



Letter to the Editor

Magnetic resonance perfusion imaging of auditory verbal hallucinations in patients with schizophrenia

Dear Editors,

Auditory verbal hallucinations (AVH) are a core symptom of schizophrenia and related spectrum-disorders. So far, magnetic resonance imaging (MRI) has been employed to study the functional neuroanatomy of AVH using two distinct methods, either by capturing symptoms during the actively hallucinating state or by investigating neural responses during explicit cognitive processing (Allen et al. 2008; Hugdahl 2009). Both approaches, however, face certain limitations. For instance, the self-identification of AVH is accompanied by the cognitive and motor response associated with this event, together with increased self-awareness. This interaction might change the participant's subjective experience and quality of the hallucinatory symptom. On the other hand, interactions between experimental stimuli and symptoms could drive activation patterns that may not represent the "pure" neural substrate of AVH. In this study, we investigated the neural correlates at rest of AVH in schizophrenia using an MRI-based technique of perfusion imaging using continuous arterial spin labelling [CASL] (Theberge 2008). The objectives of our study were threefold: first, we tested the hypothesis that patients with schizophrenia with treatment-refractory AVH would exhibit symptom-related perfusion changes within a speech-related network, as predicted by AVH models of dysfunctional speech generation and misattribution (Stephane et al. 2001; Allen et al. 2008). Second, we investigated the symptom-specificity of brain perfusion abnormalities in AVH patients by including a group of non-hallucinating schizophrenic patients. Third, we explored the relationship between regional cerebral blood flow (rCBF) and multiple dimensions of AVH, as assessed by symptom-specific psychometrics.

We studied 20 medicated patients with schizophrenia (paranoid subtype according to DSM-IV); see Supplementary material for details on inclusion/exclusion criteria, medication and psychometric scores. Patients with AVH ($n = 10$; 4 female; mean age = 36.5 years) were classified as being medication resistant for AVH, as defined by persistent symptoms in the presence of at least two clinically ineffective drug trials (each > 6 weeks of treatment) with different antipsychotics at adequate dosage. Further, patients with AVH were only included if they did not show pronounced formal thought disorder symptoms and if they had sufficient insight into their hallucinatory experience such as to provide self-reports about their symptoms. A second group of patients with schizophrenia consisted of 10 participants (2 female; mean age = 32.1 years) who either never experienced AVH or who experienced AVH in the past, while being fully remitted from AVH at least 12 months before being included in the study. The healthy control group consisted of 14 participants (7 female; mean age = 33.7 years) matched for age, education and handedness. The project was approved by the local research ethics committee. All experimental procedures were carried out with the understanding and written consent of the participants.

Imaging was performed on a 3T Magnetom Allegra (Siemens, Germany) MRI system. Scanning was performed under resting-state conditions; see also the Supplementary material for a detailed description of the technical details. Preprocessing and analyses of an MRI perfusion block of approximately 5 min were performed using Statistical Parametric Mapping (SPM5) in combination with software implemented in MATLAB 7.3 for use as a toolbox under SPM5; see also the Supplementary material for a detailed description of the data analysis. For the individual (first level) analysis, mean rCBF images were computed for each participant. Group comparisons between controls and patients were conducted at the second level using an analysis of variance. A threshold of $p < 0.005$ (uncorrected at the voxel level) and a cluster-size threshold of at least 50 contiguous voxel was chosen for all between-group comparisons. Furthermore, correlations (FDR adjusted $p < 0.0259$) were calculated using psychometric data and rCBF values extracted from clusters showing significant between-group differences.

Compared to controls, AVH patients had increased rCBF in the left inferior frontal gyrus (IFG), the left anterior cingulate cortex (ACC), the supplementary motor area (SMA), in a cluster including the left middle temporal gyrus (MTG) and superior temporal gyrus (STG), the left insula, the right MTG and the right supramarginal gyrus (SMG), extending to the right temporoparietal cortex (TPC); see Fig. 1 and Supplementary material Fig. 2, and Table 2. Compared to patients without AVH, the group of hallucinating patients exhibited significantly increased rCBF in the left STG and right SMG, extending to the right TPC (Fig. 1 and Table 2, Supplementary material). Compared to healthy participants, patients without AVH showed increased rCBF in the left MTG, left STG, left SMG and in the left insula. Patients with AVH demonstrated positive correlations between rCBF and overall AVH severity (as measured by the auditory hallucinations scale [AHS] of the Psychotic Symptoms Rating Scales [PsyRatS]) in the left STG, ACC and IFG (Fig. 2, Supplementary material). Different correlation patterns emerged when correlating rCBF values with scores from the PsyRatS-AHS emotional, physical and cognitive subscales (see Supplementary material Fig. 3).

The comparison of patients with persistent AVH against controls yielded results that support the notion of dysfunctional neural activity in brain regions associated with the generation, perception and monitoring of speech as a the central mechanism underlying AVH (McGuire et al. 1995; Stephane et al. 2006; Hugdahl 2009). Increased rCBF in non-hallucinating patients was detected in the left MTG, left STG, left SMG and left insula when compared to controls. This pattern may reflect a common neurophysiological abnormality in both groups irrespective of the presence or absence of AVH (Mechelli et al. 2007). When contrasting hallucinating against non-hallucinating patients, patients with AVH still demonstrated increased rCBF in the left STG and the right SMG/TPC, indicating two critical network nodes associated with AVH, in the presence of an otherwise comparable clinical diagnosis. This suggests that the left STG may lie at the core of a final common pathway which ultimately accounts for the perceptual nature of AVH, i.e. for the subjective experience of "hearing voices", in

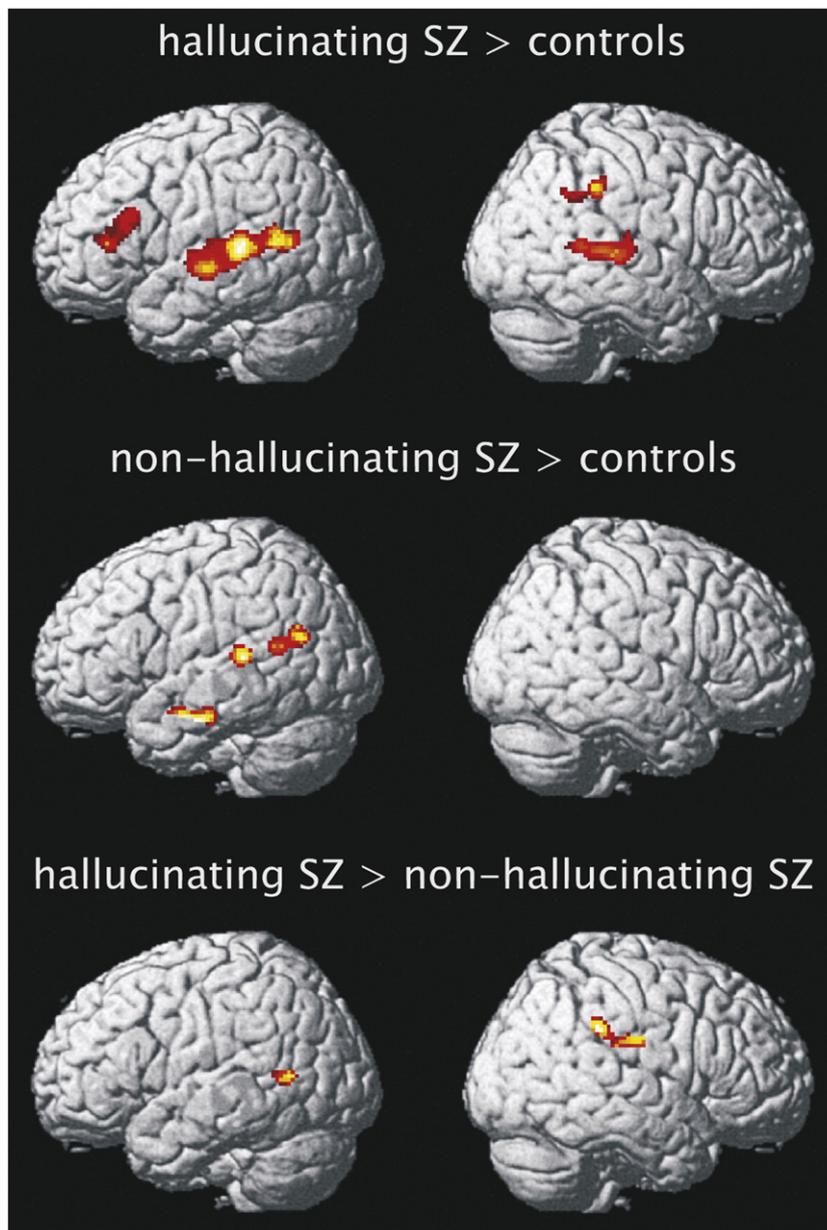


Fig. 1. Regions exhibiting abnormal rCBF in patients with schizophrenia compared to healthy participants. SZ = patients with schizophrenia. The contrast non-hallucinating SZ > hallucinating SZ did not reveal significant results. Results of the 2nd level ANOVA, $p < 0.005$ (uncorrected), cluster-extent: $k > 50$ voxel. The 2nd level maps are rendered on the anatomical template implemented in SPM5.

contrast to silently generated, but self-attributed speech. In line with previous reports (Cleghorn et al. 1990; Onitsuka et al. 2004; Plaze et al. 2006) we found that overall AVH severity was correlated with abnormal rCBF in the left STG, the ACC and the left IFG. The correlations between the emotional, physical and cognitive dimensions of AVH and rCBF further suggest that different phenomenological aspects of AVH may be related to different loci of cortical dysfunction. Interestingly, we found the ACC as the only region correlated with all three dimensions of the PsyRatS-AHS. The ACC has been associated with several cognitive processes, such as attentional control and online source and conflict monitoring (Allen et al. 2007; Mechelli et al. 2007; Simons et al. 2010), and in accordance with our findings, a recent study has reported a relationship between AVH severity and ACC connectivity during resting-state conditions (Vercammen et al. 2010). Although causality cannot be inferred from correlations, the present findings might encourage further studies to fully explore

the rich phenomenological characteristics of AVH by symptom-specific psychometric instruments.

Potential limitations of our study include the relatively small patient sample size and the fact that all of the participating patients received antipsychotic drug treatment. Moreover, previous neuroimaging studies have implicated different time courses of AVH-related activation, so that activity prior to the occurrence of AVH might differ from activity during the actual perception of AVH. With the present protocol, it was not possible to examine a specific temporal sequence of events since our patients were deliberately not instructed to indicate the occurrence of AVH while being scanned. Despite these potential shortcomings this study provided evidence for increased rCBF of frontotemporal regions in patients with treatment-resistant AVH in contrast to healthy controls. When contrasted to patients without AVH, the occurrence of AVH during scanning was still accompanied by increased perfusion in the left STG and right temporoparietal areas, indicating a critical role of these

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