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Source-based morphometry of gray matter volume in patients with schizophrenia who have persistent auditory verbal hallucinations

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ABSTRACT

Abnormal structure of frontal and temporal brain regions has been suggested to occur in patients with schizophrenia who have frequent auditory verbal hallucinations (AVH). However, it is unknown whether this is specific to this patient subgroup. This study tested the hypothesis that frontotemporal gray matter volume changes would characterize patients with persistent AVH (pAVH) in contrast to healthy controls and patients without AVH. Using structural magnetic resonance imaging at 3T, we studied 20 patients with schizophrenia and 14 matched healthy controls. Ten patients were classified as having chronic and treatment resistant AVH, whereas the remaining 10 patients either never had AVH in the past or were in full remission with regard to AVH (nAVH). Using a multivariate statistical technique for structural data, i.e. "source-based morphometry" (SBM), we investigated naturally grouping patterns of gray matter volume variation among individuals, the magnitude of their expression between-groups and the relationship between gray matter volume and AVH-specific measures. SBM identified a reduction of medial and inferior frontal, insular and bilateral temporal gray matter volume between pAVH and nAVH. This pattern did not differ between nAVH patients and controls and was associated with "physical" AVH characteristics (such as symptom duration, location, frequency and intensity) in the pAVH patient group. These results suggest that a pattern of lower gray matter volume in medial frontal, insular and bilateral temporal cortical regions differentiates between patients with persistent AVH and non-hallucinating patients. Moreover, the data support a specific role of this neural pattern in AVH symptom expression.

1. Introduction

Auditory verbal hallucinations (AVH) defined as sensory experiences in the absence of a corresponding external stimulus (Aleman and de Haan, 1998) are a core symptom of schizophrenia and related spectrum-disorders. Persistent AVH, which can be temporally defined as persistent over the course of one year despite two clinically ineffective drug trials, have to be separated from episodic hallucinations (Gonzalez et al., 2006). Hallucinations are the most common psychotic symptom, affecting about 60–80% of patients with schizophrenia and usually distressing. Moreover, in about 25% AVH are chronic and resistant to medication (Shergill et al., 1998).

Imaging brain structure in patients with schizophrenia has been shown to be successful in identifying neural correlates of the disorder. Several meta-analyses indicate widespread volume changes in frontal, temporal and parietal regions (see e.g. Glahn et al., 2008; Honea et al., 2005), yet despite this progress, the neural substrates underlying AVH in patients with schizophrenia are still poorly defined. Temporal cortical volume loss in patients presenting with persistent AVH is one of the most consistent findings (Allen et al., 2008, 2012). A recent meta-analysis of voxel-based morphometry (VBM) studies reported an association between AVH-severity and bilateral superior temporal gray matter volume loss (Modinos et al., 2013). A significant negative correlation between AVH severity and gray matter volume in the left insula and right superior temporal gyrus was highlighted by another meta-analysis (Palaniyappan et al., 2013a).

Abbreviations: AHS, Auditory Hallucinations Scale; ANOVA, analysis of variance; AVH, auditory verbal hallucinations; BPRS, Brief Psychiatric Rating Scale; COI, component of interest; DARTEL, diffeomorphic anatomic registration through exponentiated lie algebra; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, fourth edition; GMV, gray matter volume; FDR, false discovery rate; FOV, field of view; GIFT, Group ICA for fMRI Toolbox; ICA, Independent Component Analysis; MAP, maximum a posterior; MNI, Montreal Neurological Institute; MRI, magnetic resonance imaging; PANSS, Positive and Negative Syndrome Scale; PsyRatS, Psychotic Symptoms Rating Scales; PVE, partial volume estimation; SBM, source-based morphometry; TD, Talairach Daemon; TE, echo time; TI, inversion time; TIV, total intracranial volume; TR, repetition time; VBM, voxel-based morphometry.

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At present, there is a striking paucity of data addressing the specificity of structural changes for patients presenting with persistent AVH. These individuals may represent a specific schizophrenic subgroup (Mauri et al., 2008) and appear to differ from patients without AVH in terms of brain structure (Gaser et al., 2004; Shapleske et al., 2002; van Swam et al., 2013). Also, few studies have so far attempted to relate specific symptom dimensions to distinct neural substrates (Plaze et al., 2011; Vercammen et al., 2010a; Wolf et al., 2012), and this is remarkable given the phenomenological multidimensionality of AVH (Gonzalez et al., 2006; Haddock et al., 1999; Kronmuller et al., 2010). Eventually, it is noteworthy that the majority of structural findings in patients with AVH have been derived from univariate statistical approaches, such as VBM. However, structural variation in one brain region is likely to affect multiple brain areas even if it occurs in a remote location. The identification of such changes in structural networks, i.e. the relationship among multiple brain regions associated with a disorder, can therefore allow us to understand how altered inter-relationships between regions can contribute to the disorder (Kasparek et al., 2010; Xu et al., 2009).

In this study, we used a novel analysis strategy for structural MRI data, i.e. "source-based morphometry" (Xu et al., 2009), to investigate gray matter volume changes in patients with persistent AVH in comparison to patients without AVH and healthy controls. Similar to VBM, SBM does not rely on a priori definition of regions of interest and allows an automated, user-independent investigation of brain structure. Unlike VBM, however, SBM takes advantage of Independent Component Analysis (ICA) to extract spatially independent patterns that occur in structural images. Thus, in contrast to voxel-by-voxel univariate testing, SBM takes into account interrelationships between voxels to identify naturally grouped patterns of structural variation between populations. As a multivariate statistical approach, SBM can result in less-noisy sources of interest (Xu et al., 2009) and since in SBM the statistical group analysis is based on component values, i.e. on "component loadings", this technique also significantly reduces the number of multiple comparisons. Importantly, the application of SBM to schizophrenia has been shown to successfully identify distinct patterns of structural change which were not detected by VBM (Kasparek et al., 2010; Xu et al., 2009). We predicted that patients presenting with persistent symptoms would exhibit more pronounced frontotemporal gray matter volume loss in contrast to healthy individuals and schizophrenic patients without persistent AVH. In addition, we employed symptom-specific psychometric instruments to facilitate the investigation of symptom/structure relationships. Here, we expected that volume loss in AVH-related structural networks would be associated with specific symptom dimensions, such as intensity and loudness of AVH.

2. Materials and methods

2.1. Participants

We studied 20 right-handed patients with schizophrenia (paranoid subtype according to DSM-IV) who were treated at the Departments of Psychiatry II and III, Ulm University, Germany (Table 1; see also Table 3 [supplementary data] for detailed psychometric scores). Right-handedness was confirmed by the Edinburgh Handedness Inventory (Oldfield, 1971). Exclusion criteria were comorbid axis-I (except nicotine abuse or dependence) and/or axis-II disorders according to DSM-IV, neurological disorders, and an insufficient command of the German language. In all patients, symptoms were rated using the Brief Psychiatric Rating Scale (Overall and Gorham, 1976) (BPRS) and its subscores, complemented by the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1989).

Patients with persistent AVH (pAVH, n = 10) included in this study were classified as medication resistant for AVH, as defined by persistent symptoms in the presence of at least two clinically ineffective drug trials (each >6 weeks of treatment) with different antipsychotics at adequate dosage. Further, patients were only included if they did not show pronounced formal thought disorder symptoms and if they had sufficient insight into their hallucinatory experience such as to provide self-reports about their symptoms. None of the pAVH patients underwent therapeutic transcranial magnetic stimulation for AVH (Slotema et al., 2012) in the past. The duration of AVH persistence prior to scanning was retrospectively estimated based on patients self-reports. Periods of symptom persistence of at least moderate degree, as defined by the BPRS and PANSS-P hallucinations items, ranged from 8 to 72 months (median = 21 months). In pAVH patients, scores of the BPRS and PANSS-P hallucinations item indicated the presence of moderate to severe symptoms (BPRS hallucinations item range: 4–7; PANSS-P hallucinations item range: 4–6) at the time of MRI. In addition, in pAVH patients global severity of AVH was assessed using the Auditory Hallucinations Scale (AHS), as provided by the Psychotic Symptoms Rating Scales (PsyRatS) (Haddock et al., 1999). A three factor solution (Hatton et al., 2005; Kronmuller et al., 2010) from the PsyRatS-AHS was used to characterize different dimensions of AVH: (1) emotional (amount and frequency of negative content and anxiety experienced by AVH), (2) physical (duration, location, frequency and intensity of AVH), and (3) cognitive features (degree of control and repercussion, belief and location of AVH).

We included a second group of non-hallucinating patients with schizophrenia (nAVH, n = 10). These individuals either never experienced AVH during the course of the illness (n = 2) or they experienced

Table 1
Demographics and clinical scores for healthy controls and patients with schizophrenia with persistent (pAVH) and without (nAVH) auditory verbal hallucinations. BPRS: Brief Psychiatric Rating Scale; EHI: Edinburgh Handedness Inventory (Oldfield, 1971); CPZ: chlorpromazine; PANSS: Positive and Negative Syndrome Scale; PsyRatS-AHS: Psychotic Symptoms Rating Scale (emo = emotional characteristics, phys = physical characteristics, cog = cognitive characteristics). *χ^2 test.

	Controls (n = 14)		pAVH (n = 10)		nAVH (n = 10)		p-Value		
Characteristic	Mean	sd	Mean	sd	Mean	sd	Controls vs. AVH	Controls vs. nAVH	AVH vs. nAVH
Age (years)	33.7	8.6	36.5	9.0	32.1	6.2	0.45	0.62	0.22
Gender (m/f)	7/7		6/4		8/2		0.23*	0.05*	0.18*
Laterality (EHI score)	88.9	13.5	92.2	10.0	88.3	9.7	0.52	0.76	0.39
Education (years)	14.9	2.8	13.5	1.6	13.7	2.7	0.18	0.32	0.84
Duration of illness (years)			9.9	6.3	5.9	5.8			0.16
CPZ equivalents			457.3	342.1	569.8	361.9			0.48
BPRS score			48.7	10.7	38.3	9.5			0.03
BPRS AVH item			5.5	0.8	1.0	0			0.000
PANSS-P			16.0	3.4	11.2	3.2			0.004
PANSS-P AVH item			4.6	0.5	1.0	0			0.000
PANSS-N			22.0	5.5	18.8	5.7			0.22
PsyRatS total score			24.4	8.1					
PsyRatS-emo			9.1	4.1					
PsyRatS-phys			8.5	2.3					
PsyRatS-cog			9.2	3.5					