



## Resting-state functional connectivity alterations in the default network of schizophrenia patients with persistent auditory verbal hallucinations



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### ABSTRACT

To understand the neural mechanism that underlies treatment resistant auditory verbal hallucinations (AVH), is still an important issue in psychiatric research. Alterations in functional connectivity during rest have been frequently reported in patients with schizophrenia. Though the default mode network (DN) appears to be abnormal in schizophrenia patients, little is known about its role in resistant AVH. We collected resting-state functional magnetic resonance imaging (R-fMRI) data with a 3 T scanner from 19 schizophrenia patients with chronic AVH resistant to pharmacological treatment, 14 schizophrenia patients without AVH and 20 healthy controls. Using seed-based correlation analysis, we created spherical seed regions of interest (ROI) to examine functional connectivity of the two DN hub regions (posterior cingulate cortex and anteromedial prefrontal cortex) and the two DN subsystems: dorsomedial prefrontal cortex subsystem and medial temporal lobe subsystem ( $p < 0.0045$  corrected). Patients with hallucinations exhibited higher FC between dMPFC ROI and bilateral central opercular cortex, bilateral insular cortex and bilateral precentral gyrus compared to non hallucinating patients and healthy controls. Additionally, patients with hallucinations also exhibited lower FC between vMPFC ROI and bilateral paracingulate and dorsal anterior cingulate cortex. As the anterior cingulate cortex and the insula are two hubs of the salience network, our results suggest cross-network abnormalities between DN and salience system in patients with persistent hallucinations.

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### 1. Introduction

Auditory verbal hallucinations (AVH) are sensory experiences perceived in auditory modality in absence of external stimuli. They represent one of the most common and distressing symptoms of schizophrenia suffered by 60%–80% of patients (Andreasen and Flaum, 1991). Up to 25% of these patients are resistant to antipsychotic pharmacological treatment (Shergill et al., 1998).

Functional magnetic resonance imaging during resting state periods (R-fMRI) offer a fertile ground to examine multiple brain systems and alterations associated with psychiatric diseases. Measures of functional connectivity (FC) by means of R-fMRI refer to temporal correlation of low frequency fluctuations in the blood oxygen level dependent signal between two (or more) brain regions (Fox and Raichle, 2007). Previous

R-fMRI studies have investigated disruptions of FC related to patients with schizophrenia with chronic AVH as one of the symptoms, although investigating different brain regions and using a variety of methods (Lawrie et al., 2002; Mechelli et al., 2007; Gavrilescu et al., 2010; Rotarska-Jagiela et al., 2010; Vercammen et al., 2010; Hoffman et al., 2011; Wolf et al., 2011). Reduced frontotemporal FC was reported in patients with schizophrenia and AVH (Lawrie et al., 2002; Rotarska-Jagiela et al., 2010). Further, reduced interhemispheric FC of the auditory cortex was found in patients with schizophrenia or schizoaffective disorder and AVH (Gavrilescu et al., 2010). Also reduced FC between left superior temporal and anterior cingulate cortex (Mechelli et al., 2007) and between temporoparietal cortex and anterior cingulate cortex (Vercammen et al., 2010) was found in patients with schizophrenia and AVH. In contrast, stronger FC between left inferior frontal gyrus and Wernicke area was reported in patients with schizophrenia and AVH (Hoffman et al., 2011). Many factors might have been involved in such variety of results. In particular, some studies have investigated FC in treatment resistant hallucinating patients (Vercammen et al., 2010; Wolf et al., 2011)

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while others, in non refractory hallucinating patients (Lawrie et al., 2002; Mechelli et al., 2007; Gavrilescu et al., 2010; Rotarska-Jagiela et al., 2010; Hoffman et al., 2011). Another aspect is the different methodological approaches to determining FC (Independent Component Analyses (Rotarska-Jagiela et al., 2010; Wolf et al., 2011), seed region (Lawrie et al., 2002; Gavrilescu et al., 2010; Vercammen et al., 2010; Hoffman et al., 2011) or dynamic causal modeling approach (Mechelli et al., 2007)).

The dysfunction of the Default Network (DN), one of the most well-known resting state networks, seems to play a prominent role in schizophrenia (Menon, 2011; Woodward et al., 2011). This large-scale brain network appears to have increased activation during rest and decreased activation during stimulus-induced activity (Raichle et al., 2001), and comprises the medial prefrontal cortex (mPFC), posterior cingulate cortex (PCC) and medial temporal lobe (MTL) including the hippocampus and the lateral temporoparietal area (Buckner et al., 2008). This network is more activated in patients with schizophrenia and has been significantly correlated with greater psychopathology (Garrity et al., 2007; Whitfield-Gabrieli et al., 2009; Camchong et al., 2011; Bastos-Leite et al., 2014; Zhang et al., 2014). However, little is known about its role in treatment resistance AVH in patients with schizophrenia. Bearing this in mind, Northoff and Qin (2011) hypothesised that an abnormal interaction between the DN and the auditory cortex may induce hallucinations. However, a recent study (Wolf et al., 2011), which investigated several resting state networks including the DN, failed to find connectivity differences in the DN between schizophrenia patients with persistent AVH and healthy controls.

The aim of the present study is to examine the role of DN activity in schizophrenia patients with persistent AVH as compared to schizophrenia patients without previous history of hallucinations and to healthy controls. Resting state connectivity was analysed through seed region approach including manually defined regions of interest within the DN based on the validated 11 seeds (Andrews-Hanna et al., 2010). These authors described a dorsal mPFC DN subsystem that is activated when attention is directed to the self and a MTL DN subsystem that is activated when awareness is directed to the future. In a previous work we found abnormalities specific to the dMPFC DN subsystem in the early stages of psychosis (Alonso-Solis et al., 2012). We hypothesise that patients with persistent AVH may show a specific neuro-functional correlate in both subsystems compared to patients without hallucinations and healthy controls, suggesting that persistent hallucinations alters broadly the DN.

## 2. Methods

### 2.1. Participants

Thirty-three right-handed patients fulfilling DSM-IV-TR criteria for schizophrenia and aged 18 to 55 years were recruited from the outpatient service at Hospital de la Santa Creu i Sant Pau in Barcelona, Spain. The recruitment was based upon revision of clinical records and a clinical interview before entering in the study, so as to confirm that the sample comprised patients with medication-resistant AVH defined as daily presence of AVH in the past year, in face of at least two adequate trials of antipsychotic drugs (with different D2 binding profile) at equivalent doses to 600 mg/day of clozapine. Patients with no history of hallucinations and who showed good response to treatment (i.e. not showing acute psychotic symptoms in the last 12 months) were also included. Nineteen patients had persistent AVH (hallucinating patients, HP; mean age  $40.1 \pm 8.9$  years, 13 males) and fourteen were non-hallucinating schizophrenia patients (nHP; mean age  $36.4 \pm 7.1$  years, 8 males). For both groups of patients, exclusion criteria were neurological disorder that could explain the present psychopathology, mental retardation and substance use (except alcohol, tobacco or cannabis).

Clinical symptoms were quantified with the positive and negative syndrome scale (PANSS) (Kay et al., 1987).

A sample of twenty healthy controls (HC) were recruited from the local community. All of them were screened with the same study protocol. None of them had history of medical or psychiatric disorders, a drug or alcohol abuse problem, or a family history of psychiatric disorders (mean age  $37.8 \pm 7.4$  years, 13 males, all right-handed).

The local research ethics committee approved this study and all subjects provided written informed consent prior to participation. All participants could read and understand the consent form and were legally competent.

### 2.2. Image data acquisition

Participants were scanned on a 3 T Philips Achieva scanner. T1-weighted images were acquired in an axial orientation (TR/TE = 13/7.4 ms, flip angle =  $8^\circ$ , field of view (FOV) 23 cm with in-plane resolution of  $256 \times 256$  and 1-mm slice thickness). Six minute resting state functional images were collected using a gradient echo planar imaging sequence (TR/TE = 2000/30 ms, flip angle =  $90^\circ$ , FOV = 23 cm, 80 volumes). Whole-brain volumes were acquired with 40 contiguous 3.5-mm thick transverse slices. For the resting state scan, participants were instructed to close their eyes and remain awake.

### 2.3. Data processing

Image processing was performed using Analysis of Functional NeuroImages (AFNI, <http://afni.nimh.nih.gov/>) (Cox, 1996) and FSL (FMRIB Software Library, [www.fmrib.ox.ac.uk](http://www.fmrib.ox.ac.uk)) (Smith et al., 2004). Preprocessing was performed in line with previously published studies of our group (Alonso-Solis et al., 2012). Briefly, it comprised slice timing correction, motion correction, despiking (detection and reduction of extreme time series outliers using a hyperbolic tangent function), spatial smoothing (using a gaussian kernel of full width at half maximum 6 mm), mean-based intensity normalization of all volumes by the same factor, temporal bandpass filtering (0.009–0.1 Hz) and linear and quadratic detrending. Each participant's preprocessed 4-D volume was regressed on 9 nuisance covariates (global signal, cerebrospinal fluid, white matter, and motion covariates), and the resultant volume was spatially normalized by registration to the MNI152 (Montreal neurological institute) template with 2-mm<sup>3</sup> resolution, using a 12 degrees-of-freedom linear affine transformation, refined using non-linear registration.

Following our previous analysis (Alonso-Solis et al., 2012) and according to Andrews-Hanna (Andrews-Hanna et al., 2010), eleven spherical seed regions of interest (ROIs) with radius 4 mm in 2 mm<sup>3</sup> MNI space, were centered in the coordinates listed below. We examined two hub regions of the DN FC that included the posterior cingulate cortex (PCC; MNI coordinates  $-8, -56, 26$ ) and the anteromedial prefrontal cortex (aMPFC;  $-6, 52, -2$ ), and also the two DN subsystems. The first, named dorsomedial prefrontal cortex, included the following seeds: dMPFC (0, 52, 26); temporal parietal junction (TPJ;  $-54, -54, 28$ ); lateral temporal cortex (LTC;  $-60, -24, -18$ ) and temporal pole (TempP;  $-50, 14, -40$ ). The second subsystem, the medial temporal lobe (MTL), included ventral medial prefrontal cortex (vMPFC; 0, 26,  $-18$ ); posterior inferior parietal lobule (pIPL;  $-44, -74, 32$ ); retrosplenial cortex (Rsp;  $-14, -52, 8$ ); parahippocampal cortex (PHC;  $-28, -40, -12$ ) and hippocampal formation (HF;  $-22, -20, -26$ ). For each participant, and each seed, we generated an image quantifying the voxel-wise temporal correlation between the mean time series of the seed ROI and that of every other voxel in the brain. We examined motion parameters by quantifying Framewise Displacement (Power et al., 2012). Overall motion was less than the recommended value of 0.5 mm for all the three groups.

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