. These hubs highly interconnect within the same hemisphere, through both direct subcortical connections and indirect, short, cortical connections. Similarly, Salisbury et al. (2021) recent study found similar generalized fractional anisotropy (gFA) of auditory transcallosal fibers and arcuate fasciculus between first episode psychosis (FEP) patients (half of which suffered from SZ) and healthy controls. Notably, despite not finding white matter deficits, left (but not right) arcuate fasciculus deficits showed a robust association with hallucination severity: the lower the gFA, the greater the hallucination severity. In addition, a further analysis on the subsample of FEP patients with higher hallucination levels (AH + FEP group), compared with healthy controls, revealed decreased gFA in left Broca's areas to putamen fibers. As the authors highlighted, these are unidirectional fiber connections, suggesting a disconnection of (or at least reduced information flow from) language-related cortical hubs and subcortical brain nuclei. Therefore, an altered dominance of language frontal center due to the insula, angular gyrus and subcortical white matter aberrations can disrupt this complex network and affect the ability of self-monitoring inner/outer speech. In this perspective, a recent study developed a novel fMRI-capture procedure to detect AVH phenomena in SZ patients, considering an associative, speech-related functional network as a fingerprint (Fovet et al., 2022). Notably, the results revealed that increased blood-oxygen-level-dependent (BOLD) activity in Broca's area and its right homologous, supplementary (and pre-supplementary) motor area, as well as bilateral supramarginal gyri, were associated with AVH. Therefore, an aberrant hemispheric dominance for language at functional level, for example, in a state of wakeful rest (e.g., Fovet et al., 2022), may depend on AVH-SZ patients' structural atrophy in a core hub of the linguistic network, in the left hemisphere. At the same time, the linguistic posterior regions in the temporal lobe can appear over-activated because of the decreased inhibition from the anterior center. Indeed, the hemispheric dominance lies on two mechanisms, that is, the greater activation of the dominant brain region (e.g., the left frontal operculum for language) and the simultaneous inhibition of the contralateral homologous (e.g., the right frontal operculum for language) (Spironelli & Angrilli, 2015). In the present study, we found lower grey matter density in the insula and IFG, and in our case, only left hemisphere regions were associated with AVH. In line with the aphasia model (Spironelli & Angrilli, 2015), the reduced GMV of the insula that AVH-SZ patients showed could alter the whole language network and contribute to the confusion in processing internally and externally generated sensory experiences. Taken together, our results suggest that left hemisphere abnormalities, within the insula and temporo-frontal regions, contribute to the severity and persistence of AVH.

4.5. Final remarks, conclusions and limitations

Our findings revealed important structural dysfunctions in a left lateralized cluster of brain regions, including the insula and temporo-frontal regions, that significantly contribute to the severity and persistence of AVH (Fig. 4).

Arguably, a significant brain damage in the left hemisphere language network, typical of aphasia patients, does not induce hallucinatory phenomena. However, note that in neurological patients, the structural damage appears in an otherwise fully functioning and intact network (prior to the stroke or hemorrhagic event), whereas in SZ patients, the left hemisphere atrophy appears at an earlier stage of brain development (i.e., young adulthood) in individuals with systemic vulnerability. Thus, other factors contribute to the association between language network aberrations and SZ (and AVH) development. Nevertheless, we conclude that structural atrophy in circuits involved in generating and perceiving speech, as well as in auditory signal processing, might reasonably be considered a biological marker of AVH in SZ.

The two *meta*-analyses conducted in the present study investigated the anatomical correlates of AVH in SZ using a VBM approach. Focusing first on the correlation between GMV atrophy and the severity of hallucinations, and second on the differences between AVH-SZ patients and healthy controls, we provided a more fine-grained analysis of this SZ key symptom. We used a coordinate-based *meta*-analysis method that tested the convergence across experiments against a null hypothesis of random spatial associations across the whole brain, assuming that each voxel has *a priori* the same chance of being activated. Thus, we provided a quantitative summary of the neuroimaging structural results studying a particular phenomenon (Eickhoff et al., 2012). A limitation of our work consisted in the few numbers of experiments included in the two *meta*-analyses (13 for the correlation with AVH and 11 for the patients–controls comparison). However, note that our literature search considered all published studies that met our inclusion criteria, and the most recent *meta*-analyses on a similar topic covered a shorter period (Modinos et al., 2013; Palaniyappan et al., 2012). Therefore, they included a lower number of SZ patients. A second critical limitation concerned the lack of comparison between healthy adults and SZ patients without AVH. With data extracted for our second *meta*-analysis, this comparison was not allowed because only a few studies reported significant differences with controls. However, past reviews and *meta*-analyses considering brain atrophy or hypertrophy in SZ patients, regardless of positive or negative syndromes, found an extensive cluster of GMV loss bilaterally distributed, including the insula, anterior cingulate and limbic regions, frontal cortex, thalamus, amygdala and hippocampus, but also posterior cingulate and fusiform gyri (Bora et al., 2011; Ellison-Wright, Glahn, Laird, Thelen, & Bullmore, 2008; Fornito, Yücel, Patti, Wood, & Pantelis, 2009).

These findings allow us to temper a possible critical issue associated with our second *meta*-analysis. As we compared (AVH-SZ) patients and healthy controls, the results highlighted a general neuropathological mechanism associated with other symptoms that hallucinating patients experience, such as somatic hallucinations – another first-rank symptom of SZ, (Schneider, 1959) – that plausibly involve the posterior portion of the insula (e.g., Björnsdotter et al., 2009) rather than AVH. However, past reviews and *meta*-analyses conducted on SZ patients – regardless of AVH symptoms – revealed a bilateral (rather than left-lateralized) GMV atrophy of insula. Furthermore, studies conducted on individuals at clinical or genetic risk for developing psychosis revealed that subject who later converted to psychosis showed early GMV loss in right superior and middle frontal, and medial orbitofrontal regions (Cannon et al., 2015), in the cingulate cortex bilaterally (Pantelis et al., 2002), together with a greater rate of ventricle enlargement compared with subjects who did not convert to psychosis (Cannon et al., 2015). Furthermore, the rigorous inclusion/exclusion criteria adopted allowed us to consider these findings specific to AVH because we excluded studies considering hallucination phenomena other than those in the auditory-verbal sensory channel.

Finally, another important limitation concerned possible effects depending on AVH-SZ patients' antipsychotic treatment and hallucination severity, which are two important factors that were not considered as covariates in our group comparison analysis because the chlorpromazine (CPZ) equivalents were only available for two studies, whereas the average AVH severity was available for six out of eleven studies.

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.

Data availability

Data will be made available on request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2022.103241.

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