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Research report

Neuroanatomy of auditory verbal hallucinations in schizophrenia: A quantitative meta-analysis of voxel-based morphometry studies

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ABSTRACT

Introduction: Voxel-based morphometry (VBM) studies demonstrate grey matter volume (GMV) deficits in schizophrenia. This method is also applied for detecting associations between specific psychotic symptoms and brain structure, such as auditory verbal hallucinations (AVHs). However, due to differing methodological approaches, the available findings are inconsistent and difficult to integrate.

Methods: We used a novel voxel-based meta-analytical method to provide a robust quantitative review of neuroanatomical abnormalities specifically associated with the hallucinatory phenomenon in the schizophrenic brain. We reviewed all VBM studies of AVHs in schizophrenia published until July 2011 ($n = 9$). A total of 438 patients with a diagnosis of schizophrenia were included (307 with AVHs). Using a random-effects parametric voxel-based meta-analysis, coordinates of 83 foci reported as significant in the source studies were extracted and computed to estimate the brain locations most consistently associated with AVHs.

Results: Severity of AVHs was significantly associated with GMV reductions in the left ($p = .022$) and marginally with the right ($p = .062$) superior temporal gyri (STGs, including Heschl's gyri) across studies examining correlations with AVHs severity in patients ($n = 8$). Analysis of studies categorically comparing patients with and without AVHs did not reveal any significant findings, possibly due to the small number of studies using this approach ($n = 3$).

Conclusions: This meta-analysis implicates bilateral STG (including Heschl's gyri) as key areas of structural pathology in AVHs in schizophrenia. These findings support a model postulating that aberrations within neural systems involved at different levels of language processing are critical to AVHs in schizophrenia.

1. Introduction

Schizophrenia is a severe and disabling mental illness involving chronic or recurrent psychosis and long-term deterioration in functional capacity. Auditory verbal hallucinations (AVHs) are the most common psychotic symptom, affecting about 60–80% of patients with schizophrenia (Andreasen and Flaum, 1991). AVHs are defined as auditory perceptions (most typically,

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"voices") in the absence of external stimulation, and in patients with schizophrenia the content of AVHs is usually derogatory and distressing (Nayani and David, 1996). Furthermore, in about 25% of patients AVHs are medication-resistant and chronic (Shergill et al., 1998) and severely impair patients' functioning and quality of life (Hoffman, 2008).

In the last two decades, the development of neuroimaging techniques has allowed the investigation of putative abnormalities in the function, morphology and connectivity of the brains of schizophrenia patients suffering from AVHs. A recent comprehensive review of structural and functional imaging studies in patients with AVHs concluded that dysfunction in secondary (and occasionally primary) cortices in the temporal lobes is linked to the emergence of AVHs (Allen et al., 2008). In addition, non-sensory regions in prefrontal, premotor, cingulate, subcortical and cerebellar regions were also identified. A more recent meta-analysis based on functional imaging studies of patients who were experiencing AVHs during scanning highlighted aberrant activations in frontal, temporal and hippocampal regions (Jardri et al., 2011). Within the published studies examining the anatomical correlates of AVHs a range of inconsistencies is evident (with some studies highlighting associations with different non-sensory regions, e.g., Gaser et al. (2004), pointing to the right inferior frontal area, while others do not, hence evidencing significant disparity as to which regions are putatively involved) and, to date, no meta-analysis has been conducted.

Early region of interest (ROI) studies investigating putative morphological changes in patients with schizophrenia showed that AVHs were associated with volume reductions in the superior temporal gyrus (STG) and enlarged lateral ventricles (Barta et al., 1990; Flaum et al., 1995). More recently, ROI studies have reported associations between severity of AVHs and volume reductions in the left Heschl's gyrus (primary auditory cortex) (Sumich et al., 2005), and in the left anterior STG and middle temporal gyrus (MTG) (Onitsuka et al., 2004). A review of ROI studies of the STG in schizophrenia highlighted its critical involvement in the disorder, most commonly characterised by volume reductions (Sun et al., 2009). This review also showed a link between pathophysiological changes in the STG and the development of hallucinations in patients with schizophrenia, especially in the left side. A limitation of these ROI studies is that they used manual or semi-automated methods to measure the volumes of brain regions defined *a priori* as being "abnormal," hence preventing the exploration of other potentially implicated brain regions.

Fully-automated whole-brain voxel-based morphometry (VBM) methods (Mechelli et al., 2005) overcome some of the limitations of the ROI approach, and provide a powerful tool which is unbiased in its segmentation process to examine the neural substrates of psychiatric disorders and their symptomatological expressions. In their review of the literature on VBM in schizophrenia, Honea et al. (2005) reported the left STG and medial temporal lobe as key regions of structural pathology in patients relative to healthy subjects. More recently, Bora et al. (2011) provided a quantitative review of VBM studies of grey and white matter volume and concluded that schizophrenia is characterised by bilateral anterior cortical, limbic and subcortical grey matter abnormalities, and white matter changes in regions that include tracts connecting these structures within and between hemispheres. However, in these previous meta-analyses the relative associations with specific symptoms were not considered. VBM has been effective in revealing morphologic abnormalities in schizophrenia according to symptom profile (Koutsouleris et al., 2008; Lui et al., 2009) and there have been a number of studies using VBM to examine structural abnormalities in patients who experience AVHs, either by examining the *presence* (comparing patients with schizophrenia with AVHs *vs* patients without AVHs) and/or the *severity* of AVHs (relationship between GMV and AVHs severity). Unfortunately, recent applications of these novel methods are often limited by relatively small sample sizes, resulting in insufficient statistical power and increased risk of false-positive results.

Newly developed voxel-based meta-analytical methods have the potential to quantify the reproducibility of neuroimaging findings and to generate insights difficult to observe in isolated studies. In this context, what follows is a systematic literature search of papers published to date that report specific effects of AVHs on brain structure in patients with schizophrenia using VBM. The studies identified in the literature search were pooled using a novel parametric voxelwise meta-analysis method (Costafreda et al., 2009) to identify the neuroanatomical locations that are most consistently implicated in the AVHs phenomenon across studies. This method allowed performing a random-effects meta-analysis of published studies, with sample size weighting, and ensuring stringent false-positive control (Family-Wise Error rate correction - FWE).

2. Methods

2.1. *Literature selection, data collection, and preparation*

Our aim was to identify all studies fulfilling the following criteria: (1) structural magnetic resonance imaging (MRI) studies of the AVHs phenomenon, (2) investigating differences in whole-brain grey matter, (3) reporting analyses pertaining to the presence or the severity of AVHs in patients with schizophrenia, and (4) using automated VBM analysis following the general steps of normalisation, segmentation, smoothing and statistical analysis described in the early literature on the method (Ashburner and Friston, 2000; Good et al., 2001). We conducted a systematic literature search of PubMed, Science-Direct, and Scopus databases to identify relevant studies published up until July 2011 (Fig. 1). The following key words were employed: "schizophrenia", "hallucination", plus "morphometry", "voxel-based", or "voxelwise". In addition, we also conducted manual searches of the reference sections of the obtained articles. A total of 28 studies were initially identified; however some of these articles did not meet the inclusion criteria upon detailed examination and were excluded. This was the case for systematic reviews (Begré and Koenig, 2008) and articles not including original data (Gaser et al., 1999), studies exploring AVHs in people outside of the schizophrenia spectrum (Stanfield et al., 2009) or in high-risk populations (Spencer et al., 2007), studies