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Cerebral blood flow alterations specific to auditory verbal hallucinations in schizophrenia

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Background
Auditory verbal hallucinations (AVHs) have been associated with deficits in auditory and speech-related networks. However, the resting-state cerebral blood flow (CBF) alterations specific to AVHs in schizophrenia remain unknown.

Aims
To explore AVH-related CBF alterations in individuals with schizophrenia.

Method
In total, 35 individuals with schizophrenia with AVHs, 41 individuals with schizophrenia without AVHs and 50 controls underwent arterial spin labelling magnetic resonance imaging. The CBF differences were voxel-wise compared across the three groups.

Results
We found AVH-specific CBF increase in the right superior temporal gyrus and caudate, and AVH-specific CBF decrease in the bilateral occipital and left parietal cortices. We also observed consistent CBF changes in both schizophrenia subgroups (i.e. those with and without AVHs) including decreased CBF in the bilateral occipital regions, the left lateral prefrontal and insular cortices, and the right anterior cingulate cortex and increased CBF in the bilateral lateral temporal regions and putamen, the left middle cingulate cortex and the right thalamus.

Conclusions
The AVH-specific CBF increases in the auditory and striatal areas and CBF reductions in the visual and parietal areas suggest that there exists a CBF redistribution associated with AVHs.

Declaration of interest
None.

Auditory verbal hallucinations (AVHs) are one of the major positive symptoms of schizophrenia, affecting about 60–80% of individuals with schizophrenia.[1] An AVH is an experience of spoken language without corresponding external stimulus.[2,3] AVHs heavily affect the quality of life of individuals with schizophrenia,[4] and up to 25% of AVHs are resistant to conventional treatments for schizophrenia.[5] Therefore, a complete understanding of the underlying pathological process engaged in AVHs in schizophrenia may be critically important for developing specific and effective therapy, although different mechanistic models for AVHs have been proposed.[6]

A number of neuroimaging techniques have been utilised to investigate the neural substrates of AVHs in schizophrenia and have revealed structural and functional abnormalities in brain regions involving auditory processing, speech generation and perception.[7,8] Structural imaging studies have demonstrated that AVHs are associated with grey matter volume reductions in brain regions involved in speech perception, such as the superior temporal gyrus (STG) and the primary auditory cortex.[7–10] Diffusion tensor imaging studies have revealed white matter integrity disruption in the left arcuate fasciculus bundle connecting the frontal and temporal-parietal speech areas[11] and in the corpus callosum fibres connecting the bilateral auditory regions[12] in individuals with schizophrenia with AVHs. During the AVH state, functional magnetic resonance imaging (fMRI) has shown aberrant activation in the frontal-temporal speech areas[8,13,14] and the primary auditory cortex[15] in individuals with AVHs. Resting-state functional connectivity studies indicate that the core mechanism underlying AVHs involves a complex functional loop that is associated with speech areas.[16]

As the only currently available non-invasive perfusion imaging technique, arterial spin labelling (ASL) imaging has been used to investigate brain perfusion alterations in schizophrenia.[17] Both increased and decreased resting-state cerebral blood flow (CBF) alterations have been found in individuals with schizophrenia.[18–23] In a prior ASL study investigating perfusion changes associated with AVHs within an 'inner-speech' network, Wolf *et al* have observed increased CBF in the left STG and right temporoparietal cortex in individuals with AVHs compared with individuals without AVHs and controls.[24] However, a complete picture of the whole-brain perfusion alterations specific to AVHs in schizophrenia beyond the speech-related network is yet to be unveiled. In this study, we used a 3D pseudo-continuous ASL technique to perform an exploratory analysis of AVH-related CBF alterations in schizophrenia by comparing voxel-wise CBF differences among individuals with schizophrenia with AVHs, individuals with schizophrenia without AVHs and healthy controls.

Method

Participants

A total of 126 right-handed individuals were enrolled in the present study, including 76 individuals with schizophrenia and 50 healthy controls. All participants were of Han Chinese ancestry. The diagnoses of schizophrenia were determined by the consensus of two experienced clinical psychiatrists using the Structured Clinical Interview for DSM-IV (SCID).[25] All healthy controls were screened using the non-patient edition of the SCID to confirm a lifetime absence of psychiatric illnesses. Exclusion criteria for all participants were a history of head trauma with consciousness disturbances lasting more than 5 min, a history of drug or alcohol misuse, pregnancy and any physical illness such as cardiovascular disease or neurological disorders, as diagnosed by an interview

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and medical records review. In addition, all healthy controls were interviewed to exclude individuals with a known history of psychiatric illness in first-degree relatives. According to whether they had experienced AVHs, individuals with schizophrenia were subdivided into two groups: the AVH group ($n = 35$) that included individuals who experienced AVHs at least once daily, and the non-AVH group ($n = 41$) that included individuals who had never experienced AVHs or had not experienced AVHs within the 12 months prior to magnetic resonance imaging (MRI). Clinical symptoms of psychosis were quantified using the Positive and Negative Syndrome Scale (PANSS).[26] The Auditory Hallucination Rating Scale (AHRS)[27] was used to assess AVHs on seven characteristics: frequency, reality, loudness, number of voices, length, attention dedicated to the hallucinations and hallucination-induced arousal. Visual hallucinations were assessed using item six of the Scale for the Assessment of Positive Symptoms (SAPS).[28] The item requires each individual with schizophrenia to answer if he/she has seen shapes or people that are not actually present. All individuals with schizophrenia had a rating of zero (no visual hallucinations) or one (questionable) on item six of the SAPS, suggesting that none of the participants with schizophrenia had a definite experience of visual hallucinations. The antipsychotic dosages are reported as chlorpromazine equivalents, which were calculated based on clinically equivalent dosing estimates.[29] For each individual with schizophrenia, the chlorpromazine equivalent was estimated according to the antipsychotic drugs and dosages used in the last week before the MRI scan. Smoking habits were recorded in participants with schizophrenia, but the smoking status of the healthy controls was not known. Smokers were defined as individuals smoking currently and daily for more than 1 year any number of cigarettes and non-smokers were defined as individuals who did not currently smoke and had never smoked regularly or daily.[30] The Medical Research Ethics Committee of Tianjin Medical University General Hospital approved this study. After a complete description of the study, written informed consent was obtained from each participant.

MRI data acquisition

The MRI scans were performed using a 3.0-Tesla MR system (Discovery MR750, General Electric, Milwaukee, Wisconsin, USA). Tight but comfortable foam padding was used to minimise head motion and earplugs were used to reduce scanner noise. The resting-state perfusion imaging was performed using a pseudo-continuous ASL sequence with a 3D fast spin-echo acquisition and background suppression (repetition time (TR) = 4886 ms, echo time (TE) = 10.5 ms, post-label delay 2025 ms, spiral in readout of eight arms with 512 sample points; flip angle 111; field of view (FOV) = 240 × 240 mm; reconstruction matrix 128 × 128; slice thickness 4 mm, no gap; 40 axial slices; number of excitations 3; and 1.9 × 1.9 mm in-plane resolution). The total acquisition time for the resting-state ASL scan was 4 min 44 s. During the scans, all participants were instructed to keep their eyes closed, relax and move as little as possible, think of nothing in particular and not fall asleep. All images were visually inspected to ensure that only images without visible artefacts were included in subsequent analyses.

CBF calculation

The ASL difference images were calculated using a single-compartment model[31] after the subtraction of the label images from the control images. The CBF maps were subsequently derived from the ASL difference images and the proton-density-weighted reference images.[32] Statistical Parametric Mapping (SPM8)[33] was used to co-register the CBF images of the 50 healthy controls to a positron emission tomography (PET)-perfusion template in the Montreal Neurological Institute (MNI) space using non-linear transformation. The standard CBF template of the MNI was defined as the mean co-registered CBF image of the 50 healthy controls. Then the CBF images of all participants were co-registered to the standard CBF template of the MNI and resampled to a voxel size of 2 × 2 × 2 mm. Non-brain tissue was removed from each co-registered CBF map and spatially smoothed with a Gaussian kernel of 8 × 8 × 8 mm full-width at half maximum (FWHM). We normalised the CBF of each voxel by dividing the mean CBF of the whole brain.[34]

Statistical analysis

Group differences in CBF among the three groups were tested using a voxel-wise one-way analysis of covariance (ANCOVA) with age and gender as covariates followed by *post hoc* intergroup comparisons. The *post hoc* intergroup comparisons were conducted within a mask showing CBF differences from the ANCOVA analysis. Multiple comparisons were corrected using a false discovery rate (FDR) method with a significance threshold of $P < 0.05$.

To investigate the relationship between CBF and the AHRS total score, a voxel-wise multiple regression analysis was conducted in the AVH group within regions showing significant CBF differences compared with the other two groups. The gender, age and antipsychotic dosages were considered nuisance covariates. Given the importance of the frequency of AVHs in neural correlations,[35] we also performed the correlation between CBF and the frequency subscale of the AHRS. Multiple comparisons were corrected again using an FDR method.

Results

Demographic and clinical characteristics

Demographic and clinical data for the participants are presented in Table 1. The three groups were well-matched in terms of gender ($\chi^2 = 0.308$, $P = 0.857$) and age (one-way ANOVA, $F = 0.100$, $P = 0.905$). There were no significant differences in antipsychotic dosages (two sample *t*-test, $t = 1.163$, $P = 0.248$), durations of illness (two sample *t*-test, $t = -0.916$, $P = 0.363$), ratio of smoker/non-smoker ($\chi^2 = 1.484$, $P = 0.223$), PANSS negative score (two sample t-test, $t = -0.594$, $P = 0.555$), PANSS general score (two sample *t*-test, $t = 0.275$, $P = 0.784$) and PANSS total score (two sample *t*-test, $t = 0.893$, $P = 0.375$) between individuals with and without AVHs.

CBF differences across groups

A voxel-wise ANCOVA revealed that the intergroup differences in CBF were mainly located in the bilateral lateral temporal, occipital and striatal regions, the left lateral prefrontal, parietal, middle cingulate and insular cortices, and the right anterior cingulate cortex (ACC) and thalamus (FDR corrected, $P < 0.05$) (Fig. 1). Specifically, the individuals in the AVH group exhibited significantly decreased CBF in the bilateral occipital and left parietal regions and increased CBF in the right STG and caudate nucleus relative to the individuals in the non-AVH group (online Table DS1 and Fig. 1(b)). Compared with the control group, the AVH group showed significantly decreased CBF in the bilateral occipital regions, left lateral prefrontal, parietal and insular cortices and the right ACC and increased CBF in the bilateral lateral temporal regions and putamen, the left middle cingulate cortex (MCC) and the right thalamus (online Table DS2 and Fig. 1(c)). Similarly, the non-AVH group had significantly decreased CBF in the bilateral occipital regions, the left lateral prefrontal and insular cortices, and the right

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Table 1 Demographic and clinical characteristics of the sample[a]

Characteristics	AVH group ($n = 35$)	Non-AVH group ($n = 41$)	Control group ($n = 50$)	P[b]
Age, years: mean (s.d.)	31.5 (7.7)	32.3 (5.7)	32.0 (8.2)	0.905
Gender, women/men: *n*	14/21	17/24	18/32	0.857
Antipsychotic dosage,[c] mg/d: mean (s.d.)	518.1 (395.6)	429.9 (259.5)	N/A	0.248
Duration of illness, months: mean (s.d.)	101.4 (94.3)	118.8 (71.7)	N/A	0.363
Ratio of smoker/non-smoker, *n*	21/14	30/11	N/A	0.223
Positive and Negative Syndrome Scale, mean (s.d.)			N/A	
Total	73.2 (23.6)	68.4 (23.0)		0.375
Positive score	20.1 (7.7)	14.8 (7.6)		0.004
Negative score	18.8 (8.2)	20.2 (9.2)		0.555
General score	34.3 (11.5)	33.6 (10.5)		0.784
Auditory Hallucination Rating Scale total score, mean (s.d.)	23.9 (8.4)			

N/A, not applicable.
a. All participants are of Han Chinese ancestry.
b. One-way ANOVA was used to test the difference in age across the three groups. Chi-square test was used to test the difference in gender across the three groups. Two-sample *t*-test was used to compare the differences in antipsychotic dosage, duration of illness and PANSS scores between the two schizophrenia groups. Chi-square test was used to test the difference in the ratio of smokers/non-smokers between the two schizophrenia groups.
c. Antipsychotic dosages are reported as chlorpromazine equivalents calculated based on clinically equivalent dosing estimates.

ACC and increased CBF in the bilateral lateral temporal regions and putamen, the left MCC and the right thalamus compared with the control group, but the spatial extent was smaller than that in the individuals in the AVH group (online Table DS3 and Fig. 1(d)).

Notably, both the schizophrenia groups showed an overlapping reduction of CBF in the bilateral occipital regions, the left lateral prefrontal and insular cortices, and the right ACC and an overlapping increase of CBF in the bilateral lateral temporal regions and putamen, the left MCC and the right thalamus, which were defined as common CBF alterations shared by individuals with and without AVH (Fig. 2(a)). Compared with both the non-AVH and control groups, the AVH group exhibited decreased CBF in the bilateral occipital and left parietal regions and increased CBF in the right STG and caudate, which were defined as exclusive CBF alterations in individuals with AVH (Fig. 2(b)).

Associations between CBF and AVH severity in the AVH group

In brain regions demonstrating AVH-exclusive CBF alterations, we did not find any significant correlation between CBF and AVH severity (both ARHS total score and ARHS frequency subscale) in the AVH group.

Discussion

Main findings

In this study, we adopted a 3D-ASL approach to study the whole-brain CBF patterns in individuals with schizophrenia with AVHs, individuals with schizophrenia without AVHs and healthy controls. Although the two schizophrenia groups showed widespread common CBF alterations in the frontal, temporal, occipital, insular and subcortical regions, the AVH group exhibited exclusive alterations, including increased CBF in the STG and caudate nucleus, and decreased CBF in the occipital and parietal cortices.

Common CBF alterations in individuals with schizophrenia with and without AVHs

Our findings of decreased CBF in the ACC, lateral prefrontal cortex, insular and occipital cortices and increased CBF in the lateral temporal cortex, putamen and thalamus in both schizophrenia groups provide further evidence that CBF impairments in these regions may be at the root of pathogenesis of schizophrenia, which was consistent with our prior study.[23] The hypoperfusion in the lateral prefrontal cortex, the salience network (including the dorsal ACC and the anterior insular) and the visual region may contribute to deficits of cognitive processing,[36] switching between central-executive and default-mode networks[37] and visual processing[38] in schizophrenia. The lateral temporal cortex, thalamus and putamen are involved in processes of multimodal sensory integration, modulation of multiple functional circuits and dopamine function; hyperperfusion in those regions may lead to disturbances in their functions in schizophrenia.[39–41] Thus, perfusion abnormalities in these brain circuits may contribute to the occurrence of schizophrenia irrespective of the presence of AVHs.

CBF alterations specific to AVHs in schizophrenia

We found that individuals with AVHs showed CBF increases in the right STG and caudate nucleus when compared with individuals without AVH and healthy controls, these findings are inconsistent with a previous CBF study within the 'inner-speech' network showing that the increased CBF in the left STG and right temporoparietal cortex were specific to AVHs in schizophrenia.[24] The discrepancy may be related to differences in multiple aspects between the two studies: sample size (35 individuals with AVHs and 41 individuals without AVHs in our study *v.* 10 individuals in each group in Wolf *et al*'s study), schizophrenic subtypes (mixed subtypes *v.* paranoid subtype), gender (matched *v.* unmatched between groups), ASL techniques (3D-pseudo-continuous ASL *v.* continuous ASL) and correction for multiple comparison (corrected *v.* uncorrected). Sommer and colleagues have noted that the right homologues of the language areas (including the right STG), rather than the language areas in the left hemisphere, were mainly activated while individuals with schizophrenia experienced AVHs in a scanner.[42,43] In an early fMRI report, Woodruff *et al* have found that AVHs predominantly activate the right language areas including the right temporal cortex, whereas auditory perception of speech activates the left ones.[44] Although several structural imaging studies have reported that individuals with schizophrenia with AVHs exhibit decreased volume[8,9] and cortical thickness[45] in the bilateral STG, a meta-analysis has reported that there is a significant negative correlation between the severity of auditory hallucinations and grey matter

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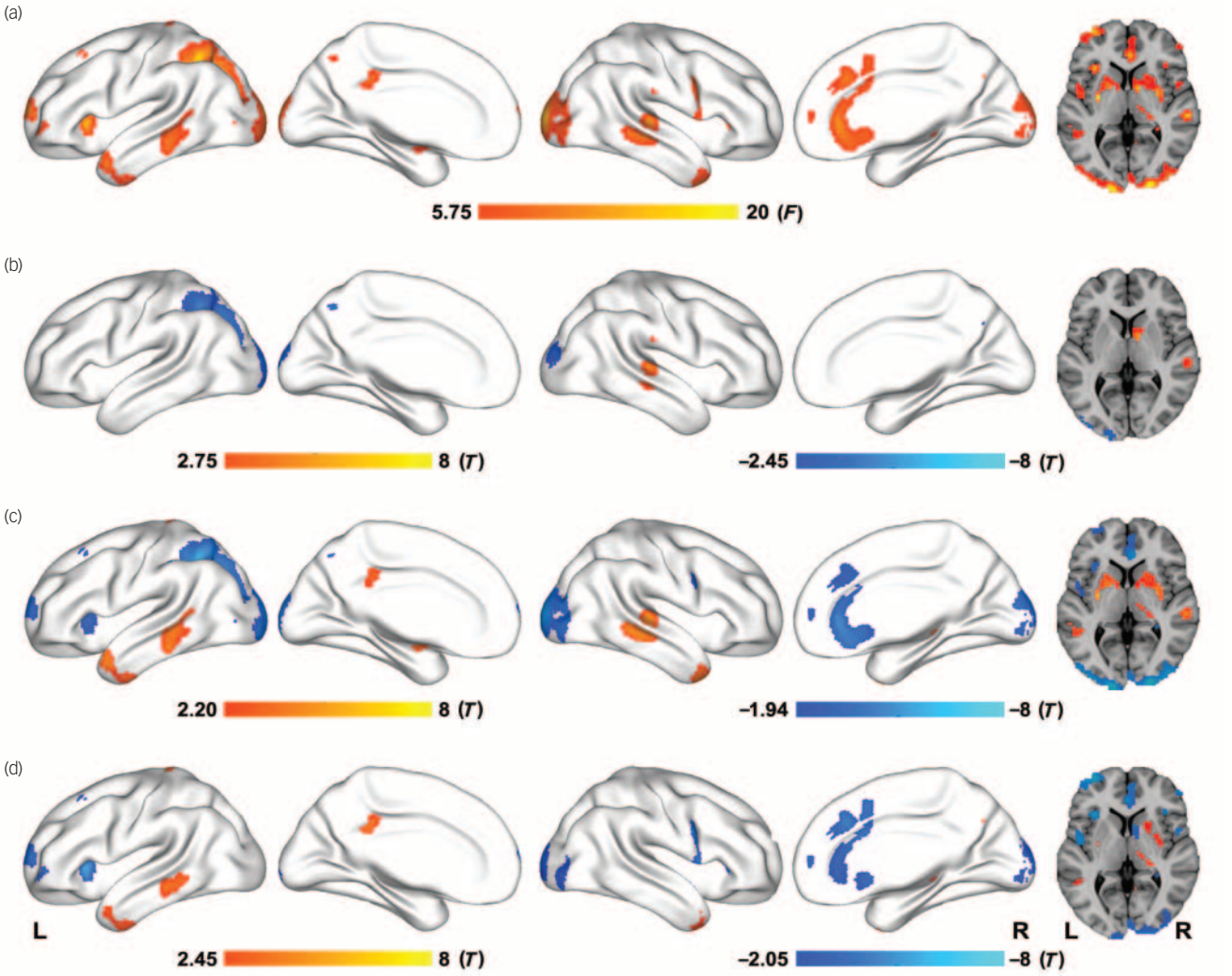

Fig 1. Brain regions exhibiting cerebral blood flow (CBF) differences among the auditory verbal hallucination (AVH), non-AVH and control groups.

(a) One-way analysis of covariance (ANCOVA) reveals brain regions with significant CBF differences among the three groups. *Post hoc* two-sample *t*-tests show brain regions with significant CBF differences between (b) the AVH and non-AVH groups, (c) the AVH and control groups, and (d) the non-AVH and control groups. The minimum values in the colour bars indicate statistical thresholds (*F* or *T*) of $P<0.05$ (false discovery rate (FDR) corrected). L, left; R, right.

volume in the right STG in schizophrenia, suggesting that volume reduction in the right STG is likely to be specific to the symptoms of AVHs.[10] This paradox of functional and structural findings may indicate a disruption of the normal structure–function relationship or a decoupling between blood supply and brain structural topology. The left STG, including the primary and association auditory cortices, has been repeatedly found to play a prominent role in the aetiology of AVHs.[7,8] The right STG is also implicated in auditory and language processing, particularly of the emotional and prosodic aspect of speech stimuli.[46] In most right-handed people, the left hemisphere dominates over the right one in language production and perception.[47] However, dysfunction of the right hemisphere language areas is capable of producing some single words or truncated sentences typically with a negative emotional content,[48,49] for example swear words or terms of abuse. AVHs experienced by individuals with schizophrenia usually consist of these kinds of short phrases of low linguistic complexity,[50,51] indicating that they may indeed be the product of the right language-related regions including the right STG.[43] Another possible interpretation of our right lateralised findings is that according to the 'callosal relay' model, auditory signals must be dominantly transferred from the right hemisphere to the left side for processing.[12,52,53] So it is conceivable that hyperfunction of the right STG may be capable of producing or amplifying AVH-related speech in the case of normal function of the left side. Converging evidence points towards the potential role of the caudate nucleus in the pathophysiology of AVHs. For example, several reports have shown that individuals with schizophrenia experiencing AVHs have significantly higher metabolic rates[54] and grey matter volume[55] in the caudate nucleus. Considering that the caudate nucleus has a central role in linguistic processes[56] and regulating language switch,[57,58] its dysfunction could be a key factor in the development and maintenance of AVHs.[54]

We also found decreased CBF in the parietal cortex in individuals with AVHs compared with individuals without AVHs and healthy controls. This cluster is located at the superior parietal lobule and the intra-parietal sulcus[59–61] and is involved in top–down attention, working memory, motor coordination, numerical calculation, tool use and language.[59,62.63] Most of these functions have been reported to be impaired in individuals with schizophrenia.[64–67] Among these functions, the deficits in top–down attention[68,69] and working memory[70,71] are closely associated with AVHs. Thus, the reduced CBF in the superior

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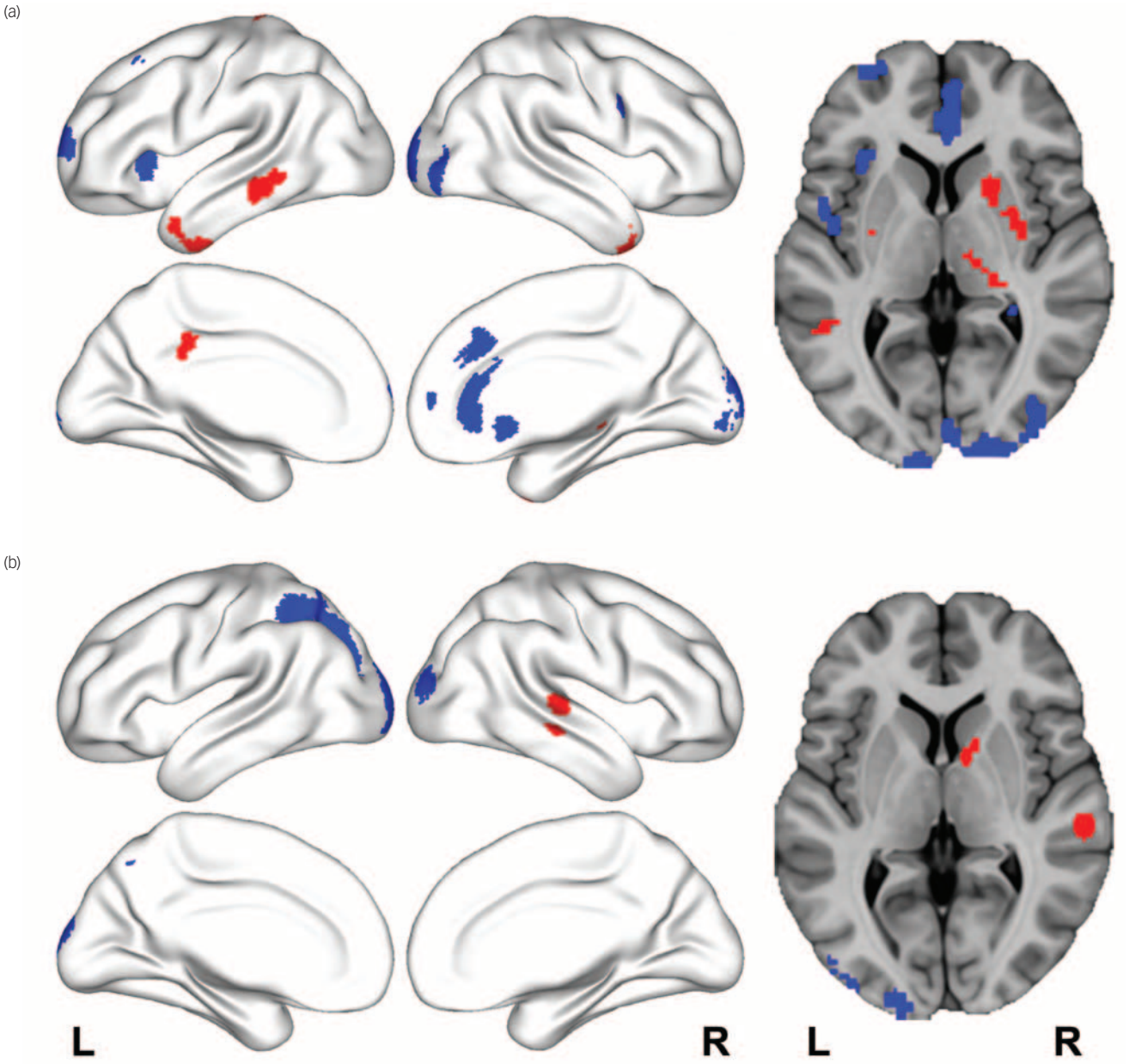

Fig. 2. Brain regions with (a) common and (b) exclusive cerebral blood flow (CBF) alterations in individuals with auditory verbal hallucinations (AVHs).

(a) Common CBF alterations in schizophrenia are defined as the overlapping regions between CBF-difference maps ($P<0.05$, false discovery rate (FDR) corrected) of the AVH–Control and non-AVH–Control groups (red represents CBF increase and blue means CBF reduction in both schizophrenia groups). (b) Exclusive CBF alterations are defined as the overlapping regions between CBF-difference maps ($P<0.05$, FDR corrected) of AVH–non-AVH and AVH–Control groups (red represents CBF increase and blue means CBF reduction in the AVH group compared with both the non-AVH and control groups). L, left; R, right.

parietal lobule and the intra-parietal sulcus may be a candidate explanation for the attention and working memory deficits in individuals with schizophrenia with AVHs.

Associations between CBF and AVH severity

In our study, we did not find a correlation between CBF values of these AVH-exclusive brain areas and severity of auditory hallucinations assessed by the ARHS total score and frequency subscale in individuals with AVHs. These findings indicate that aberration of resting-state CBF may be a stable trait characteristic of AVH schizophrenia regardless of its severity. However, we cannot rule out the possibility that there is a complex relationship between CBF and AVH severity beyond a simple linear correlation. Thus, more complex models, such as a quadratic regression model, are needed to clarify the relationship between them.

Limitations

Several limitations must be noted when interpreting the results of the present study. First, the majority of the participates with schizophrenia received antipsychotic drug treatment and its effect on the CBF in schizophrenia is still unclear. Although the effect of this is likely to be relatively small, because there was no difference in antipsychotic dosage between the individuals with and without AVHs, future studies should focus on drug-naive individuals with schizophrenia to clarify the uncertainty. Second, we did not assess the psychotic symptoms, including AVHs, during the MRI scan, which means that some individuals with schizophrenia may have experienced AVHs and others may not while in the MRI scanner. Instead, we assessed AVHs and other symptoms of psychosis in all the individuals with schizophrenia before the MRI procedure. Third, individuals with schizophrenia who had not experienced

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AVHs within 12 months prior to MRI scanning were included in this study. These individuals may have experienced auditory hallucinations earlier in their psychotic illness, and they may still have trait characteristics of hallucinations. Finally, although the sample sizes of 35 individuals with AVHs and 41 individuals without AVHs are sufficient to compare intergroup differences, 35 individuals with AVHs might not be sufficient to investigate within-group correlation with symptom severity. This might be the reason for the lack of significant correlations between CBF and the AHRS scores. Future studies with a larger sample size of individuals with AVHs are needed to validate our findings.

Implications

In summary, in this study we present evidence that individuals with schizophrenia with and without AVHs share common CBF alterations in widespread brain regions including the frontal, temporal, occipital, insular and subcortical regions. More importantly, individuals with AVHs show exclusive CBF alterations consisting of an increase in the right auditory and striatal areas, and a reduction in the visual and parietal areas, indicating that there exists a CBF redistribution associated with AVHs.

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