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Altered amplitude of low frequency fluctuations in schizophrenia patients with persistent auditory verbal hallucinations

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ABSTRACT

The aim of this study is to analyze the differences in low frequency fluctuation (LFF) values between schizophrenia patients with and without auditory verbal hallucinations (AVH). Nineteen schizophrenia patients with persistent AVH (HP), fourteen non-hallucinating schizophrenia patients (nHP) and twenty healthy controls (HC) underwent R-fMRI. LFF values were calculated in the slow frequency band (0.01–0.08 Hz). By means of group level contrasts, we performed direct voxel-wise group comparisons. Both groups of patients showed decreased amplitude LFF (ALFF) values in the occipital pole and lingual gyrus compared to HC, whereas increased ALFF values were found in the temporal pole and fusifom gyrus. Schizophrenia patients exhibited decreased fractional ALFF (fALFF) values in the precuneus, occipital pole and bilateral occipital cortex, and increased fALFF in the insula compared to HC. There were also differences between patients with and without AVH. (Ok to start with lower case?) fALFF values were higher in the putamen and insular cortex and lower in the frontal pole in HP compared to nHP and HC. ALFF increased in HP patients in the bilateral thalamus and bilateral parahippocampal gyrus, compared to nHP patients and HC. Our results suggest that altered dynamics in low-frequency fluctuations may play a key role in the neurophysiology of auditory hallucinations.

1. Introduction

Auditory verbal hallucinations (AVH) are one of the most common and distressing symptoms of schizophrenia. Defined as the experience of "hearing voices" in the absence of external stimuli that cause them, AVH are suffered by 60%–80% of patients (Andreasen and Flaum, 1991) and often induce discomfort, functional impairment and behavioural alterations (Nayani and David, 1996). Furthermore, in approximately 30% of patients who experience this type of hallucinations, these are refractory to antipsychotic pharmacological treatment (Shergill et al., 1998).

Resting state functional magnetic resonance imaging (R-fMRI) techniques have recently been used to elucidate the pathophysiology of several diseases such as schizophrenia. Evidence is building up that spontaneous low frequency (0.01–0.1 Hz) fluctuations (LFF) of the human brain measured with R-fMRI are physiologically meaningful and related to neural spontaneous activity (Biswal et al., 1995). Previous studies have identified altered patterns in t functional connectivity (FC), which is the temporal correlation of these LFF of the BOLD (Blood Oxygen Level Dependent) signal between different brain areas, in schizophrenia patients with AVH (Gavrilescu et al., 2010; Hoffman et al., 2011; Lawrie et al., 2002; Mechelli et al., 2007; Rotarska-Jagiela et al., 2010; Vercammen et al., 2010; Wolf et al., 2011). We recently described a pattern of FC for patients with schizophrenia and persistent auditory verbal hallucinations in regions which encompass the salience processing system and the default mode network (Alonso-solís et al., 2015). In order to go further in the study of the neural mechanisms that underlie AVH, we shift our focus from measures of functional connectivity during rest, to regional properties of the brain's intrinsic functional dynamics. Although functional connectivity measures can provide us with more holistic information on a set of brain regions within a network, the relative magnitude of these fluctuations can differ between brain regions and between subjects, and thus may act as a marker of individual differences (Zou et al., 2008). In this regard, Zang et al. developed an index, called amplitude of LFF (ALFF), for detecting the regional intensity of spontaneous fluctuation within the BOLD signal (Zang et al., 2007). Later on, Zou et al. proposed a better approach for detecting regional

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signals of changes in spontaneous activity, called the fractional ALFF (fALFF), which can supply a more accurate measure of low-frequency oscillatory phenomena (0.01–0.1 Hz) (Zou et al., 2008). Although the fALFF index has proved to be less sensitive to spurious signals (Zou et al., 2008), both measures are test-retest reliable across time and are likely to be potential biomarkers of mental illnesses (Hoptman et al., 2010; Huang et al., 2010; Lui et al., 2010; Mennes et al., 2010).

Recent studies have reported differences in both ALFF and fALFF values between patients with schizophrenia and healthy controls (Hare et al., 2016; Hoptman et al., 2010; Turner et al., 2013; Yu et al., 2012). The prevailing literature supports the notion that posterior brain areas show decreased ALFF and fALFF values in patients with schizophrenia, while anterior brain areas are more likely to show increments of these values. The particular location of these increases and decreases has varied across studies (Turner et al., 2013). A recent meta-analysis demonstrated that ALFF and fALFF values were decreased in the bilateral occipital cortex and posterior parietal cortex, while the bilateral striatum, medial temporal cortex and medial prefrontal cortex were increased in patients with schizophrenia (Xu et al., 2015). In another study, Hoptman and colleagues found that frontal and temporal regions, previously associated with the disorder, displayed increased amplitude of LFF (Hoptman et al., 2010). In this regard, Whitfield-Gabrieli reported a dysregulation of medial frontal regions associated with self-directed thoughts, leading to confusion between internal and external stimuli, providing neurophysiologically-based hallucinations (Whitfield-Gabrieli et al., 2009). Due to the fact that schizophrenia with AVH is a very common phenotype, it would be very interesting to study the ALFF and fALFF values in schizophrenia patients with AVH and schizophrenia patients without AVH. Considering that schizophrenia patients with persistent AVH is a more severe manifestation of the illness, it is interesting that a previous work (Turner et al., 2012) found that ALFF was a reliable measure for chronic schizophrenia. Therefore, the persistence of AVH could lead to specific alterations in the LFF. A recent study examining the relation between hallucinations and ALFF in schizophrenia suggested that altered LFF in the left hippocampus may play a crucial role in the development and sustained propensity to hallucinate (Hare et al., 2016).

In order to shed new light on the pathophysiological mechanisms underlying AVH, the aim of this work is to analyze differences in ALFF and fALFF values in schizophrenia patients with and without AVH. Based on our previous findings, we hypothesize that patients with persistent AVH will show greater alterations in ALFF and fALFF values compared to patients without AVH and to healthy controls.

2. Methods

2.1. Participants

Nineteen schizophrenia patients (mean age 40.1 ± 8.9 years, 13 males, all right-handed) with persistent AVH (HP) and fourteen individuals with schizophrenia but without AVH (nHP; mean age 36.4 ± 7.1 years, 8 males, all right-handed) were recruited from the outpatient services at Hospital de la Santa Creu i Sant Pau in Barcelona, Spain, to participate in an R-fMRI study. All patients met DSM-IV-TR criteria for schizophrenia and were aged 18 to 55 years. All hallucinating patients were resistant to antipsychotic medication, as confirmed by daily episodes of AVH over the previous twelve months and a minimum of two different D2 binding profile antipsychotic drug having been tested (at equivalent doses to 600 mg/day of chlorpromazine). Non-hallucinating schizophrenia patients had no previous history of AVH and showed a good response to pharmacological treatment. Exclusion criteria comprised neurological disorder possibly related with the present psychopathology, mental retardation and the use of substances not including tobacco, alcohol or cannabis. The Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) was used to quantify clinical symptoms in patients. When scanning was conducted, the majority of patients were treated with second-generation antipsychotic drugs. In some cases, antidepressants, anticholinergic drugs, stabilizers or benzodiazepines were being administered. Mean time evolution for schizophrenia was 16.1 ± 9.3 years in HP patients and 8 ± 6.2 years in nHP patients. Mean age at onset of the illness was 23.4 ± 4.5 years for HP patients and 27.8 ± 7.5 years for nHP patients (See Table 1 for more complete clinical and demographical data).

Twenty healthy controls were also recruited from the local area (HC; mean age 37.8 ± 7.4 years, 13 males, all right-handed). All these healthy individuals were screened following the same procedure. None of these participants had a record of medical or psychiatric illnesses or problems with drugs or alcohol.

This investigation was carried out in accordance with the latest version of the Declaration of Helsinki. Before entering the study, all participants provided written informed consent and were legally competent. The study was approved by the local Research Ethics Committee.

2.2. MRI data acquisition

T1-weighted MRIs and six-minute resting state functional images were acquired in a 3T Philips Achieva scanner. T1 images were obtained in an axial orientation: TR/TE = 13/7.4 ms, flip angle = 8°, field of view = 23 cm, resolution = 256 × 256, slice thickness = 1 mm. Six minute resting state MRIs were obtained using a gradient echo planar imaging sequence: TR/TE = 2000/30 ms, flip angle = 90°, FOV = 23 cm, 180 volumes of 128 × 128 of in-plane resolution and 40 contiguous 3.5 mm thick transverse slices.

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) (Smith et al., 2004). Pre-processing was performed in line with previously published studies of our group (Alonso-solís et al., 2012, Alonso-solís et al., 2015). It comprised slice-timing correction, motion correction, despiking of extreme time series outliers using a hyperbolic tangent function, removal of linear trends in time-series, spatial smoothing (using a Gaussian kernel of FWHM = 6 mm) and global intensity normalisation of the entire data set by a single scaling factor

For ALFF and fALFF calculation, power spectrum at the slow frequency band (0.01–0.08 Hz) was then computed. ALFF was obtained by summing the amplitudes in the low frequency band and afterwards fALFF was calculated as ALFF/amplitude of total frequency. ALFF and fALFF were z-normalised across full brain and finally non-linearly registered to standard space. “Gray matter mask was obtained by binarizing the gray matter tissue prior provided by FSL avg152T1_gray.img using a threshold of 100 (1 for voxels > 100)”.

2.4. Group level analysis

Firstly, group model was set up using FSL FEAT. Then, group-level analyses were performed using FSL's FLAME (FMRIB's Local Analysis of Mixed Effects) ordinary least squares model (OLS), using a gray matter mask. Voxel-wise group analyses were carried out to test for significant differences between groups, performing firstly an ANOVA test with three groups (HP, nHP and HC) and then post-hoc analyses. Results were corrected for multiple comparisons at cluster level using Gaussian random field theory (min Z N 2.3; cluster significance: p = 0.05, corrected). Automated anatomical labeling was conducted with autoaq of FSL, using Harvard-Oxford Cortical Structural Atlas and Harvard-Oxford Subcortical Structural Atlas, reporting the most significant structures to which each cluster belongs.

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