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Brief report

# Frequency domains of resting state default mode network activity in schizophrenia

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ABSTRACT

Probabilistic independent component analysis was applied to identify the default mode network (DMN) in resting state data obtained with functional magnetic resonance imaging from 25 DSM-IV schizophrenia and 25 matched healthy subjects. Power spectrum analysis showed a significant diagnosis × frequency interaction and higher power in one frequency band, indicating an alteration of DMN frequency spectrum in schizophrenia.

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## 1. Introduction

Spontaneous fluctuations of the blood oxygenation level dependent (BOLD) signal have been used to analyse low-frequency signals in resting state functional magnetic resonance imaging (fMRI) series (Auer, 2008). Among several resting state networks identified in healthy subjects, the default mode network (DMN) has been defined as a set of brain regions showing higher coherent activity during non-task-driven cognitive states (Raichle and Snyder, 2007). There are now several studies suggesting alterations in DMN activity in schizophrenia (Broyd et al., 2009), although these differences have been analysed in different cognitive states (e.g., resting state, working memory tasks) and with different techniques (Bluhm et al., 2007; Calhoun et al., 2008; Lui et al., 2010; Mingoia et al., 2012; Rotarska-Jagiela et al., 2010; Zhou et al., 2007).

Recent studies reported reduced amplitudes of low-frequency oscillations during the resting state in several cortical areas in schizophrenia patients (Hoptman et al., 2010), and elevated amplitudes in first-episode patients (Huang et al., 2009). There is also evidence that the amplitude of low frequency fluctuations in chronic schizophrenia might be a relatively stable marker with moderate to high test-retest stability (Turner et al., 2012). However, the relation between DMN dysfunction and the frequency domains of low-frequency BOLD fluctuations remains unclear.

Here, we analysed the power for different frequency bands from DMN time series extracted using a probabilistic independent component analysis (pICA) of fMRI data, in order to test the hypothesis of altered frequency power in the DMN under resting state conditions.

## 2. Methods

### 2.1. Study participants

We analysed resting-state functional magnetic resonance imaging (fMRI) data obtained from 25 DSM-IV schizophrenia patients (8 female/15 male; mean age 30 y, S.D. 7.3; age range 21–49 y) and 25 healthy controls (10 female/15 male; mean age 30.1 y, S.D. 8.6; age range 22–55 y), matched for age and gender; handedness was assessed with the Edinburgh Handedness Inventory (Oldfield, 1971) and showed no group difference (three left-handers in the patient group, none in the control group; Fisher's Exact Probability Test: $p > 0.23$). All study participants

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provided written informed consent to a protocol approved by the Ethics Committee of the Medical School of Jena University. None of the subjects had any history of traumatic brain injury with loss of consciousness, neurological or major medical conditions, or active substance abuse/dependence, and all had a pre-morbid IQ well above 80 (estimated using the German MWT-B). All patients were on stable antipsychotic medication.

### 2.2. MRI data acquisition

All subjects underwent a 9-min resting state fMRI using a 3 T whole-body MRI system (Magnetom Tim Trio, Siemens, Erlangen, Germany) equipped with a 12-channel head matrix coil and applying a standard BOLD-sensitive EPI sequence (207 volumes, TR: 2550 ms; TE: 30 ms; flip angle: 90°; 45 contiguous 3-mm axial slices with no gap, $64 \times 64$ matrix; in-plane resolution $3\,\text{mm} \times 3$ mm; field-of-view 192 mm $\times$ 192 mm). A high-resolution $T_1$-weighted structural scan was acquired for co-registration (3D MPRAGE; 192 contiguous sagittal 1-mm slices; TR: 2300 ms; TE: 3 ms; TI: 900 ms; echo time 8.9 ms; flip angle 9°; matrix size $256 \times 256$; isotropic $1 \times 1 \times 1\,\text{mm}^3$ voxels).

### 2.3. fMRI data preprocessing and pICA

Data were pre-processed with SPM8 (Institute of Neurology, London, UK) and analysed using FSL software (FMRIB, Oxford, UK), as described in a previously published report on a pICA of DMN differences in the same sample (Mingoia et al., 2012). Briefly, the processing pipeline included removal of the first three images of the time series, and realignment and six-parameter rigid body spatial transformation, as well as 8-mm Gaussian kernel smoothing. High-pass ($f > 0.009$ Hz) and low-pass filters ($f < 0.18$ Hz) were applied to ensure removal of signal drifts and cardiac/breathing artefacts, respectively; the attenuation of higher frequency will facilitate ICA to better identify relevant components removing sources of no interest.

pICA, as implemented in the FSL MELODIC software, was then used to extract independent components of the BOLD time series, and an automated algorithm developed in Matlab (www.mathworks.com) was used to select the component representing the DMN, based on a comparison to an anatomical DMN template. This processing resulted in an independent component reflecting a temporal correlation between fluctuations in the BOLD signal of discrete areas representing the DMN. Group comparisons of the regions and network connectivity have been published previously (Mingoia et al., 2012).

### 2.4. Power spectral density analysis

We then analysed the frequency domains for the extracted DMN, estimating the power of the signal at different frequencies. For this purpose, the time course associated with each individual's DMN component was transformed from the time domain to the frequency domain using Welch's method (Welch, 1967). Frequency distribution of time courses was evaluated by computing the power spectral density (PSD) of each subject's DMN time course. The power spectrum of the time course was generated by pwelch, a Matlab signal processing toolbox, which estimates the power spectral density of the input signal dividing it into eight sections of equal length, each with 50% overlap. The fMRI run was composed by 207 points, then the length $N$ of the FFT = 64 points, with overlap window of 32 points. This setting produced a high resolution of specific observation of the power spectrum density with 33 bins of 0.0061 Hz, ranged from 0 to 0.196 Hz. Even if the conventional frequency range of resting state fMRI is included between 0.01 and 0.1 Hz, we decided to include the entire frequency spectrum generated by pwelch toolbox for subsequent analysis. Similar approaches have recently been used in the analysis of paediatric fMRI data (Fransson et al., 2013). Power values for all bins were compared between patients and controls performing a multivariate ANOVA (applying Pillai's Trace) with power values as dependent variables, frequency as within-subject factor and diagnosis as between-group factor. $T$-tests (two-tailed) were carried out post-hoc between groups comparing powers for each of the 33 frequency bins.

### 2.5. Head-movement estimation

To exclude effects related to head movement, we first calculated maximal displacement from reference image, and secondly estimated and compared micro-movements between groups based on the derivative of motion parameters as described previously by Power et al. (2012), and in more detail in the Supplementary Material.

## 3. Results

Power spectral density analysis provided 33 frequency bins. About 95% of the total power (96.2% for healthy controls, 95.7% for patients) was described by first 10 frequencies values, from 0 to 0.0551 Hz. MANOVA analysis revealed a different power spectral density between patients and controls with significant diagnosis $\times$ frequency interaction ($F(33, 16) = 2.729$, $p = 0.018$). $T$-tests performed post-hoc at each frequency bin showed that the schizophrenia group exhibited significantly higher spectral power than controls at a frequency bin 0.0797 Hz ($F = 6.261$, $p = 0.016$) and 0.0858 Hz ($F = 5.405$, $p = 0.024$). The power distribution in the frequency domain of the DMN component for healthy subjects and patients with schizophrenia is shown in Fig. 1. Head-movement analyses showed that no subject exhibited larger translation than 3 mm or rotation than 3°. Also, there was no significant group difference in micromovements, as analysed by PSD (Power et al., 2012) (see also Supplementary Material).

## 4. Discussion

Analysing the DMN component of a pICA-based analysis of resting state fMRI data, we found schizophrenia patients to show significantly altered spectral power in the frequency domain, unrelated to cardiac or breathing artefacts. While healthy controls exhibit high power at a restricted range of frequency, patients with schizophrenia have a more wide spread frequency spectrum with higher power at residual higher frequencies (0.07966 and 0.08578 Hz). So far, most resting state studies have either focused on (whole-brain) amplitude analyses, or have provided group comparisons of the DMN regions based on seed regions.

While our results replicate and extend previous studies in chronic schizophrenia patients (Hoptman et al., 2010), they provide a first analysis that specifically focuses on power spectrum analyses of the DMN only. As a main finding, our results demonstrate that at least a part of the low-frequency alterations found in schizophrenia (Bluhm et al., 2007; Hoptman et al., 2010; Zhou et al., 2007) can be specifically attributed to DMN dysfunction. In contrast to previous studies on low-frequency BOLD fluctuations, our pICA approach selected only the signals related to the DMN (i.e. the voxels included in the DMN component). It therefore also excluded signals that may occur in some areas of the DMN (such as the precuneus) which do not specifically reflect DMN activity (but rather belong to another resting state network).

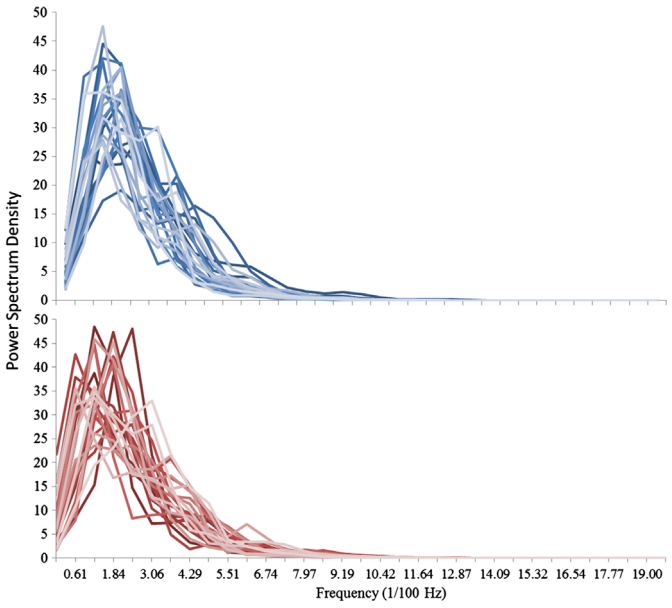


**Fig. 1.** Bar diagrams of power in different frequency ranges ("bins") based on the DMN component of the BOLD signal extracted from a resting state fMRI series.

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Since our data were obtained during a resting state, it is also unlikely that task-driven cognitive activity would have interfered with the time course in the DMN regions. For example, in DMN analyses based on cognitive fMRI data, the BOLD signal time course in DMN areas might include changes induced by cognitive tasks.

While the power differences in our results appeared to be rather specific to a particular frequency band, the role of this (and its specificity to either group differences or DMN function) remains unclear and will need further investigations.

As studies of the default mode network are gaining increasing importance in schizophrenia and other psychiatric disorders, they offer not only potential information of regional dysfunctions, but also allow characterisation of spontaneously occurring signal fluctuations, which might be related to specific neural networks. This study has investigated the frequency domain of the DMN, which seems to be, together with the space and time domain, a promising tool to better explain schizophrenia.

Finally, we also need to consider some limitations of the study. Although our study sample was carefully selected to include a rather homogenous group (chronic schizophrenia, no current psychotic episode, few positive symptoms), the sample size was limited. Furthermore, all patients were on stable antipsychotic medication; recent studies suggest that at least some properties relevant to resting state analyses indeed change with antipsychotic medication, although probably also with clinical symptoms and restricted to some cortical areas (Lui et al., 2010). Also, frequency power differences may be markedly different in first-episode patients (Huang et al., 2009). Therefore, different stage or clinical states might impact on DMN activity, or vice versa. While further research is desirable, our findings nevertheless underline the usefulness of assessing different dimensions of the DMN and spontaneous activity in these brain areas in schizophrenia.

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## Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.pscychresns.2013.05.013.

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