Anisotropy of local functional connectivity (LFC) in resting state fMRI time series: what does it say about the fmri signal?

Michael J. Tobia[1], David Gallagher[1], Rahul Dewal[1], Prasanna Karunanayaka[1], Sebastien Rupprecht[1], and Qing X. Yang[1]
[1]*Center for NMR Research, Penn State University, Hershey, PA, United States*

Target Audience: Scientists interested in the origins of the fmri signal, functional connectivity during resting state, and white matter fiber tractography.

Purpose: The blood oxygenation level dependent (BOLD) contrast mechanism of the fMRI signal is well established for task activation paradigms [1-3], but the contrast mechanism giving rise to spatially organized functional connectivity in gray matter (GM) during the resting state has been debated [4,5], and its presence in white matter is usually dismissed due to the low blood flow and metabolic demand relative to GM [3,6-7]. However, it was recently reported that local functional connectivity (LFC) was anisotropic, more so in WM more than GM, and tensors derived from these LFCs could be used for tractography in WM [8]. Given the lack of expected BOLD contrast in WM, especially during resting state, these data demonstrating increased anisotropy of LFC along WM fibers reinvigorates the question: what's in the noise? We investigated the purported WM LFC anisotropy in resting state fMRI in vivo, and explored an alternative contrast mechanism responsible for generating anisotropic LFCs in a phantom study.

Methods: GE-EPI BOLD time series were collected from humans and a custom phantom on a 3T Siemens Tim Trio (8-channel head coil; 3.3mm^3 voxels, TR/TE=2.0s/20ms). The phantom was oriented either perpendicular or parallel to the B_o field (figure 2, top). An electrical signal of 1 mA at a frequency of 0.5 Hz and pulse duration of 30µs was passed through a 40 gauge uninsulated copper wire loop inside a 2.0% agar gel phantom using a grass stimulator. In vivo data were collected from 5 human subjects (1 female) during eyes-closed resting state for 6 min. Preprocessing followed standard resting state fMRI protocols, including: detrending, bandpass filtered .008-.1 Hz, global signal regression, and smoothing 8mm^3. The LFC tensor is computed from a single local temporal correlation map of T2* image time series using the Pearson correlation and a radius of 2 voxels. Tensor and anisotropy calculations (fractional anisotropy & absolute anisotropy) were computed according to [8,9], respectively.

Results: Figure 1 shows the resultant anisotropy maps from a human subject derived from LFC and DTI. LFC fractional anisotropy (LFC-FA) ranged 0-.83. Visual inspection of the LFC-FA map reveals similarities and differences to FA derived from DTI. The caudate head (red arrow) shows strong LFC-FA, whereas it is invisible in DTI. Part of the optic tract extending into the occipital cortex (yellow arrow) is characterized by high LFC-FA, similar to DTI, but also by very low LFC-FA in the medial aspect of corpus callosum (blue arrow), which is dissimilar to DTI. The LFC-FAV1 map shows that the anterior-posterior direction (green) dominates, and that left-right (red) and inferior-superior (blue) are fewer. Figure 2 (bottom) shows the LFC absolute anisotropy (AA) map (left panel) in an axial slice of the phantom. It shows elevated LFC-FA near the wires when carrying an electric current perpendicular to the main field (B_o), which was not found with an open circuit or constant current, nor when the current was in parallel to B_o. The 'fiber tracts' derived from the LFC Tensor run along the direction of the wire (lower right panel).

Discussion: The LFC anisotropy of T2* time series was investigated. Contrary to previous reports, elevated LFC-FA values were not limited to WM voxels. The elevated LFC-FA in GM does not appear to be solely attributable to edge artifacts. Results from the phantom experiment show that a fluctuating electrical current perpendicular to B_o is sufficient to engender LFC anisotropy in GE-EPI time series near the electric current. Tractography based on these signals isolates the pathway carrying the electrical current in the phantom. In vivo, the distribution of anisotropic correlations among GM and WM voxels demonstrates that LFC anisotropy only partially conforms to DTI-based anisotropy. The causes of LFC anisotropy here are apparently different from DTI [9] or orientation-dependent methods such as T2*-fiber mapping [10], and susceptibility tensor imaging [11].

Conclusion: The in vivo data showing anisotropic correlations are not restricted to WM, and phantom data showing that electric current in the absence of neurobiological vasculature also generates anisotropic LFCs from fMRI noise, together suggest that correlations of resting state fMRI, especially in WM, arise in part due to neuroelectric activity. Thus, there is more information in the T2*-weighted fMRI signal than just BOLD effects, and further investigations of LFC anisotropy may reveal novel insights into dynamic brain networks beyond current resting state analyses.

Figure 1

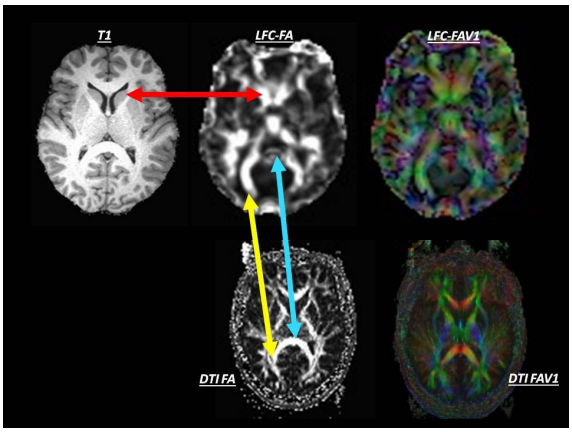
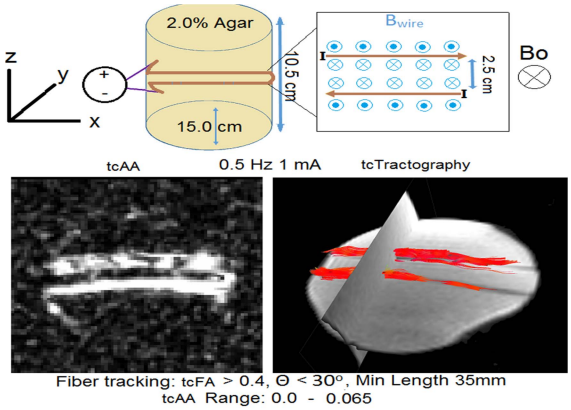


Figure 2



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