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Visualizing functional pathways in the human brain using correlation tensors and magnetic resonance imaging

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ABSTRACT

Functional magnetic resonance imaging usually detects changes in blood oxygenation level dependent (BOLD) signals from T_2^*-sensitive acquisitions, and is most effective in detecting activity in brain cortex which is irrigated by rich vasculature to meet high metabolic demands. We recently demonstrated that MRI signals from T_2^*-sensitive acquisitions in a resting state exhibit structure-specific temporal correlations along white matter tracts. In this report we validate our preliminary findings and introduce spatio-temporal functional correlation tensors to characterize the directional preferences of temporal correlations in MRI signals acquired at rest. The results bear a remarkable similarity to data obtained by diffusion tensor imaging but without any diffusion-encoding gradients. Just as in gray matter, temporal correlations in resting state signals may reflect intrinsic synchronizations of neural activity in white matter. Here we demonstrate that functional correlation tensors are able to visualize long range white matter tracts as well as short range sub-cortical fibers imaged at rest, and that evoked functional activities alter these structures and enhance the visualization of relevant neural circuitry. Furthermore, we explore the biophysical mechanisms underlying these phenomena by comparing pulse sequences, which suggest that white matter signal variations are consistent with hemodynamic (BOLD) changes associated with neural activity. These results suggest new ways to evaluate MRI signal changes within white matter.

1. Introduction

Functional magnetic resonance imaging (fMRI) usually detects hemodynamic changes associated with neural activity on the basis of blood oxygenation level dependent (BOLD) contrast, and is well established as the primary neuroimaging technique for studying the functional architecture of the brain and correlating regional activities over time [1–3]. Since 1990, fMRI has been widely adopted by the neuroscience community, and has permeated many aspects of brain research, including studies of human sensory and cognitive processes and their changes with development, aging or pathological disorders.

The vast majority of fMRI studies have been focused on brain gray matter [4], in which significant changes in blood flow and oxygenation in response to variations in neural activity are known to occur, and there have been only a very limited number of reports of corresponding changes in white matter to date [5–7]. The dearth of fMRI literature on white matter is conventionally attributed to an absence of significant hemodynamic changes within white matter in response to changes in electrical activity, so that any corresponding weak BOLD signals are not reliably detectable by current means. Compared to gray matter, white matter is irrigated by much less dense vasculature [8], with blood flow approximately one-fourth of that in the gray matter [9]. Even if BOLD changes occur, they may produce much smaller effects. However, despite this four-fold reduction in blood flow, it has been found that the oxygen extraction fraction is relatively uniform in the resting brain [9]. Thus it is at least plausible that white matter may also elicit BOLD signals that may be

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detected with more sensitive technology or more appropriate processing algorithms. Indeed, recent investigations in which high field MRI and prudently chosen task paradigms were employed have reported reliable detection of white matter activations [10]. However, we also should emphasize that task-evoked activation is not a necessary prerequisite for the existence of resting state correlations in baseline signals.

We first reported our preliminary observations that MRI signals from T_2*-sensitive acquisitions in a resting state exhibit structure-specific temporal correlations in white matter by examining a small set of normal brains at rest [11], but we hypothesized that appropriate analysis of such signals may reveal new insights into white matter structure and represent an important type of functional synchrony which heretofore has been overlooked. In this report, we confirm the validity and significance of resting state correlations, and provide evidence of the biophysical basis of their origins. We introduce a new mathematical construct we call functional correlation tensors (FCTs) that quantifies the correlational anisotropy of resting state MRI signals among neighboring voxels in the brain. In gray matter these tensors tend to be isotropic except at the boundaries of functional domains. In white matter, the tensors tend to be anisotropic with the dominant direction grossly consistent with that of local fibers found independently by diffusion tensor imaging. These FCTs can thus be used not only to visualize white matter structures over large distances, but also to provide an entirely new way to characterize functional organization in the human brain.

We first demonstrate the ability of FCTs for depicting various fiber pathways that include the genu and splenium of corpus callosum, cingulum fibers, portions of arcuate fasciculus, and sub-cortical U-fibers, based solely on analysis of anisotropic resting state correlations of MRI signals *without any prior knowledge and without any use of diffusion-encoding gradients*. Second, we stimulate localized functional activity and demonstrate how these FCTs change with engagement of function and can be used to highlight pathways that are involved in these tasks. To evaluate the underlying biophysical mechanisms, we have carried out multi-echo imaging experiments with T_2*- and T_2-sensitive acquisitions acquired at different echo times, and examined the impact of different levels of T_2* and T_2 contrast on the correlational anisotropy of the signals in white matter.

2. Methods

Human MRI data were acquired from 22 healthy subjects whose age spanned from ten years to middle-aged adults. Prior to imaging, informed consent was obtained from each subject according to protocols approved by the Vanderbilt University Institutional Review Board. All human imaging was performed on a 3 T Philips Achieva scanner (Philips Healthcare, Inc., Best, Netherlands) using a 32-channel head coil. Subjects lay in a supine position with eyes closed except when performing functional tasks.

All fMRI time series acquired were corrected for slice timing and head motion using SPM software (http://www.fil.ion.ucl.ac.uk/spm/software) with our standard protocol [12]. Subjects with head motion more than 4 mm of translation or 4° of rotation in any direction were excluded. Prior to analysis, a global time course of each dataset was removed by intensity normalization. Voxels in each time series were band-pass filtered to retain frequencies only of 0.01-0.08 Hz. To provide anatomical references, 3D high resolution T_1-weighted images were acquired using a multi-shot gradient echo (GE) sequence at voxel size of $1 \times 1 \times 1$ mm^3, and co-registered with the mean fMRI data volume from the same subject. The subjects participated in four experimental studies, with details of imaging and analysis procedures given below.

2.1. Imaging in a resting state

T_2*-sensitive data from ten college students (5 males, age range = [18, 23]) in a resting state were collected, as well as diffusion weighted images (DWI) that were acquired during the same session.

2.1.1. Imaging protocol

Images sensitive to BOLD contrast were acquired using a GE, echo planar imaging (EPI) sequence and the following parameters: TR = 2 s, TE = 35 ms, matrix size = 80×80, FOV = 240×240 mm^2, 34 axial slices of 3.5 mm thick with a 0.5 mm gap, and 300 volumes. DWIs were obtained using a single-shot, spin echo (SE) EPI sequence with $b = 1600$ s/mm^2, 92 diffusion-sensitizing directions, TR = 8.5 s, TE = 65 ms, SENSE factor = 3, matrix size = 96×96, voxel size = 2.5×2.5 mm^2, 50 axial slices of 2.5 mm thick with zero gap.

2.1.2. Image processing

First, diffusion tensors were constructed from the DWI data using linear least squares fitting [13]. Then slice timing and motion corrected T_2*-weighted data were co-registered with the b = 0 DWI volume, along with T_1-weighted images acquired.

2.1.3. Construction of spatio-temporal functional correlation tensors

Methods for constructing FCTs from T_2*-weighted time series were described in detail earlier [11]. Briefly, to capture intrinsic synchronization and signal correlation profiles, we measure temporal correlations among neighboring voxels and construct a tensor that characterizes directional biases of the correlations. More specifically, for each voxel, we first define a set of unit direction vectors that point to the voxels in its neighborhood, and then compute temporal correlations in T_2*-weighted signals along each of the directions. For a correlation tensor $\mathbf{T}$ to be constructed, the estimated correlation C_i projected along a direction vector $\mathbf{n}_i$ is

$$C_i = \mathbf{n}_i \cdot \mathbf{T} \cdot \mathbf{n}_i^t, \quad (1)$$

where t denotes transpose.

Given a set of measured C_i, tensor $\mathbf{T}$ can be solved analytically, similar to the construction of diffusion tensors [13]. $\mathbf{T}$ characterizes the local profile of temporal correlations in MRI signals, with the major eigenvector representing the dominant direction of temporal correlations.

In this experiment, we used a first tier neighborhood of 26 voxels for tensor construction, and chose C to be the squared Pearson's linear correlation coefficient. Constructions of correlation tensors with the closest 26 neighboring voxels allow analysis of local profiles of MRI signal correlations at the finest scale available from the imaging data. To improve signal-to-noise ratio, the MRI signals were spatially smoothed prior to tensor constructions with a Gaussian filter at a small size of FWHM = 3 mm.

2.2. Imaging in a resting state and with visual stimulations

T_2*-weighted images were acquired from two adults (1 male, age = 36; 1 female, age = 25) both at a resting state and with visual stimulation, along with DWI data for structural references of fiber pathways.

2.2.1. Imaging protocol

Images sensitive to BOLD contrast were acquired using a T_2*-weighted GE EPI sequence with the following parameters: TR = 3 s, TE = 45 ms, matrix size = 128×128, FOV = 240×240 mm^2, 34 axial slices of 4 mm thick with zero gap, and 200 volumes. DWIs were acquired with $b = 1000$ s/mm^2, 32