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Detecting resting-state brain activity by spontaneous cerebral blood volume fluctuations using whole brain vascular space occupancy imaging

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ABSTRACT

Resting-state brain activity has been investigated extensively using BOLD contrast. However, BOLD signal represents the combined effects of multiple physiological processes and its spatial localization is less accurate than that of cerebral blood flow and volume (CBF and CBF, respectively). In this study, we demonstrate that resting-state brain activity can be reliably detected by spontaneous fluctuations of CBV-weighted signal using whole-brain gradient and spin echo (GRASE) based vascular space occupancy (VASO) imaging. Specifically, using independent component analysis, intrinsic brain networks, including default mode, salience, executive control, visual, auditory, and sensorimotor networks were revealed robustly by the VASO technique. We further demonstrate that task-evoked VASO signal aligned well with expected gray matter areas, while blood-oxygenation level dependent (BOLD) signal extended outside of these areas probably due to their different spatial specificity. The improved spatial localization of VASO is consistent with previous studies using animal models. Moreover, we showed that the 3D-GRASE VASO images had reduced susceptibility-induced signal voiding, compared to the BOLD technique. This is attributed to the fact that VASO does not require T_2^* weighting, thus the acquisition can use a shorter TE and can employ spin-echo scheme. Consequently VASO-based functional connectivity signals were well preserved in brain regions that tend to suffer from signal loss and geometric distortion in BOLD, such as orbital prefrontal cortex. Our study suggests that 3D-GRASE VASO imaging, with its improved spatial specificity and less sensitivity to susceptibility artifacts, may have advantages in resting-state fMRI studies.

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Introduction

There has been growing interest in intrinsic brain activities revealed by spontaneous fluctuations in resting-state functional MRI (rs-fMRI) signals (Biswal et al., 1995; Fox et al., 2005; Greicius et al., 2003). The human brain has been shown to be composed of multiple coherent networks that support sensory, motor and cognitive functions (Buzsáki and Draguhn, 2004; De Luca et al., 2006; Smith et al., 2009). These brain networks appear to be consistent across time within and between individuals (Chen et al., 2008; Damoiseaux et al., 2006), and constrained to anatomically connected regions (Greicius et al., 2009; Honey et al., 2009). Interestingly, the strength of functional connectivity in these networks at "rest" is able to predict relevant task-induced activation and behavioral performance (Hampson et al., 2006; Zou et al., in press). Alterations of resting-state activity in these brain networks are associated with various neurological and psychiatric disorders (Buckner et al., 2008; Menon, 2011), suggesting that intrinsic brain activities may be used as a system-level biomarker for diagnosing diseases and monitoring treatment outcomes.

Although intrinsic brain activity can be assessed using various modalities, including electrophysiology (Arieli et al., 1996; Fiser et al., 2004), positron emission tomography (Raichle et al., 2001) and voltage-sensitive dye imaging (Mohajerani et al., 2010), the majority of current knowledge about it has been acquired from resting-state blood-oxygenation level dependent (BOLD) imaging studies (Biswal et al.,

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1995; Fox et al., 2005), which constitute a growing proportion of functional brain imaging literature over the past years. However, BOLD signal represents the combined effects of cerebral blood volume (CBV), cerebral blood flow (CBF) and cerebral metabolic rate of oxygen ($CMRO_2$) (Davis et al., 1998), which may be difficult to interpret without knowing the complex interplay of these physiological parameters. Therefore, imaging techniques based on a less confounding (ideally single), well-interpretable physiological parameter (such as CBV, CBF or $CMRO_2$) are needed. Recently, arterial spin-labeling (ASL) perfusion imaging has been used to investigate resting-state brain activities (Chuang et al., 2008; Viviani et al., 2011; Zou et al., 2009), demonstrating the viability of characterizing intrinsic brain activities with CBF contrast, though low temporal resolution, low contrast-to-noise ratio, and contamination of BOLD signal remain challenging in these techniques. Like CBF, CBV could be another important, single physiological parameter to characterize brain activities with improved spatial specificity (Jin and Kim, 2008), but so far, there is no CBV-based resting-state fMRI study reported in humans yet.

Vascular space occupancy (VASO) imaging was originally proposed to measure task-induced brain activation based on CBV changes from the baseline to an activated state (Donahue et al., 2009; Hua et al., 2013; Lu et al., 2003; Wu et al., 2007; Yang et al., 2005). Evoked fMRI experiments on cat brains showed that VASO signal was primarily located in the middle layers of the cortex (closer to neural cells), whereas BOLD signal based on a gradient-echo sequence was more on the surface layer (closer to blood vessels) (Jin and Kim, 2008), suggesting that VASO has better spatial localization than BOLD. Compared to ASL techniques, which usually need a pair of images to obtain CBF, a single-shot VASO imaging may provide higher temporal resolution.

Theoretically, VASO imaging can be used to measure intrinsic brain activities reflected by fluctuations of CBV, but practically it was limited to only a few brain slices if traditional multi-slice echo-planner imaging (EPI) sequences are used. This is due to the fact that VASO exploits an inversion recovery pulse sequence to acquire images at a limited time duration (blood nulling time) when blood signal is suppressed. However, three-dimensional gradient- and spin-echo (3D-GRASE) VASO sequence (Günther et al., 2005; Poser and Norris, 2009) acquires images in a 3D fashion, and therefore data from the entire brain can be collected at the blood nulling time, implying the possibility of observing changes of CBV in the entire brain.

In this study, we seek to detect resting-state brain activities by spontaneous CBV fluctuations, using 3D-GRASE VASO imaging. Specifically, intrinsic brain networks, including cognitive control, visual, and sensorimotor networks were assessed using a single-shot, whole-brain VASO technique. The CBV-based resting-state brain networks were subsequently compared with the BOLD-based ones obtained from the same participants.

Methods

Subjects and fMRI paradigms

Eighteen healthy subjects (9 males; mean age 22.8 ± 1.8 years) were scanned with normal or correct-to-normal vision after providing written informed consent. Foam pads were used to restrain head motions and scanner noise was attenuated by earplugs. Two resting scans (with VASO and BOLD contrasts respectively) were acquired followed by two task scans (VASO and BOLD respectively), so that the resting-state scans would not suffer from the potential 'footprints' of task performance. The order of VASO and BOLD scans was pseudo-randomized among participants. The subjects were instructed to close their eyes and not to fall in sleep during the resting scans. In the task scans, a block-design visual task with dark-gray and light-gray checkerboard flashing at 8 Hz was used, which began with a 30-s "off" block (with a fixation cross at the center of the screen) and consisted of twelve cycles of alternated 20-s "on" and 20-s "off" blocks. The subjects were asked to tap their fingers simultaneously while viewing the visual stimuli.

VASO and BOLD data acquisition

Experiments were performed on a Siemens 3 T TIM Trio scanner (Siemens, Erlangen, Germany) using the body coil for transmission and a 12-channel head coil for reception. VASO data were acquired using a single-shot 3D GRASE sequence with a non-selective adiabatic inversion pulse, followed by an inversion time (TI) to null the blood signal (Poser and Norris, 2009). Gradients compensating the imbalance in Maxwell terms due to the EPI readout were not used in this GRASE implementation. The body coil-transmitted inversion pulse nulls the blood in a relatively large volume (within an FOV of about 40 cm) and thus reduces inflow effects in the VASO signal. After a spectral-selective saturation pulse for fat suppression, the imaging volume was excited by a slab-selective 90° sinc RF pulse with 5.12 ms duration, subsequently refocused by a 180° sinc pulse that was surrounded by crusher gradients on the z-axis. During each spin echo, an entire k_x–k_y plane was acquired using an EPI readout. Centric order encoding along k_z-direction was used to minimize TE effects and maximize SNR. To avoid blurring due to T_2 decay during the long readout train that was required for a large number of slices, parallel imaging capability was added to allow undersampling in primary (k_y) phase-encoding direction, as well as partial Fourier acquisition along the secondary (k_z) phase-encoding direction.

The acquisition parameters of the VASO sequence were: matrix size $64 \times 64 \times 22$ with 2 additional slices for oversampling, FOV = $220 \times 220 \times 110$ mm^3, voxel size = $3.4 \times 3.4 \times 5$ mm^3, TR/TE/TI = 2500/14.6/742 ms, GRAPPA factor along $k_y = 3$, partial Fourier along $k_z = 6/8$, readout bandwidth = 2694 Hz/pixel, and total readout length = 280 ms. The total acquisition time for both resting and task scan was 8 min and 30 s. TI was determined based on the blood T_1 of 1627 ms (Lu et al., 2004; Poser and Norris, 2011). A gradient-echo EPI sequence was used for BOLD imaging acquisition. For comparison, most acquisition parameters of the BOLD were the same as those of VASO, except for TE (30 ms) and GRAPPA factor (no parallel imaging was used). Finally, a conventional 3D MP-RAGE sequence of 6-min was performed to acquire T_1-weighted images which were used as anatomic reference (voxel size = 1 mm^3 isotropic, TI = 1100 ms, TR = 2530 ms, flip angle = 7°, $256 \times 256 \times 176$, GRAPPA factor = 2).

Task-based fMRI data analyses

The task-based VASO and BOLD data were preprocessed using Matlab (The MathWorks, Inc., MA, USA) and SPM8 (http://www.fil.ion.ucl.ac.uk/spm/), which included slice timing correction (only for BOLD data), image realignment, coregistration of structural and functional data, and normalization to the MNI space. Spatial smoothing with a 6-mm full-width-at-half-maximum (FWHM) Gaussian kernel along x and y directions was applied to VASO data, while the BOLD data were smoothed with a 3-D 6-mm Gaussian kernel. There was no large head motion observed (>2 mm), and all data were included in the following analysis.

The hemodynamic response function (HRF) of VASO signals (with inverted sign) may differ slightly from that of BOLD (Lu et al., 2003). However, in this study we adopted a block-design paradigm, which would be insensitive to the minor differences in the hemodynamic responses of VASO and BOLD signals, and thus the same HRF by default in SPM was used for the both contrasts. Since VASO signal decreases in activated condition, first-level statistical analysis defined the 'on's as −1 and 'off's as 0 for VASO-based task data, and 'on's as 1 and 'off's as 0 for BOLD-based ones. The timing of block conditions took into account inversion time in VASO. A group-level statistics was then performed to obtain the activation maps for VASO and BOLD contrasts, respectively. Average VASO and BOLD percentage changes were calculated in a region

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