

Decreased Spontaneous Low-frequency BOLD Signal Fluctuation in First-episode Treatment-naïve Schizophrenia *

Luo Ouyang¹, Wei Deng², Ling Zeng¹⁺, Dongming Li³, Qing Gao¹, Lijun Jiang², Ling Zou³,
Liqian Cui², Xiaohong Ma², Xiaoqi Huang^{2,3}

¹ School of Life Science and Technology, University of Electronic Science and Technology of China, Chengdu, P.R.China

² Department of Psychiatry, and ³ Department of Radiology, West China Hospital, Sichuan University, Chengdu, P.R.China

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Abstract. The default mode of brain function hypothesis has been readdressed from the perspective of the presence of low-frequency blood oxygenation level-dependent (BOLD) functional magnetic resonance imaging (fMRI) signal changes (0.01-0.1Hz) in the resting healthy brain. In this study, a newly reported cosine- statistical parameter mapping (SPM) approach is presented to measure the temporal low-frequency blood oxygenation level-dependent (BOLD) signal for exploring the brain activity of schizophrenia in a resting state with subjects' eyes closed. Firstly, the nine cosine functions with frequency between 0.01 and 0.1Hz are specified as the design matrix of the general linear model, then fMRI data is analyzed by SPM method. Nine first-episode treatment-naïve schizophrenia patients and nine healthy subjects participated in this study. The results showed diminished low-frequency spontaneously activity in schizophrenia.

Keywords: MRI, BOLD, default.

1. Introduction

Currently, fMRI research of resting state has attracted more and more attention due to its practical advantage in clinical application, especially for those traditionally so called non-organic disorders in psychiatry [1-3]. Abnormal brain activity in the resting state of schizophrenia has been detected by various methods such as electroencephalography (EEG) [4], positron-emission tomography (PET) [5], single photon emission computed tomography (SPECT) [6, 7] and also by fMRI. Different analysis method has been applied to explore the deficit of spontaneous low-frequency fluctuation (LFF) in blood oxygenation level-dependent (BOLD) signal of schizophrenia patients. For example, resting state fMRI study had found a decreased regional homogeneity of LFF in schizophrenia patients [8].

Recently, a new cosine-SPM method is proposed to analyze the LFF of BOLD signals [9]. The cosine-SPM method assumes that the discrete cosine basis set constituted an effective model of any signal change within the given frequency range (0.01-0.1Hz) as a linear combination of the individual basis functions. So it can be a tool to detect the subtle BOLD signal changes and thus represent the functional activity of brain. In the present study, we try to use this new method of data analysis to explore the properties of the spontaneous LFF of BOLD in first episode drug-naïve schizophrenia patients.

2. Material and Methods

2.1. Subjects

Nine first-episode treatment-naïve schizophrenia patients (aged 29.8 ± 11.9 years, range 17-51 years, 4 males,

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+ Corresponding author. *E-mail address:* Zengling@uestc.edu.cn.

5 females; all right handed, diagnosis were made according to diagnostic criterion of DSM-IV) and nine age-, sex- and handedness- matched normal controls (aged 31.3 ± 10.5 years, range 18-55 years) were recruited in our study. The study was approved by the local ethical committee and written informed consent was obtained from all subjects before the study and the subjects were scanned within the West China Hospital, Sichuan University.

2.2. Paradigm Design

All subjects underwent whole brain MRI scanning during which they kept their eyes closed throughout the entire scanning session. Subjects were asked explicitly to refrain from engaging in any cognitive task or otherwise related effort and not to move during scanning, while they had to stay awake at all time. After scanning, all subjects were asked to describe: (1) whether they were able to stay fully awake through all scanning sessions; (2) how well they thought they have achieved the instruction to do nothing. All subjects reported that during scanning they stayed awake and experienced frequent episodes of thoughts that could be described as self-referential mental processing.

2.3. MR Image Acquisition

EPI sequences (TR=2000 ms, TE=30 ms, FA=90°, 200 runs) were performed using a 3T MR imaging system (EXCITE, General Electric, Milwaukee, USA) with an 8 channel phase array head coil. The slice thickness was set to 5 mm (without slice gap) with a matrix size of 64×64 and a field of view (FOV) of 240×240 mm², resulting a voxel size of 3.75×3.75×5 mm³. Each brain volume is comprised of 30 axial sections and each functional run contained 200 image volumes.

2.4. Data Preprocessing and Analysis

Image preprocessing and statistical inference was carried out using the SPM2 software package (Wellcome Department of Imaging Neuroscience; <http://www.fil.ion.ucl.ac.uk/spm>). For each subject, data processing included: (1) head-motion correction; (2) re-sampling (3×3×3mm³) and spatial normalization to Talairach space; (3) spatially smoothing (FWHM = 9 mm). Low-frequency spontaneous BOLD signal fluctuations levels were modeled using a discrete cosine basis set containing 10 regressors within the frequency range of 0.01-0.1 Hz, which is specified as the design matrix of the general linear model in Fig.1. The discrete cosine basis set constituted an effective model of any signal change (within the given frequency range) as a linear combination of the individual basis functions. Individual statistical parametrical maps were created using F test containing the frequency range of 0.01-0.1 Hz and threshold at $P < 0.001$ uncorrected for multiple comparisons.

Multi-subject analysis was therefore taken using a masking procedure. A binary mask was created from each individual F-contrast image by setting each pixel value to one if the corresponding F value exceeded 3.13; otherwise, it was set to zero. A final mask was calculated by multiplying the binary values of all of the individual masks. The result was a mask that showed voxels in the brain for which the corresponding F value exceeded 3.13 in all subjects that participated in the study. Although the masking procedure was a less statistically rigorous approach, it allowed for investigation of brain areas that exhibited slow oscillations in the BOLD signal during rest that generalized to the subjects that participated in the study.

3. Results

Fig.2a. shows the spontaneous, low frequency BOLD signal fluctuation at a multi-subject level within control group. The most extensive areas of activity are observed in the bilateral occipital lobes extending to PCC and precuneus. Other smaller extensive areas are scattered in the bilateral frontal lobes and the left caudate nucleus. Fig.2b. shows extensive areas of activity at a multi-subject level within patients group. The corresponding results of the patients group yielded much smaller regions of activity, including the occipital cortex, temporal cortex, parietal and frontal lobes bilaterally. The activity of precuneus/PCC, the most important component of default mode as observed in normal controls, disappeared in patients with schizophrenia and the activity cluster in bilateral occipital lobes was smaller in patients group.

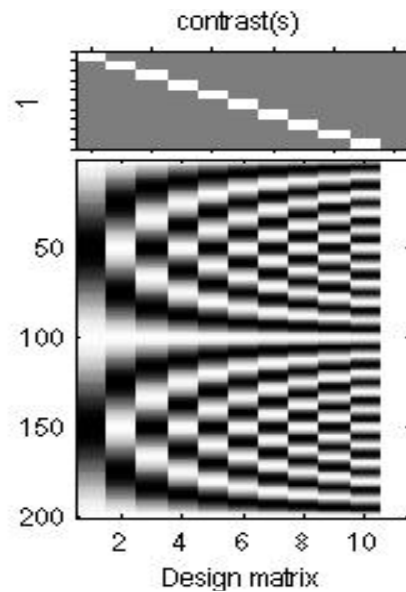


Fig.1: The design matrix for general linear model.

4. Conclusion

In the present study, a new cosine-SPM method is proposed to investigate the low-frequency fluctuation of BOLD signal in schizophrenia patients in resting state. And our result showed similar abnormality in brain activity of schizophrenia patients in the resting state. And it proved that cosine-SPM method may be a new useful way to be applied in future resting state fMRI study of neuro-psychiatric diseases.

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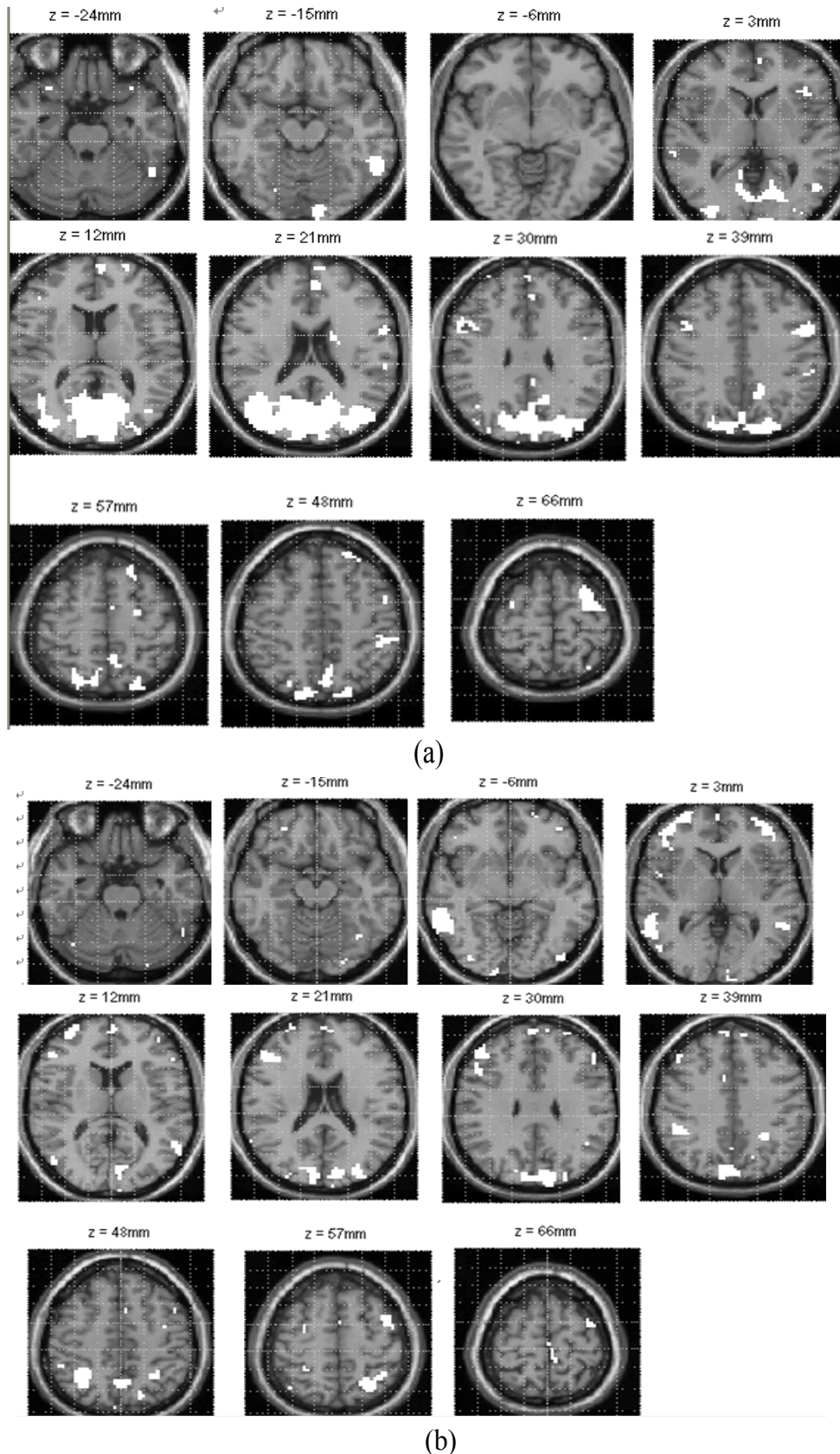


Fig 2: Multi-subject analysis of BOLD signal fluctuations during rest with eyes closed. A binary mask for each subject was created by thresholding the individual F-contrast images at $F \leq 4.27$ ($P \leq 0.05$ corrected). A final binary mask image showing voxels in the brain exhibiting low-frequency fluctuations in all controls (a) patients and (b) at the specified statistical threshold was constructed by multiplying together all the individual binary mask images. Voxels that met these criteria are depicted in white.