Default Mode Network alterations underlie auditory verbal hallucinations in schizophrenia

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Abstract

Although alterations of the default mode network (DMN) in schizophrenia (SZ) have been largely investigated, less research has been carried out on DMN alterations in different sub-phenotypes of this disorder. The aim of this pilot study was to compare DMN features among SZ patients with and without auditory verbal hallucinations (AVH). Three groups of 17 participants each were recruited: patients with hallucinations (AVH-SZ), patients without hallucinations (nAVH-SZ) and age-matched healthy controls (HC). The DMN spatial pattern was similar between the nAVH-SZ and HC, but the comparison between these two groups and the AVH-SZ group revealed alteration in the left Angular Gyrus (lAG) node of the DMN. Using a novel approach based on normalized fractional Amplitude of Low-Frequency Fluctuations (fALFF), the AVH-SZ subgroup showed altered spectral activity in the DMN compared with the other two groups, especially in the lower-frequency bands (0.017-0.04 Hz). Significant positive correlations were found for both SZ groups collapsed, and for the nAVH-SZ group alone between delusional scores (PANSS-P1) and slow fALFF bands of the DMN. Narrowing the analysis to ROI centered on the lAG, significant correlations were found in the AVH-SZ group for hallucination scores (PANSS-P3) and Slow-5 and Slow-4 (both positive), and Slow-3 (negative) fALFF bands. Our results reveal the central role of the left AG in relation with hallucinations, an important cortical area connecting auditory cortex with several hubs (including frontal linguistic centers) and involved in auditory process monitoring.

Keywords: Default Mode Network (DMN); Schizophrenia; Auditory Verbal Hallucinations (AVH); functional Magnetic Resonance Imaging (fMRI); Independent Component Analysis (ICA); fractional Amplitude of Low-Frequency Fluctuations (fALFF).

1. Introduction

Schizophrenia (SZ) is a psychotic disorder that consists of a variety of syndromes, essentially marked by negative and/or positive symptoms (Andreasen, 1990; Kay et al., 1987; McGrath et al., 2008), such as affective flattening and apathy, and delusions and hallucinations, respectively. SZ patients may also exhibit cognitive deficits, including impaired working memory, attention, and executive functions. Among all symptoms, auditory verbal hallucinations (AVH), defined as the experience of "hearing voices" in the absence of external stimuli that cause them, are one of the most common and distressing symptoms of SZ, affecting about 60%–90% of patients (Alderson-Day et al., 2015), and inducing discomfort, functional impairment and behavioral alterations (Nayani and David, 1996). Since AVH is directly associated with a disruption of language-related functional areas and networks (Ćurčić-Blake et al., 2017; Hugdahl, 2009; Jardri et al., 2011; Kompus et al., 2011), inter- and intra-hemispheric connectivity might show different dysfunctional patterns in SZ patients suffering from hallucinations (AVH-SZ), as opposed to patients without hallucinations (nAVH-SZ). In this context, various sub- phenotypes of SZ may have unique (dys)functional patterns depending on presenting or not AVH symptoms.

Several past neuroimaging studies suggest that SZ patients suffer from deficiencies in hemispheric brain communication, and that this disruption may be related to the occurrence of AVHs. This key symptom has been associated with decreased functional left hemispheric laterality of speech perception areas in the temporal lobes (Crow, 1997; Green et al., 1994; Hugdahl et al., 2008; Mitchell and Crow, 2005; Sommer et al., 2001). Furthermore, this altered symmetrical activation was correlated with the progression of the disease (Lam et al., 2012), as revealed by

disorganized speech pattern and thought disorders. Notably, this has been studied for the language network in a variety of tasks (Alary et al., 2013; Liemburg et al., 2012), but a growing number of studies have also sought to directly link resting-state characteristics to the propensity for hallucinations (Cavelti et al., 2018; Liemburg et al., 2012; Sabb et al., 2010; Weber et al., 2020). Resting state represents a baseline condition in correspondence of which the brain is not engaged in external demands from the environment, and its activity is functionally organized in networks, including the default-mode network (DMN) (Raichle et al., 2001). The DMN includes a set of brain regions, comprising left and right angular gyrus (lAG and rAG), posterior cingulate cortex (PCC), and medial prefrontal cortex (mPFC), and is known to correlate negatively with task-positive activity, prompting the concept of "default state". In particular, the DMN is active in a range of internally-directed cognitive processes, including mind-wandering, and introspective thought, and it is often anti-correlated with externally-guided activity (Buckner et al., 2008; Fox et al., 2005). Due to the intra-personal and self-directed nature often characterizing AVH-SZ patients (Ffytche and Wible, 2014; Vercammen et al., 2010), it is plausible that an atypical modulation of the DMN – either via an altered interaction between the DMN and other networks at rest (Northoff and Qin, 2011; Hugdahl et al., 2015) or a failure to maintain the DMN in a stable state (Jardri et al., 2013) – could give rise to internal cognition being mistakenly processed in sensory association areas, which could contribute to the hallucinatory experience (Waters et al., 2012).

Indeed, alterations in the DMN have been reported in SZ patients (Hu et al., 2017; Kindler et al., 2015) and a relationship between symptoms severity and functional connectivity has been found (Garrity et al., 2007). However, most of these studies have

used mixed SZ groups (Rotarska-Jagiela et al., 2010), which did not enable to disentangle the specific features associated with hallucinations. Growing interest has been focused on the study of SZ sub-phenotypes to identify brain biomarkers, which may characterize the emergence of a specific symptomatology. By constraining the SZ sample to separately include a group of AVH-SZ patients (Sommer et al., 2012; Vercammen et al., 2010) and a clinical control group of nAVH-SZ patients (Gavrilescu et al., 2010; Hoffman et al., 2011), it emerged that bilateral insula, parahippocampal areas, and regions belonging to the DMN, including PCC, showed increased activity in AVH-SZ patients only. It was further found increased functional connectivity between the insula and both angular gyri (Mallikarjun et al., 2018), suggesting that asymmetries in DMN activity may be involved in the generation of AVH.

In this pilot study, we aimed to investigate DMN altered spatial and spectral features in relation to hallucinations using a new approach focusing on fMRI low-frequency fluctuations within the DMN in two groups of SZ patients, i.e., with and without hallucinations (AVH-SZ and nAVH-SZ patients, respectively), and in a group of healthy controls (HC). In particular, we firstly aimed to test whether DMN symmetry, in topology and activity, is preserved or shows differences between SZ patients and HC, and between the two SZ patient subgroups. Finally, we investigated how altered low-frequency DMN fluctuations correlated with severity of hallucinatory symptoms.

2. Material and Methods

2.1. Participants

De-identified and anonymized data from two subgroups of Norwegian SZ

patients were included, the first subgroup with a predominance of AVH and positive symptoms (AVH-SZ group), the second subgroup without AVH and with predominantly negative symptoms (nAVH-SZ group). These SZ patients represent a sub-group of the patient group considered in the study by Weber et al. (2020). In the present study, inclusion criteria were: (a) scores ≥ 4 on both the P1 (Delusions) and P3 (Hallucinations) items of the Positive and Negative Syndrome Scale (PANSS (Kay et al., 1987) and scores ≤ 4 on both the the PANSS N1 (Blunted Effect) and N2 (Emotional Withdrawal) items (AVH-SZ group); (b) scores ≤ 4 on either the PANSS P1 (Delusions) or P3 (Hallucinations) items, and scores ≥ 3 on both the PANSS N1 (Blunted Effect) and N2 (Emotional Withdrawal) items (nAVH-SZ group); (c) the SZ patients included in different subgroups were mutually exclusive: if a patient was assigned to the AVH-SZ subgroup he/she had low scores on the PANSS negative scale and the other way around, so that there were no mixed-scoring patients. Seventeen SZ patients for each subgroup satisfied the criteria, showing similar age, educational level and gender distribution (average group means ± Standard Deviations, SD, in Table 1). All patients were under medical treatment on second-generation antipsychotics, primarily aripiprazole, amisulpride, or olanzapine, but a few were also prescribed clozapine, quetiapine or risperidone (see Definition of Daily Doses, DDD, in Table 1). The patient subgroups were compared with an age-matched control-group of 17 healthy individuals. Transfer of data to University of Padua was approved by the Regional Committee for Medical Research Ethics in Western Norway (REK-Vest, # 04052020-6822).

Table 1
Socio-demographical characteristics and medical treatment of clinical and control groups. Mean ± standard deviations (SD).

	Group			
	AVH-SZ (n = 17)	**nAVH-SZ (n = 17)**	**HC (n = 17)**	**Statistics**
Age	25.94 ± 8.56	28.38 ± 11.80	28.12 ± 7.36	$F_{2,48} = 0.34$, *n.s.*
Education	13.09 ± 3.74	11.91 ± 2.29	16.06 ± 1.09	$F_{2,47} = 11.15$, $p < 0.001$[a]
Gender	6 F; 11 M	4 F; 13 M	5 F; 12 M	all $\chi^2 < 1.0$, *n.s.*
DDD	0.50 ± 0.34	0.96 ± 0.56	-	$_{t26} = -2.66$, $p = 0.013$[b]
PANSS				
P1	*4.53 ± 0.80*	*3.06 ± 1.20*		$t_{32} = 4.21$, $p < 0.001$
P3	*4.71 ± 0.59*	*2.06 ± 1.20*		$t_{32} = 8.18$, $p < 0.001$
Mean Positive	***4.62 ± 0.45***	***2.56 ± 0.86***		$t_{32} = 8.71$, $p < 0.001$
N1	*2.29 ± 1.10*	*3.71 ± 0.85*		$t_{32} = -4.17$, $p < 0.001$
N2	*2.12 ± 1.11*	*3.53 ± 0.62*		$t_{32} = -4.57$, $p < 0.001$
Mean Negative	***2.21 ± 0.71***	***3.62 ± 0.52***		$t_{32} = -6.64$, $p < 0.001$

Note: AVH-SZ = SZ patients with Auditory Verbal Hallucination; nAVH-SZ = SZ patients without Auditory Verbal Hallucination; HC = Healthy controls; DDD = Definition of Daily Doses; PANSS = Positive and Negative Syndrome Scale; P1 = Delusions; P3 = Hallucinations; N1 = Blunted Effect; N2 = Emotional Withdrawal.

[a] Tukey HSD post hoc: AVH-SZ = nAVH-SZ (*n.s*).; AVH-SZ < HC ($p = 0.048$); nAVH-SZ < HC ($p < 0.001$). Note: education years from a nAVH-SZ patient were missing.

[b] DDD data from some SZ patients (i.e., 2 AVH and 4 nAVH) were not available.

2.2. MRI data acquisition

Magnetic resonance (MR) data were acquired with a 3T MR scanner (GE Discovery MR750 - GE Healthcare, Waukesha WI, USA) at the Haukeland University Hospital in Bergen, Norway. The acquisition protocol included functional MR imaging (fMRI) in the eyes-close resting state condition for 5 minutes and 20 seconds. One hundred and sixty whole brain volumes were acquired, with 30 slices with a 0.5 mm gap (voxel size 1.72x1.72x3 mm^3) with the following parameters: TR = 2000 ms, TE = 30 ms, Flip Angle (FA) = 90°, and Field of View (FOV) = 220 mm. In addition, a structural T1-weighted image was acquired (7.42 min) using a 3D Spoiled Gradient-Recalled Echo (SPGR) sequence with the following parameters: TR = 7.78 ms, TE = 2.94 ms, FA = 14°, and FOV = 256 mm, with isotropic voxel size of $1mm^3$. During all scans, subjects were asked to simply stay motionless, awake and relaxed with their eyes closed; no visual or auditory stimuli were presented at any time during functional scanning. None of participants in the study moved, fall asleep[1], or reported anxiety or other particular emotions during scanning.

[1] The patients were watched by the responsible MR-technician through a window into the scanner chamber, although not overtly monitored. It is unlikely that the patients fell asleep due to the background noise caused by the scanner, and no patient was found sleeping when the scanning session was over.

2.3. Clinical Assessment

The Positive and Negative Syndrome Scale (PANSS) was used to quantify clinical symptoms in patients. More in detail, hallucination severity was assessed with the P3 item (Kay et al., 1987). The PANSS P3 item assesses hallucinations in different modalities but has a particular focus on auditory hallucinations and hearing voices, since these are the most common type of hallucination in psychotic patients, and the way that the interview questions are organized reflects AVH to a greater degree than other sensory modalities. Together with P3, we also considered the PANSS P1 item relevant, as it assesses severity of delusional thoughts. All PANSS raters were trained and certified, and satisfactory inter-rater reliability was documented. For all patients, PANSS data were collected on the day of fMRI scanning.

2.4. MRI data processing

Processing of MRI data was carried out using built-in MATLAB (MathWorks, Natick, MA, United States) functions and by using the Statistical Parametric Mapping 12 (SPM12) software. Structural MRI (sMRI) data preprocessing included Intensity Non-Uniformity (INU) correction and image segmentation, which were performed by using the unified segmentation algorithm implemented in SPM12, with a regularization parameter equal to 0.0001 and a smoothing parameter equal to 40 mm Full-Width Half-Maximum (FWHM). fMRI data were preprocessed by means of an automated pipeline developed using SPM12, including spatial alignment to sMRI, motion correction, bias field correction, spatial smoothing (6 mm FWHM), and co-registration to standard space (Mantini et al., 2013; Marino et al., 2019). The fMRI images were analyzed to obtain Default Mode Network spatial maps from each individual, as well as a Default

Mode Network map at the group-level. A connectivity analysis was performed separately for each subject, using spatial Independent Component Analysis (sICA). sICA was used for decomposing the fMRI data into brain activity patterns starting from the spatial covariance of the measured signals (McKeown et al., 1998). The number of ICs was estimated by using the minimum description length criterion (Calhoun et al., 2001). Accordingly, 24 to 68 ICs were extracted, depending on the specific fMRI dataset. The Fast ICA algorithm was used to calculate ICs, with a hyperbolic tangent non-linearity and a deflation approach (Esposito et al., 2005). For each IC, a spatial map (that expresses the intensity of the activity across the voxels of that pattern) and an associated time series (the pattern course over time) were extracted (Mantini et al., 2009; Mantini et al., 2007). The spatial map was converted to z-scores by subtracting the average intensity across voxels and dividing the resulting map by the standard deviation across voxels. An automated template-matching procedure, in which the considered DMN-template was derived from previous fMRI study (Mantini et al., 2013) was used to identify the IC corresponding to the DMN. Specifically, it was identified as the IC showing the highest spatial correlation with the corresponding template map in Montreal Neurological Institute (MNI) space.

2.5. Testing for between-group differences in DMN spatial map

Starting from the individual DMN spatial map, we derived DMN group-level correlation map by performing a one-sample t-test, using a mass-univariate analysis. According to this approach, each voxel displayed as significant in the results indicates that there was significant correlation at the group level. We corrected the significance level for multiple comparisons (for multiple voxels involved in the analysis) between single-subject z-scores correlation maps using the Benjamini-Hochberg false discovery

rate (BH-FDR) procedure (Benjamini and Hochberg, 1995), which does not make any assumptions about sample dependency. The significance threshold for the DMN group-level correlation map derived from the fMRI data was set to $p< 0.05$, BH-FDR corrected. This was performed separately for each group to visualize average DMN functional connectivity pattern both for the HC and the SZ groups, i.e. combined AVH-SZ and nAVH-SZ subgroups. We then performed a DMN between-subject comparison between the HC and the SZ patient groups by using a two-sample t-test on the individual DMN maps belonging to each group to detect regional differences in the DMN map between the three groups. More specifically, between-group differences were tested for HC and nAVH-SZ, HC and AVH-SZ, and AVH-SZ and nAVH-SZ. Due to significant differences in the two subgroups of SZ patients, in the AVH-SZ and nAVH-SZ comparison we included the DDD as covariate.

2.6. Fractional Amplitude of Low-Frequency Fluctuations

Starting from the individual time-series associated with the DMN (Marino et al., 2021), the frequency spectrum was computed using the Fast Fourier Transform (FFT) function to estimate the Fractional Amplitude of Low-Frequency Fluctuations (fALFF). The fALFF was computed for the whole detectable frequency range, which was subdivided into four separate bands: slow-5 (0.01–0.027 Hz), slow-4 (0.027–0.073 Hz), slow-3 (0.073–0.198 Hz) and slow-2 (0.198– 0.25 Hz). This separation was first suggested by Zou et al., (2008) (Zou et al., 2008) to provide a better discrimination compared to the canonical fALFF, which is computed for the frequency range 0.01-0.1 Hz. To limit the effect of individual confounds, the fALFF values in the four frequency bands were normalized with respect to the canonical fALFF (Esposito et al., 2013; Zuo et al., 2010). We performed a between-group comparison between the fALFF values of

each group for each frequency using a two-sample t-test. More specifically, we tested for between-group differences for HC and nAVH-SZ, HC and AVH-SZ, and AVH-SZ and nAVH-SZ.

2.7. Correlation of fALFF with PANSS data

To identify relevant relationship between neuroimaging measurements and behavioral scores for SZ patients, we performed Spearman correlation analyses between the normalized fALFF frequency band values and, separately, the P1 and P3 items from the PANSS administered during the interview.

3. Results

No significant socio-demographical differences between the HC and SZ patient groups were found (all *F*-values and χ^2 values < 1.0; group means ± SD in Table 1). Considering SZ subgroups, nAVH-SZ patients were prescribed higher dosages of second-generation antipsychotics, as revealed by significantly greater DDD, than the AVH-SZ patients (*t* test = 2.63, $p = 0.01$; group means ± SD in Table 1). Furthermore, all PANSS scores revealed expected significant differences (all *t* tests > 4.00, $p<0.001$), P1-P3 scores were higher in the AVH-SZ group than the nAVH-SZ group, and vice versa for the negative symptoms, as expected, N1-N2.

Figure 1 shows the DMN random-effects group-level t-maps for the HC group (panel A, top row), the nAVH-SZ patients (panel A, middle row), and the AVH-SZ patients (panel A, bottom row). Similarly, the random-effects group-level t-maps for the comparison between HC and nAVH-SZ patients (panel B, top row), HC and AVH-

SZ patients (panel B, middle row), and AVH-SZ and nAVH-SZ subgroups (panel B, bottom row).

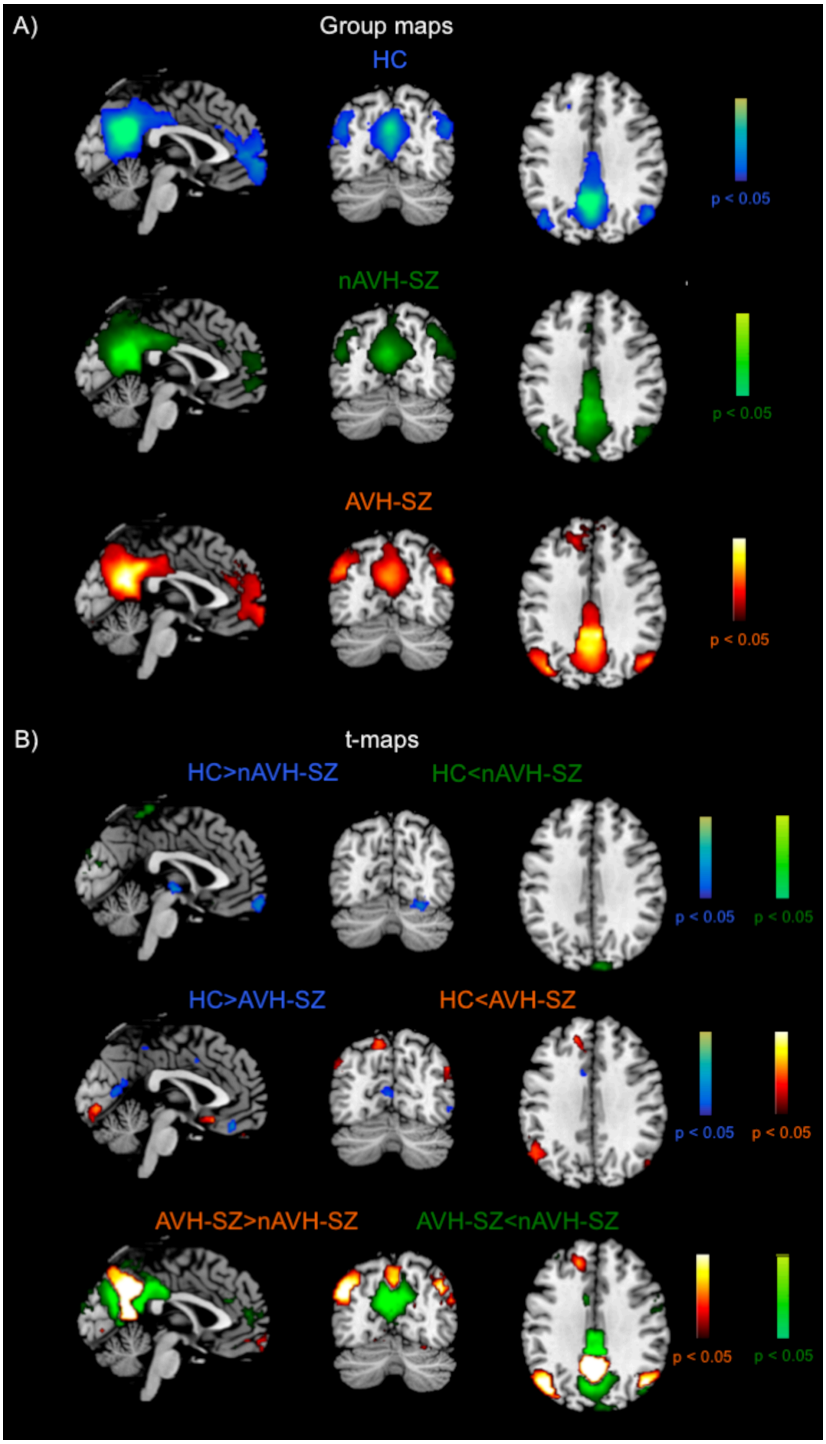

Figure 1. Panel A: Random-effects group-level maps for the DMN for HC (top row, winter color scale), nAVH-SZ patients (middle row, green color scale), and AVH-SZ patients (bottom row, hot color scale). Panel B: random-effects group-level t-map for the difference between HC and nAVH-SZ patients (winter/green color scales depending on the group contrast), between HC and AVH-SZ patients (winter/hot color scales depending on the group contrast), and between AVH-SZ and nAVH-SZ patients (hot/green color scales depending on the group contrast). The reported *p*-values ($p<0.05$) were FDR-corrected, both for the random-effects group-level t-maps of each group and for the random-effects group-level t-map of their comparison.

Consistent with previous studies (Esposito et al., 2005; Mantini et al., 2007) the DMN recruited the PCC and ACC and bilaterally the rAG and lAG in all groups. However, the between-group analyses for HC and AVH-SZ groups revealed spatial differences in correspondence with two regions belonging to the DMN: compared with HC, AVH-SZ had significant greater activation in lAG (MNI coordinates: -45, -66, 42) but lower activation in PCC (MNI coordinates: -3, -68, 12) (Figure 1B, middle row, hot and winter color scale, for AVH-SZ>HC and AVH-SZ<HC contrasts, respectively). The first region also showed greater activation in the between-group comparison for the AVH-SZ and nAVH-SZ groups (Figure 1B, bottom row, hot and green color scale, for AVH-SZ>nAVH-SZ and AVH-SZ<nAVH-SZ contrasts, respectively). Furthermore, other regions apart from the DMN showed between group differences: compared with HC, AVH-SZ showed lower activation in right frontal area (MNI coordinates: 42, 42, 17).

Considering the normalized fALFF analysis computed from the DMN time-series, AVH-SZ patients showed significantly lower slow fluctuation amplitudes compared to both the HC and nAVH-SZ groups between 0.005 and 0.01 Hz, and at around 0.06 Hz, and significantly higher amplitude at around 0.05 Hz (Figure 2). The nAVH-SZ and HC groups did not differ significantly for any frequency, whereas the AVH-SZ and nAVH-SZ subgroups differed significantly for the frequency range between 0.017 and 0.04 Hz (Figure 2).

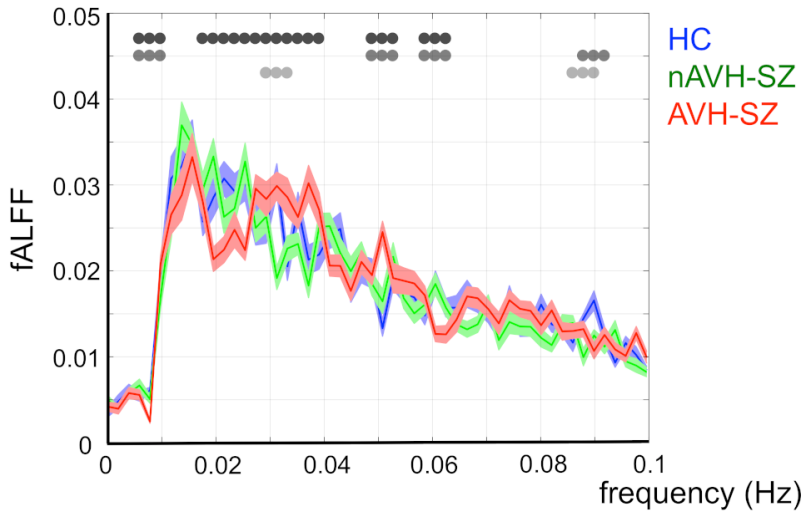

Figure 2. Normalized fALFF analysis carried out on DMN time series in AVH-SZ patients, nAVH-SZ patients and HC (red, green, and blue lines, respectively). Significant differences between the AVH-SZ and nAVH-SZ groups, theHC and AVH-SZ groups, and the HC and nAVH-SZ groups, are highlighted by black, dark-gray, and light-gray dots, respectively.

With respect to possible associations with PANSS scores, we found that the P1 (delusional thoughts) item score was significantly positively correlated with Slow-4 when considering both patient groups together (Figure 3A), but only for the nAVH-SZ group when considering the groups separately (Figure 3B). This suggests that the correlation for both groups is mainly driven by the nAVH-SZ subgroup. No significant correlations were found for the N1 and N2 PANSS items.

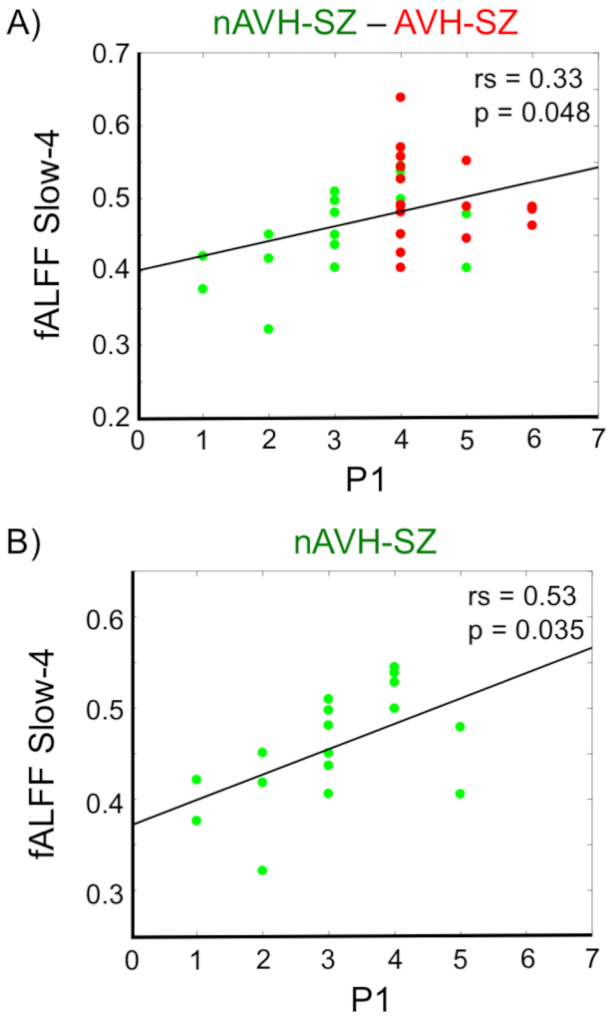

Figure 3. Significant Spearman correlations ($p<0.05$) between normalized fALFF bands (DMN analysis) and the PANSS, considering: A) the Slow-4 for both patient populations (nAVH-SZ and AVH-SZ) together, and B) separately for the nAVH-SZ group alone.

Starting from the statistical t-maps that showed between-group differences between AVH-SZ and HC, and between AVH-SZ and nAVH-SZ, we decided to carry out an additional analysis focused on the AVH-SZ patients' greater DMN activation in the lAG region. In particular, under the hypothesis that regional (a)symmetry in bilateral brain connectivity may be related to the occurrence of hallucinations, we investigated the group differences of ALFF measurements detected from the lAG. This ROI was chosen for further analysis as the most relevant cortical difference detected between the AVH-SZ group and the other two groups. Therefore, we set a region of

interest (ROI), defined as a 6 mm radius sphere, in this brain region to compare the fALFF spectral power of both the lAG (MNI coordinates: -45, -66, 42), as well as the contralateral ROI in rAG (MNI coordinates: 45, -66, 42), both belonging to the DMN. For each ROI, and separately for each subject, fALFF values were calculated within the defined ROI and then normalized by the mean of the whole-brain fALFF computed across the whole detectable frequency range (Huang et al., 2017; Meda et al., 2015). Figure 4 shows the fALFF band analyses for, the left ROI (left panel) and the Right ROI (right panel) separately for the three groups, i.e., HC group, AVH-SZ and nAVH-SZ patient subgroups. Significant differences were found in the left ROI between the AVH-SZ patients and both the HC and nAVH-SZ groups, for very low-frequency fluctuations (<0.015 Hz).

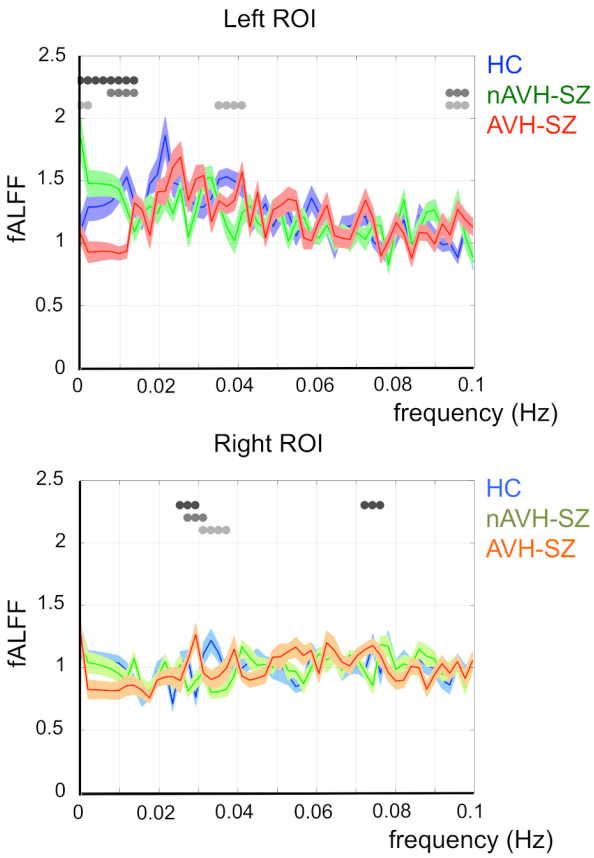

Figure 4. Normalized fALFF analysis carried out on left and right ROIs time series (MNI coordinates: -45, -66, 42 and 45, -66, 42, respectively) in AVH-SZ patients, nAVH-SZ patients and HC (red/orange, green/light-green and blue/light-blue lines, respectively). Significant differences between the AVH-SZ and nAVH-SZ groups, the HC and AVH-SZ groups, and the HC and nAVH-SZ groups, are highlighted by black, dark-gray, and light-gray dots, respectively.

Considering associations with symptoms, we found that P3 scores showed significant positive correlation with the Slow-5 and Slow-4 measurements derived from activation in the left ROI, in the AVH-SZ group (Figure 5A and 5B), and negative significant correlation with the Slow-3 measurement, also derived from the left ROI, in the same patient group (Figure 5C).

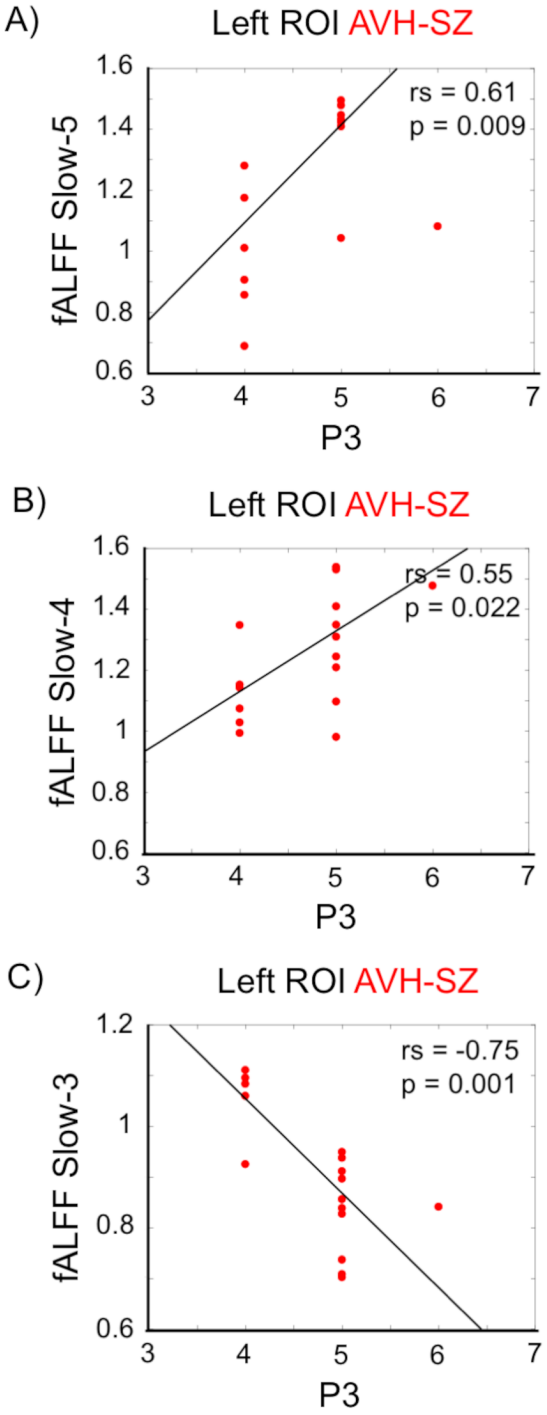

Figure 5. Significant Spearman correlations ($p<0.05$) between normalized fALFF bands (ROI analysis) and the PANSS. Correlations were significant only for the Left ROI between P3 scores and A) Slow-5

(positive), B) Slow-4 (positive), and C) Slow-3 (negative).

4. Discussion

In this pilot study, we investigated DMN alterations in different sub-phenotypes of SZ, by investigating the fALFF within the DMN in two subgroups of patients, with and without AVH, compared to HC, with the goal of linking altered DMN fluctuations to patients' clinical symptoms. The involvement of DMN connectivity in SZ symptomology is supported by the results showing associations between inter-hemispheric connectivity of DMN regions and PANSS scale scores. We explored brain function within DMN by using the fALFF, which reflects low-frequency fluctuations of spontaneous neural activity (Logothetis et al., 2001; Yang et al., 2007). The fALFF analysis included two incremental steps. First, we focused on overall DMN network fluctuations, by calculating the fALFF from the time-course associated with the DMN spatial pattern, which was derived from data-driven ICA-based functional connectivity, thus avoiding the influence of physiological noise confounds (Esposito et al., 2013; Marino et al., 2021). Then, the fALFF analysis was carried out not only on the DMN time series, but also in a *post hoc* ROI analysis following the identification of an extra region in the DMN spatial map, i.e., the lAG, which was not found neither in the HC and nAVH-SZ groups. This suggests that the altered DMN might be a hallmark of the presence of hallucinations in SZ patients. Interestingly, lAG is a region involved in inner speech monitoring (Cui et al., 2017; Mallikarjun et al., 2018) and associated with language (Price, 2012) and memory and/or self-referential (Buckner et al., 2008) processing, and it has been previously identified in literature as an area involved in alterations linked to AVH in schizophrenia (Cui et al., 2017). In addition, we showed that altered inter-hemispheric functional connectivity in the DMN might be linked to

the presence of AVH events in SZ patients.

Recent studies have reported differences in both ALFF and fALFF values between patients with SZ and healthy controls (Hoptman et al., 2010; Turner et al., 2013; Yu et al., 2014), also in regions belonging to the DMN, including the PCC (Achard et al., 2006), the medial prefrontal cortex (Fryer et al., 2015), and the ACC (Alonso-Solís et al., 2015), revealing increased fALFF values in the anterior brain areas, especially for hallucinating patients. When correlating with clinical scores, the low-frequency fluctuation alterations within the DMN are often associated with positive symptom ratings (Garrity et al., 2007; Kindler et al., 2015), but contradictory results have also been reported for clinical symptoms (Hare et al., 2019; Zhou et al., 2019). However, these inconsistencies may partly be due to the differences in the implemented approaches. In addition, there is the issue of heterogeneity of SZ populations, disease courses, use of antipsychotics, and frequency and severity of auditory hallucinations. Aiming to overcome these limitations, we split SZ patients in two subgroups (AVH-SZ and nAVH-SZ) and compared them with a matched group of healthy adults.

We reported changes in DMN spatial pattern for AVH-SZ patients compared to both HC and nAVH-SZ groups (Figure 1) and altered fALFF compared to nAVH-SZ for a relatively low-frequency range (<0.05Hz) (Figure 2). In particular, previous literature have shown that altered bilateral DMN connectivity may underlie hallucinations, delusions, thought disturbances, and negative symptoms involved in SZ (Cui et al., 2017; Wang et al., 2015), and may be crucial to whether AVH develop (Chang et al., 2015). Consistently with this, we showed that the nAVH-SZ group was not significantly different from the HC group. This suggests that alterations in the DMN associated with SZ may be driven by the occurrence of auditory hallucinatory events.

Indeed, also at the ROI level, the AVH-SZ subgroup showed decreased spectral activity in the lAG compared with the other two groups, especially when considering the lower frequency part of the frequency spectrum (Figure 4). At the network level, correlation analysis with PANSS scores showed significant associations between positive symptom scores (PANSS subscale P1) and DMN fALFF (Slow-4) for the nAVH-SZ group, but not for the AVH-SZ group. This suggests that fALFF alterations, specifically for the nAVH-SZ group, may be mainly underlying delusional thoughts (Figure 3). However, when pushing the investigation further with the *post hoc* ROI analysis, the ROIs fALFF analyses revealed significant correlations with hallucinations (PANSS subscale P3), suggesting a relationship between larger amplitudes of fALFF and severity of clinical signs. In particular, we found that increased fALFF was associated with a more severe hallucinations when considering the left ROI for the lower frequency bands (Figure 5). This suggests that the lAG may play a relevant role in the generation of hallucinatory events, since significant correlations with the clinical scores were only reported for the AVH-SZ group. This supports the hypothesis of an unbalanced leftward activity in patients with AVH, occurring also within the DMN as showed in the current study.

Previous fMRI studies of AVH have identified activity in brain regions involving auditory processing, language, memory and areas of the DMN, including the lAG (Bohlken et al., 2017; Ćurčić-Blake et al., 2017; Zhou et al., 2019), which has also been shown to be functionally connected to the insula. The fact that the fALFF in the insula is specifically altered in AVH-SZ patients supports the presence of a more complex neural circuit which involves other brain networks in addition to the DMN, such as the salience network (Alonso-Solís et al., 2015; Alonso-Solís et al., 2017). Indeed, occurrence of auditory hallucinations may be generated from distorted

integration of information in attention-related networks (Bastos-Leite et al., 2015; Pankow et al., 2015), such as the salience network. Furthermore, the insula – which notably belongs to this network – plays a key role in monitoring information from both the internal and external environment to decide which information requires further processing (Menon and Uddin, 2010), and might explain impaired self-monitoring observed in SZ patients compared to healthy individuals. Indeed, the reduced activity in the lAG, an important hub connecting posterior with anterior linguistic centers, supports the view that hallucinations arise also when within-dominant-hemisphere connectivity is disrupted. Indeed, as temporal lobe areas are important for the comprehension of what is produced from linguistically anterior output regions, this would lead to loss of the ability to recognize self-generated speech as ones own speech. This suggests that future works should be investigate interactions between regions belonging to anatomically different – but functionally linked – networks, which could provide further evidences to understand the processes underlying the insurgence of auditory hallucinations.

Our study suffers from some limitations, especially the relatively small sample size, which might have influenced the statistical power. Furthermore, as the AVH-SZ patients were not at their first episode (Cui et al., 2017), medication usage might have affected the entity of the altered fluctuations (Baker et al., 2014; Hadley et al., 2014). However, the nAVH-SZ patients would act as an alternative control group to investigate the emergence of the AVH events, on the one hand, by controlling the drug usage confounds on the other hand. We therefore consider the focus on separate SZ subgroups as a strength of our experimental approach, rather than a limitation, that may (at least) partially compensate the relatively small sample size. Also, since hallucinatory experiences are intrinsically transient and unpredictable phenomena

(Hugdahl et al., in press), the presence of hallucinations during the scanning, and of the time-course of neural networks prior to hallucination occurring, would have been interesting aspects to investigate, but which could not be considered in this study.

5. Conclusions

Our findings suggest that the fALFF represents a viable approach to identify relevant features from resting state connectivity, providing clinically useful information for studying various SZ symptoms. In line with this, the implementation of such as framework could find broad application in the field of psychiatry to identify state-specific functional abnormalities, and to longitudinally monitor the evolution of network functioning and symptomatology, which could be helpful in the investigation of many psychotic disorders.

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