Impaired brain white matter and functional networks in healthy individuals with auditory verbal hallucinations

Xiao-Dong Lin[1], De-Guo Jiang[1], Lang-Lang Cheng[1], Ce Chen[1], Chong-Guang Lin[1], Chuan-Jun Zhuo[1,2]

[1]Department of Psychiatry, Psychiatric-Neuroimaging-Genetics Laboratory, Wenzhou seventh People's Hospital, Wenzhou, Zhejiang 325000, China;
[2]Department of Psychiatric-Neuroimaging-Genetics and Comorbidity Laboratory, Tianjin Mental Health Centre, Tianjin Anding Hospital, Tianjin 300222, China.

To the Editor: Auditory verbal hallucinations (AVHs) are experienced concomitantly with various neuropsychiatric diagnoses including schizophrenia, bipolar disorder, major depression disorder, post-traumatic stress disorder, and borderline personality disorder.[1] Notably, AVHs are also experienced by individuals without a neuropsychiatric diagnosis.[1,2] According to the strictest diagnostic criterion ("Did you at any time hear voices saying quite a few words or sentences when there was no one around that might account for it"), the prevalence of AVHs in the general population is 0.7%. According to the normal criterion ("Over the past year, have there been times when you heard or saw things that other people could not"), the prevalence of AVHs in the general population is 4.2%.[3] Otherwise healthy individuals who experience AVHs can be called healthy individuals with AVH (H-AVHs).[3] The 6.2% to 20.0% of H-AVHs have been reported to develop psychosis within 2 to 5 years of AVH onset. In the absence of psychosis, a minority H-AVH subjects need clinical care.[4,5] Nonetheless, research on AVHs in healthy populations is helpful for elucidating treatment effects on AVHs in clinical populations.[5]

Structural and functional alterations have been found in the brains of H-AVHs in previous neuroimaging studies. A study found that brain structural alterations related to the H-AVH condition were located mainly in a region of the supplementary motor area associated with speech and language.[6] Spray *et al*[7] reported that H-AVHs exhibited left superior temporal gyrus impairment. The other study reported that H-AVHs might experience functional disturbances affecting auditory, memory, and language areas as well as areas in the default mode network and salience network.[8] However, to the best of our knowledge, no study has reported brain structural and functional alterations in Chinese H-AVHs.

This study was conducted in accordance with the *Declaration of Helsinki* and was approved by the Ethics Committee of Wenzhou Seventh People's Hospital. Written informed consent was obtained from each subject. The study was conducted from July 2017 to October 2018. All data were acquired at Wenzhou Seventh People's Hospital. The present study included 24 H-AVHs (meeting the aforementioned strictest criterion) and 29 demographically matched healthy controls. The demographic and clinical characteristics of the 2 groups are reported in Table 1.

This study used tract-based spatial statistics (TBSS) to investigate differences in white matter between H-AVH subjects and matched healthy controls, as described in a previous study.[9] GRETNA software (http://www. nitrc. org/projects/gretna/)[10] was employed to define functional networks and compare functional networks alterations between H-AVH subjects and healthy controls. The scans were performed with a 3.0-T MR system (Discovery MR750, General Electric, Milwaukee, WI, USA). A 3-dimensional T1-weighted brain volume (BRAVO) sequence with 188 sagittal slices was obtained for each subject with the following parameters: repetition time = 8.2 ms; echo time = 3.2 ms; inversion time = 450 ms; flip angle = 12°; field of view = 256 mm × 256 mm; matrix = 256 × 256; slice thickness = 1 mm; and no gap. MRI data analysis was performed at Tianjin Mental Health Center. The images were processed in PANDA software, which is a MATLAB toolbox that integrates the FSL (https://fsl. fmrib.ox.ac.uk/fsl/fslwiki), Diffusion Toolkit (http://www. trackvis.org/dtk/), and MRIcron (https://www.nitrc.org/ projects/mricron) programs. Distances from individual voxels to the image skeleton were used to project DTI metric values onto the original mean fractional anisotropy skeleton according to the TBSS protocol. Resting-state

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.1097/CM9.0000000000000106

Correspondence to: Prof. Chuan-Jun Zhuo, Department of Psychiatry, Psychiatric-Neuroimaging-Genetics Laboratory, Wenzhou seventh People's Hospital, Wenzhou, Zhejiang 325000, China; Department of Psychiatric-Neuroimaging-Genetics and Comorbidity Laboratory, Tianjin Mental Health Center, Tianjin Anding Hospital, Tianjin 300222, China
E-Mail: chuanjunzhuotjmh@163.com

Chinese Medical Journal 2019;132(5)

Received: 10-11-2018 **Edited by:** Xin Chen

Table 1: Demographic and clinical characteristics of the study groups.

Characteristics	H-AVH subjects ($n=24$)	Healthy controls ($n=29$)	Statistical values	*P*
Male/female, *n*	8/16	14/15	1.208*	0.272
Age (years), mean ± SD	32.1 ± 11.0	32.4 ± 6.9	0.076	0.939
Education time (years), mean ± SD	10.9 ± 2.9	11.3 ± 4.2	0.420	0.667
Illness duration (years), mean ± SD	10.0 ± 2.7	–	–	–
AVH scores, mean ± SD	34.1 ± 6.2	–	–	–

* χ^2 value, otherwise *t* value. AVH: Auditory verbal hallucination; –: Not applicable; SD: Standard deviation.

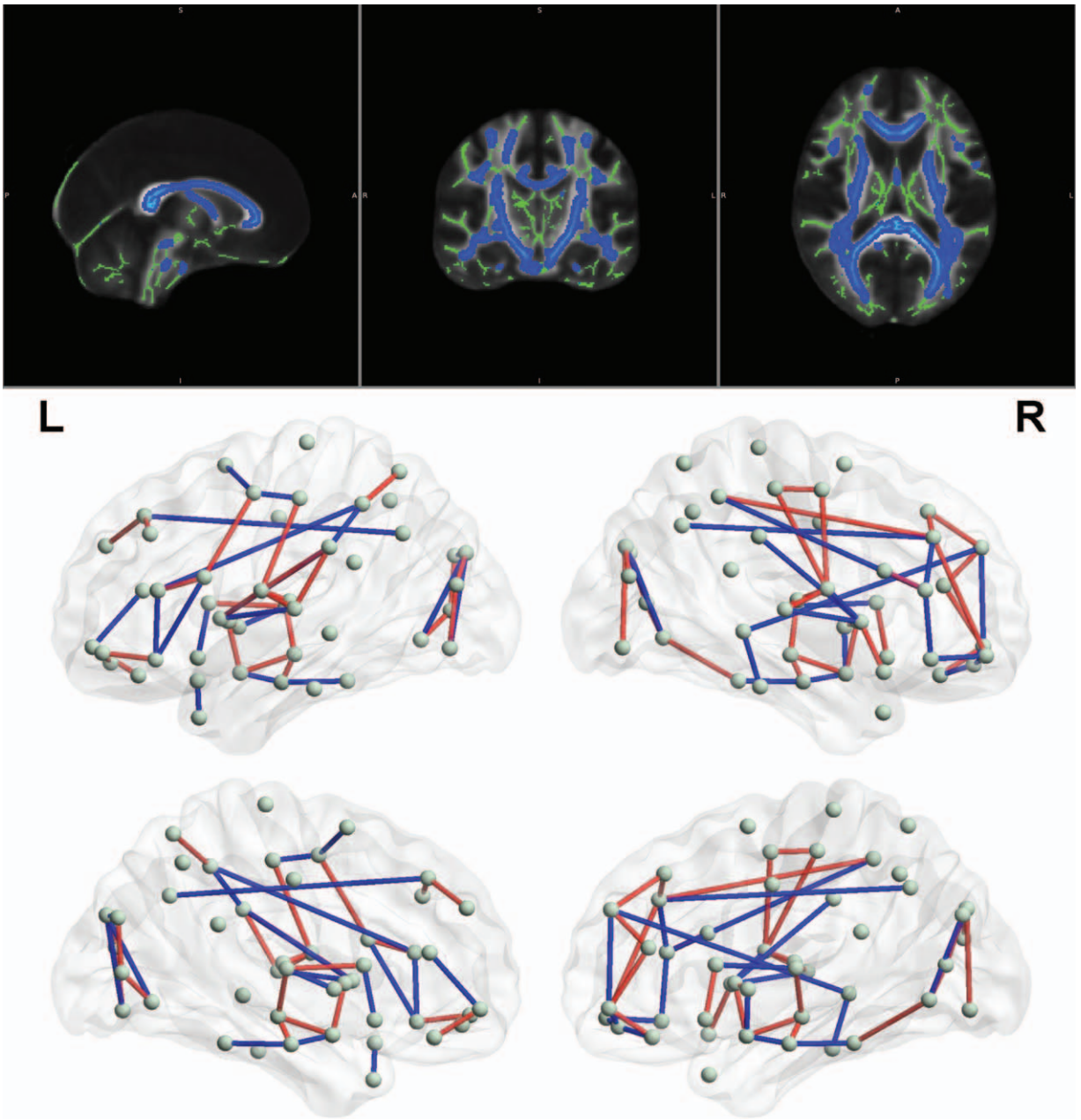

Figure 1: Differences in white matter tracts and functional connectivity networks of H-AVHs compared with healthy controls. In the 3 black-background images (above), blue indicates areas of white matter impairment. In 4 node-vertex images (below), blue indicates decreased connectivity and red indicates increased connectivity in the H-AVH group relative to healthy controls. H-AVH: Healthy individuals with auditory verbal hallucination.

BOLD data were preprocessed in Statistical Parametric Mapping 8. All participants' BOLD data were within the defined motion thresholds (translational and rotational movements <2 mm and <2°, respectively). Several nuisance covariates (6 motion parameters, their first-time derivations, the global brain signal, the white matter signal, and the cerebrospinal fluid signal) were regressed out of the data. The whole-brain network was constructed in GRETNA 2 software. To further denoise spurious interregional correlations, only those correlations with significance levels that survived a $P < 0.05$ (Bonferroni corrected) threshold were retained, a well-established brain network analysis threshold.

We found white matter disruptions affecting widespread brain regions, including the corpus callosum, arcuate fasciculus, cortico-spinal tracts, anterior commissure, and posterior commissure, in the H-AVH group. These alterations were far more extensive than we had expected, suggesting a need for the development of preventive measures to protect white matter tracts in healthy individuals who experience AVHs. With respect to functional networks, we found markedly decreased functional connectivity among parietal, occipital, temporal, and frontal regions in the H-AVH group relative to the control group [Figure 1].

As far as we know, this pilot study first investigated AVH-associated WM impairment and functional network alterations in Chinese Hi-AVH subjects. We found WM alterations impacting almost all of the major tracts of the brain in our H-AVH subjects together with complex disturbance pattern in functional networks. These findings indicated that H-AVH subjects had structural and functional impairments affecting essentially the whole brain. Consistent with previous studies,[2-5] the present findings supported the hypothesis that AVHs were accompanied by structural and functional impairments affecting many important neural circuits and brain networks, with prominent involvement of regions in the frontal and temporal lobes that were important components of auditory processing circuitry.

This study had several limitations. First, we enrolled subjects with persistent AVH symptoms who might thus present more obvious alterations and brain network impairments than healthy individuals with infrequent AVHs. This characteristic of our study sample could have biased our neuroimaging data. Second, although we repeated our analyses 3 times, our work did not encompass the complexity of graph theory analysis, which would be expected to provide greater detail regarding inter-group differences. In the future, we plan to collaborate with professors who are proficient in graph theory analysis to explore the pathological features of AVHs further. Third, we did not assess what other symptoms the H-AVHs were experiencing, such as distress, anxiety, and depression. Because these factors may influence our findings, we will consider these factors in our future work. Last, our sample was relatively small. Larger cohorts will be enrolled in future studies.

In conclusion, despite the aforementioned limitations, this study revealed, for the first time, structural and functional impairments affecting many key neural circuits and networks in H-AVHs. These findings contributed to the elucidation of the pathological features of AVHs.

Funding

This work was supported by grants from the Tianjin Health Bureau Foundation (No. 2014KR02), Wenzhou Science and Technology Project (No. ZS2017011), and the National Natural Science Foundation of China (No. 81871052).

Conflicts of interest

None.

References

1. Upthegrove R, Broome MR, Caldwell K, Ives J, Oyebode F, Wood SJ. Understanding auditory verbal hallucinations: a systematic review of current evidence. Acta Psychiatr Scand 2016;133:352–367. doi: 10.1111/acps.12531.
2. Sommer IE, Daalman K, Rietkerk T, Diederen KM, Bakker S, Wijkstra J, *et al*. Healthy individuals with auditory verbal hallucinations; who are they? Psychiatric assessments of a selected sample of 103 subjects. Schizophr Bull 2010;36:633–641. doi: 10.1093/schbul/sbn130.
3. Johns LC, Kompus K, Connell M, Humpston C, Lincoln TM, Longden E, *et al*. Auditory verbal hallucinations in persons with and without a need for care. Schizophr Bull 2014;40:S255–S264. doi: 10.1093/schbul/sbu005.
4. Daalman K, Diederen KM, Hoekema L, van Lutterveld R, Sommer IE. Five year follow-up of non-psychotic adults with frequent auditory verbal hallucinations: are they still healthy? Psychol Med 2016;46:1897–1907. doi: 10.1017/S0033291716000386.
5. Baumeister D, Sedgwick O, Howes O, Peters E. Auditory verbal hallucinations and continuum models of psychosis: a systematic review of the healthy voice-hearer literature. Clin Psychol Rev 2017;51:125–141. doi: 10.1016/j.cpr.2016.10.010.
6. Diederen KM, van Lutterveld R, Sommer IE. Neuroimaging of voice hearing in non-psychotic individuals: a mini review. Front Hum Neurosci 2012;6:111. doi: 10.3389/fnhum.2012.00111.
7. Spray A, Beer AL, Bentall RP, Sluming V, Meyer G. Microstructure of the superior temporal gyrus and hallucination proneness - a multi-compartment diffusion imaging study. Neuroimage Clin 2018;20:1–6. doi: 10.1016/j.nicl.2018.06.027.
8. Alderson-Day B, Diederen K, Fernyhough C, Ford JM, Horga G, Margulies DS, *et al*. Auditory hallucinations and the brain's resting-state networks: findings and methodological observations. Schizophr Bull 2016;42:1110–1123. doi: 10.1093/schbul/sbw078.
9. Zhu J, Zhuo C, Qin W, Wang D, Ma X, Zhou Y, *et al*. Performances of diffusion kurtosis imaging and diffusion tensor imaging in detecting white matter abnormality in schizophrenia. Neuroimage Clin 2015;7:170–176. doi: 10.1016/j.nicl.2014.12.008.
10. Xu J, Chen F, Lei D, Zhan W, Sun X, Suo X, *et al*. Disrupted functional network topology in children and adolescents with post-traumatic stress disorder. Front Neurosci 2018;12:709. doi: 10.3389/fnins.2018.00709.

How to cite this article: Lin XD, Jiang DG, Cheng LL, Chen C, Lin CG, Zhuo CJ. Impaired brain white matter and functional networks in healthy individuals with auditory verbal hallucinations. Chin Med J 2019;132:606–608. doi: 10.1097/CM9.0000000000000106