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Auditory hallucinations in first-episode psychosis: A voxel-based morphometry study

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ABSTRACT

Background: Auditory hallucinations (AH) are a core symptom of psychosis. The brain abnormalities responsible for AH remain controversial due to inconsistent and conflicting findings across studies, with substantial confounding factors, such as chronicity. Few studies have examined the pathological changes that occur in the gray matter (GM) of patients with first-episode psychosis (FEP) and AH. The present study aims to validate the presence and characteristics of these structural abnormalities in relation to the intensity of psychotic symptoms and AH in a larger homogeneous sample than those of previous studies.
Methods: A magnetic resonance voxel-based morphometric analysis was applied to a group of 215 patients with FEP (93 patients with AH and 122 patients without AH) and 177 healthy controls. The patients were evaluated using the PANSS scale. Results: Patients with FEP exhibited greater reductions in GM concentrations in the temporal, frontal, cingulate and insular areas than the healthy controls did. No specific differences were found between the patients with FEP and AH and the patients without AH. In addition, total scores on the PANSS were negatively correlated with GM reductions in the FEP group. No correlations were found between the severity of the AH and the GM volumes.
Conclusions: As in previous studies, reductions in the GM concentrations in patients with FEP suggest that alterations are present in the early stages of psychosis, and these alterations are correlated with the severity of the illness. The GM reductions were not found to be related to the presence or severity of AH.

1. Introduction

Hallucinations are considered a fundamental symptom within psychiatry (Waters et al., 2012). Specifically, auditory hallucinations (AH) are the most common psychotic symptom, affecting approximately 60–80% of patients with schizophrenia (Andreasen and Flaum, 1991).

Currently, the mechanism and pathophysiology of AH are still largely unknown. Neuroimaging studies of AH, have improved the

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Table 1
Clinical and demographic variables.

	FEP patients with auditory hallucinations ($N = 93$)	FEP patients without auditory hallucinations ($N = 122$)	Control subjects ($N = 177$)	ANOVA (F; p value; degrees-of-freedom) or $\chi 2$
Age in years: mean (SD)	22.85 (6.25)	23.39 (6.22)	24.58 (6.70)	$F = 2.534$; $p = 0.810$; $df = 389$
Sex: no. (%)				$\chi 2 = 2.26$; $p = 0.324$
Male	58 (62.4)	85 (67.9)	109 (61.6)	
Female	35 (37.6)	37 (30.3)	68 (38.4)	
Ethnicity: no. (%)				$\chi 2 = 21.10$; $p = 0.099$
Caucasian	75 (80.6)	110 (90.2)	158 (89.3)	
Other	18 (19.4)	12 (9.8)	19 (10.7)	
Highest degree attained: no. (%)				$\chi 2 = 80.23$; $p < 0.001$
Some graduate-level degree	31 (33.3)	26 (21.3)	13 (7.3)	
High school diploma	39 (41.9)	46 (37.7)	37 (20.9)	
Bachelor's or associate's degree	12 (12.9)	30 (24.6)	38 (21.5)	
Master's degree	11(11.8)	20 (16.4)	89 (50.3)	
Antipsychotic medication (mg)				
Total cumulative dose: mean (SD)	44,069.45 (51,829.94)	41,361.93 (74,012.17)	–	$F = 0.080$; $p = 0.778$; $df = 389$
Total intracranial volume (TIV) in milliliters: mean (SD)	1410.83 (143.55)	1420.12 (147.08)	1438.86 (135.22)	$F = 1.379$; $p = 0.253$; $df = 389$
PANSS score at baseline evaluation: mean (SD)				
Total	90.43 (23.49)	62.01 (19.57)	–	$F = 93.50$; $p < 0.001^{**}$; $df = 389$
Positive	24.33 (6.55)	13.71 (6.08)	–	$F = 150.22$; $p < 0.001^{**}$; $df = 389$
Negative	21.75 (8.75)	16.41 (7.95)	–	$F = 21.82$; $p < 0.001^{**}$; $df = 389$
General	44.34 (13.75)	31.89 (10.02)	–	$F = 59.03$; $p < 0.001^{**}$; $df = 389$

** $p < 0.0005$.

understanding of the brain regions and networks involved in this symptom. The temporal and frontal lobe brain areas have been implicated in AH in repeated functional and structural imaging studies, reporting alterations in sensory regions, mainly in the superior temporal gyrus (STG) and the middle temporal gyrus (MTG), and these findings have been confirmed by two meta-analyses (Jardri et al., 2011; Modinos et al., 2013). Volumetric and functional changes in nonsensory regions have also been reported.

Structural Magnetic Resonance imaging (MRI) studies have tried to correlate volumetric changes with AH in patients with schizophrenia (Modinos et al., 2013). Most of them have found, specific relationships between gray matter (GM) volume reductions in the left STG and marginally with the right STG and AH severity (Modinos et al., 2013). A reduction in the left Heschl's gyrus has also been found to be specifically related to AH (Sumich et al., 2005; Modinos et al., 2013). Our group previously showed that GM reductions (bilateral insula, bilateral STG and left amygdala) were correlated specifically with the severity of AH in a highly homogeneous group of chronic patients with persistent hallucinations (García-Martí et al., 2008). In addition, specific relationships between the left inferior frontal and right postcentral gyri reductions and the severity of AH were observed.

Although morphometric studies have demonstrated evidence of cerebral deficits in patients with schizophrenia and AH, these studies have mainly been performed with chronic hallucination patients. Confounds associated with illness chronicity and prolonged exposure to antipsychotic medications may have, therefore, influenced the results. Compared to the studies of chronic patients, relatively few attempts have been made to investigate GM deficits in patients with first-episode psychosis (FEP) and AH (Shin et al., 2005; Chen et al., 2015; Huang et al., 2015). However, the study of first-episode schizophrenia seems important for elucidating the core pathophysiology of this illness (Whitford et al., 2005). GM volume reductions in the right temporal, left anterior cingulate and cerebellar and insular regions may underlie the onset of psychosis. GM reductions in the temporal regions have been shown to be inversely correlated with the severity of psychotic symptoms (Fusar-Poli et al., 2012).

As described above, it seems that imaging studies with FEP patients using voxel-based morphometry (VBM) may be one of the best ways to shed light on certain aspects of the pathophysiology of AH that remain unclear. Three studies have explored GM volume changes in FEP with and without AH (Shin et al., 2005; Chen et al., 2015; Huang et al., 2015). Shin et al. (2005) measured the volumes of cerebral and cerebellar regions in FEP patients with ($n = 17$) and without ($n = 8$) AH. They found that patients with AH showed larger frontal and temporal GM volumes than patients without AH. Chen et al. (2015) applied a surface-based analysis approach in a sample of 49 patients with FEP and 50 matched controls. They found that a subgroup of 18 patients suffering from persistent AH showed lower cortical thickness in the right Heschl's gyrus. This reduction was correlated with AH severity. Huang et al. (2015) conducted a VBM analysis in 36 drug naïve patients (18 with AH) and 18 controls and found that patients with and without AH exhibited reduced GM volumes relative to the controls in the left STG and the frontal, cerebellar, caudate and thalamic regions, showing also correlation with the severity of the illness. No significant differences were found between patients with and without AH. Of note, the power of these studies may have been limited by their small sample sizes.

The present study explores the relationship between AH and structural brain abnormalities through a VBM study in FEP patients with

Table 2
Areas of GM density reduction in the FEP patients (with and without AH) compared to the control subjects. $p < 0.05$ FWE-corrected, $k = 90$, degrees of freedom = 390.

Label	Right/left	MNI coordinates (x,y,z)	Brodmann area	Student's t-value	Cluster size (voxels)	Uncorrected p	FWE-corrected p
Superior frontal medial	Right	(14, 52, 2)	10	7.51	5366	<0.001	0.028
Middle temporal gyrus	Right	(60, −10, −8)	22	7.35	1584	<0.001	0.026
Superior frontal gyrus	Left	(−21, 62, 1)	11	7.20	5366	<0.001	0.031
Insula	Right	(36, 25, 1)	48	7.18	1584	<0.001	0.033
Insula	Left	(−48, −2, 3)	32	7.09	3155	<0.001	0.041
Inferior frontal operculum	Left	(−41, 10, 28)	44	7.07	3511	<0.001	0.039
Superior temporal gyrus	Right	(51, −3, 6)	48	7.01	3511	<0.001	0.042

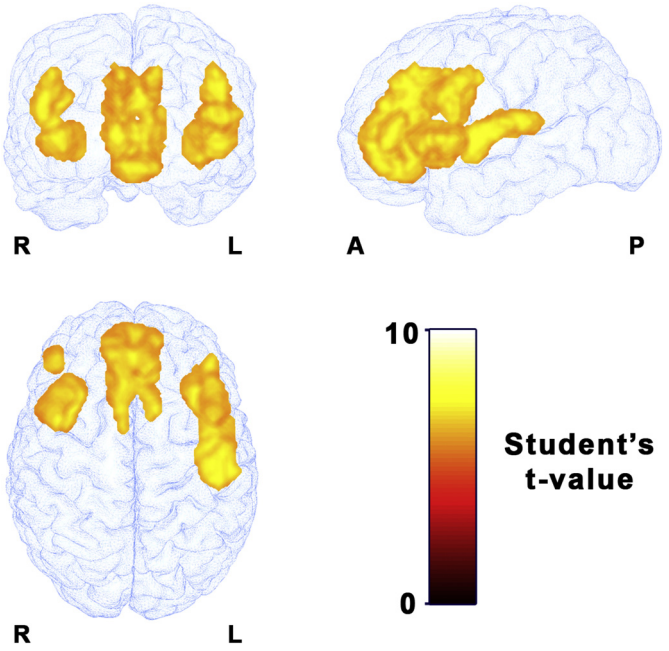

Fig. 1. Areas with GM density reduction in the FEP patients (with and without AH) compared to the control subjects. p < 0.05 FWE-corrected, k = 90.

and without AH in a large sample from a two-year multicenter, naturalistic, prospective study. Additional aims include studying how brain changes are correlated with the severity of illness and severity of AH using the PANSS scale.

2. Methods

2.1. Subjects

The subjects of this study participated in the "Phenotype-genotype and environmental interaction. Application of a predictive model in first psychotic episodes" study. This was a two-year, multicenter, naturalistic, prospective study, with 335 FEP patients and 253 healthy controls (HC) (Bernardo et al., 2013).

The inclusion criteria for the patients were as follows: (1) an age of 7–35 years old at the time of the first evaluation, (2) a diagnosed (DSM-IV) psychotic disorder of <12 months duration, (3) the ability to speak Spanish correctly, and (4) the provision of written informed consent. The exclusion criteria for the patients were: (1) mental retardation (DSM-IV), (2) a history of head trauma with a loss of consciousness, and (3) systemic disease with impact on mental health. A sample of HC matched for age, sex, ethnicity and handedness was recruited from the same geographic areas as the patients. The inclusion criteria for the HC were the same as those for the patients, except for past or present psychotic symptoms. The exclusion criteria were the same as those for the patients but also included (1) past or present psychotic symptoms or major depressive disorder, and (2) having a first-degree relative with a history of a diagnosed psychotic disorder.

A complete description of the study design, recruitment and assessment procedures is provided elsewhere (Bernardo et al., 2013) (Pina-Camacho et al., 2016). At baseline, a complete evaluation (structured interview, clinical scales, family environment, prognostic and premorbid adjustment scales, genetic and analytic) was performed (see Table 1 in Bernardo et al., 2013). Drug abuse was evaluated in every visit by a fragment of the European Adaptation of a Multidimensional Assessment Instrument for Drug and Alcohol Dependence (EuropAsi) (Kokkevi and Hartgers, 1995) and the Scale of the Udvalg for Kiniske Undersogelser (UKU), a comprehensive rating scale designed to assess general side effects of psychotropic drug (Lingjaerde et al., 1987). The assessment of drugs misuse interview was evaluated at baseline, 2 months, 6 months, 1 and 2 year. Eleven of the 16 sites within the PEPs Project (Bernardo et al., 2013) participated in the neuroimaging module (PEPs-Img study). Subjects were scanned on 6 scanner platforms. To minimize the effects of time since the FEP onset, the analysis was restricted to patients with less than an 18-month duration from the onset of positive psychotic symptoms to the scan acquisition (i.e., a maximum of 12 months from onset to recruitment, as per the inclusion criteria, plus a maximum of 6 months from study inclusion to the scan). A sample of 353 subjects—196 patients (12-month follow-up diagnosis of schizophrenia spectrum (SSD): $n = 92$, 12-month follow-up diagnosis of affective psychosis (AFP): $n = 32$, and other psychoses (OP): $n = 72$) and 157 HC—was included in the PEPs-Img study.

We added 39 subjects (19 FEP patients and 20 HC) from our own sample with the same criteria, achieving a final sample of 392 subjects, 215 patients with FEP and 177 healthy control subjects matched for age, sex and ethnicity. Of the patients, 122 had AH, and 93 did not have AH. Clinical characteristics were assessed using the Scale for Positive and Negative Symptoms in schizophrenia (PANSS) (Kay et al., 1990). The criterion for patients with AH was a score of >2 on item P3 of the PANSS. Table 1 shows the clinical and demographical variables of the enrolled subjects.

The study was approved by the institutional review boards of the participant sites and was conducted according to the provisions of the World Medical Association's Declaration of Helsinki. Written informed consent was obtained from all adult participants and from the parents/legal guardians of children under 16 years of age.

2.2. Scanning protocol

T1 images were used for the morphometric analysis. A previous reliability study was performed to ensure homogeneity across centers by exploring 6 control subjects who were scanned twice at each hospital. Details about the reproducibility study and the complete list of MR parameters can be found in Pina-Camacho et al. (2016). The representative sequence acquired in the 3-Tesla magnets was as follows: 3D spoiled gradient-echo sequence (TE = 7.38 ms; TR = 13.18 ms; flip angle = 8°, NEX = 1, 160 contiguous slices with no-gap, matrix = 256 × 256, FOV = 240 mm, and voxel size = 0.90 × 0.90 × 1 mm). For the 1.5-Tesla scanners, the sequence was a 3D spoiled gradient-echo (TE = 9.21 ms; TR = 25 ms; flip angle = 30°, NEX = 1, with 175 contiguous slices with no-gap, matrix = 256 × 256, FOV = 240 mm, and voxel size = 1x1x1 mm).

Table 3
Areas of GM density reduction in the FEP patients with AH compared to the control subjects. p < 0.05 FWE-corrected, k = 85, degrees of freedom = 268.

Label	Right/left	MNI coordinates (x,y,z)	Brodmann area	Student's t-value	Cluster size (voxels)	Uncorrected p	FWE-corrected p
Insula	Right	(39, 14, 1)	48	7.15	1777	<0.001	0.033
Inferior frontal triangularis	Right	(41, 20, 24)	48	7.02	1777	<0.001	0.036
Superior temporal gyrus	Right	(52, −4, 4)	48	6.77	1777	<0.001	0.041
Anterior cingulum	Right	(−9, 38, −14)	32	6.62	5214	<0.001	0.041
Superior frontal gyrus	Right	(11, 50, 6)	10	6.58	5214	<0.001	0.043
Insula	Left	(−37, −161, 12)	48	6.32	3294	<0.001	0.042
Inferior frontal operculum	Left	(−43, 17, 24)	48	5.99	3294	<0.001	0.044

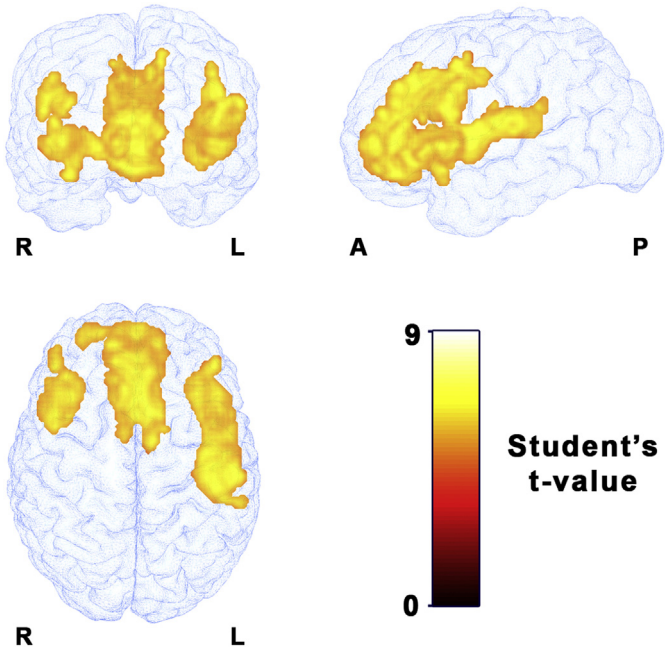

Fig. 2. Areas with GM density reduction in the FEP patients with AH compared to the control subjects. $p < 0.05$ FWE-corrected, $k = 85$.

2.3. Image processing

The data were processed with SPM8 (Statistical Parametric Mapping, Wellcome Institute, UK) and MATLAB (The MathWorks, USA). First, images were qualitatively reviewed by a radiologist and a computer engineer, who were both blind to the clinical data, in order to ensure the quality of the data. No images were labeled as outliers.

The VBM method was implemented directly through the SPM8 interface. First, a custom template dataset was obtained to reduce the bias associated with the use of predefined and standardized templates (Shen et al., 2007). This process involves the normalization of the raw images to the standard MNI template using affine transformations. The resulting images were then segmented and averaged using a Gaussian filter with an 8 mm FWHM (full width at half maximum) to generate whole-brain and tissue-specific GM and white matter (WM) templates.

Afterward, the T1-raw images for each participant were normalized and segmented using the custom template using DARTEL (Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra) (Ashburner, 2007) strategy. The segmented GM and WM maps were newly registered to construct a more accurate diffeomorphic template. The original images were then warped to this DARTEL template using flow fields that encoded the spatial deformations. The voxel size of the normalized images was set to $1.5 \times 1.5 \times 1.5$ mm. The final step included a Jacobian modulation with point-by-point contractions and expansions to preserve the total amount of tissue in the normalized images. Finally, images were smoothed with 10 a FWHM kernel.

2.4. Statistical analysis

The statistical models were designed and estimated according to the general linear model (GLM) framework (Friston et al., 1995). Two different stages were considered in the statistical evaluation. First, an ANCOVA model was constructed to evaluate the morphometric GM differences between groups (FEP patients with AH, FEP patients without AH and controls). This model included four covariates of interest (age, sex, total intracranial volume (TIV) and the center where the image was acquired). The cumulative antipsychotic dose was also considered as a nuisance variable when doing comparisons between FEP patients with and without AH (not considering controls). The TIV value was computed from the GM, WM and cerebrospinal fluid (CSF) maps by integrating the probability value of each voxel with the voxel size. Analyses were conducted with an initial uncorrected threshold of $p < 0.001$. Then a correction at the cluster level was applied considering significant those voxels that survived a family-wise error (FWE) rate correction of $p < 0.05$. Additionally, an extent threshold filter was applied to minimize spurious findings, considering only those clusters with a minimum size (k) calculated for each comparison as the expected number of voxels per cluster provided by SPM.

Second, a regression model was designed to assess the specific relationships between the PANSS scores and the GM volume variability. This model included only images from the FEP group and the same set of nuisance variables from the ANCOVA model. A parametric mask was applied to limit the regression analysis to the areas that previously showed significant GM differences between the FEP patients and controls. This brain mask was created from the output thresholded map provided by SPM during the comparison between FEP patients and controls ($p < 0.05$, FWE). All voxels with non-zero Student's *t*-values were set to 1 in the final binary mask.

The results were labeled with custom software adapted from the Automated Anatomical Labeling (AAL) toolbox for SPM (Tzourio-Mazoyer et al., 2001). For each cluster, the maximum Student's t-value was used to identify and to label the brain area.

3. Results

3.1. GM differences between the FEP patients (with and without AH) and HC

The overall sample of FEP patients (with and without AH) showed significant GM volume reductions ($p < 0.05$ FWE, $k = 90$) in several areas compared with the HC. Statistical contrasts were adjusted to minimize the residual effects of the site covariate between groups ($\chi^2 = 3.03$; $p = 0.695$). The most relevant findings showing differences were located in the frontal, temporal and insular regions (Table 2 and Fig. 1). No significant differences were found when testing for the opposite contrast (GM volume increments in the overall group of FEP versus HC).

3.2. GM differences between the FEP patients with AH and the HC

A significant GM volume reduction ($p < 0.05$ FWE, $k = 85$) was found in the FEP patients with AH compared with HC after correcting

Table 4
Areas of GM density reduction in the FEP patients without AH compared to the control subjects. $p < 0.05$ FWE-corrected, $k = 65$, degrees of freedom = 297.

Label	Right/left	MNI coordinates (x,y,z)	Brodmann area	Student's t-value	Cluster size (voxels)	Uncorrected p	FWE-corrected p
Insula	Right	(35, 24, 1)	48	7.31	1898	<0.001	0.029
Superior frontal gyrus	Right	(13, 49, 5)	10	7.19	4211	<0.001	0.031
Anterior cingulum	Right	(7, 45, 6)	32	6.38	4211	<0.001	0.036
Inferior frontal operculum	Left	(−43, 9, 30)	44	6.32	2940	<0.001	0.033
Insula	Left	(−33, 18, 3)	48	6.29	2940	<0.001	0.037
Superior temporal gyrus	Right	(51, −10, 3)	48	6.24	1898	<0.001	0.038

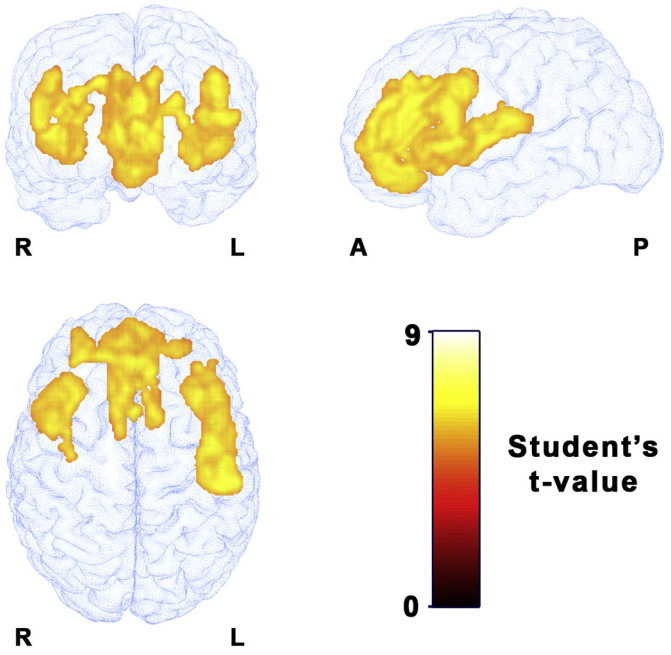

Fig. 3. Areas with GM density reduction in the FEP patients without AH compared to the control subjects. $p < 0.05$ FWE-corrected, $k = 65$.

for the residual effects of the site covariate between the groups ($\chi^2 = 2.41$; $p = 0.790$). This reduction was mainly distributed in the frontal, cingulate, insula and temporal areas (see Table 3 and Fig. 2). No differences were found when testing for GM volume increments in the group of FEP patients with AH versus the HC.

3.3. GM differences between the FEP patients without AH and the HC

The morphometric results for the FEP patients without AH versus the HC were virtually identical to the comparisons of FEP patients with AH, showing GM reductions in the insula, frontal, cingulate and temporal regions ($p < 0.05$ FWE, $k = 65$) after correcting for the residual effect of the site ($\chi^2 = 5.63$; $p = 0.344$). See Table 4 and Fig. 3 for more details. No significant GM increments were found in the group of patients compared to HC.

3.4. GM differences between the FEP patients with AH and the FEP patients without AH

The total cumulative dose of antipsychotic medication was similar in both groups ($F = 0.080$; $p = 0.778$). A specific vector contrast was tested to determine potential positive (1) or negative (−1) effects between this nuisance variable and the GM distribution, not showing significant results. The VBM method did not show GM differences between the FEP patients with and without AH with the considered statistical criterion ($p < 0.05$ FWE-corrected, $k = 55$). Neither were GM increases nor decreases observed between these groups.

3.5. PANSS score regression with GM variability

A statistically significant correlation was found between the PANSS total scores and focal GM volume reductions in FEP patients. The correlation was negative; the higher the score on the PANSS total scale, the lower the GM volume. The effect was mainly located in the left STG, right medial frontal gyrus and left anterior cingulate gyrus. Similar results were obtained for the group of FEP patients with AH (Table 5, Fig. 4) and for FEP patients without AH (Table 6, Fig. 4). No significant correlations were found when testing for item 3 (hallucinatory behavior) of the PANSS scale and the GM volume. Only significant effects that survived the correction for multiple comparisons at the cluster level were considered.

4. Discussion

We found GM volume reductions in the temporal, frontal, insular and cingulate areas in patients with FEP compared to HC but found no differences between patients with FEP with and without AH.

In addition, we found correlations between the GM reductions in the left STG, right medial frontal gyrus and left anterior cingulate gyrus and the severity of illness in general, but not in relationship to the severity of the AH.

Our data did not support the results of three previous studies of volumetric measures and AH in FEP. Shin et al. (2005) found GM differences between patients with and without AH (an increase in GM volume in frontal temporal gray matter areas in patients with AH). Chen et al. (2015) found lower cortical thickness in the right Heschl's gyrus in patients with AH and a correlation between reductions in the cortical thickness and the severity of AH in 49 FEP patients. In a study of 36 naïve FEP patients, Huang et al. (2015) found a reduction in the thalamic volume only in patients with AH.

There may be several explanations for these contradictory findings. First, the sample size may have played a role. The patient sample used in our study was four times larger than those used in the studies of Shin et al. (2005), Chen et al. (2015) and Huang et al. (2015). Therefore, the results of these studies may have been false positives. Second, differences in the methodology may explain the differences. Shin et al. (2005) used a semi-automated Talairach atlas-based segmentation technique with fuzzy-logic, which is conceptually different from a VBM analysis. Additionally, the authors noted that the larger GM volumes in the patients with AH may have been explained by the clinical characteristics, as the inclusion criteria included only unmedicated FEP patients. Chen et al. (2015) used only cortical thickness measures, while in this work, we used a VBM approach that provided a combination of different measurements of GM, including cortical folding, as well as cortical thickness. Huang et al. (2015) included only naïve patients, and in our study, the majority of the patients were taking antipsychotic medication. The role played by antipsychotic treatment in the pathophysiologic trajectory of brain abnormalities in schizophrenia is currently a matter of lively debate. The findings from the largest meta-analysis of cross-sectional studies on schizophrenia performed to date indicated that the reduction in whole-brain GM volume is associated with the dose of antipsychotics taken at the time of scanning (Haijma et al., 2013; Vita et al., 2015). In Huang's study, due to the relatively small number of subjects, the results appeared without any correction for multiple

Table 5
Areas with a negative correlation between the PANSS total score and the adjusted GM values in the FEP patients with AH. $p < 0.05$ FWE-corrected, $k = 85$, degrees of freedom = 91.

Label	Right/left	MNI coordinates (x,y,z)	Brodmann area	Student's t-value	Cluster size (voxels)	p value (cluster level)	Pearson coefficients (r/R^2)
Medial frontal gyrus	Right	(34, 55, 3)	10	6.55	98	0.016	−0.453/0.205
Superior temporal gyrus	Left	(−55, −1, 0)	48	6.52	124	0.018	−0.402/0.162
Anterior cingulum	Left	(−7, 41, 2)	11	6.10	95	0.021	−0.389/0.151

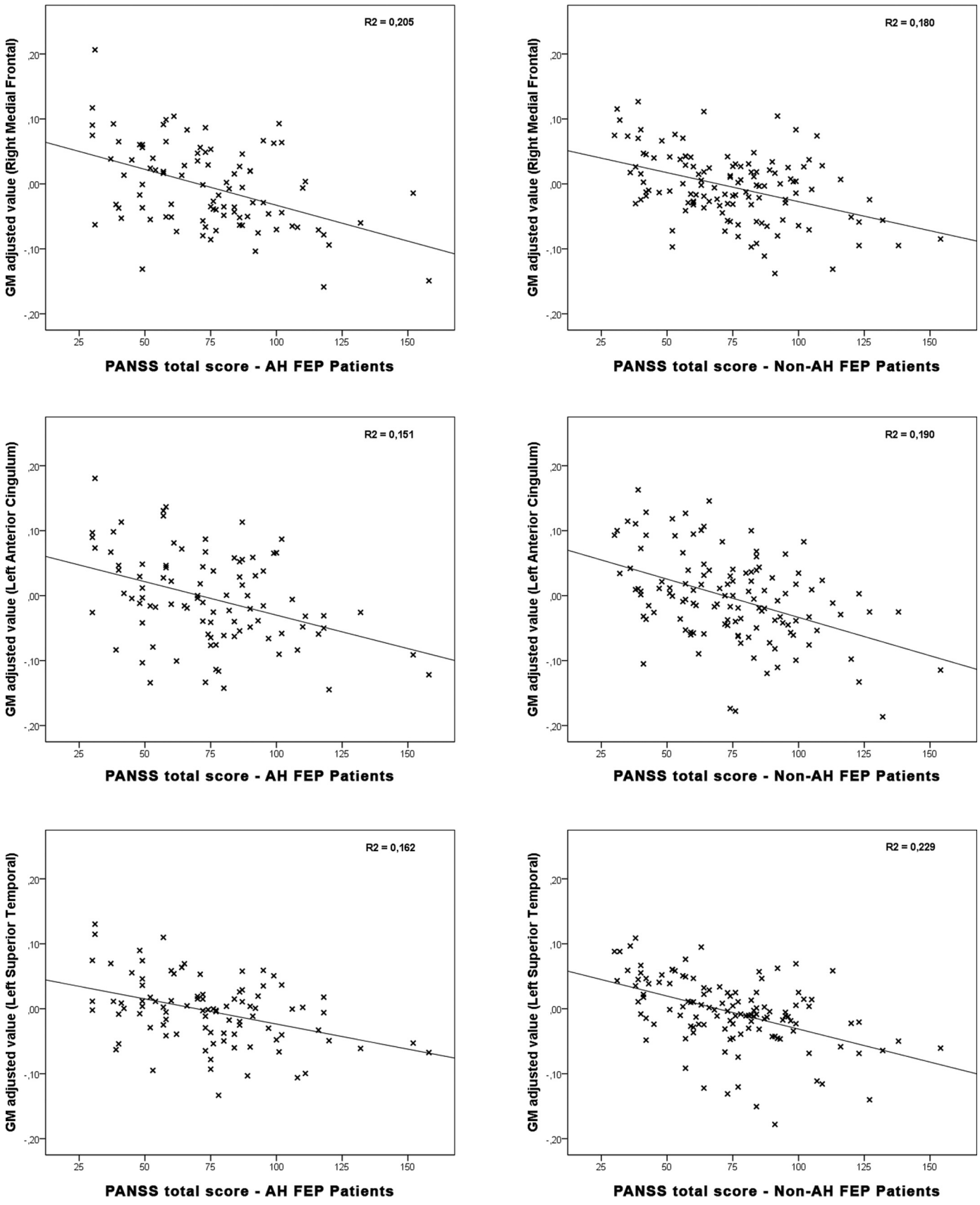

Fig. 4. Scatterplot of adjusted GM values (arbitrary units) negatively correlated with the PANSS total score in patients with FEP. Left column: FEP patients with AH ($p < 0.05$ FWE-corrected, $k = 85$), and right column: FEP patients without AH ($p < 0.05$ FWE-corrected, $k = 65$). Top row: right medial frontal correlation, middle row: left anterior cingulum correlation, and bottom row: left superior temporal correlation.

Table 6
Areas with a negative correlation between the PANSS total score and the adjusted GM values in the FEP patients without AH. $p < 0.05$ FWE-corrected, $k = 65$, degrees of freedom = 120.

Label	Right/left	MNI coordinates (x,y,z)	Brodmann area	Student's t-value	Cluster size (voxels)	p value (cluster level)	Pearson coefficients (r/R^2)
Superior temporal gyrus	Left	(−55, −1, 0)	48	6.98	77	0.012	−0.478/0.229
Anterior cingulum	Left	(−7, 41, 2)	11	6.74	110	0.017	−0.435/0.190
Medial frontal gyrus	Right	(34, 55, 3)	10	6.66	95	0.015	−0.424/0.180

comparisons. Thus, the ratio of false positives was not taken into account.

The results of this study were in accordance with those of a meta-analysis of the neuroanatomical map of the onset of psychosis suggested by Fusar-Poli et al. (2012). These authors proposed that GM reductions in several brain areas may underlie the onset of psychosis. The specific areas that they suggested play a role include the temporal, anterior cingulate, cerebellar and insular regions. We found reductions in all of these areas except the cerebellum, in which we instead found a GM decrease in the frontal area.

Moreover, we found a significant relationship between the PANSS total score and the degree of GM reduction. This was consistent with previous findings reported in the literature (Whitford et al., 2005; Lui et al., 2009; Fusar-Poli et al., 2012; Ren et al., 2013).

Our results indicated a different pattern of GM reductions in FEP patients compared with chronic patients with hallucinations. In a preliminary study conducted with chronic patients with hallucinations, we found a specific relationship between the GM reductions and the severity of AH (García-Martí et al., 2008). This relationship was confirmed in posterior meta-analyses (Modinos et al., 2013).

Our finding that the right STG is reduced in the FEP group was consistent with the work of Fusar-Poli et al. (2012), who found GM volume reductions in the right temporal region in previous studies of the onset of psychosis. We found that the GM reductions in the left temporal regions were inversely correlated with the severity of psychotic symptoms in the same direction, as was reported in a previous study (Fusar-Poli et al., 2012). This finding confirmed that the GM reductions are more related to the psychosis and are not specific to the AH at the beginning of the illness.

Most previous studies have found a relationship between GM volume reductions in the left and marginally in the right STG and AH severity (Modinos et al., 2013). However, we did not find this correlation. Instead, we found a relationship between GM reductions and the severity of psychosis.

Our finding that the GM volumes of the right superior frontal gyrus and the right and left inferior frontal gyri were reduced was consistent with the findings reported by Huang et al. (2015). They found that patients with FEP with and without AH exhibited reduced GM volumes relative to controls in frontal regions. We also found that the reduced GM volume in the right medial frontal gyrus was related to the severity of illness but not to the severity of the AH.

The anterior cingulate is a key region involved in emotional processing and higher executive function (Bush et al., 2000) and several studies have identified volume reductions this area in schizophrenia (Baiano et al., 2007). A study of the anterior cingulate cortex in first-episode schizophrenia patients identified reduced cortical thickness (Fornito et al., 2008) but not reduced GM volume. Our results were consistent with these findings.

The insular cortex is a limbic integration region that engages in emotional and cognitive functions. Structural imaging techniques using MRI have consistently found decreased GM in the insula (Wylie and Tregellas, 2010). These deficits are usually bilateral, present in first-episode schizophrenia, and progressive in chronic schizophrenia (Ellison-Wright et al., 2008; Chan et al., 2011). Our results were consistent with previous studies with FEP, but we did not find a relationship between the insula and the presence or severity of AH, which was contradictory to previous studies of chronic patients (Shapleske et al., 2002; García-Martí et al., 2008). The patients included in this study were FEP patients, and the influence of chronicity might help to explain this discrepancy.

This study had several limitations worth noting. First, all patients included in the study were medicated, although the equivalent dose of antipsychotics did not influence the results ($F = 0.080$; $p = 0.778$). Second, the patients were assessed with the PANSS scale, and more accurate scales to measure AH will be needed in future studies. Third, this was a cross-sectional study, and we hypothesized progressive decreases in GM in patients with persistent AH based on previous cross-sectional studies of chronic patients. Longitudinal studies should, thus, be designed to study the longitudinal progression of the GM aspect in patients with AH. Fourth, the sample included in this study was very heterogeneous in terms of psychosis, and only a fraction of the patients had schizophrenia, but is a value added that the sample is homogeneous in terms of inclusion/exclusion of patients with AH. The structural basis of AH may not be the same in an acute and remitting condition as it is in a more continuous condition. Fifth, methodologically in the framework of the random field theory the cluster-based statistics are controversial in VBM because data can be not uniformly smooth. We assume that the large number of degrees of freedom (data size) used in this work probably has minimized the possible effect of the lack of smoothness in the results. Sixth, correlations were tested only in areas previously reported as significant by the VBM comparison between FEP patients and control. We have considered that prior results as a basis to test for correlations, following a 'hypothesis-testing' strategy. Although the considered binary masks are quite large compared to the whole brain, as it includes relative big regions of interest, we cannot discard a residual effect of circularity or non-independence over data (Kriegeskorte et al., 2009).

However, as mentioned above, it is important to highlight the strengths of this study in testing our hypothesis. This was a study of FEP patients diagnosed with psychotic disorders, according to the DSM-IV criteria, of less than a 12-month duration. This study was conducted with a large sample size and a short treatment duration. The enrolled patients were treated mostly with atypical antipsychotics and were scanned using a high-resolution, technique and the data were analyzed using a VBM approach. This methodology permitted us to segment brain tissues and to study the whole brain.

To conclude, in this VBM study of patients with FEP and AH, we found reductions in GM in the early stages of psychosis. However, these alterations were not specific to the presence of AH. Future VBM prospective studies comparing patients who develop chronic schizophrenia with persistent AH to patients who do not develop this type of schizophrenia should improve our understanding of the pathophysiology of schizophrenia and may aid in the development of personalized therapeutic approaches that target the early stages of the psychotic process.

Contributors

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Declaration of Competing Interest

The authors declare no conflicts of interest.

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