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Technical Note

Static and dynamic characteristics of cerebral blood flow during the resting state

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ABSTRACT

In this study, the static and dynamic characteristics of cerebral blood flow (CBF) in the resting state were investigated using an arterial spin labeling (ASL) perfusion imaging technique. Consistent with previous PET results, static CBF measured by ASL was significantly higher in the posterior cingulate cortex (PCC), thalamus, insula/superior temporal gyrus (STG) and medial prefrontal cortex (MPFC) than the average CBF of the brain. The dynamic measurement of CBF fluctuations showed high correlation (functional connectivity) between components in the default mode network. These brain regions also had high local temporal synchrony and high fluctuation amplitude, as measured by regional homogeneity (ReHo) and amplitude of low-frequency fluctuation (ALFF) analyses. The spatial pattern of the static CBF correlated well with that of the dynamic indices. The high static and dynamic activities in the PCC, MPFC, insula/STG and thalamus suggest that these regions play a vital role in maintaining and facilitating fundamental brain functions.

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Introduction

There has been growing interest in resting brain activity (Raichle et al., 2001; Fox and Raichle, 2007; Greicius, 2008). Positron emission tomography (PET) first demonstrated that a set of brain regions including posterior cingulate cortex (PCC), medial prefrontal cortex (MPFC), thalamus and insula exhibit higher cerebral blood flow (CBF) than the whole brain average in the resting state (Raichle et al., 2001). CBF in the majority of these regions decreases from its baseline level during a wide range of goal-directed tasks (Shulman et al., 1997; Mazoyer et al., 2001). Together, these brain regions have been called the default mode network (DMN). In contrast to the observation of static CBF in PET studies, dynamic interactions between brain regions have been revealed using resting-state functional magnetic resonance imaging (fMRI) (Biswal et al., 1995). Most of these fMRI studies utilized the synchrony of spontaneous fluctuations in the blood oxygenation level dependent (BOLD) signal to identify coherent brain networks and to assess alterations in connectivity strength in various brain disorders (e.g., Greicius et al., 2004; Bluhm et al., 2007; Greicius, 2008; Hong et al., 2009). While the dynamic signals in the DMN are highly correlated (Greicius et al., 2003; Fransson, 2005; Fox et al., 2005; Beckmann et al., 2005), the static and dynamic characteristics of resting-state signals have not been systematically studied under a single modality within the same subjects.

Perfusion imaging based on arterial spin labeling (ASL) has been widely used to measure resting-state blood flow in the brain (Detre etal., 1992). ASL approaches can also be utilized to measure dynamic, spontaneous CBF changes in the resting state. An early study demonstrated that spontaneous low frequency (<0.1 Hz) flow-weighted fluctuations are highly synchronized within the motor system (Biswal et al., 1997). De Luca et al. (2006) observed several brain networks using resting-state ASL data from a single subject. Recently, Chuang et al. (2008) developed a strategy to reduce BOLD contamination in the resting-state CBF fluctuations and reported connectivity within the sensorimotor network.

Using ASL, we investigated the spatial distribution of static and dynamic CBF in the resting state within the same subjects. A multi-slice, pulsed ASL (PASL) technique was utilized to collect CBF time courses from healthy subjects. Static CBF was measured by voxel-wise averaging the CBF values over the time domain. Dynamic characteristics of the brain were assessed using three methods. Classic cross-correlation analysis with a predefined "seed" was used to examine functional connectivity to the seed. We also assessed the characteristics of the CBF dynamic fluctuations from the aspect of local information, which might provide novel and complementary information to the correlation analysis. Amplitude of low-frequency

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fluctuations (ALFF) (Zang et al., 2007), which quantifies the strength of the fluctuations in each voxel, was adopted in the current study to depict the local intensity of CBF fluctuations. Regional homogeneity (ReHo) (Zang et al., 2004), which reflects local synchrony by calculating similarity of dynamic fluctuations of voxels within a given cluster, was also used in the analysis to reveal local synchrony of CBF fluctuations. Since CBF is a single physiological parameter (vs. BOLD which is a composite of several parameters) and is probably more closely related to cerebral metabolism than BOLD, ReHo and ALFF results from CBF data may be more physiologically relevant than those from BOLD.

Materials and methods

Participants

Twelve healthy subjects (26.3 ± 6.4 years old, 9 females, and 3 males) participated in the study. All subjects were screened with a questionnaire to ensure no history of neurological illness, psychiatric disorders or past drug abuse. They were recruited under a protocol approved by the Institutional Review Board of the Intramural Research Program of the National Institute on Drug Abuse. Signed informed consent was obtained from all participants prior to study enrollment.

Data acquisition

Functional MRI data were collected on a 3 T Siemens Allegra MR scanner (Siemens, Erlangen, Germany) equipped with a quadrature volume head coil. A PASL sequence based on the flow-sensitive alternating inversion recovery (FAIR) echo-planar imaging (EPI) method was adopted for functional scans. Arterial blood was labeled with alternating slice-selective inversion recovery (label, SIR) and non-slice-selective inversion recovery (control, NSIR) scans. Important components of QUIPSS II (Wong et al., 1998), such as additional saturation pulses to control the time duration of the tagged bolus, were added into the sequence. These components make the PASL technique relatively insensitive to transit delays and improve the quantification of perfusion. Imaging parameters of the PASL sequence were as follows: TE (echo time)/TR (repetition time)/TI (inversion time) = 33/2000/1400 ms, flip angle = 90°, bandwidth = 4112 Hz/pixel. The saturation pulse to control the tagged bolus was applied at TI1 = 700 ms, with a saturation thickness of 100 mm and a gap of 12 mm to the imaging slab. Ten oblique imaging slices (thickness/gap = 6/0 mm, field of view = 220 × 220 mm^2, in-plane resolution = 3.44 × 3.44 mm^2) were prescribed to cover a large part of the default mode network (Raichle et al., 2001). The slab thickness for the SIR scans was approximately 1.4 times the imaging slab (84 mm thickness in total) to avoid artifacts in perfusion images due to imperfect transition of the slab profile (Yang et al., 1998). Head movement was minimized by using a polyurethane foam helmet individually made for each participant. Before the resting-state scan, subjects were instructed to rest with their eyes closed, not to think of anything in particular, and not to fall asleep during the acquisition period. Twelve minutes of continuous ASL data were acquired for each subject, corresponding to 360 measurements.

After the functional scans, a total of 19 NSIR-EPI images were acquired with multiple TIs (30, 80, 130, 180, 230, 330, 430, 530, 630, 730, 830, 1030, 1230, 1530, 1830, 2230, 2730, 3230 and 3830 ms) to generate T_1 maps for image segmentation. For registration purposes, a set of high-resolution anatomical images were acquired using a 3-D magnetization prepared rapid gradient echo (MPRAGE) T_1-weighted sequence (256 × 192 × 160 matrix size; 1 × 1 × 1 mm^3 in-plane resolution; TI/TR/TE = 1000/2500/4.38 ms; flip angle = 8°) on each subject.

Data preprocessing

A T_1 map was curve-fitted for each subject using the NSIR-EPI images with multiple TIs, which was then used for structural segmentation into maps of gray matter, white matter, and cerebrospinal fluid (CSF) using a custom linear decomposition algorithm in MATLAB (MathWorks, Inc., CA).

The resting-state PASL data were preprocessed using the Analysis of Functional Neuroimaging (AFNI) software package (Cox, 1996), including the following: (1) slice time correction for acquisition time differences between slices; (2) head motion correction for head movement during the scan; (3) linear detrending of signal drift; (4) spatial normalization to standard Talairach and Tournoux (TT) space with a resampled resolution of 3 × 3 × 3 mm^3 to facilitate group analysis; and (5) spatial smoothing with a 6-mm Gaussian kernel to minimize individual variance and enhance the signal-to-noise ratio (SNR). Potential contamination from BOLD was removed using the method proposed by Chuang et al. (2008). Each PASL dataset was high-pass filtered at the cutoff frequency of 0.125 Hz (corresponding to $\frac{1}{4TR}$) using Chebyshev type II filters in MATLAB. The PASL signal was demodulated to low frequency by multiplying $\cos(\pi n)$ (n is the scan number). Note that high-pass filtering followed by demodulation is the same as demodulation followed by low-pass filtering, and this process will produce similar results to sinc interpolation of the ASL time course to create time-matched control and label images followed by subtraction (Aguirre et al., 2002; Liu and Wong, 2005; Chuang et al., 2008). Potential contamination from physiological noise was reduced using independent component analysis (ICA) at a group level (Beckmann and Smith, 2004), provided in the FMRIB Software Library (FSL; http://www.fmrib.ox.ac.uk/fsl/melodic/index.html). The resting-state PASL data of 12 subjects were automatically decomposed into 20 components. High spatial correlation of the components with CSF and/or vascular maps suggested the components to be artifact instead of representing neuronal activity (Stevens et al., 2009). One component that had the highest average z-score in the thresholded vessel mask (http://www.bic.mni.mcgill.ca/brainweb/anatomic_normal_20.html) and another component that had the highest average z-score in the cerebrospinal fluid (CSF) mask (prior probability template provided by FSL, and thresholded at 0.5) were considered irrelevant to neuronal function (Fig. 1). The majority of the voxels in the two components are located in the respective masks, although a small portion of the voxels (especially the CSF component) does not seem to overlap with the masks, probably due to imperfections of the ICA source separation. These two components were regressed out from the data using dual regression (Beckmann et al., 2009) as follows: a subject specific time course of each component was created by regressing the group component maps against the individual data (using fsl_glm implemented in FSL). Then the time courses corresponding to these two noise components were filtered out of each subject's data (using fsl_regfilt implemented in FSL).

Data analysis

Average CBF map (static CBF map) was calculated for each subject from the ICA denoised data. Similar to PET analyses (Raichle et al., 2001), the static CBF map of each subject was divided by the mean CBF values of that subject in a brain mask that was the intersection of scanned brain regions in all subjects. To reveal brain regions with CBF significantly higher than the global mean CBF, a voxel-wise one-sided one-sample t-test against 1 was performed on the normalized CBF maps (Raichle et al., 2001).

To evaluate the dynamic characteristics of CBF, three approaches were used to analyze the PASL data after ICA denoising:

(1) Seed-based correlation analysis was employed to examine the temporal relationship between the PCC and other brain regions.