



# Resting-state functional connectivity in medication-naïve schizophrenia patients with and without auditory verbal hallucinations: A preliminary report



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## ABSTRACT

Auditory verbal hallucinations (AVH) are a cardinal feature of schizophrenia that has been associated with activation in language processing areas, in concert with higher-order cognitive brain networks. It remains to be determined whether, and if so how, the functional dynamics between these brain regions contributes to the emergence of AVH. The current study recruited 36 first-episode medication-naïve schizophrenia patients, including 18 patients with AVH, 18 patients free of AVH and 18 controls matched on age, gender and level of education. Resting-state functional MRI images were acquired for every subject and used to map functional brain connectivity. We compared functional connectivity in 18 bilateral regions of interest implicated by previous AVH studies among the three subject groups, with the aim of detecting patterns of dysconnectivity unique to or most pronounced in AVH patients. Results showed that AVH patients are characterized by dysconnectivity in neural circuitry involving the anterior cingulate cortex, insular cortex and language-related regions, comparing with both controls and non-AVH patients. Current findings suggest that abnormality in speech-sensitive areas and their functional cooperation with cortical regions involving in source monitoring and salience detection functions may contribute to the occurrence of AVH.

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## 1. Introduction

Auditory verbal hallucinations (AVH), or ‘hearing voices’, are the perception of speech in the absence of an external auditory stimulus. AVH are common to schizophrenia, affecting between 40% to 80% of patients (Aleman and Larøi, 2008), but also occur in various other clinical disorders (Larøi, 2012) and even in a subpopulation of healthy individuals (Sommer et al., 2010).

Investigating the neural mechanism of AVH with magnetic resonance imaging (MRI) has been gaining in popularity in recent years. Meta-analyses of functional MRI (fMRI) and positron-emission tomography (PET) studies suggested that auditory hallucinations were associated with abnormal focal activations in language related areas (e.g., inferior frontal gyrus, superior temporal gyrus and nearby cortical

areas) and other regions of the cortex (Jardri et al., 2011; Kompus et al., 2011; Kühn and Gallinat, 2010). Abnormal functional connectivity among these brain regions has also been proposed to contribute to hallucinatory experiences (Clos et al., 2014; Hoffman and Hampson, 2012; Sommer et al., 2012; Vercammen et al., 2010). For example, studies have suggested that AVH may result from hyperactivity of the auditory cortex (bottom-up) in combination with abnormal (top-down) modulation by higher-order cognitive brain regions within the default-mode network and salience network (Alderson-Day et al., 2015; Allen et al., 2008; Northoff and Qin, 2011). However, challenges remain in functional connectivity studies of AVH, including the prevalent use of antipsychotic medications in schizophrenia patients, which has been suggested to alter resting-state functional connectivity (Bolding et al., 2012; Lui et al., 2010; Sambataro et al., 2010). Moreover, as direct comparisons of patients with versus those without AVH are scarce, it is difficult to determine whether the observed abnormalities in functional connectivity are AVH-specific, or a general aspect of schizophrenia.

In the current study, we examined patterns of dysconnectivity related to AVH among regions consistently implicated by previous AVH studies, including the superior and middle temporal gyrus, inferior parietal lobule, inferior frontal cortex (pars triangularis and pars

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opercularis), anterior cingulate cortex (caudal and rostral part), postcentral gyrus and insula. To examine functional dysconnectivity in the absence of the potential confounds of psychotropic medications, we acquired resting-state fMRI data in first-episode medication-naïve schizophrenia patients and a group of demographically matched healthy controls. Comparing patients with versus those without AVH and healthy controls, we aim to identify functional dysconnectivity unique to, or most pronounced in, patients with AVH.

## 2. Methods

### 2.1. Subjects

A total of 54 subjects participated in this study, including 36 first-episode medication-naïve schizophrenia patients – 18 with auditory verbal hallucinations (AVH group) and 18 without hallucinations (non-AVH group) – and 18 healthy controls (CON group). These subjects were selected from a larger sample of 120 first-episode schizophrenia patients from a National Basic Research Program of China (No. 2011CB707805). The majority of patients had taken anti-psychotic medications at the time of recruitment, but only unmediated patients were selected for this current study, as described previously in a study on inter-hemispheric connectivity (Chang et al., 2015). The study was approved by the ethics committee of the Xijing Hospital, affiliated with the Fourth Military Medical University, Xi'an, China. All participants gave their written informed consent.

Patients were recruited from the outpatient clinic of the psychiatry department, meeting a diagnosis of schizophrenia through consensus of two senior clinical psychiatrists using the Structural Clinical Interview for DSM-IV (SCID) (First et al., 1995). Symptom severity was assessed using the Positive and Negative Syndrome Scale (Kay et al., 1987). Patients scoring 3 or more on PANSS hallucination item P3 were further evaluated for hallucination content and frequency. Those experiencing AVH at least once a day in the past four weeks were recruited in the AVH group. The non-AVH group included patients who scored 1 on P3 (absence of symptom) and did not experience hallucinations in the two years before recruitment. Healthy volunteers were recruited via advertisements and screened for the absence of DSM-IV axis I and II disorders. Exclusion criteria for all participants included a history of a neurological or severe medical disorder, substance abuse or dependency, prior electroconvulsive therapy or head injury resulting in loss of consciousness. All included participants were right-handed, matched on age, gender and education level (Table 1).

### 2.2. Image acquisition

Resting-state fMRI images and structural T1 scans were acquired for every subject on a 3.0-T Siemens Magnetom Trio Tim scanner. During image acquisition, the participants were instructed to lie still and keep their eyes closed without falling asleep. Subjects were judged to be awake at the start and end of scanning. Earplugs and a MRI-compatible

head coil were used to minimize head motion and attenuate scanner noise.

Resting-state functional scans were collected using a gradient-echo echo-planar imaging (EPI) sequence (TR = 2000 ms, TE = 30 ms, flip angle = 90°, FOV = 220 × 220 mm<sup>2</sup>). Whole-brain volumes comprised 33 contiguous transverse slices with 4 mm thickness, 0.6 mm gap and 3.40 × 3.40 mm<sup>2</sup> in-plane resolution. For every subject, 240 whole-brain volumes were acquired. T1-weighted high-resolution structural images were obtained using a three dimensional magnetization prepared rapid acquisition gradient echo (3D MPRAGE) sequence with the following parameters: TR = 2530 ms, TE = 3.5 ms, flip angle = 7°, FOV = 256 × 256 mm<sup>2</sup>, slice thickness = 1 mm, 192 slices with 0.5 mm gap.

### 2.3. Image preprocessing

Data preprocessing was performed using the SPM8 software package (<http://www.fil.ion.ucl.ac.uk/spm/>). Resting-state time-series were realigned to the first volume and then co-registered with the T1 image. Nuisance correction, including six realignment parameters, CSF and white matter signals was performed by linear regression. To further minimize the influence of head motion on resting-state fMRI data, each slice with a framewise displacement exceeding 0.5 – indicating excessive movement – was scrubbed following the procedure of Power et al. (2012), with framewise displacement defined as the sum of the absolute values of the derivatives of the six realignment parameters (Power et al., 2012; Van den Heuvel et al., 2013). There were no significant group-differences in either the number of deleted scans ( $F = 1.52$ ,  $p = 0.23$ ), or motion parameters after scrubbing ( $F = 0.60$ ,  $p = 0.56$ ). More detailed information is provided in the Supplementary Table 1. Time-series were bandpass filtered (0.01–0.05 Hz) to eliminate low frequency noise and influences of frequencies reflecting possible cardiac or respiratory oscillations.

### 2.4. Functional brain network reconstruction

Automated parcellation of the cortex into coherent regions was performed using Freesurfer's Desikan-Killiany atlas (Desikan et al., 2006), resulting in 82 brain areas for every subject. Functional connectivity between each pair of brain regions was defined as Pearson's correlation coefficient of regional time-series after Fisher's  $r$ -to- $z$  transformation. Both negative and positive correlation values (i.e. the full connectivity matrix) were included and constituted a functional network for every subject.

### 2.5. Regions of interest

As implicated by previous research, the emergence of AVH has been related to abnormalities in brain regions underlying language processing and higher order functions (Allen et al., 2012). To investigate the association between functional interaction among these regions and AVH

**Table 1**

Demographic and clinical characteristics of patients with AVH ( $n = 18$ ), patients without AVH ( $n = 18$ ), and healthy controls ( $n = 18$ ).

Characteristics	AVH patients	non-AVH patients	Controls	$p$ value
Age	22.56 ± 6.73	22.67 ± 3.80	24.44 ± 3.73	0.46
Sex (male/female)	10/8	9/9	10/8	0.93
Education (years)	12.44 ± 2.31	12.56 ± 2.20	13.89 ± 3.50	0.22
Duration of illness (months) <sup>a</sup> median (IQR)	5 (1.5, 6)	4.5 (2.25, 12)	–	0.54
PANSS Total Score <sup>b</sup>	106.44 ± 13.55	88.06 ± 23.90	–	0.01
PANSS Positive Score <sup>b</sup>	31.11 ± 6.92	18.61 ± 8.68	–	0.00
PANSS Negative Score	25.78 ± 3.87	22.06 ± 10.43	–	0.17
PANSS General Psychopathology	49.56 ± 9.01	47.39 ± 9.84	–	0.49

<sup>a</sup> Duration of illness was determined from first meeting schizophrenia diagnoses until recruitment into this study. Due to non-normal distribution of illness duration, median and interquartile range (IQR) were reported instead of mean and standard deviation. Group comparison was performed using Kruskal-Wallis H test.

<sup>b</sup> Patients with AVH have significantly higher Positive and Negative Syndrome Scale (PANSS) total and positive symptoms than patients without AVH. Groups were matched for age, gender, and education level.

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