Aberrant Functional Connectivity Patterns of Default Mode Network May Play a Key Role in the Interaction between Auditory Verbal Hallucinations and Insight

Ri-Xing Jing[1,2], Shen Li[3,4], Xin-Jun Zhang[3], Jing Long[3], Tian-Hong Zhou[3], Chuan-Jun Zhuo[3]

[1]Department of Pattern Recognition, National Laboratory of Pattern Recognition, Institute of Automation, Chinese Academy of Sciences, Beijing 100190, China
[2]Department of Pattern Recognition, University of Chinese Academy of Sciences, Beijing 100049, China
[3]Tianjin Mental Health Center, Psychiatric Neuroimaging Laboratory, Tianjin Anding Hospital, Tianjin 300222, China
[4]Department of Psychiatry, College of Basic Medical Sciences, Tianjin Medical University, Tianjin 300070, China

Ri-Xing Jing and Shen Li contributed equally to this work.

Previous studies have reported that auditory verbal hallucinations (AVHs) may be caused by resting-state neuronal hyperactivity in the default mode network (DMN). Abnormally increased functional connectivity (FC) between the DMN and other cortical regions may cause disturbances in neuronal network architecture and interactions. Subsequently, disturbed neuronal network architecture and interactions may induce increased activation in auditory and speech perception areas in the absence of external auditory stimuli as well as reduced activation in the same areas in the presence of external auditory stimuli. These disturbances may be the neural basis of AVHs.[1] In addition, insight, which is another core characteristic of schizophrenia, has been associated with treatment compliance, relapses, long-term outcomes, and global functioning ability. Some studies have reported that insight is also related to disturbance of the DMN, especially self-monitoring: poor insight is associated with increased connectivity between the self-referential network and the left insula.[2] The self-referential network may be considered a component of the DMN.[2,3] Based on the aforementioned findings, we found that DMN alteration is associated both with AVHs and with insight. However, to the best of our knowledge, no one has yet studied FC patterns (FCPs) between the DMN and other brain regions associated with AVHs in schizophrenic patients with and without insight. Aberrant FCPs between DMN and other brain regions might play a key role in the interaction between AVHs and insight.

Based on previous studies[4] we conducted an exploratory pilot study to investigate FCPs between the DMN and other brain regions related to schizophrenics' experiences of AVHs with and without insight using the FC map technique. We hypothesized the existence of distinct FCPs between the DMN and other brain regions related to schizophrenics' experiences of AVHs with and without insight.

For this pilot study, we selected seven AVH-schizophrenic patients without insight, six AVH-schizophrenic patients with insight and 22 healthy controls (HCs) from our database for inclusion in FCP analysis. All subjects provided written informed consent prior for this study, and the protocol was approved by the Committee on Studies Involving Human Beings at Tianjin Anding Hospital. The mean antipsychotic dosage (chlorpromazine equivalents) was 374.0 ± 163.8 mg/d in AVH-schizophrenic patients without insight and 375.2 ± 190.5 mg/d in AVH-schizophrenic patients with insight ($P = 0.98$ for a contrast between the two patient groups). There were no significant differences in age, gender, or education level among the three groups.

Preprocessing was performed with Statistical Parametric Mapping software (SPM8, http://www.fil.ion.ucl.ac.uk/spm/software/spm8/), the Analysis of Functional NeuroImage (AFNI, http://afni.nimh.nih.gov/afni) package, and the

Address for correspondence: Dr. Chuan-Jun Zhuo,
Tianjin Mental Health Center, Psychiatric Neuroimaging Laboratory,
Tianjin Anding Hospital, Tianjin 300222, China
E-Mail: chuanjunzhuotjmh@163.com

FMRIB Software Library (FSL, http://fsl.fmrib.ox.ac.uk/fsl). The first 10 images were discarded. Images were then corrected for slice-timing and motion. Each functional magnetic resonance imaging (fMRI) scan was intensity-scaled to have a whole brain mean value of 10,000. Temporal bandpass filtering (0.01–0.08 Hz) was performed, and 6 affine motion parameters from the data were also regressed. Removal of linear and quadratic trends was also performed. Single-subject images were spatially normalized to the Montreal Neurological Institute space using the DARTEL algorithm in SPM8, resampled to 3 mm × 3 mm × 3 mm during normalization, and smoothed with a 6-mm full-width at half-maximum Gaussian kernel. The maximum frame-wise displacement (FD) between time points was computed for each subject, and the subjects excessive movement (FD >3 mm) were excluded from the study.

The posterior cingulate cortex (PCC) forms a central node of the DMN and has an important role in schizophrenia. In this study, the PCC was used as the seed region for FC map analysis to assess FCPs s in DMN related to schizophrenics' experiences of AVHs with and without insight. We chose the bilateral PCC as a whole-brain seed region from an Anatomical Automatic Labelling template. For each scan, the mean time series of voxels in the PCC was applied as a seed to produce whole-brain voxel-wise FC maps using Pearson's correlation. Then, Fisher's z transformation was used to transform Pearson's correlation to z-values.

Considering the limited sample size, we investigated group differences in fMRI results between each pair of groups (AVH-schizophrenic patients without insight vs. HCs, AVH-schizophrenic patients with insight vs. HCs, and AVH-schizophrenic patients without insight vs. AVH-schizophrenic patients with insight) using Statistical nonParametric Mapping (SnPM13, http://warwick.ac.uk/snpm), which provides an extensible framework for nonparametric permutation tests based on the general linear model as well as pseudo t-statistics for independent observations. A two-tailed, pseudo voxel-level one-sample t-test was first performed on the whole-brain FC maps of HCs with age and sex as covariates ($n = 1000$ permutations, family-wise error (FWE)-corrected, $P < 0.05$). Then, between-group analyses were conducted using pseudo voxel-level two-sample t-tests within a mask including brain regions in which HCs showed statistically significant FC measures, with age, sex, and illness duration as covariates ($n = 1000$ permutations, cluster size >30 for AVH-schizophrenic patients without insight vs. AVH-schizophrenic patients with insight, $P < 0.01$; cluster size >50 for comparisons of AVH-schizophrenic patients without insight vs. HCs and AVH-schizophrenic patients with insight vs. HCs, $P < 0.01$).

The primary finding of this pilot study is that when compared with the AVH-schizophrenic patients with insight, patients without insight demonstrated increased FC in the PCC-frontal lobe-cingulate cortex circuit; in addition, decreased FC was observed in the PCC-right cerebrum circuit [Figure 1a]. When compared to HCs, AVH-schizophrenic patients without insight did not display any differences in FC [Figure 1b]. However, more interestingly, AVH-schizophrenic patients with insight demonstrated decreased FC relative to HCs in the PCC-frontal lobe-angular gyrus circuit [Figure 1c].

The preliminary findings indicated that AVH-schizophrenic patients without insight demonstrated an increased FCP in the PCC-frontal lobe-cingulate cortex circuit. This circuit is a key component of the DMN; thus, this finding strongly supports the hypothesis that increased spontaneous neural activity of DMN is the neural basis of AVHs as well as the hypothesis of increased spontaneous neural activity in the self-referential network. In combination, the above findings suggest that DMN hyperactivity might play a key role in the interaction between AVHs and poor insight. In contrast, we found decreased FC in the PCC-frontal lobe-angular gyrus circuit. This finding provides converging support for our suggestion that DMN hyperactivity may play a key role in the interaction between AVHs and poor insight.[1-5]

However, there are several limitations to the pilot study. First, the small sample size may affect the strength of our findings. These findings provide only initial evidence for further study. In future studies, we will consider this flaw and address this gap. Second, in this pilot study, we only enrolled chronic patients, and selection bias may reduce the strength of our findings. In further studies, we will conduct a well-designed long-term follow-up study enrolling a large sample to further explore mechanisms of AVHs, insight, and the interaction between AVHs and insight. We will acquire baseline MRI data from these drug-naïve first-episode patients, and MRI data will then be acquired once every 6 months for 2–3 years. Through these data, we can characterize the dynamic trajectory of patients' symptoms and brain characteristics (such as the specific trajectory of neural markers of AVHs in schizophrenic patients and the specific trajectory of neural markers of insight in schizophrenic patients). Although such a study will be extremely time-consuming and laborious, it can precisely identify specific pathological targets and provide an objective index for precise treatment strategies, thereby elevating the early remission rate.

Although many flaws exist in this preliminary study and future studies are needed to clarify the results, our preliminary findings tend to support the hypothesis that aberrant FCPs in DMN might play a key role in the interaction between AVHs and insight. Although the findings of this pilot study are limited by the small sample size and other flaws, they may nevertheless provide useful clues for further study.

Conflicts of interest
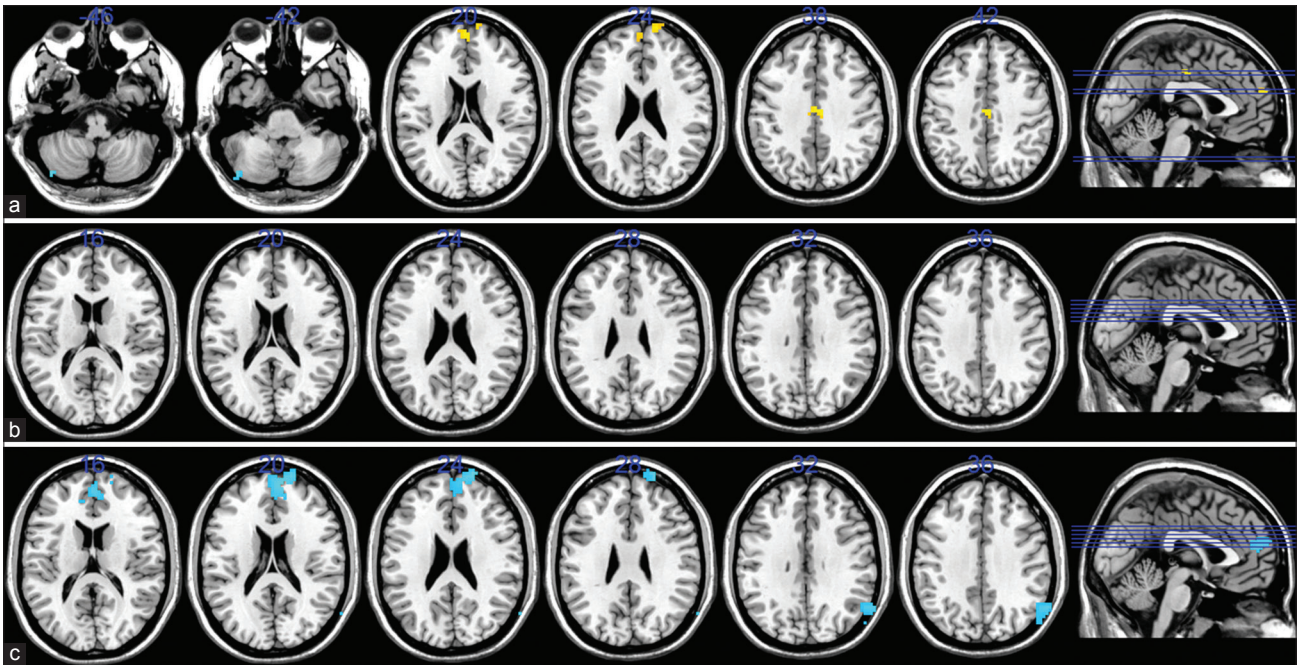There are no conflicts of interest.

Figure 1: DMN functional connectivity patterns differences between AVH-schizophrenic patients without insight, AVH-schizophrenic patients with insight and healthy controls. (a) When compared with the AVH-schizophrenic patients with insight, patients without insight demonstrated increased FC in the PCC-frontal lobe-cingulate cortex circuit; in addition, decreased FC was observed in the PCC-right cerebrum circuit. (b) When compared with HCs, AVH-schizophrenic patients without insight did not display any differences in FC. (c) AVH-schizophrenic patients with insight demonstrated decreased FC relative to HCs in the PCC-frontal lobe-angular gyrus circuit. AVH: Auditory verbal hallucination; DMN: Default mode network. FC: Functional connectivity; PCC: Posterior cingulate cortex; HCs: Healthy controls.

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