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The Identification of Default Mode Network in Rhesus Macaque Using Resting-State fMRI

Xiao-wei FU[1], Cheng-zhen GUO[1], Peng-cheng LI[3], Dan-zhou YANG[2] and Ying ZHANG[3,a,*]

[1]College of Computer Science and Technology, Hubei Province Key Laboratory of Intelligent Information Processing and Real-time Industrial System, Wuhan University of Science and Technology, Wuhan 430065, China

[2]College of Pharmacy, Purdue University, West Lafayette 47907, USA

[3]Institute of Biophysics, State Key Laboratory of Brain and Cognitive Science, Chinese Academy of Science, Beijing 100101, China

[a]ying.zhang.j@gmail.com

*Corresponding author

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Abstract. To investigate Default Mode Network (DMN) in healthy rhesus monkey brain using Resting-State functional Magnetic Resonance Imaging (RS-fMRI). Under anesthesia, two healthy rhesus macaques underwent RS-fMRI at 7.0T using equal imaging parameters. The functional images were first spatially normalized to the standard rhesus monkey template 112SM-RL-T1, and the GIFT software was utilized to carry out group-level Independent Component Analysis (group-ICA) on all preprocessed functional images. The results demonstrated that our method can obtain functional connectivity maps of the resting-state networks. Among them, the DMN bilaterally includes posterior cingulate cortex, anterior cingulate cortex, medial parietal cortex, retrosplenial cortex, arcuate sulcus, ventral intraparietal area, temporo-parietal area, superior temporal sulcus dorsal bank and a portion of visual cortex. With the help of cutting-edge 7.0T fMRI technology, our result confirms that the DMN of the monkey brain highly resembles the ones in human; it supports the notion that non-primates are useful models for neuropharmacological and neurocognitive studies.

Introduction

Owing to its non-invasive nature, Blood-Oxygenation Level-Dependent functional Magnetic Resonance Imaging (BOLD-fMRI) has been applied worldwide for the clinical and basic research of neurosurgery in recent decades. The examinations of intrinsic brain activity and functional connectivity have been conducted on human subjects or non-human primates by task-related fMRI and Resting-State fMRI (RS-fMRI). RS-fMRI is simply a period of recording in the absence of any explicit task paradigm. Investigations are undertaken without specific task-stimuli and subjects are free to cycle through normal cognitive processes while passively lying awake in the scanner with eyes open and fixating or closed. Compared to task-related fMRI, RS-fMRI avoids brain activation differences caused by different subjects taking the initiative to perform a specific task or to accept a certain stimulus generated, and hence becoming more preferred in neuropharmacology research [1]. At present, the early qualitative analysis and treatment of most diseases are clinically carried out by fMRI

equipment with field strength less than 3.0T. It is shown that the higher the field strength of fMRI equipment, the faster the imaging speed and the higher the quality of collected images [2]. fMRI equipment at 7.0T can acquire images of superior quality, and its powerful processing system can facilitate the device to complete almost all advanced MRI sequences and pop experiments. However, it is still unknown if excessive field strength will damage the human body and if there exist differences in data collected by fMRI at 7.0T. The literature [3] proposed non-human primates to be the best-suited model for exploring these unresolved resting-state concerns. Default Mode Network (DMN) is the most commonly investigated and perhaps most controversial among all resting-state networks. However, there are few references describing how to preprocess monkey brain fMRI data for DMN extraction. Based on this, a novel preprocessing method is presented in this paper for the identification of DMN in macaques. RS-fMRI data were first collected from two healthy anesthetized macaques using MRI at 7.0T with identical imaging parameters. Then, the DPARSF software package [4], SPM12 [5], FSL 5.0.9 [6] and marsbar_0.44 [7] were utilized to preprocess both functional images and structural images. Finally, the DMN was extracted by group-level Independent Component Analysis (group-ICA) using GIFT [8] toolbox.

Materials and Methods

Animals

All RS-fMRI data were acquired from two adult healthy anesthetic macaque monkeys (M1&M2, both male) whose weights are 8.7 kg and 9.7 kg, respectively. The surgical and experimental procedures were carried out in accordance with Beijing Regulations on Animals Management and were in line with the ethics committee rules of Institute of Biophysics, Chinese Academy of Sciences.

In preparation for image acquisition, each monkey underwent fasting for 12 hours and restriction of water for 3 hours, followed by intravenous administration of propofol (1 mg/ml) to carry out basic anesthesia for establishing a continuous intravenous infusion channel. Continuous intravenous anesthesia was then maintained with propofol (at an infusion rate of 0.3 mg/kg/min, about 3 drops/kg/min) using an infusion pump. In order to ensure that the animal head was located in the magnet bore of the MRI equipment during the scanning process, all monkeys were first placed prostrate on a custom-built experimental rig and their teeth were fixed on a special denture to allow unobstructed breathing. Then, animals were positioned on a specially designed workbench for fMRI. Respiratory rate was continuously observed, while corneal reflexes and the behavioral response to skin irritation were monitored intermittently. The anesthetic infusion rate was dynamically adjusted to maintain sustained and stable narcotism for about 30 minutes, followed by moving the monkeys into the scanning device to collect fMRI data.

Data Acquisition

All experimental data were collected on the SIEMENS MAGNETOM Investigational_Device_7T syngo MR B17 equipment (manufactured in Germany) at the Institute of Biophysics, Chinese Academy of Sciences. An in-house designed and manufactured conformal three-channel primate-head RF coil was utilized for all experiments. For each monkey, we applied an echo-planar imaging (EPI) sequence in

axial orientation to acquire resting-state functional data, which contained 6 sessions of 336 continuous functional volumes. The scanning parameters were as follows: Repetition Time (TR) was 6,000 ms; Echo Time (TE) was 23 ms; Flip Angle (FA) was 90°; in-plane resolution was $1\times1mm^2$; Filed of View (FOV) was $96\times90mm^2$; the number of slices were 76; slices thickness was 1mm. EPI images were acquired with GRAPPA at an acceleration factor of 2. For each monkey, a high-resolution T1-weighted structural volume was acquired as anatomical reference along the same orientation as the functional images with a Magnetization Prepared Rapid Gradient Echo (MPRAGE) acquisition scheme. The scanning parameters were as follows: TR was 2200ms; TE was 3.22ms; Inter-volume time was 1050ms; FA was 7°; in-plane resolution was $0.7\times0.7mm^2$; FOV was $135\times135mm^2$; the numbers of slices were 176; slices thickness was 0.7mm.

Date Preprocessing

DPARSF 4.0 for monkey data in DPABI_V2.0 toolbox, SPM12, FSL 5.0.9 and marsbar_0.44 were used to preprocess all RS-fMRI data of monkey brain based on MATLAB 7.11 (R2010b). The preprocessing procedure consist of data preparation, brain extraction, removing first 6 (approximately) time points, slice timing, head motion correction, re-orientation, co-registration, segmentation, normalization and smoothing. An overview of the proposed preprocessing method is shown in Fig. 1, in which the blue boxes on left and the gray boxes on right represent the steps that resting-state function data and structural data were performed, respectively. The processes performed with both are described in red boxes. Details are as follow:

① Data preparation: Most acquired data from MRI devices are usually in DICOM format. Before data analysis is performed using DPARSF 4.0 for monkey data in DPABI_V2.0 toolbox, each session of 336 volumes in 3D NIfTI format were transformed into 4D NIfTI format by means of running dcm2niigui in MircroN software [9]. In addition, both functional data in 4D NIfTI format and structural data in 3D NIfTI format of each monkey were sorted according to the software requirements.

② Brain extraction: Integrated skull tissue can be observed in both functional EPI images and structural images at a high field of 7.0T, which had great influences on subsequent data processing and analysis. Conventional brain extraction schema for human or non-human primates can not eliminate all skull signals in monkey data at high field effectively. In this paper, we initially adopted BET in the FSL 5.0.9 kit to prevent skull tissue from interfering with brain tissue signal. Then, if a residual skull tissue was still observed in the structural images, marsbar_0.44 and SPM12 were combined to further strip the image. DPARSF 4.0 for monkey was applied to further process functional data or structural data according to next steps.

③ Removing first 6 (approximately) time points: The first six volumes of each functional session were often discarded to eliminate magnetic saturation effects.

④ Slice timing and head motion correction: The functional data of each monkey underwent slice timing, following by head motion correction. For each monkey, we excluded the session with head translation >1mm or head rotation $>1^{o}$.

⑤ Re-orientation: The re-orientations of functional images and structural images are crucial for subsequent spatial normalization of functional images. Since there were large differences between the origin of collected data and that of monkey brain template 112SM-RL-T1 [10] used in DPARSF 4.0 for monkey data, both functional data and structural data need to be reoriented separately. The origin of 112SM-RL-T1 [10] monkey brain template can be observed through Viewer in DPABI toolbox. We first set

suitable values of pitch, roll and yaw in reorientation interface to align the orientation of functional images or structural images with the 112SM-RL-T1 template and then adjust the values of right, forward and up so that the origin was close to that of 112SM-RL-T1 template.

⑥ Co-registration: The reoriented functional images were co-registered to corresponding individual anatomical images.

⑦ Segmentation: Using prior probabilistic distributions of white matter, gray matter and cerebrospinal fluid [10] to segment co-registered structural images.

⑧ Spatial normalization: All functional volumes were spatially normalized to 112SM-RL-T1 template by selecting normalization method using T1 image unified segmentation and resample the voxel size to $2\times2\times2mm^3$.

⑨ Smoothing: Finally, the Gaussian filter was used for spatial smoothing to suppress noise and effects due to residual differences in functional and gyral anatomy during inter-subject averaging (FWHM 3mm).

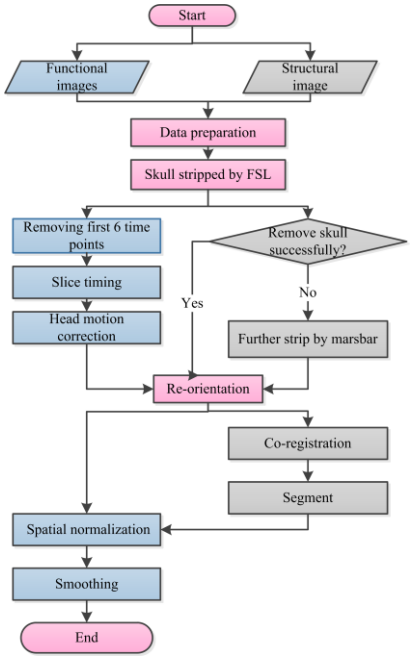

Figure 1. The preprocessing flow chart for RS-fMRI macaque data

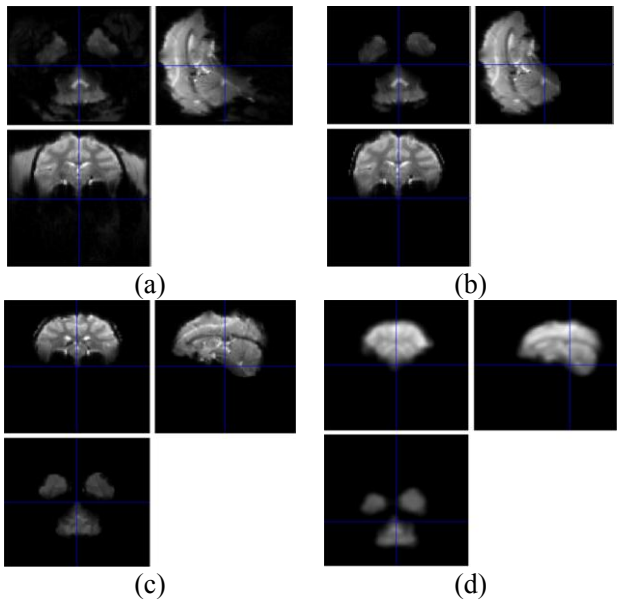

Figure 2. (a) Original functional images. (b)-(d) processed image obtained by brain extraction, reorientation and spatial normalized with smoothing, respectively.

Independent Component Analysis for DMN Extraction

With the help of the GIFT software package [8], group-ICA was conducted on preprocessed resting-state functional images to extract the DMN of rhesus monkey. There were a total of 8 sessions of functional data to be concatenated for group-ICA after head motion correction. First, the number of group-level Independent Components (group-ICs) was estimated to be 12 using the MDL standard in the GIFT package. Then, the temporal dimension of this aggregated data set was reduced by means of Principal Component Analysis (PCA). This was followed by spatial component estimation to obtain 12 group-ICs using the Infomax algorithm. Since the ICA is a stochastic estimation process, the final calculated component maps depend on the initial algorithm conditions. In order to ensure the quality of decomposition, the ICASSO toolkit was used to iterate ICA algorithm for 20 times. Finally, 12 ICs of each animal were

back-reconstructed from group-ICs, each pf them contained a spatial map and corresponding time course. To facilitate comparison between individuals, the spatial map of each IC was converted to z-scores. The larger the z-scores, the stronger the functional connectivity. We set the threshold ($z > 1.5$) to acauire functional connectivity map of DMN in macaque monkey brain.

Results

Since brain size, shape, orientation and gyral anatomy differ greatly across various monkeys; their functional volumes usually were spatially normalized to the standard 112SM-RL-T1 template for inter-subject comparison. For example, we took functional images of M1 to demonstrate the experimental results of the proposed preprocessing method, as shown in Fig. 2. Fig. 2(a) shows original functional images, Fig. 2(b)-(d) show processed image obtained by brain extraction, reorientation and spatial normalized with smoothing, respectively. It can be observed that although original functional images contained skull in addition to brain signal, the described methods can effectively extraction whole brain signals. In data preprocessing process, results of the reorientation have great influences on subsequent spatial normalization. The monkey standard template 112SM-RL-T1 can be previewed by virtue of Viewer in the DPABI toolbox. Comparing Fig. 2(c) with 112SM-RL-T1 template, it can be seen that the origin of functional images after reorientation was approximately the same as the one of standard 112SM-RL-T1 template and functional images were successfully transformed into the monkey template, as shown in Fig. 2(d).

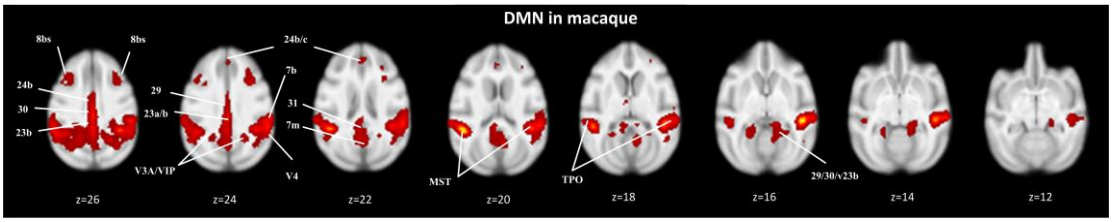

Figure 3. The DMN in macaque

After data preprocessing, the GIFT software package was utilized to carry out spatial group-ICA, and we successfully obtained 12 component time-courses and corresponding spatial maps. Fig. 3 shows the result that axial spatial functional connectivity maps of DMN overlaid on 112SM-RL-T1 template. Atlas of the rhesus monkey brain [11] was used to locate brain area of DMN, which contains posterior cingulate cortex (PCC, area 23a/b), anterior cingulate cortex (ACC, area 24b/c), medial parietal cortex (area 7m), retrosplenial cortex (area 29/30) in the posterior midline, and arcuate sulcus (area 8bs), ventral intraparietal area (area VIP), superior temporal sulcus dorsal bank (area TPO, TEa), temporo-parietal area (area MST) and a portion of visual cortex (area V3A, V4 and 7b).

Discussions

The activities of brain regions within DMN exhibit significant increase in the resting-state fMRI experiments, which demonstrates that there still exist many high-order cognitive processes when subjects task requirements are absent. DMN is the most commonly investigated and perhaps most controversial among all resting-state networks. However, there is no definitive definition of rhesus monkey brain DMN at

present, though a consensus is beginning to emerge. In this paper, we used the cutting-edge 7.0T fMRI equipment to investigate the DMN of macaque. The identification of DMN can be conducted by seed-based or ICA approaches. Through the seed selection, the seed-region based correlation analysis method aims to calculate the degree of functional correlations between brain regions and the seed. Vincent et al [12] first reported a DMN-like network in anesthetized macaques. They placed an anatomically seed in the posterior midline containing regions of the PCC (areas 23 and 31) and a portion of the PGm (area 7m), and found that it functionally connected with lateral temporoparietal cortex (including area 7a and superior temporal gyrus), posterior parahippocampal cortex (PPHC) and the dorsal medial prefrontal cortex (dmPFC; area 9) that overlapped with the anterior cingulate cortex (ACC) (area 24c). Using the same dataset, Margulies et al [13] restricted seed to the PCC (area 23/31) and advanced the idea that DMN included PCC, the ventral medial PFC (vmPFC; areas 10m, 32, and 14r), dorsolateral prefrontal cortex (dlPFC), and inferior parietal lobule but lateral temporoparietal cortex and hippocampal formation connectivity. Besides, their results also proposed a notion that the PGm is not in fact a component of the DMN [14]. From the above literatures, it can be observed that the functional connectivity maps greatly depended on the selection of the seed.

Compared to the seed-region based analysis method, the ICA method can decompose the resting-state functional data of monkey into multiple ICs, each IC reflects an integrative network configurations. In this paper, group-ICA was utilized to investigate which brain regions DMN include in macaque. Our results demonstrated that the DMN bilaterally includes PCC, ACC, medial parietal cortex, retrosplenial cortex, arcuate sulcus, ventral intraparietal area, temporo-parietal area, superior temporal sulcus dorsal bank and a portion of visual cortex. The biggest difference from the above findings was that the DMN obtained in this paper contained a part of visual cortex. In summary, it can be seen that the brain regions of DMN in monkey mainly distributed in the midline of the brain, including PCC, ACC, medial parietal cortex and retrosplenial cortex. In humans, it bilaterally encompassed PCC/retosplenial cortex/precuneus (PGm), ventral and dorsal medial prefrontal cortex, inferior parietal lobule, lateral temporal cortex, and hippocampal formation [14]. Our result confirms that the DMN of the monkey brain highly resembles the ones in human, it supports the notion that non-primates are useful models for neuropharmacological and neurocognitive studies.

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