Magnetic Resonance Imaging 34 (2016) 1235–1241

Contents lists available at ScienceDirect

Magnetic Resonance Imaging

journal homepage: www.mrijournal.com

Effects of anesthesia on resting state BOLD signals in white matter of non-human primates

Tung-Lin Wu [a,b,*], Feng Wang [a,c], Adam W. Anderson [a,b,c], Li Min Chen [a,c], Zhaohua Ding [a,c], John C. Gore [a,b,c]

[a] Vanderbilt University Institute of Imaging Science, Nashville, TN, United States
[b] Biomedical Engineering, Vanderbilt University, Nashville, TN, United States
[c] Radiology and Radiological Sciences, Vanderbilt University, Nashville, TN, United States

ARTICLE INFO

Article history:
Received 11 July 2016
Accepted 17 July 2016
Available online xxxx

Keywords:
fMRI
White matter
Monkeys
Anesthesia

ABSTRACT

Resting state functional magnetic resonance imaging (rsfMRI) has been widely used to measure functional connectivity between cortical regions of the brain. However, there have been minimal reports of bold oxygenation level dependent (BOLD) signals in white matter, and even fewer attempts to detect resting state connectivity. Recently, there has been growing evidence that suggests that reliable detection of white matter BOLD signals may be possible. We have previously shown that nearest neighbor inter-voxel correlations of resting state BOLD signal fluctuations in white matter are anisotropic and can be represented by a functional correlation tensor, but the biophysical origins of these signal variations are not clear. We aimed to assess whether MRI signal fluctuations in white matter vary for different baseline levels of neural activity. We performed imaging studies on live squirrel monkeys under different levels of isoflurane anesthesia at 9.4 T. We found 1) the fractional power (0.01–0.08 Hz) in white matter was between 60 to 75% of the level in gray matter; 2) the power in both gray and white matter low frequencies decreased monotonically in similar manner with increasing levels of anesthesia; 3) the distribution of fractional anisotropy values of the functional tensors in white matter were significantly higher than those in gray matter; and 4) the functional tensor eigenvalues decreased with increasing level of anesthesia. Our results suggest that as anesthesia level changes baseline neural activity, white matter signal fluctuations behave similarly to those in gray matter, and functional tensors in white matter are affected in parallel.

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1. Introduction

Functional magnetic resonance imaging (fMRI) records bold oxygenation level dependent (BOLD) magnetic resonance (MR) signals, and has been widely exploited by the neuroscience community for identifying patterns of neural activation in the brain. The magnitude of BOLD hemodynamic effects has previously been directly related to the level of underlying electrical activity [1]. Resting state fMRI has been used to quantify inter-voxel and inter-areal correlations of fluctuations in BOLD signals, which are then interpreted as indications of functional connectivity between cortical regions [2]. White matter possesses a sparse vasculature compared to gray matter with an approximately four-fold decrease in blood flow, so in general there have been very few investigations of BOLD signals in white matter, and even fewer attempts to detect resting state connectivity. In addition, the presence of action potentials in white matter instead of post-synaptic potentials, which are believed to be the primary source of fMRI signals, further complicates and questions the possibility of detecting BOLD signals in white matter [3]. However, BOLD fMRI has also been found to correlate with mostly spiking activity [4]. Indeed, there is growing evidence that suggests that reliable detection of white matter BOLD signals may be possible [5]. For example, fMRI activation in the genu of the corpus callosum has been well-established when subjects are exposed to the Poffenberger paradigm [6]. This finding has been confirmed in other studies [7,8], providing strong evidence that fMRI activations may be detectable in white matter. Moreover, Fabri et al. investigated functional topological mapping of the corpus callosum with fMRI data, and found that activation at discrete regions of the corpus callosum were consistently detected [9]. Beyond the corpus callosum, several studies have also found BOLD fMRI activation in the internal capsule associated with swallowing [10] as well as finger tapping [11,12]. More recently, Astafiev et al. found that the most consistent BOLD signal changes between healthy controls and chronic mild traumatic brain injury patients were localized in

* Corresponding author at: Vanderbilt University Institute of Imaging Science, B0104 MC, 1161 21st Ave South, Vanderbilt University, Nashville, TN, 37232-2310. Tel.: +1 919 491 1858.
E-mail address: tung-lin.wu@vanderbilt.edu (T-L. Wu).

http://dx.doi.org/10.1016/j.mri.2016.07.001
0730-725X/Published by Elsevier Inc.

white matter while performing visual tasks [13]. However, it should be emphasized that the production of focal task-derived activation is neither a necessary nor sufficient condition for detecting steady state correlations in fluctuations in a baseline signal.

We have previously reported our observations that variations in T_2^* weighted MRI signals in a resting state show comparable intensity and temporal variability profiles in both white and gray matter. The voxel-averaged temporal variations of MRI signals in white matter are ~80% those in gray matter [14]; analyses of the power spectra of BOLD signals from both white matter and gray matter show that the ratio of signal power in the low frequency range of 0.01 to 0.08 Hz to total variance is comparable [14]. These indicate that resting state variations that potentially reflect neural activity in gray matter may also be detectable in white matter. Moreover, we have shown that inter-voxel correlations of resting state signals from white matter exhibit spatial anisotropy and reveal distinct underlying structures [14,15]. Based on these observations, we have proposed that appropriate analysis of resting state acquisitions may reveal signal variations within white matter that reflect functional activity. However, the basis for this hypothesis demands further investigation.

It has been recognized that anesthesia reduces spontaneous neural electrical activity in the brain [16]. Indeed, the effects of increased anesthesia on fMRI signals have been demonstrated in both human and animal studies. For example, it has been shown that with increased anesthesia levels, functional connectivity decreases between cortices in macaque monkeys [17]. Similarly, we have also reported diminishing contributions of low frequency fluctuations and correlation strengths between regions in the primary somatosensory cortex of squirrel monkeys as anesthesia levels were increased [18]. A recent observational study in rhesus monkeys on dose-dependent effects of anesthesia on regional activity also demonstrated a similar phenomenon [19]. However, these previous studies did not assess possible changes within white matter. Thus, by carrying out imaging studies on live squirrel monkeys under different levels of anesthesia, we aimed to assess changes in MRI signals from white matter for different baseline levels of neural activity. In particular, we aimed to compare how different anesthesia levels modulate fractional power and spatio-temporal correlation tensors in white matter in a resting state.

2. Materials and method

2.1. Animals and preparation

Four adult male squirrel monkeys were studied for functional MRI scans at decreasing isoflurane levels (1.25%, 0.875% and 0.5%). Each animal was sedated with ketamine hydrochloride (10 mg/kg)/atropine (0.05 mg/kg) before it was maintained on mechanical ventilation (40 bpm) with isoflurane anesthesia (0.5%–1.25%) delivered in a 70:30 N_2O/O_2 mixture. After intubation, each animal was placed in a custom-designed MR cradle where the head was secured with ear and head bars to prevent any motion related artifacts. A solution of 2.5% dextrose in saline solution was also infused intravenously (3 ml/kg/h) throughout the imaging session. Vital signs of the animal including peripheral oxygen saturation and heart rate, EKG, end-tidal CO_2, and respiratory pattern were continuously monitored. Temperature of the animal was kept between 37.5 and 38.5 °C with a circulating water blanket. All procedures were in compliance with the Society for Neuroscience guidelines for animal use in research and were approved by the Institutional Animal Care and Use Committee (IACUC) at Vanderbilt University.

2.2. Variation of isoflurane levels

Multiple functional MRI scans (runs) at each decreasing isoflurane level (1.25%, 0.875% and 0.5%) were acquired. Before image acquisition at each isoflurane level, at least 10 min were allocated for the stabilization of anesthesia and animal's physiological condition through monitoring of vital signals such as the heart rate, end tidal CO_2 and respiration patterns.

2.3. MRI data acquisitions

All scans were acquired on a 9.4 T magnet with a quadrature birdcage volume coil (inner diameter = 85 mm) and Varian/Agilent MR spectrometer. Structural T_1-weighted images were collected using a fast inversion recovery gradient echo sequence (TR/TE = 3000/2.8 ms, echo train length ETL = 4, inversion recovery time TI = 600 ms, flip angle = 80 degrees, resolution of $0.5 \times 0.5 \times 0.5$ mm^3), while structural T_2^*-weighted images were collected using a gradient echo sequence (TR/TE = 500/10 ms, NEX = 2, flip angle = 35 degrees, resolution of $0.125 \times 0.125 \times 0.125$ mm^3). Resting state BOLD-sensitive axial images were acquired using a T_2^*-weighted GE-EPI sequence (TR/TE = 750/16 ms, 2 shots, resolution of $1 \times 1 \times 1$ mm^3, 1.5 s/volume). Each imaging run contained 300 image volumes.

2.4. fMRI data pre-processing and power analyses

Slice timing correction was performed with *spm8* in Matlab followed by motion correction (three translations and three rotations) and isotropic smoothing with a full width at half maximum of 1.5 mm. A temporal 128 s high pass filter along with linear detrending was applied before resting state power analyses were performed. RETROICOR [20] was then applied in *spm8* with custom scripts [21] to correct for cardiac and respiratory interferences. Fractional power maps were computed by transforming each voxel time series into its power spectral density via a Fourier Transform, and dividing the integrated power amplitudes in the low frequency range (0.01–0.08 Hz) by the sum over the entire frequency range (0.01–0.33 Hz). Power measures were subsequently normalized within each monkey by computing relative z-scores before combining the runs for group analyses.

2.5. Region of interest selection/segmentation

White and gray matter voxels in the brain were segmented using high resolution T_2^*-weighted anatomical images. Intensity histogram thresholding was first used for segmenting gray matter before manually selecting and removing voxels subject to partial volume effects. Similarly, manual selection of white matter was performed. The full segmentation of white matter for each monkey is presented in Supplementary Information I. The segmented white matter masks were further subjected to a morphological erosion algorithm using the Matlab function *imerode* with 2×2 structuring element (Supplementary Information III). This was performed to remove outermost voxels and further ensure the absence of partial volume effects. As control reference regions, adjacent muscle voxels were also selected with the functional images; care was taken to avoid any gray matter partial volumes (Supplementary Information II).

2.6. Calculation of spatio-temporal correlation tensors

After slice timing and motion correction, the resting state data were subjected to isotropic smoothing with a full width at half maximum of 2 mm, and a bandpass filter of 0.01–0.08 Hz was then applied to each voxel time series. Spatio-temporal correlation tensors were constructed using the method reported in Ding et al. [14]. Briefly, each voxel in the fMRI signal exhibits a series of small amplitude fluctuations. Since each voxel has 26 nearest neighbors, a total of 26 cross-correlation coefficients can be estimated that