Abberant inverted U-shaped brain pattern and trait-related retinal impairment in schizophrenia patients with combined auditory and visual hallucinations: a pilot study

Chuanjun Zhuo1,2,3,4,5,6,7, Bo Xiao8, Ce Chen2, Deguo Jiang2, Gongying Li1, Xiaoyan Ma3, Ranli Li3, Lina Wang3, Yong Xu4, Chunhua Zhou9, Xiaodong Lin2

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Abstract
Schizophrenic patients often experience auditory hallucinations (AHs) and visual hallucinations (VHs). However, brain and retinal alterations associated with combined AHs and VHs in schizophrenic patients are unknown. This study aimed to investigate brain and retinal alterations in first episode un-treated schizophrenic patients with combined AHs and VHs (FUSCHA V). FUSCHA V patients (n = 120), divided into four groups according to severity of AH and VH symptoms, were compared to healthy controls (n = 30). Gray matter volume (GMV) and global functional connectivity density (gFCD) were recorded to reflect brain structure and functional alterations. Total retinal thickness was acquired by optical coherence tomography to assess retinal impairment. The majority of FUSCHA V patients (85.8%) demonstrated both GMV reduction and gFCD increases along with retinal thinning compared to healthy controls. The severity of GMV reduction and gFCD increase differed between patient groups, ranked from highest to lowest severity as follows: severe AHs combined with severe VHs (FUSCHASV, 20 patients), moderate AHs combined with severe VHs (FUSCHMASV, 23 patients), severe AHs combined with moderate VHs (FUSCHSAMV, 28 patients), and moderate AHs combined with moderate VHs (FUSCHMAMV, 26). Retinal impairment was similar among the four FUSCHA V groups. GMV reduction and gFCD increases in the frontal-parietal lobule show an inverted U-shaped pattern among FUSCHA V patients according to AH and VH severity, while retinal impairment remains stable among FUSCHAV groups. These findings indicate a reciprocal deterioration in auditory and visual disturbances among FUSCHA V patients.

Keywords Schizophrenia · Auditory hallucinations · Vision hallucinations · GMV · gFCD
Introduction

Auditory perceptual disturbances in patients with schizophrenia are generally experienced as auditory hallucinations (AHs) (Pinheiro et al. 2019). The prevalence of AHs is greater than 40% in patients with schizophrenia (Upthegrove et al. 2016), and prevalence in first episode, un-medicated schizophrenic patients is even higher (Zhuo et al. 2019). Increasingly, studies have focused on the brain pathology associated with AHs and several hypotheses have been established (Baumeister et al. 2017; Blom 2015; Hugdahl and Sommer 2018; Northoff 2014). While these hypotheses have not been met with full acceptance, these prior studies have provided many important findings on the brain mechanisms associated with AHs (Huang et al. 2019; Stephane 2019; Zmigrod et al. 2016).

Visual perceptual disturbances in schizophrenia are experienced as visual hallucinations (VHs) and vision distortions (Green et al. 2012). The prevalence of VHs in schizophrenia patients is approximately 25–30% (Waters et al. 2014). Prior studies have reported that VHs are experienced in multiple stages of schizophrenia, and has also been reported in children, adolescents, and young adults at high-risk for schizophrenia (Grano et al. 2015; Hebert et al. 2010; Mittal et al. 2015). Furthermore, according to some reports, visual disturbances can be used as an index for symptoms, endophenotypes, biomarkers, and predictors for the study of the clinical, pathological and physiological features of schizophrenia (Garcia-Portilla et al. 2019; Guidotti and Grayson 2011).

In the last decade, imaging studies using both magnetic resonance imaging (MRI) and optical coherence tomography (OCT), have focused on brain and retinal aberrations in schizophrenia. Specifically, studies about the relationship between brain and retinal aberrations and the symptoms of visual disturbances have reported that patients with schizophrenia present with brain functional disturbances and retinal thickness impairment (Calderone et al. 2013; Lencer et al. 2005; Nagel et al. 2007; Omitsuka et al. 2007; Silverstein et al. 2009, 2010). These findings provide pivotal information for further study. The poor treatment outcome of schizophrenic patients with a combination of auditory and visual system disturbances support the above mentioned findings (Silverstein 2016).

Hence, the current study investigated the pathological features of schizophrenic patients presenting with both AHs and VHs. Specifically, first-episode unmedicated patients were studied to avoid influences of previous interventions.

Inspired by Silverstein (2016), who stated that without radical re-visioning of research ideas, it is difficult to achieve scientific advancement (Silverstein 2016), we conducted a pilot study to investigate pathological features of the first episode of un-medicated schizophrenic patients with combined auditory and visual disturbance. Unlike prior studies that separated patients into those experiencing visual disturbances and those experiencing auditory disturbances, the current study investigated whole-brain and retinal aberrations in patients with a combination of both auditory and visual disturbances. Three hypotheses were tested. Our first hypothesis was that first episode untreated schizophrenic patients with AHs and VHs (FUSCHAV patients) would demonstrate brain structural/functional and retina alterations. Our second hypothesis was that brain and retinal alteration patterns would differ according to severity of AHs and VHs. Finally, our third hypothesis was that auditory and visual hallucinations may show reciprocal deterioration in FUSCHAV patients.

Methods

Patients were recruited between January 2018 and July 2019 from five institutes (Tianjin Mental Heal Center, the School of Mental Health at Jining Medical University, Wenzhou Seventh People’s Hospital, Tianjin Kangtai Hospital, The First Hospital of Shanxi Medical University) to participate in the study. The ethics committee of all five institutes approved study methods. All MRIs and OCTs were conducted by one technician.

The inclusion criteria for FUSCHAV were as follows: 1) fully meets the DSM-IV diagnostic criteria for SCH; 2) first schizophrenia diagnosis in a mental health professional hospital; 3) no antipsychotic therapeutics for at least three weeks prior to the study; 4) simultaneously experiences AHs and VHs; 5) aged 18 to 30 years; 6) no substance abuse; 7) no other systemic disease, chronic disease, or head trauma; 8) no other diseases which can cause AHs and VHs; and 9) no other diseases which can cause retinal disease. Healthy controls were recruited from hospital staff and adult medical students. The healthy controls did not have any psychiatric disorders or first-degree relatives with psychotic disorders as assessed by two professional psychiatrists using the SCI-D NP version. The exclusion criteria for patients and healthy controls were as follows: 1) moderate to severe physical disease (e.g. respiratory, cardiovascular, endocrine, neurological, liver, or kidney disease); 2) currently receiving electroconvulsive therapy; 3) a history of loss of consciousness for more than five minutes for any cause; 4) left-handedness, as determined by the Annett Hand Preference Questionnaire; 5) ophthalmic disease; 6) high myopia; 7) any magnetic resonance imaging (MRI) contraindication, including claustrophobia; and 8) IQ < 80.

MRI data acquisition

The 3.0-Tesla MR system (Discovery MR750, General Electric, Milwaukee, WI, USA) was used to collect MRI data. Functional magnetic resonance imaging (fMRI) was performed using a GE Healthcare Discovery MR750 3 T MRI
system (General Electric, Milwaukee, WI, USA) with an eight-channel phased-array head coil. Participants lay in a supine position and were asked to restrict thoughts and head movements during imaging. The imaging parameters were as follows: 2000 ms repetition time (TR), 45 ms echo time (TE), 32 slices, 4 mm slice thickness, 0.5 mm gap, field of view (FOV), 64 × 64 acquisition matrix, and 90° flip angle. SENSitivity Encoding (SENSE), with a SENSE factor of 2 and parallel imaging were used for all scans. Images were obtained with a high-resolution, three-dimensional turbo-fast echo T1-weighted sequence with the following parameters: 8.2/3.2-ms TR/TE, 188 slices, 1 mm thickness, no gap, 256 × 256 FOV, 256 × 256 acquisition matrix, and 12° FA.

**OCT data acquisition**

OCT data were acquired with the OCT 4000 system (Zeiss, Germany (premierop.com/zeiss-cirrus-hd-oct-4000-used)) which collects retinal scans of both eyes of participants. The hand-held probe was mounted and subjects were positioned on a chin-head rest and asked to focus on a fixation target. A 5-s volumetric 10 mm × 5 mm scan of the foveal center, marked by outer segment layer (OSL) thickening, was captured. Each scan consisted of 500 A-scan/B-scans, 50 B-scans and five frames/B-scan, with acceptable scans containing ≥ five consecutive B-scan frames of the foveal center with no movement artefacts.

**Psychotic, auditory and visual hallucination symptoms severity assessment**

Total severity of schizophrenia was assessed by the Positive and Negative Symptoms Scale (PANSS) (Fleischhacker et al. 2019). The scale for the Assessment of Positive Symptoms (SAPS) (Kumari et al. 2017) was used to measure the severity of AHs and VHs. Cognitive ability was assessed with the MATRICS Consensus Cognitive Battery (MCCB) (Lees et al. 2015). The Global Assessment of Functioning (GAF) was used to assess global function (Gspinl et al. 2018).

Patients were categorized into four groups according to the severity of AHs and VHs as measured by the SAPS items of visual and auditory hallucination. Scores of AHs and VHs above 4 were defined as severe. Patients who scored between 2 and 3 on AHs and VHs were defined as middle to moderately severe AHs and VHs, respectively. According to the above classification rule, we established four groups: severe AHs combined with severe VHs (FUSCHSASV, 20 patients); middle to moderate AHs combined with severe VHs (FUSCHMASV, 23 patients); severe AHs combined with middle to moderate VHs (FUSCHSAMV, 28 patients); and middle to moderate AHs combined with middle to moderate VHs (FUSCHMAMV, 26 patients).

**sMRI data processing**

Analysis of differences in brain volume was performed by voxel-based morphometry (VBM), using SPM8 (Statistical Parametric Mapping; v5; Institute of Neurology, London, UK). Bias correction, spatial normalization, segmentation into gray and white matter, imaging of cerebrospinal fluid, and intensity modulation were performed on 3D-FSPGR images in native space using SPM8. The DARTEL (Diffeomorphic Anatomical Registration Through Exponential Lie Algebra) toolbox (as proposed by Ashburner,) was used in a high-dimensional normalization protocol. Intensity modulation was performed by multiplying voxel values of the segmented images by the measure of warped and unwarped structures derived from the nonlinear step of the spatial normalization. During this step, relative regional gray matter density was converted into absolute gray matter density, and expressed as the amount of gray matter per unit volume of brain tissue before spatial normalization. The resulting modulated gray and white matter images were smoothed with a 6 mm Gaussian kernel. A multiple pattern recognition analysis was used to regress out covariate influences on gray matter. Significance threshold was set at $p < 0.05$, FEW-corrected. Covariates were: age, gender, education level, symptoms severity, GAF scores, and MCCB scores.

**fMRI data pre-processing**

Resting-state fMRI scans were processed using Statistical Parametric Mapping 8 (SPM8; http://www.fil.ion.ucl.ac.uk/spm). The first 10 scan volumes were discarded to allow stabilization of the scanner and to allow patients to acclimate to the testing situation. The remaining volumes were corrected for slice timing and motion artifacts. Allowable motion thresholds (translational and rotational motion <2 mm and 2°, respectively) were checked for all fMRI data. Six of the motion parameters and the average blood oxygen level-dependent signals of the ventricles and white matter were removed. Data with specific-volume framewise displacement values >0.5 were excluded from analysis. Bandpass frequencies ranging from 0.01 to 0.08 Hz were used to filter data. Individual structural images were coregistered to the mean functional image, and the transformed structural images were co-registered to the Montreal Neurological Institute (MNI) space using linear registration. The motion-corrected functional volumes were spatially normalized to the MNI using parameters estimated during linear co-registration. Finally, the functional images were re-sampled into 3 mm cubic voxels for further analysis.
Global functional connectivity density (gFCD) calculation

The gFCD was calculated for each voxel using a customized Linux script (Zhuo et al. 2014). A Pearson’s linear correlation was used to explore functional connectivity between voxels, with a correlation coefficient threshold of $r > 0.6$. Only voxels within the cerebral grey-matter mask were used in calculations of gFCD, and the gFCD for any given voxel ($x_0$) was calculated as the total number of functional connections $k(x_0)$ between $x_0$ and all other voxels using a growth algorithm. This procedure was repeated for all voxels. To increase normality of the distribution, each gFCD value was divided by the mean value of all included voxels. A $6 \times 6 \times 6$ mm$^3$ Gaussian kernel was used to spatially smooth the gFCD maps to minimize the impact of anatomical differences between participants (Zhuo et al. 2014).

OCT data analysis

A blind process of manual segmentation of individual retinal layers was performed by allocating random numbers to B-scan images prior to analysis. An ImageJ macro (http://imagej.nih.gov/ij/) (Jerotic et al. 2019) was used for segmentation. Average individual and combined layer thickness measurements were extracted from three macular regions relative to the foveal center (0 μm): (1) foveal region = −750 to 750 μm, (2) nasal parafoveal region = −1500 to −750 μm and (3) temporal parafoveal region = 750 to 1500 μm.

Statistical analyses

One-way analyses of variance (ANOVA) were used to analyse demographic and clinical characteristics of participants (McHugh 2011). The Mann-Whitney test was used to compare GMV and gFCD between groups (Matsouaka and Betensky 2015). Gender differences were explored using Chi square analysis between two groups (Thomas 1990), correcting for GMV and gFCD. A $p$ value <0.05 was considered significant.

Results

Demographic and clinical characteristics of participants

MRI data from five patients and OCT data from two patients were excluded from analysis due to poor acquisition quality. Among the remaining 113 patients, 109 patients demonstrated brain gray matter reduction and 97 patients demonstrated brain and retina co-structural impairment. Data from these 97 patients were used for analysis. Two independent psychiatrists with no involvement in the current study tested the validity of patient subtype divisions using the Auditory Hallucination Rating Scale (Haddock et al. 1999) and the PANSS P3 VHs (Fleischhacker et al. 2019) item to distinguish AH and VH severity. The four resulting symptom combination groups and diagnostic

| Variable | HCs $n = 30$ | FUSCHSASV $n = 20$ | FUSCHMASV $n = 23$ | FUSCHSAMV $n = 28$ | FUSCHMAMV $n = 26$ | $F$ | $P$ |
|----------|--------------|---------------------|---------------------|---------------------|---------------------|-----|-----|
| Age, years Mean (SD) | 25.4(0.5) | 22.0(4.2) | 26.4(3.0) | 25.2(1.2) | 27.9(3.9) | 63.40 | <0.001 |
| Gender (Femal/Male) | 15/15 | 9/11 | 11/12 | 14/14 | 11/15 | 24.23 | <0.001 |
| Education level, years Mean (SD) | 16.1(2.5) | 14.5(2.0) | 15.0(3.5) | 14.5(2.5) | 15.5(1.5) | 23.12 | <0.001 |
| Duration of illness, Months, Mean (SD) | N/A | 2.4(1.8) | 3.2(2.0) | 4.3(1.5) | 6.2(2.7) | 47.21 | <0.001 |
| PANSS score Mean (SD) | N/A | 78.9(1.5) | 80.1(6.8) | 79.5(5.9) | 76.8(9.9) | 127.73 | <0.001 |
| SAPS-AHs | N/A | 4.6(0.2) | 2.2(0.4) | 4.5(0.1) | 1.9(0.4) | 27.73 | <0.001 |
| SAPS-VHs | N/A | 4.2(0.3) | 3.7(0.2) | 2.0 (0.5) | 2.1 (0.3) | 21.56 | <0.001 |
| GAF | 100.0(0.0) | 78.0(13.5) | 72.0(10.5) | 76.5(6.7) | 80.2(9.9) | 45.13 | <0.001 |
| MCCB score Mean (SD) | Speed Processing | 48.0(4.5) | 30.1(8.5) | 36.5(7.0) | 38.5(8.0) | 40.3(8.0) | 99.66 | <0.001 |
| Attention | 47.5(11.5) | 20.3(4.3) | 22.0(2.7) | 23.8(6.5) | 34.0(2.0) | 100.10 | <0.001 |
| Working Memory | 50.0(11.2) | 21.2(4.6) | 24.0(5.2) | 34.0(4.3) | 30.2(8.2) | 98.96 | <0.001 |
| Verbal Learning | 49.50(5.0) | 30.4(5.5) | 33.2(9.4) | 37.4(2.5) | 32.2(8.4) | 77.52 | <0.001 |
| Visual Learning | 45.0 (9.0) | 24.0(3.3) | 29.2(4.8) | 30.0(4.1) | 32.2(2.3) | 111.10 | <0.001 |
| Problem Reasoning | 45.6(4.5) | 30.0(7.3) | 32.0(6.5) | 35.5 (7.3) | 37.0(10.2) | 93.89 | <0.001 |
| Social Cognition | 47.5(1.5) | 30.5(10.0) | 34.4(8.2) | 33.4(8.5) | 36.9(12.0) | 112.99 | <0.001 |
assessments of the psychiatrists affirmed our artificial divisions. While the patient groups significantly differed compared to healthy controls on MCCB and GAF, there were significant differences in these measures among the four patient groups. Detailed information is listed in Table 1.

**GMV reduction**

Compared to the healthy control group, all four patient groups demonstrated GMV reduction. GMV reduction was mainly observed in the temporal, frontal, parietal, and occipital lobes with the greatest extent of GMV reduction located in the frontal-parietal lobe across all four groups (Fig. 1a). The four groups ranked by the extent of GMV reduction according to the peak value of reduction in the frontal-parietal lobe is as follows: FUSCHSASV, FUSCHMASV, FUSCHSAMV, and FUSCHMAMV. The extent of GMV reduction demonstrates an inverted U-shape pattern (Fig. 1b).

**gFCD alterations**

Compared to the healthy control group, all four patients groups demonstrated gFCD increase. As with GMV alterations, the increase in gFCD was mainly observed in the temporal, frontal, parietal, and occipital lobes (Fig. 1c) with the greatest extent of gFCD increase in the frontal-parietal lobe across all four patient groups. The four groups ranked by the extent of gFCD increase in the frontal-parietal lobe according to peak value (greatest increase to lowest) is as follows: FUSCHSASV, FUSCHMASV, FUSCHSAMV, and FUSCHMAMV. As with GMV decrease extent, the extent of gFCD increase demonstrates an inverted U-shape pattern (Fig. 1b).

**GMV differences among the four patient groups**

Alterations in GMV volume were compared among patient groups (Fig. 1d, top). While the extent of GMV volume alterations in some brain regions differed between
patient groups, the largest GMV alterations remained in the frontal and parietal lobes.

**gFCD alterations among the four patient groups**

gFCD alterations were compared among all patient groups. While the extent of gFCD alterations in some brain regions differed between patient groups, the largest gFCD alteration were also mainly located in the frontal, parietal, and occipital cortices (Fig. 1d, bottom).

**Retinal alterations**

All four patient groups showed significant retinal nerve fiber layer (RNFL) thinning compared to the healthy control group (Fig. 2 and Table 2). While overall, the RNFL did not significantly differ among patient groups, there was a regional complex pattern of RNFL alterations among groups (Table 3).

**Discussion**

The present study investigated brain and retinal alterations in first episode schizophrenic patients with auditory and visual hallucinations. All four groups of FUSCHAV patients demonstrated GMV reduction, primarily located in the temporal, occipital, frontal, and parietal lobes. These findings indicate that the primary auditory and visual cortex are impaired in FUSCHAV patients (Bernardin et al. 2019; Csaszar et al. 2019; Moseley et al. 2018). The first episode of schizophrenic patients with congenital deficiency or serious brain damage is generally severe auditory and visual hallucinations.

![Fig. 2 Total retinal thickness and the pattern of retinal thinning in patients and healthy controls. A The maximum impairment of total retinal thickness in FUSCHSASV (a), FUSCHMASV (b), FUSCHSAMV (c), and FUSCHMAMV (d) and the minimum total retinal thickness of healthy controls (e). B The pattern of retinal thinning in patients and healthy controls](image-url)
notably, the GMV reduction in the frontal and parietal lobes suggests that cortex involved in higher integration is affected. The patients in the current study were experiencing their first episode of schizophrenia and were unmedicated and therefore, these findings suggest that GMV reduction was present prior to the psychotic episode (Bordier et al. 2018; Zmigrod et al. 2016) and that there may be a brain-based pathology associated with the onset of AHs and VHs. Moreover, FUSCHA V patients demonstrated increased gFCD in the same brain regions showing GMV reduction suggesting that functional hyperactivity may compensation for structural impairment (Cao et al. 2018; Collier et al. 2014; Csaszar et al. 2019; Kremlacek et al. 2016; Xu et al. 2016). Interestingly, FUSCHA V groups differed in GMV and gFCD alterations in some brain regions. These alterations may be a distinguishing pattern for different patient groups. In addition to alterations in brain gray matter and connectivity, total retinal thickness was decreased in FUSCHA V patients compared to healthy controls, suggesting brain and eye co-impairment.

There were three major findings that we will address. First, GMV reduction and gFCD increases in the frontal-parietal lobule of FUSCHA V patients demonstrates an inverted U-shape pattern according to severity combinations of AHs and VHs. This inverted U-shape pattern suggests that visual disturbances are accompanied by relatively severe brain structural impairment and relatively strong functional compensation. However, GMV alterations in FUSCHSASV are more severe than in FUSCHSAMV indicating that the severity of VHs may enhance structural brain impairments and functional compensation. The second major finding suggests that auditory and visual disturbances may be reciprocal and reflected as inverted U-shaped patterns of GMV and gFCD. These findings provide new clues for the further study of the mechanisms of the interaction between AHs and VHs in schizophrenia. Third, although brain alterations in FUSCHA V patients demonstrated an inverted U-shape according to severity of AHs and VHs, the retinal impairment in these patients did not differ. This finding suggests that while combinations of different severities of AHs and VHs are related to brain alterations, retinal thickness may be more of a trait marker and not related to symptom severity. This idea is consistent with prior research in first episode un-medicated patients (Bernardin et al. 2019; Moseley et al. 2018; Thomas 1990). However, contrary to this theory, other studies have reported that retinal thickness and brain GMV reduction are affected by treatment with antipsychotics (Bordier et al. 2018; Cao et al. 2018; Collier et al. 2014; Csaszar et al. 2019; Kremlacek et al. 2016; Xu et al. 2016). Further cohort studies are needed to fully characterize the dynamical trajectory of brain and retinal alterations, to further understand the reciprocal action between the severity of AHs and VHs in patients with schizophrenia.

| Variable                  | Temporal parafoveal region | Foveal region     | Nasal parafoveal region |
|---------------------------|---------------------------|-------------------|-------------------------|
| FUSCHSASV                 | 276.0 μm ± 15.0 μm        | 250.9 μm ± 20.9 μm| 310.3 μm ± 10.7 μm     |
| FUSCHMASV                 | 280.3 μm ± 28.3 μm        | 253.5 μm ± 15.0 μm| 312.2 μm ± 14.5 μm     |
| FUSCHSAMV                 | 274.0 μm ± 19.5 μm        | 257.1 μm ± 16.5 μm| 317.2 μm ± 25.4 μm     |
| FUSCHMAMV                 | 275.5 μm ± 10.0 μm        | 254.5 μm ± 12.0 μm| 310.5 μm ± 10.7 μm     |
| Healthy controls (HCs)    | 315.5 μm ±15.0 μm         | 268.3 μm ± 25.0 μm| 330.5 μm ± 11.5 μm     |
| Four FUSCHA V groups vs. HCs | F 17.56                  | 21.03             | 30.03                   |
|                           | P <0.001                  | <0.001            | <0.001                  |
| FUSCHSASV vs. FUSCHMASV   | t-test 0.757              | 0.720             | 0.580                   |
|                           | P 0.456                   | 0.780             | 0.611                   |
| FUSCHSASV vs. FUSCHSAMV   | t-test 0.605              | 0.742             | 0.647                   |
|                           | P 0.576                   | 0.631             | 0.599                   |
| FUSCHSASV vs. FUSCHMAMV   | t-test 0.553              | 0.653             | 0.580                   |
|                           | P 0.428                   | 0.524             | 0.413                   |
| FUSCHMASV vs. FUSCHMAMV   | t-test 0.620              | 0.753             | 0.673                   |
|                           | P 0.413                   | 0.786             | 0.527                   |
| FUSCHMASV vs. FUSCHSAMV   | t-test 0.703              | 0.603             | 0.499                   |
|                           | P 0.670                   | 0.570             | 0.553                   |
| FUSCHSAMV vs. FUSCHMAMV   | t-test 0.996              | 0.569             | 0.666                   |
|                           | P 0.878                   | 0.578             | 0.591                   |
**Limitations**

There are several limitations to the current study that must be considered when interpreting the results. First, the method used to group patients in the current study is novel and therefore further research needs to confirm the validity of this method. We have started to investigate this method by observing the evolution of symptoms in 51 patients for 6-month after starting anti-psychotic medication. We found varying degrees of alleviation from AVs and VHs, with VHs showing greater treatment resistance than AHs. These observations lend support for the group division method used in the current study.

Second, the small sample size of each group limits the significance of the findings. Third, total retinal thickness was used to assess eye impairment. The retina was not divided into layers to more precisely clarify retinal impairment and as such, our results may not provide the full picture of retinal impairment in FUSCHA V patients. We lacked access to software that can reliably divide the retina into fine slices for a more in-depth analysis. We are currently applying to the Zeiss OCT Institute for access to software that will enable us to further divide the layers of the retina to increase resolution in a future study of FUSCHA V patients.

Fourth, we calculated correlational coefficients to investigate potential relationships between GMV/gFCD, retinal thickness, and clinical symptoms (as measured by severity of AHs/VHs). In agreement with prior research (Lui et al. 2009; Milev et al. 2003), there were no significant correlations found between GMV/gFCD and clinical symptoms in agreement with prior research. In addition, we found no significant correlations between retinal thickness and clinical symptoms. Prior research investigating this topic has yielded inconsistent results. The lack of significant correlations between clinical symptoms and GMV/gFCD or retinal thickness may indicate that these alterations are related to trait aspects of symptoms rather than to symptom severity.

Fifth, an important limitation of the current study is the lack of a group of schizophrenic patients without AHs and VHs for comparison. Such a group would enable further characterization of pathological features in our study population. We are working on enrolling such a comparison group for a future study.

**Conclusion**

Despite the above described limitation, the current study reports on three important findings: 1) GMV reduction and gFCD increases in the frontal-parietal lobule of FUSCHA V patients demonstrate an inverted U-shape pattern according to differences in AH and VH severity, indicating functional compensation correlated with volume reduction, 2) There appears to be reciprocal deterioration in auditory and visual disturbances among FUSCHA V patients as observed through both brain and retinal aberrations, 3) Although brain alterations in FUSCHA V patients differ with degree of AH and VH severity, retinal impairment remains constant among FUSCHA V groups.

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Compliance with ethical standards

Conflict of interest  The authors declare that they have no conflict of interest.

Ethical approval  The ethics committee of all five institutes approved study methods. All procedures performed in studies involving human participants were in accordance with the ethics standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethics standards.

Informed consent  Written informed consent was obtained from all individual participants included in the study.

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References

Baumeister, D., Sedgwick, O., Howes, O., & Peters, E. (2017). Auditory verbal hallucinations and continuum models of psychosis: A systematic review of the healthy voice-hearer literature. Clinical Psychology Review, 51, 125–141.

Bernardin, F., Schweitzer, T., Angioi-Duprez, K., Giersch, A., Jansen, C., Schwan, R., et al. (2019). Retinal ganglion cells dysfunctions in schizophrenia patients with or without visual hallucinations. Schizophrenia Research.

Blom, J. D. (2015). Auditory hallucinations. Handbook of Clinical Neurology: 129, 433–455.

Bordier, C., Nicoliti, C., Forcellini, G., & Bifone, A. (2018). Disrupted modular organization of primary sensory brain areas in schizophrenia. NeuroImage: Clinical, 18, 682–693.

Calderone, D. J., Martínez, A., Zemon, V., Hofstam, M. J., Hu, G., Watkins, J. E., et al. (2013). Comparison of psychophysical, electrophysiological, and fMRI assessment of visual contrast responses in patients with schizophrenia. Neuroimage, 67, 153–162.

Cao, H., Wang, R., Luo, X., Li, X., Hallett, M., Thompson-Westra, J., et al. (2018). A voxel-based magnetic resonance imaging morphometric study of cerebral and cerebellar gray matter in patients under 65 years with essential tremor. Medical Science Monitor, 24, 3127–3135.

Collier, A. K., Wolf, D. H., Valdez, J. N., Turetsky, B. I., Elliott, M. A., Gür, R. E., & Gür, R. C. (2014). Comparison of auditory and visual oddball fMRI in schizophrenia. Schizophrenia Research, 158(1–3), 183–188.

Csaszar, N., Kapocs, G., & Bokon, I. (2019). A possible key role of vision in the development of schizophrenia. Reviews in the Neurosciences, 30(4), 359–379.

Fleschhacker, W., Galderisi, S., Laszlovszky, I., Szatmari, B., Barabasy, A., Acsaï, K., et al. (2019). The efficacy of cariprazine in negative symptoms of schizophrenia: Post hoc analyses of PANSS individual items and PANSS-derived factors. European Psychiatry, 58, 1–9.

Garcia-Portilla, M. P., Garcia-Alvarez, L., de la Fuente-Tomás, L., Velasco-Iglesias, A., Saiz, P. A., Gonzalez-Blanco, L., et al. (2019). Could structural changes in the retinal layers be a new biomarker of mental disorders? A systematic review and thematic synthesis. Revista de Psiquiatría y Salud Mental, 12(2), 116–129.

Grano, N., Salmijari, L., Karjalainen, M., Kallionpaa, S., Roine, M., & Taylor, P. (2015). Early signs of worry: Psychosis risk symptom visual distortions are independently associated with suicidal ideation. Psychiatry Research, 225(3), 263–267.

Green, M. F., Hellemann, G., Horan, W. P., Lee, J., & Wynn, J. K. (2012). From perception to functional outcome in schizophrenia: Modeling the role of ability and motivation. Archives of General Psychiatry, 69(12), 1216–1224.

Gspandl, S., Peirson, R. P., Nahhas, R. W., Skale, T. G., & Lehner, D. S. (2015). Power and sample size calculations for the Wilcoxon-Mann-Whitney test in the presence of tied observations. Statistical Medicine, 29(5), 1216–1224.

Huang, J., Zhuo, C., Xu, Y., & Lin, X. (2019). Auditory verbal hallucination and the auditory network: From molecules to connectivity. Neuroscience, 410, 59–67.

Hugdahl, K., & Sommer, I. E. (2018). Auditory verbal hallucinations in schizophrenia from a levels of explanation perspective. Schizophrenia Bulletin, 44(2), 234–241.

Jerotic, S., Ristic, I., Pejovic, S., Mihaljevic, M., Pavlovic, Z., Britvic, D., et al. (2019). Retinal structural abnormalities in young adults with psychosis spectrum disorders. Progress in Neuro-Psychopharmacology & Biological Psychiatry, 98, 109825.

Kremlacke, J., Kreegipuu, K., Tales, A., Astikainen, P., Poldyer, N., Naatanen, R., et al. (2016). Visual mismatch negativity (vMMN): A review and meta-analysis of studies in psychiatric and neurological disorders. Cortex, 80, 76–112.

Kumar, S., Malik, M., Florival, C., Manalai, P., & Sonje, S. (2017). An assessment of five (PANSS, SAPS, SANS, NSA-16, CGI-SCH) commonly used symptoms rating scales in schizophrenia and comparison to newer scales (CAINS, BNSS). Journal of Addiction Research & Therapy, 8(3), 324.

Lees, J., Applegate, E., Emsley, R., Lewis, S., Michalopoulou, P., Collier, T., Lopez-Lopez, C., Kapur, S., Pandina, G. J., & Drake, R. J. (2015). Calibration and cross-validation of MCCB andCogState in schizophrenia. Psychopharmacology, 232(21–22), 3873–3882.

Lencer, R., Nagel, M., Sprenger, A., Heide, W., & Binkofski, F. (2005). Reduced neuronal activity in the V5 complex underlies smooth-pursuit deficit in schizophrenia: Evidence from an fMRI study. NeuroImage, 24(4), 1256–1259.

Lui, S., Deng, W., Huang, X., Jiang, L., Ma, X., Chen, H., Zhang, T., Li, X., Li, D., Zou, L., Tang, H., Zhou, X. J., Mechelli, A., Collier, D. A., Sweeney, J. A., Li, T., & Gong, Q. (2009). Association of cerebral deficits with clinical symptoms in antispsychotic-naive firstepisode schizophrenia: An optimized voxel-based morphometry and resting state functional connectivity study. The American Journal of Psychiatry, 166(2), 196–205.

Matouaka, R. A., & Betensky, R. A. (2015). Power and sample size calculations for the Wilcoxon-Mann-Whitney test in the presence of tied observations. Statistical Medicine, 29(5), 1216–1224.

Velasco-Iglesias, A., Saiz, P. A., Gonzalez-Blanco, L., et al. (2018). A voxel-based magnetic resonance imaging morphometric study of cerebral and cerebellar gray matter in patients under 65 years with essential tremor. Medical Science Monitor, 24, 3127–3135.

Collier, A. K., Wolf, D. H., Valdez, J. N., Turetsky, B. I., Elliott, M. A., Gür, R. E., & Gür, R. C. (2014). Comparison of auditory and visual oddball fMRI in schizophrenia. Schizophrenia Research, 158(1–3), 183–188.

Csaszar, N., Kapocs, G., & Bokon, I. (2019). A possible key role of vision in the development of schizophrenia. Reviews in the Neurosciences, 30(4), 359–379.

Fleschhacker, W., Galderisi, S., Laszlovszky, I., Szatmari, B., Barabasy, A., Acsaï, K., et al. (2019). The efficacy of cariprazine in negative symptoms of schizophrenia: Post hoc analyses of PANSS individual items and PANSS-derived factors. European Psychiatry, 58, 1–9.
of death-censored observations. *Statistics in Medicine*, 34(3), 406–431.
McHugh, M. L. (2011). Multiple comparison analysis testing in ANOVA. *Biochem Med (Zagreb)*, 21(3), 203–209.
Milev, P., Ho, B. C., Arndt, S., Nopoulos, P., & Andreasen, N. C. (2003). Initial magnetic resonance imaging volumetric brain measurements and outcome in schizophrenia: a prospective longitudinal study with 5-year follow-up. *Biological Psychiatry*, 55(6), 608–615.
Mittal, V. A., Gupta, T., Keane, B. P., & Silverstein, S. M. (2015). Visual context processing dysfunctions in youth at high risk for psychosis: Resistance to the Ebbinghaus illusion and its symptom and social and role functioning correlates. *Journal of Abnormal Psychology*, 124(4), 953–960.
Moseley, P., Mitrenga, K. J., Ellison, A., & Fernyhough, C. (2018). Investigating the roles of medial prefrontal and superior temporal cortex in source monitoring. *Neuropsychologia*, 120, 113–123.
Nagel, M., Sprenger, A., Nitschke, M., Zapf, S., Heide, W., Binkofski, F., & Lencer, R. (2007). Different extraretinal neuronal mechanisms of smooth pursuit eye movements in schizophrenia: An fMRI study. *Neuroimage*, 34(1), 300–309.
Northoff, G. (2014). Are auditory hallucinations related to the brain’s resting state activity? A Neurophenomenal resting state hypothesis. *Clinical Psychopharmacology and Neuroscience*, 12(3), 189–195.
Onitsuka, T., McCarley, R. W., Kuroki, N., Dickey, C. C., Kubicki, M., Demeo, S. S., et al. (2007). Occipital lobe gray matter volume in male patients with chronic schizophrenia: A quantitative MRI study. *Schizophrenia Research*, 92(1–3), 197–206.
Pinheiro, A. P., Farinha-Fernandes, A., Roberto, M. S., & Kotz, S. A. (2019). Self-voice perception and its relationship with hallucination predisposition. *Cognitive Neuropsychiatry*, 24(4), 237–255.
Silverstein, S. M. (2016). Visual perception disturbances in schizophrenia: A unified model. *Nebraska Symposium on Motivation*, 63, 77–132.
Silverstein, S. M., Berten, S., Essex, B., Kovacs, I., Susmara, T., & Little, D. M. (2009). An fMRI examination of visual integration in schizophrenia. *Journal of Integrative Neuroscience*, 8(2), 175–202.