

## Relationship of auditory verbal hallucinations with cerebral asymmetry in patients with schizophrenia: An event-related fMRI study

Zhijun Zhang<sup>a,b,\*</sup>, Jiabo Shi<sup>b</sup>, Yonggui Yuan<sup>b</sup>, Guifeng Hao<sup>a</sup>, Zhijian Yao<sup>b</sup>, Ning Chen<sup>b</sup>

<sup>a</sup> *The Department of Neuropsychiatry, Affiliated ZhongDa Hospital of Southeast University, Nanjing, China*

<sup>b</sup> *The Department of Psychiatry, Affiliated Brain Hospital of Nanjing Medical University, Nanjing, China*

Received 5 September 2006; received in revised form 2 March 2007; accepted 18 April 2007

### Abstract

The purpose of this study was to explore whether there are differences in cerebral asymmetry between subgroups of schizophrenic patients with or without auditory verbal hallucinations (AVHs) and normal controls by using event-related functional magnetic resonance imaging (efMRI). A total of 26 Chinese Han male patients with paranoid schizophrenia (diagnosed by DSM IV, including 13 patients with AVHs and 13 patients without) and 13 matched normal controls were recruited for the present study. The participants had been instructed to listen to short sentences from left or right side and to indicate laterality during efMRI scanning. Functional data were acquired using a 1.5 T MR, and were analyzed using statistical parametric mapping. A random-effect model was employed to assess the difference in blood oxygen level dependent response between “left-sided” and “right-sided” conditions. The results from the present study have shown (1) within group comparisons: right precuneus and right superior parietal lobule were significantly activated showed significantly greater activation by left-sided voices than right-sided ones in controls. However, no significant difference in activation was found in any brain region between left and right-sided voices in either of the two patient subgroups, (2) between group comparisons: in comparison with AVHs patients, right middle frontal gyrus (MFG) was markedly activated when control subjects were differentiating right-sided voices. In comparison with patients without AVHs, right-side stimuli significantly activated bilateral MFG and left postcentral gyrus in control group. Furthermore, compared to the non-hallucination group, left Wernicke’s area, including supramarginal gyrus, angular gyrus and superior temporal gyrus, was significantly activated by both left and right-sided voices in the hallucination group. In summary, auditory-related asymmetry in control subjects is attenuated in schizophrenic patients. The symptoms of AVHs in schizophrenia are possibly correlated with left hemispheric, particularly auditory and language-related areas dysfunction.

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**Keywords:** Auditory verbal hallucinations; Schizophrenia; Functional magnetic resonance imaging; Cerebral asymmetry

### 1. Introduction

Auditory verbal hallucinations (AVHs) refer to the experience of perceiving speech in the auditory modality without corresponding external stimuli. Tien (1991) reports that hallucinations of all modalities occur in

the general population at an annual incidence of 4–5%. AVHs are common features of psychotic illness and reportedly occur in 74% of subjects with schizophrenia in the International Pilot Study of Schizophrenia (Wing et al., 1974). The critical importance of AVHs as a discriminating diagnostic entity for schizophrenia is framed in the DSM-IV (American Psychiatric Association, 1994). Patients may become confused when experiencing AVHs, and these AVHs, especially auditory command hallucinations may be dangerous to community, family, and patients themselves.

\* Corresponding author. Address: The Department of Neuropsychiatry, Affiliated ZhongDa Hospital of Southeast University, Nanjing, China. Tel.: +86 25 83272023; fax: +86 25 83285132.

E-mail address: [zhijunzhang838@yahoo.com.cn](mailto:zhijunzhang838@yahoo.com.cn) (Z. Zhang).

In the previous studies, many attempts have been made to elucidate the pathogenesis of AVHs, but, to date, the neurocognitive and neurophysiological bases of AVHs remain obscure. However, neuropsychology combined with electrophysiology and neuroimaging have provided valuable research strategies. At present the asymmetry abnormalities, inner speech disorder and disinhibition hypotheses of AVHs are popular (David, 1999; Stephane et al., 2001). Research approaches are particularly focused on abnormalities of asymmetry in temporal cortical and related language areas such as Wernicke's area.

Growing evidence from several lines indicate that the pathogenesis of schizophrenia may involve abnormality and dysfunction of the left hemisphere (Crow, 1990; Bogerts, 1997), with less abnormality in the right hemisphere (Mitchell and Crow, 2005). Structural neuroimaging and neuropathologic studies demonstrated reduction in size of the left hemisphere including frontal, lingual, temporal and occipital lobes (reviewed by Antonova et al., 2004, 2005) and the inferior parietal lobe (Niznikiewicz et al., 2000) in schizophrenics. However, some studies emphasize left-sided temporal lobe abnormalities in addition to more diffuse brain abnormalities (Woodruff, 1995). Particularly, a significant reduction in the size of the left planum temporale (and hence reduced asymmetry) was found in post-mortem (Falkai et al., 1995) and in structural MRI studies (Petty et al., 1995; Barta et al., 1997). The planum temporale, the posterior superior surface of the superior temporal gyrus, is usually larger on the left and has a critical role in supporting language function. Significant correlations between volume reductions of left anterior superior temporal gyrus and severity of AVHs have been reported (Rajarethinam et al., 2000) with inconsistent results (Shapleske et al., 2001). Most recently, Neckelmann et al. (2006) reported grey matter volume reductions in the left STG associated with severity of hallucination in patients with schizophrenia, and proposed that reductions in grey matter might be instrumental in generating spontaneous neuronal activity that is associated with speech perception experiences in the absence of an external acoustic stimulus.

The evidence raised from studies of brain function has led to suggestions that deficits of left temporal lobe language areas could account for a number of alterations in functional asymmetry in hallucination-prone schizophrenic individuals, such as reduced right ear (left hemisphere) advantage on dichotic listening tasks (Green et al., 1994; Loberg et al., 2004) and reduced left temporal cortical activation when listening to single words or when monitoring inner speech (Malaspina et al., 2000; Aydin et al., 2001). In addition, electrophysiology studies have found strong association of the left superior temporal cortex with the experience of AVH in schizophrenics by magnetoencephalography measurement (Ishii et al., 2000). Decrement of the auditory P300 component of the event-related potentials is a robust finding in schizophrenic patients and seems to be most pronounced in the left temporal region particularly in the hallucinating individuals (Havermans et al., 1999).

The study of brain lateralization with functional magnetic resonance imaging (fMRI) has demonstrated variation in healthy subjects, ranging from strong leftward lateralization (in most subjects) to bilateral processing, and in rare cases to rightward lateralization (Springer et al., 1999). In addition, fMRI studies have found increased activation in frontal areas, particularly in the left inferior frontal gyrus, when subjects listen to words or sentences contrasted with sequences of silence or reversed speech. Jancke et al. (2003) further reported extended activations in a fronto-temporal cortical network in response to dichotic presentations of consonant-vowel (CV) syllables in neurologically intact subjects. So far, functional neuroimaging studies have produced these behavioral findings by showing a relationship between AVHs and dysfunction of left temporal lobe asymmetry for auditory stimuli, with reduced functions (Woodruff et al., 1997; Sommer et al., 2001; Plaze et al., 2006) and enhancement of activations (McGuire et al., 1993; Silbersweig et al., 1995; Dierks et al., 1999; Shergill et al., 2001). The experience of AVHs itself may involve cortical language regions, particularly in the left temporal lobe (Lennox et al., 1999). Shergill et al. (2004) reported that activation in the left inferior frontal and right middle temporal gyri was evident 6–9 s before onset of hallucinations, whereas activation in the bilateral temporal gyri and the left insula coincided with the perception of the hallucination.

The aim of the study is to use event-related fMRI to explore whether there are regional differences in brain activation by left-sided and right-sided voice stimulation between subgroups of schizophrenic patients with or without AVHs and normal controls, and further test whether abnormalities of asymmetry in schizophrenic patients may be related to production of AVHs.

## 2. Methods

### 2.1. Subjects

Twenty-six Chinese Han male inpatients with DSM-IV diagnoses of paranoid schizophrenia were recruited from the Psychiatry Department of Affiliated Brain Hospital of Nanjing Medical University from November 2004 to August 2005. All patients were assessed clinically by two senior psychiatrists (JB Shi and ZJ Yao) within 1 day of testing using the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1983a) and the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1983b). According to the AVH score of the SAPS, the patients were divided into two subgroups named hallucination group and non-hallucination group, in which the patients with a score >4 for AVHs on the SAPS and a history of AVHs for at least 2 weeks, were classed as hallucination group ( $n = 13$ ), and those who scored 0 for auditory hallucinations on the SAPS and without a history of AVHs were classed as non-hallucination group ( $n = 13$ ). In the hallucination group, 10 patients were first episode and 3

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