Research article

Depressive symptoms combined with auditory hallucinations are accompanied with severe gray matter brain impairments in patients with first-episode untreated schizophrenia – A pilot study in China

Chuanjun Zhuoa,b,c,*,1, Xuexin Xud,1, Xiaodong Linb,1, Min Chenb, Feng Jia, Deguo Jiangb, Yong Xued,f, Lina Wangc, Yancheng Lic, Hongjun Tianc, Wenqiang Wangg, Chunhua Zhouh

a Department of Biological Psychiatry, School of Mental Health, Jining Medical University, Jining 272191, Shandong Province, China
b Department of Psychiatry and Neuroimaging Center, Wenzhou Seventh People’s Hospital, Wenzhou, 325000, Zhejiang Province, China
c Psychiatric-Neuroimaging-Genetics and Comorbidity Laboratory (PNGC_Lab), Tianjin Anding Hospital, 300300 Tianjin, China
d Department of Radiology, MRI Center, Tianjin Children Hospital, Tianjin Medical University Affiliated Tianjin Children Hospital, Tianjin 300444, China
e Department of Psychiatry, First Hospital/First Clinical Medical College of Shanxi Medical University, Taiyuan, China
f MDT Center for Cognitive Impairment and Sleep Disorders, First Hospital of Shanxi Medical University, Taiyuan 030001, China
g Canada and China Joint Laboratory of Biological Psychiatry, Xiamen Xianye Hospital, Xiamen 361000, Fujian Province, China
h Department of Pharmacology, The First Hospital of Hebei Medical University, Shijiazhuang 050000, Hebei Province, China

ARTICLE INFO

Keywords:
Auditory hallucination
Depressive symptom
Schizophrenia

ABSTRACT

Background: Depressive symptoms and auditory hallucinations (AHs) are often accompanied by gray matter volume (GMV) alterations in schizophrenia. However, little is known about the effects of concurrent depressive symptoms and AHs on the GMV of patients with schizophrenia.

Aim: To investigate the pathological features of gray brain matter in patients with first-episode untreated schizophrenia (FUSCH) who have concurrent moderate-to-severe depressive symptoms and AHs (FUSCH-DAH).

Methods: The Calgary Depression Scale for Schizophrenia (CDSS) and Auditory Hallucinations Rating Scale (AHRS) were adopted. Voxel-based morphometry (VBM)-based GMV analyses were used to measure cortical alterations. FUSCH-DAH patients were compared to FUSCH patients with depressive symptoms but without AHs, denoted as FUSCH-D, along with healthy controls.

Results: GMV reductions were more substantial in the FUSCH-DAH patients than FUSCH-D patients or healthy controls. Both FUSCH-DAH and FUSCH-D groups showed GMV reductions of the parietal, frontal, and temporal lobes, which were not apparent in the healthy controls. Compared to FUSCH-D patients, FUSCH-DAH patients demonstrated more substantial GMV reductions in the Broca area, Wernicke region, insular lobe, and prefrontal lobe. The GMV reductions were 1.06% and 0.58% in FUSCH-DAH and FUSCH-D patients, respectively, as compared with the healthy controls.

Conclusions: This is the first report showing that concurrent depressive symptoms and AHs leads to severe GMV deterioration in FUSCH-DAH patients. Hence, there is a reciprocal relationship between AHs and depressive symptoms in FUSCH-DAH patients. However, the potential additive effects of concurrent AHs and depressive symptoms require further investigation in order to identify future targeted therapies for schizophrenia.

1. Introduction

The impact of depressive symptoms on the progression and treatment of schizophrenia remains to be fully understood [1]. Several findings have converged to demonstrate that depressive symptoms can decrease the efficacy of most schizophrenia therapies used in the clinic [2]. In addition, depressive symptoms increase the risk of self-harm and suicide in patients with schizophrenia [1]. Despite the connection between schizophrenia and depression, the combination of antipsychotic agents with antidepressants is often ineffective for patients with schizophrenia who have depressive symptoms [3–5]. Depressive symptoms may occur during any stage of schizophrenia, including the prodromal stage, episode stage, and remission, and result in a significantly elevated risk of developing psychosis [1,6]. More notably, depressive
symptoms in patients with schizophrenia usually cause treatment difficulty, with some patients developing treatment resistance [2,4,5,7]. Hence, there is an urgent need for new treatment strategies for improving the outcomes of patients with schizophrenia who have depressive symptoms.

Auditory hallucinations (AHs) are highly prevalent in patients with schizophrenia [7,8]. Previous studies reported that AHs can impact the depressive symptoms in patients with schizophrenia and further deteriorated their social interaction with the real world. This can ultimately impact the other abilities of these patients with schizophrenia, further deteriorating the prognosis of these patients in the clinic [2-5]. The relationship between AHs and depressive symptoms can be reciprocal deteriorated. This relationship between depressive symptoms and AHs can further increase suicidal ideation in patients with schizophrenia who have concurrent depressive symptoms and AHs [9-13]. Conventional treatments for AHs may slightly reduce depressive symptoms and improve the quality of life in patients with schizophrenia [4,5,7]. However, the effects of conventional treatments in FUSCH-DAH patients are limited [14]. Currently, the primary treatment strategies for FUSCH-DAH patients include augmentation with antipsychotic agents [14], transcranial direct current stimulation (tDCS) treatment [15,16], repetitive transcranial magnetic stimulation (rTMS) treatment [17,18] and ECT treatment [19,20]. All the studies mentioned above converge to suggest that the co-occurrence of depressive symptoms and AHs may be a predictor of treatment-resistant schizophrenia. A better understanding of the brain-based pathological features associated schizophrenia may aid in the development of new treatment strategies in the future.

In the past decade, mounting evidence has shown that schizophrenia is associated with widespread gray matter volume (GMV) reductions of the brain [21-25]. According to the neuro-developmental hypothesis of schizophrenia, GMV reductions may develop in patients during adolescence or early adulthood, when the psychotic symptoms are not readily apparent. In addition, a lot of studies have reported that GMV reduction can occur during any stage of schizophrenia, and also can be deteriorated by antipsychotic treatment and duration of treatment [26-29]. GMV reductions are primarily located in occipital lobe, parietal lobe, temporal lobe and frontal lobe. Simultaneously, several studies reported that GMV reductions were observed in the patients with major depression. GMV reductions were primarily located in the regions of prefrontal cortex, the hippocampus, and the striatum [30]. In addition, GMV reduction can be observed during the first episode of depression and may deteriorate with antidepressants treatment [31]. Previous studies reported that GMV reductions in patients with schizophrenia with depressive symptoms was more serious than patients with schizophrenia without depressive symptoms [32,33], even in the first episode patients [34]. Simultaneously, several studies have reported that auditory verbal hallucinations (AVHs) in patients with schizophrenia are normally accompanied by substantial GMV reductions [22-24]. However, to the best of our knowledge, few studies have focused on GMV alterations in FUSCH patients with co-occurred depressive symptoms and auditory verbal hallucinations (FUSCH-DAH) and FUSCH patients with depressive symptoms but without AHs (FUSCH-D).

In this brief report, we have conducted a pilot study to investigate GMV alterations in FUSCH-DAH and FUSCH-D patients. We hypothesized as the following: 1) FUSCH-DAH patients would display substantial GMV differences than FUSCH-D patients, 2) the reciprocal deterioration of depressive symptoms and AHs may be associated with related GMV alterations, 3) the GMV differences between two groups may be related to the severity of depressive symptoms or AHs.

2. Materials and methods

From July 2016 to July 2019, 60 patients and 50 healthy controls were enrolled from the inpatient and outpatient departments of five institutes including (1) Jining Medical University, (2) Tianjin Anding Hospital, (3) Wenzhou Seventh People’s Hospital, (4) Xiamen Xianyue Hospital, and (5) the First Hospital of Shanxi Medical University. All participants volunteered to participate in this study and provided written informed consent prior to inclusion in the study. This study was approved by the Ethics Committee of Jining Medical University, Tianjin Anding Hospital, Wenzhou Seventh People’s Hospital, Xiamen Xianyue Hospital, and the Shanxi Medical University Joint Project Group (No. JTWXS-001). The same magnetic resonance imaging (MRI) systems and parameters were used in all five institutions to assure high consistency between the objective indices.

2.1. Participants

The patients had to meet the criteria including: (1) between 18–30 years of age; (2) meet the diagnostic criteria of schizophrenia according to the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV-TR; (3) had first-episode schizophrenia, which is defined as the psychotic symptoms of schizophrenia presented in the past 6 months, with the severity of the symptoms reaching the diagnostic criteria of schizophrenia, and impairment of global function, as compared to the time before the psychotic symptoms [35]; (4) schizophrenia must be accompanied by moderate-to-severe depressive symptoms based on the Calgary Depression Scale for Schizophrenia (CDSS); (5) the intelligence quotient (IQ) cutoff was set to 2 standard deviations below the mean to prevent potential intellectual disability as a confound, as assessed by the Wechsler Adult Intelligence Scale-IV [36,37]; (6) did not receive any treatment with pharmacological agents or physical therapies, such as ECT and rTMS, in more than 3 weeks before the study [38]; (7) no contraindications for MRI; (8) no history of substance abuse; (9) no any other systemic diseases, chronic diseases, or head trauma.

Patients with concurrent AHs were scanned first due to the difficulty of recruiting these patients. According to the CDSS and AHRS cutoff points, “CDSS scores ≥6”, “AHRS > 0” was the criteria of FUSCH-DHA. CDSS scores < 6”, “AHRS = 0” was the criteria of FUSCH-D.

Healthy controls were recruited from our hospital staff and adult medical students. The healthy controls did not have any psychiatric disorders or first-degree relatives with psychotic disorders, as distinguished by two professional psychiatrists using the Structured Clinical Interview from the DSM-IV-TR (SCID-IV) Non-Patient (NP) edition [39]. The exclusion criteria were as follows: (1) moderate-to-severe physical diseases, such as respiratory, cardiovascular, endocrine, neurological, liver, or kidney disease co-morbidities; (2) history of electroconvulsive therapy; (3) history of loss of consciousness for greater than 5 min by any cause [40]; (4) left-handedness, as determined with the Annett Hand Preference Questionnaire [41]; (5) ophthalmic diseases, (6) high myopia with eye glasses above 600 degrees [42]; and (7) MRI contraindications, including claustrophobia.

2.2. MRI data acquisition

MRI was performed using the Discovery MR750 3.0-Tesla MRI system (General Electric, Milwaukee, WI, USA). Tight, but comfortable, foam padding was used to minimize head motion, and earplugs were used to reduce scanner noise. Sagittal 3D T1-weighted images were acquired using a brain volume sequence with the following parameters: repetition time (TR) = 8.2 ms; echo time (TE) = 3.2 ms; inversion time (TI) = 450 ms; flip angle (FA) = 12°; field of view (FOV) = 256 mm × 256 mm; matrix = 256 × 256; slice thickness = 1 mm; no gap; and 188 sagittal slices.

2.3. MRI data processing

The structural MRI data were preprocessed using the CAT12 (http://dbm.neuro.uni-jena.de/cat) method from the Statistical Parametric Mapping software package (SPM12, http://www.fil.ion.ucl.)
ac.uk/spm/software/spm12/). All images were reoriented to the same origin point and spatial orientation, and the non-linear deformation field was reckoned that prime overlaid the probability maps of tissues on the individual images. Three tissue components, including the cerebral spinal fluid, GMV, and white matter volume, were classified. Next, we registered the native-space tissue segments to the standard Montreal Neurological Institute (MINI) template with the affine registration algorithm and corrected for individual differences caused by head motion artifacts. The diffeomorphic anatomical registration was used to refine the inter-individual registration of GMV changes with the exponentiated Lie algebra (DARTEL) toolbox. Modulating the intensity of the gray matter images with the surrounding voxels compressed or expanded. The relative GMV corrected for individual differences in brain size, while gray matter tissues were modulated using a non-linear deformation approach. After completing the pre-processing pipeline, the quality check was performed using the CAT12 toolbox to evaluate the homogeneity of the gray matter tissues. The gray matter tissue segments were smoothed with an 8-mm Gaussian Kernel for the group analysis, which increased the signal-to-noise ratio and decreased the misregistration between images and benefits of the statistical normality. The automated anatomical labeling atlas software and anatomical atlas were used to determine the most significant clusters [43,44].

2.4. Assessment of illness severity assessment

The Positive and Negative Symptoms Scale (PANSS) [45] was adopted to assess the total psychotic symptoms of patients. Some examples of negative symptoms associated with schizophrenia include apathy, anhedonia, emotional blunting, cognitive deficits, and inattentiveness. The CDSS [46] and Auditory Hallucinations Rating Scale (AHRS) were used quantitatively assess the severity of AH. In this pilot study, we used AHRS as a tool to assess the severity of AH symptoms [47].

2.5. Statistical analysis

To precisely characterize the influence of AHs on the brain, we ensured that age, sex, education level, illness duration, and depressive symptom scores remained as covariates in the final analysis. We also used two-sample t-tests to compare the GMV differences between each group and adopted the one-way analysis of variance (ANOVA) to test the GMV differences among the three groups. The clinical and demographic data of the three groups were compared using two-sample t-tests. First, GMV differences in FUSCH-DAH patients were compared with those from the healthy controls. Secondly, the FUSCH-D patients were compared to the healthy controls. Third, GMV differences in the FUSCH-DAH were compared to those of the FUSCH-D patients. All of the GMV alterations were compared using voxel-wise two-sample t-tests, with total intracranial volume, age, gender, PANSS scores, CDSS scores, AHRS scores as covariates of no interest [48-50]. The significance level was set at $P < 0.05$ and corrected according to the Gaussian random field theory with a voxel significance of $P < 0.001$ and cluster significance of $P < 0.05$ for multiple comparisons using the REST software. GMV reductions and clinical ratings were analyzed and correlation coefficients $<0.2$ were defined as insignificant. In addition, the Bonferroni correction was used to limit type I errors.

3. Results

3.1. Socio-demographics and clinical features of patients and healthy controls

It is difficult to locate FUSCH patients in China due to the stigma associated with the disease and the presence of traditional Chinese medicines. In addition, a few FUSCH patients were willing to seek the medical diagnosis or treatment from our mental health hospital when their psychotic symptoms first appeared. For this study, several factors were matched between the groups, including age, sex, educational level, illness duration, and symptoms of depressive symptoms, yet this made it more challenging to recruit patients. In this pilot study, although we attempted to recruit well-matched patients and healthy controls, we enrolled 60 patients and 40 healthy controls. The MRI data of 20 patients did not meet the inclusion criteria. Therefore, the data of 20 FUSCH-DAH patients, 20 FUSCH-D patients, and 25 healthy controls were analyzed further. The MRI data was used to assess GMV difference.

3.2. Differences in clinical information between the two patient groups

Compared to patients with FUSCH-D, no significant differences were observed in the patients with FUSCH-DAH, in terms of age, gender, educational level, illness duration, or severity of psychotic and depressive symptoms [age, FUSCH-DAH (20.5 ± 1.5) vs. FUSCH-D (21.9 ± 2.0); gender, FUSCH-DAH (10 male and 10 female) vs. FUSCH-D (10 male and 10 female); Educational level, FUSCH-DAH (16.5 ± 3.0) vs. FUSCH-D (16.5 ± 4.2); illness duration, FUSCH-DAH (12.5 ± 2.0) vs. FUSCH-D (12.0 ± 2.5); PANSS, FUSCH-DAH (75.2 ± 5.7) vs. FUSCH-D (76.0 ± 8.6); CDSS, FUSCH-DAH (18.5 ± 2.2) vs. FUSCH-D (18.0 ± 3.2)]. The detailed information is shown in Table 1. We calculated the scores of items in the CDSS and compared them between the two groups. We found scores of hopelessness and suicide in FUSCH-DAH patients were significantly higher than FUSCH-D patients, while the scores of early waking and self-deprecation were significant higher in FUSCH-D patients (Table 2).

3.3. GMV differences among the three groups

In this pilot study, we observed FUSCH-DAH patients had more widespread GMV reductions in the entire posterior parietal lobe, frontal lobe, and temporal lobe, as compared to the healthy controls. We also observed that FUSCH-DAH patients demonstrated more substantial

| Table 1 | Socio-demographics and clinical features of 20 FUSCH-DAH patients, 20 FUSCH-D patients, and 25 healthy controls. |
|-----------------|-------------------------------------------------|-----------------|-----------------|-----------------|-----------------|
| Age (years)     | 20.5 ± 1.5                                      | 21.9 ± 2.0       | 21.0 ± 2.5       | 0.899<sup>f</sup> | 0.991           |
| Gender (M/F)    | 10/10                                           | 10/10            | 12/13           | 0.477<sup>f</sup> | 0.503           |
| Educational level (year) | 16.5 ± 3.0                                  | 16.5 ± 4.2       | 16.0 ± 2.5       | 0.805<sup>f</sup> | 0.900           |
| Illness duration (week) | 12.5 ± 2.0                                   | 12.0 ± 2.5<sup>f</sup>| 0.213           | 0.188           |
| IQ scores       | 92.2 ± 5.4                                      | 91.52 ± 3.8      | 0.110           | 0.884           |
| PANSS            | 75.2 ± 5.7                                      | 76.0 ± 8.6       | N/A             | 0.277           | 0.389           |
| CDSS            | 18.5 ± 2.2                                      | 18.0 ± 3.2<sup>f</sup>| 0.555           | 0.233           |
| AHRS            | 20.0 ± 2.0                                      | 0.0 ± 0.0        | N/A             | N/A             |

FUSCH, first episode untreated schizophrenia; PANSS, Positive and Negative Symptoms Scale; CDSS, Calgary Depression Scale for Schizophrenia; AHRS, Auditory Hallucinations Rating Scale.
4. Discussion

supports the neurodevelopmental hypothesis of schizophrenia [53–55].
GMV reductions in the parietal, frontal, and temporal lobes, suggesting that grey matter impairments may be a precursor of psychotic symptoms in FUSCH-D patients. This finding is consistent with previous studies and supports the neurodevelopmental hypothesis of schizophrenia [53–55]. The affected brain regions (i.e., parietal, frontal, and temporal lobes) play essential roles in cognition, emotional processing, executive functioning, and perception processing [56–58]. Hence, GMV reductions in these regions may disrupt the proper functioning of these brain regions, which may lead to the development of schizophrenia symptoms. However, our findings from this initial pilot study suggest that specific indexes, such as GMV, may be used to screen the patients at most risk of developing schizophrenia, which may aid as an objective index to diagnose and prevent the prodromal stage of schizophrenia.

Secondly, FUSCH-DAH patients have more substantial GMV reductions in the entire posterior parietal lobe, Broca area, Wernicke region, frontal lobe, and temporal lobe, and insular lobe, which are central components of the executive control network and primary auditory cortex. The abnormal and reciprocal activity between these regions supports the hypothesis that the interaction between speech generation and speech perception processes gives rise to the experience of sound in the absence of external stimuli. This interaction between speech generation and speech perception is the common pathway of many hypotheses of auditory hallucinations. For example, the resting state hypothesis of auditory verbal hallucinations [59], top-down processes disturbance of the hypothesis of AHs [60], and the frontal-temporal brain structural abnormality hypothesis of AHs [61–67].

Based on these findings, we postulate that depressive symptoms and AHs might have reciprocal deteriorative actions in FUSCH-DAH patients. This hypothesis requires further investigation, as it may aid the development of new preventative and treatment strategies for patients with schizophrenia. Considering the fact that GMV reduction are observed during any stage of schizophrenia and may be deteriorated by antipsychotics treatment, it is likely that the GMV reductions are linked to illness duration, especially in schizophrenic patients with persistent AHs or depressive symptoms [26–28]. Future studies should focus on the development of optimal personalized treatment strategies for patients in these diagnostic categories.

4.1. Limitations

There were several limitations in this pilot study. First, the sample size was relatively small in this study, and future studies would enroll more samples. Secondly, this pilot study was lack of a group of patients without depressive symptoms. However, our primary aim in this pilot study was to investigate the reciprocal deterioration of depressive symptoms and AHs in FUSCH patients. Third, we only investigated the total GMV reductions between the two patient groups, while total GMV indexes, such as GMV, may be used to screen the patients at most risk of developing schizophrenia, which may aid as an objective index to diagnose and prevent the prodromal stage of schizophrenia.

Table 2: CDSS scores differences between differences in each dimension (each item of CDSS).

| CDSS dimensions (Items) | FUSCH-DAH (n = 20) | FUSCH-D (n = 20) | t    | P       |
|------------------------|-------------------|-----------------|------|---------|
| Depression             | 2.0 ± 0.1         | 2.0 ± 0.3       | 0.115| 0.835   |
| Hopelessness           | 2.5 ± 0.4         | 1.7 ± 0.2       | 2.203| 0.023   |
| Self-depreciation      | 1.9 ± 0.1         | 2.3 ± 0.1       | -1.770| 0.039  |
| Guilty ideas of reference | 2.3 ± 0.2      | 2.0 ± 0.5       | 0.012| 0.987   |
| Pathological guilt     | 2.0 ± 0.1         | 2.0 ± 0.3       | 0.007| 0.995   |
| Morning depression     | 2.0 ± 0.7         | 2.0 ± 0.5       | 0.001| 0.997   |
| Early awakening        | 1.8 ± 0.2         | 2.5 ± 0.4       | -2.136| 0.010  |
| Suicide                | 2.0 ± 0.5         | 1.5 ± 0.3       | 2.135| 0.007   |
| Observed depression    | 2.0 ± 0.5         | 2.0 ± 0.2       | 0.100| 0.898   |

GMV reductions in the Broca region, Wernicke region, insular lobe, and prefrontal lobe when compared to FUSCH-D patients (Fig. 1).

Table 2: CDSS scores differences between differences in each dimension (each item of CDSS).

In this pilot study, there is one important phenomenon. We observed that the average GMV reduction in the FUSCH-DAH group was 1.06% when compared with the healthy controls; however, the average GMV reduction in FUSCH-D patients was 0.58% when compared with the healthy controls.

In our previous studies, GMV reductions are found in 1.06% when compared with the healthy controls. Based on these findings, we postulate that depressive symptoms and AHs might have reciprocal deteriorative actions in FUSCH-DAH patients. This hypothesis requires further investigation, as it may aid the development of new preventative and treatment strategies for patients with schizophrenia. Considering the fact that GMV reduction are observed during any stage of schizophrenia and may be deteriorated by antipsychotics treatment, it is likely that the GMV reductions are linked to illness duration, especially in schizophrenic patients with persistent AHs or depressive symptoms [26–28]. Future studies should focus on the development of optimal personalized treatment strategies for patients in these diagnostic categories.

4.1. Limitations

There were several limitations in this pilot study. First, the sample size was relatively small in this study, and future studies would enroll more samples. Secondly, this pilot study was lack of a group of patients without depressive symptoms. However, our primary aim is this pilot study was to investigate the reciprocal deteriorative actions of depressive symptoms and AHs in FUSCH patients. Third, we only investigated the total GMV reductions between the two patient groups, while total GMV values obtained from the healthy controls were used as the references. Fourth, in this pilot study, MRI was performed on the evening of the recruitment day and before the treatment. The consistency of our MRI data may be influenced by the different MRI time points, yet the data still allows for an analysis of GMV differences between patients. In
future studies, we will consider methods to lessen the potential influence differences in MRI scanning times. Fifth, although we postulated that AHs and depressive symptoms in FUSCH-DAH patients might have a reciprocal deterioration relationship via GMV reductions, we did not confirm which trigger induced the complementary effect. Future studies using animal models may help solve this limitation. Lastly, since atrophy is noted in depressive patients even outside the realm of schizophrenia, AHs can also be observed in patients with depression disorders. In future studies, we will further assess this question to better understand the role of atrophy.

5. Conclusion

This is the first report showing that concurrent depressive symptoms and AHs lead to severe GMV deterioration in FUSCH-DAH patients. Hence, there is a reciprocal relationship between AHs and depressive symptoms in FUSCH-DAH patients. However, the potential additive effects of concurrent AHs and depressive symptoms require further investigation in order to identify future targeted therapies for schizophrenia.

CRediT authorship contribution statement

Chuanjun Zhuo: Conceptualization, Data curation, Funding acquisition, Resources, Project administration, Supervision, Validation, Visualization, Writing - original draft, Drafting - review & editing.
Xuexin Xu: Conceptualization, Data curation, Validation, Visualization, Writing - original draft, Writing - review & editing.
Xiaodong Lin: Conceptualization, Data curation, Funding acquisition, Validation, Visualization, Writing - original draft, Writing - review & editing.
Xuexin Xu: Conceptualization, Data curation, Validation, Visualization, Writing - original draft, Writing - review & editing.
Feng Ji: Data curation, Formal analysis, Validation, Writing - review & editing.
Deguo Jiang: Data curation, Formal analysis, Validation, Writing - review & editing.
Yong Xu: Investigation, Methodology, Funding acquisition, Validation, Writing - review & editing.
Lina Wang: Investigation, Methodology, Validation, Writing - review & editing.
Yancheng Li: Investigation, Methodology, Validation, Writing - review & editing.
Hongjun Tian: Investigation, Methodology, Validation, Writing - review & editing.
Wenqiang Wang: Investigation, Methodology, Validation, Writing - review & editing.
Chunhua Zhou: Investigation, Methodology, Validation, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

Acknowledgements

This work was supported by grants from the National Natural Science Foundation of China (81871052 to C.Z., 81801679 and 81571319 to Y.X.), the Key Projects of the Natural Science Foundation of Tianjin, China (17JCZDJC35700 to C.Z.), the Tianjin Health Bureau Foundation (2014KR02 to C.Z.), Tianjin Anding Hospital Award320000 Yuan to C.J., the National Key Research and Development Program of China (2016YFC1307004 to Y.X.), the Shaxi Science and Technology Innovation Training Team’s Multidisciplinary Team for Cognitive Impairment (201705D131027 to Y.X.), the Zhejiang Public Welfare Fund Project (LG18H090002 to D.J.), and the Key Project of the Wenzhou Science and Technology Bureau (ZS2017011 to X.L.).

References

[1] R. Upthegrove, S. Marwaha, M. Birchwood, Depression and schizophrenia: cause, consequence, or trans-diagnostic issue? Schizophr. Bull. 43 (2017) 240–244.
[2] S.E. Herrman, K. Allott, L.J. Phillips, S.J. Wood, J. Uren, S.R. Mallawaarachchi, S.M. Cotton, Depressive psychopathology in first-episode schizophrenia spectrum disorders: a systematic review, meta-analysis and meta-regression, Psychol. Med. 49 (2019) 2463–2474.
[3] J. Firth, S.B. Teasdale, K. Allott, D. Sinkind, W. Marx, J. Cotter, N. Veronese, F. Schuch, L. Smith, M. Solmi, The efficacy and safety of nutrient supplements in the treatment of mental disorders: a meta-review of meta-analyses of randomized controlled trials, World Psychiatry 18 (2019) 308–324.
[4] A. Gregory, P. Mallikarjun, R. Upthegrove, Treatment of depression in schizophrenia: systematic review and meta-analysis, Br. J. Psychiatry 211 (2017) 198–204.
[5] B. Helfer, M.T. Samara, M. Huhn, E. Klupp, C. Leucht, R.R. Engel, S. Leucht, Efficacy and safety of antidepressants added to antipsychotics for schizophrenia: a systematic review and meta-analysis, Am. J. Psychiatry 173 (2016) 876–886.
[6] P. Fuaar-Poli, S. Borgwardt, A. Bechtold, J. Addington, A. Riecher-Rossler, F. Schulz-Lutter, M. Keshavan, S. Wood, S. Ruhrmann, L.J. Seidman, The psychosis high-risk state: a comprehensive state-of-the-art review, JAMA Psychiatry 70 (2013) 107–120.
[7] K.M. Kubera, M. Rashidi, M.M. Schmitgen, A. Barth, D. Hirjak, F. Sambataro, V.D. Calhoun, R.C. Wolf, Structure-function interrelationships in patients with schizophrenia who have persistent auditory verbal hallucinations: A multimodal MRI study using parallel ICA, Prog. Neuropsychopharmacol. Biol. Psychiatry 93 (2019) 114–121.
[8] C. Zhuo, Y. Xu, L. Zhang, R. Jing, C. Zhuo, The effect of dopamine antagonists treatment on auditory verbal hallucinations in healthy individuals is clearly influenced by comorbid psychopathology and associated structural and functional alterations: an artificially controlled pilot study, Front. Genet. 10 (2019).
[9] R. Tourino, F.J. Acosta, A. Giraldèz, J. Alvarez, J.M. González, C. Abelleira, N. Benitez, E. Boena, J.A. Fernandez, C.J. Rodriguez, Suicidal risk, hopelessness and depression in patients with schizophrenia and internalized stigma, Actas Esp. Psiquiatr. (2018).
[10] E.E. Kilicaslan, A.T. Esen, M.I. Kasal, E. Ozelci, M. Boysan, M. Gulec, Childhood trauma, depression, and sleep quality and their association with psychotic symptoms and suicidality in schizophrenia, Psychiatry Res. 258 (2017) 557–564.
[11] A. Nagyu, A. Al-Rabie, Suicidality and survivability in schizophrenia, J. Nerv. Ment. Dis. 205 (2017) 585.
[12] E. Kjellby, I. Sinkevicic, F. Gjestad, R. Krokene, E.-M. Leberg, H. Jørgensen, K. Hugdahl, E. Johnsen, Suicidality in schizophrenia spectrum disorders: the relationship to hallucinations and persecutory delusions, Eur. Psychiatry 30 (2015) 830–836.
[13] B. Togay, H. Noyan, R. Taskelen, A. Ucok, Clinical variables associated with suicide attempts in schizophrenia before and after the first episode, Psychiatry Res. 229 (2015) 252–256.
[14] R.D. Gibbons, C.H. Brown, K. Hur, S.M. Marcus, D.K. Bhaumik, J.A. Erkens, R.M. Herings, J.J. Mann, Early evidence on the effects of regulators’ suicidality warnings on SSR1 prescriptions and suicide in children and adolescents, Am. J. Psychiatry 164 (2007) 1356–1363.
[15] J.T. Kantrowitz, P. Sehatpour, M. Avisar, G. Horga, A. Gwad, M.J. Hopman, O. Begell, R.R. Girgis, B. Vail, G. Silipo, Significant improvement in treatment-resistant auditory verbal hallucinations after 5 days of double-blind, randomized, sham controlled, fronto-temporal, transcranial direct current stimulation (tDCS): a pilot investigation extension study, Brain Stimul. 12 (2019) 981–991.
[16] K. Kunzelmann, L. Meier, M. Grieder, Y. Morishima, T. Dierks, No effect of transcranial direct current stimulation of the auditory cortex on auditory-evoked potentials, Front. Neurosci. 12 (2018) 880.
[17] S. Dolfius, N. Jafandi, O. Guillin, B. Tjojak, M. Plaze, G. Saba, C. Nauczyciel, A. Montagne Larmurier, N. Chastan, V. Meille, High-frequency neurostimulated tTMS in auditory verbal hallucinations: a pilot double-blind controlled study in patients with schizophrenia, Schizophr. Bull. 44 (2018) 505–514.
[18] W. Niewendorp, S. Koops, M. Somers, L.E. Sommer, Transcranial magnetic stimulation, transcranial direct current stimulation and electroconvulsive therapy for medication-resistant psychosis of schizophrenia, Curr. Opin. Psychiatry 28 (2015) 222–228.
[19] M. Rohlenk, K. Hugdahl, I. Sommer, Auditory verbal hallucinations: neuroimaging and treatment, Psychol. Med. 47 (2017) 199–208.
[20] P.A. Thomann, R.C. Wolf, H.M. Nolte, D. Hirjak, S. Hofer, U. Seidl, M.S. Depping, B. Stiefels, K. Maier-Hein, F. Sambataro, Neuro modulation in response to electroconvulsive therapy in schizophrenia and major depression, Brain Stimul. 10 (2017) 637–644.
[21] C.C.Y. Leung, R. Gadelrab, C.U. Nthpe, P. Mcguire, A. Demjaha, Neurobiology, clinical course, and therapeutic approaches of treatment resistant schizophrenia: towards an integrated view, Front. Psychiatry 10 (2019) 601.
[22] A. de Bartolomeis, C. Avagliano, G. Duro, O. Beggel, R.R. Girgis, B. Vail, G. Silipo, Significance of improvement in treatment-resistant auditory verbal hallucinations after 5 days of double-blind, randomized, sham controlled, fronto-temporal, transcranial direct current stimulation (tDCS): a pilot investigation extension study, Brain Stimul. 12 (2019) 981–991.
[23] A. Deol, N. Jafandi, O. Guillin, B. Tjojak, M. Plaze, G. Saba, C. Nauczyciel, A. Montagne Larmurier, N. Chastan, V. Meille, High-frequency neurostimulated rTMS in auditory verbal hallucinations: a pilot double-blind controlled study in patients with schizophrenia, Schizophr. Bull. 44 (2018) 505–514.
[24] B.J. Kikonen, The Group of Treatment Resistant Schizophrenia. Heterogeneity in Treatment Resistant Schizophrenia (TRS), Front. Psychiatry 9 (2018) 757.
[25] J. Huang, C. Zhuo, X. Song, Y. Li, R. Jing, H. Tian, L. Wang, F. Mao, S. Li, R. Jiang, Does depressive-type schizophrenia exist? How do we prove it?: an updated review and overview, J. Nerv. Ment. Dis. 207 (2019) 555–560.
