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Functional connectivity and activity of white matter in somatosensory pathways under tactile stimulations

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ABSTRACT

Functional MRI has proven to be effective in detecting neural activity in brain cortices on the basis of blood oxygenation level dependent (BOLD) contrast, but has relatively poor sensitivity for detecting neural activity in white matter. To demonstrate that BOLD signals in white matter are detectable and contain information on neural activity, we stimulated the somatosensory system and examined distributions of BOLD signals in related white matter pathways. The temporal correlation profiles and frequency contents of BOLD signals were compared between stimulation and resting conditions, and between relevant white matter fibers and background regions, as well as between left and right side stimulations. Quantitative analyses show that, overall, MR signals from white matter fiber bundles in the somatosensory system exhibited significantly greater temporal correlations with the primary sensory cortex and greater signal power during tactile stimulations than in a resting state, and were stronger than corresponding measurements for background white matter both during stimulations and in a resting state. The temporal correlation and signal power under stimulation were found to be twice those observed from the same bundle in a resting state, and bore clear relations with the side of stimuli. These indicate that BOLD signals in white matter fibers encode neural activity related to their functional roles connecting cortical volumes, which are detectable with appropriate methods.

Introduction

Functional magnetic resonance imaging (fMRI) is well established as a primary neuroimaging technique for detecting neural activities in the human brain. Based on blood oxygenation level dependent (BOLD) signal changes associated with hemodynamic responses to stimuli, fMRI has been widely used to localize and quantify regional activities and to assess synchronous activities across time (Ogawa et al., 1990; Biswal et al., 1995; Gore, 2003; Fox and Raichle, 2007). However, the tremendous successes over the past quarter of a century have focused on studies of cortical gray matter, and the detection of functional activities in white matter has rarely been reported in the literature. The paucity of reports on white matter activities is presumably partly attributed to the much lower blood flow and volume in white matter (Nonaka et al., 2003a, 2003b), and therefore much lower BOLD signal changes than in gray matter consistent with lower metabolic demands.

We have recently reported our observations that MRI signals from T_2*-sensitive acquisitions in a resting state exhibit structure-specific anisotropic temporal correlations in white matter (Ding et al., 2013; Ding et al., 2016). Based on these observations, we proposed a concept of spatio-temporal correlation tensors that characterize correlational anisotropy in white matter BOLD signals. Moreover, we found that directional preferences of spatio-temporal correlation tensors along many white matter tracts are grossly consistent with those revealed by diffusion tensors, and that evoked functions selectively enhance visualization of relevant fiber pathways. These tend to suggest that

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BOLD signals in white matter may encode neural activity as well, and may be detectable using appropriately sensitive imaging and analysis techniques such as improved imaging hardware (Mazerolle et al., 2013), pulse sequences (Gawryluk et al., 2009), stimulation and analysis strategies (Tettamanti et al., 2002; Weber et al., 2005; D'Arcy et al., 2006; Yarkoni et al., 2009; Marussich et al., 2017).

Over a decade ago, despite the presence of large differences in vascular density between gray matter and white matter, the oxygen extraction fraction was shown to be relatively uniform throughout the parenchyma of a resting brain (Raichle et al., 2001). Furthermore, the BOLD signal changes in white and gray matter in response to hypercapnia are largely comparable when normalized with regional cerebral blood flow (Rostrup et al., 2000). We have observed that BOLD signals in a resting state exhibit similar temporal and spectral profiles in both gray and white matter of the human brain (Ding et al., 2013), and that their relative low frequency (0.01–0.08 Hz) signal powers are comparable (Ding et al., 2016). In addition, our recent experiments with anesthetized squirrel monkeys demonstrate that low frequency activity in both gray and white matter vary similarly with the level of anesthesia (Wu et al., 2016). Taken together, these findings converge to support the view that variations in BOLD signals that are believed to reflect neural activities in gray matter may also be detectable in white matter.

In this work, we further explore BOLD signal properties in brain white matter under functional loading. We hypothesize that functional loading should enhance the detectability of BOLD signals along white matter pathways that are relevant to specific evoked functions. To examine this hypothesis we imaged a cohort of normal human subjects subject to tactile stimulation of the palm, and then analyzed the temporal and frequency profiles of BOLD signal fluctuations in the somatosensory system. We specifically investigated whether there are significant temporal correlations in BOLD signals between the primary somatosensory cortex and projection pathways that are connected to it, and whether there are common signal characteristics that are shared between them. We compared the results of somatosensory stimulations to both palms, and to resting conditions. In particular, we used conventional stimulus-evoked functional MRI to identify cortical volumes in the primary somatosensory system. We used separate diffusion MRI acquisitions to identify relevant white matter tracts between these regions and thalamus and pons. We then examined the task and resting state correlations between the BOLD signals from the cortical volumes and the white matter tracts and compared them to volumes in white matter elsewhere.

Methods

Data acquisition

Full brain MRI data were acquired from twelve healthy (six males and six females), and right-handed adult volunteers (mean age = 27.8 yrs, stdev=4.8 yrs). No subjects had a history of neurological, psychiatric or medical conditions as determined by interview. Prior to imaging, informed consent was obtained from each subject according to protocols approved by the Vanderbilt University Institutional Review Board. All imaging was performed on a 3T Philips Achieva scanner (Philips Healthcare, Inc., Best, Netherlands) using a 32-channel head coil.

Three sets of images sensitive to BOLD contrast were acquired using a T_2*-weighted (T_2* w) gradient echo (GE), echo planar imaging (EPI) sequence with TR=3 s, TE=45 ms, matrix size=80×80, FOV=240×240 mm^2, 34 axial slices of 3 mm thick with zero gap, and 145 volumes. During the same imaging session, diffusion weighted images (DWI) were obtained using a single-shot, spin echo EPI sequence with b=1000 s/mm^2, 32 diffusion-sensitizing directions, TR=8.5 s, TE=65 ms, SENSE factor=3, matrix size=128×128, FOV=256×256, 68 axial slices of 2 mm thick with zero gap. To provide anatomical references, 3D high resolution T_1-weighted (T_1w) images were also acquired using a multi-shot 3D GE sequence at voxel size of 1×1×1 mm^3. The order of image acquisitions was T_1w, resting state, tactile stimulations to the right palm, DWI and tactile stimulations to the left palm. The three functional runs had the same time duration of 435 seconds.

Sensory stimuli were prescribed in a block design format, which started with 30 seconds of palm stimulations by continuous brushing followed by 30 seconds of no stimulation, and so on. Prior to administration of the stimuli, five volumes were acquired in a resting state. During the image acquisitions, subjects lay in a supine position with eyes closed (in resting state), or fixed on a cross in the middle of the screen (no stimulus) or on an arrow sign (with stimulus).

Image preprocessing

Once acquired, all BOLD time series were corrected for slice timing and subject's head motion, and subsequently smoothed with a Gaussian kernel at FWHM=4 mm using SPM12. The smoothed BOLD signals were then linearly detrended and normalized into unit variance voxel-wise. Meanwhile, diffusion tensors were fit from the DWI data using a least squares approach (Jones and Cercignani, 2010) with in-house software. Finally, the T_1w images were segmented into gray and white matter and cerebrospinal fluid images using SPM12, all of which, along with the original T_1w images, were co-registered with the b=0 DWI data individually for each subject.

Characterization of BOLD signals in time and frequency domains

BOLD signals were characterized in both the time and frequency domains. In the time domain, temporal correlations between the resting state and stimulus evoked BOLD signals from identified white matter tracts and those from the primary somatosensory cortex (S1) were analyzed. In the frequency domain, power spectra of the BOLD signals were computed for each voxel, and the magnitude of the frequency corresponding to the fundamental frequency of the periodic stimuli was determined, yielding three magnitude maps of stimulus frequency respectively for the three sets of T_2*w images acquired.

The S1 region was initially defined in MNI space as a combination of Brodman's areas (BA) 1, 2 and 3 in the postcentral gyrus of each hemisphere, using the PickAtlas tool (Maldjian et al., 2003) supplied with SPM12. The initial S1 was then transformed into the space of the BOLD data acquired with tactile stimulations to the contralateral palm. Finally, the transformed S1 region was multiplied by the magnitude map of the stimulus frequency and was thresholded at 80% maximum magnitude, to generate an activation adjusted S1 region. This process reduced false positives in the S1 region due to misregistration from the MNI space to the native space of individual subjects.

Within the S1 region defined above, the first principal component of all BOLD signal time courses was derived, with which three maps of Pearson linear correlations were computed:

M1: Correlations of BOLD data from left palm stimulations with S1 in right hemisphere.

M2: Correlations of BOLD data from right palm stimulations with S1 in left hemisphere.

M3: Correlations of BOLD data from resting state with S1in both hemispheres[2].

Prior to computations of the correlations, all the BOLD signals were band-pass filtered to retain frequencies only of 0.01–0.08 Hz. This frequency band contained the principal stimulation frequency of 0.016 Hz (and its low order harmonics). To suppress potential confounding signals from adjacent but functionally unrelated white matter

[2] In this map, the principal component of S1 was computed with the two hemispheres pooled together, with the S1 in each hemisphere "copied" from its corresponding activation adjusted region in the stimulated images by image co-registration.