# Functional Pathways in Monkey Brain Mapped Using Resting State Correlation Tensors

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**Target Audience:** Investigators who are interested in new methods for measuring brain structure and function.

**Background**: We recently reported our remarkable discovery that anisotropic correlations between resting state signals within a local region of white matter can be used to drive functional structures that closely resemble DTI data but without the use of diffusion gradients [1]. Resting state functional magnetic resonance imaging (rsfMRI) has previously been widely used for measuring functional connectivity between cortical regions only [2], and there have been no reports of rsfMRI in white matter, presumably because of the sparse vasculature in white matter relative to gray, and the consistent failure to observe significant hemodynamic responses from tasks within white matter. To date, the architecture that underlies functional connectivity across cortical regions has to be determined by using other techniques such as diffusion tensor imaging (DTI) [3]. Recently, we demonstrated a technique that is able to delineate the functional architecture of the brain, especially white matter, purely on the basis of fMRI data. Specifically, we derive local spatio-temporal correlation tensors from fMRI time series obtained in a resting state which reveal intrinsic anisotropic synchronizations of MRI signals that depict an underlying structure.. Our previous studies of human brains have demonstrated these functional structures are comparable to those obtained from DTI data [3] and potentially arise from BOLD (blood oxygenation level dependent) effects. To further explore and verify the biophysical mechanisms for the observed spatio-temporal correlations in white matter signals, we carried out imaging studies on live anesthetized squirrel monkeys and compared spatio-temporal correlation tensors from T2* and cerebral blood volume (CBV)-weighted fMRI.

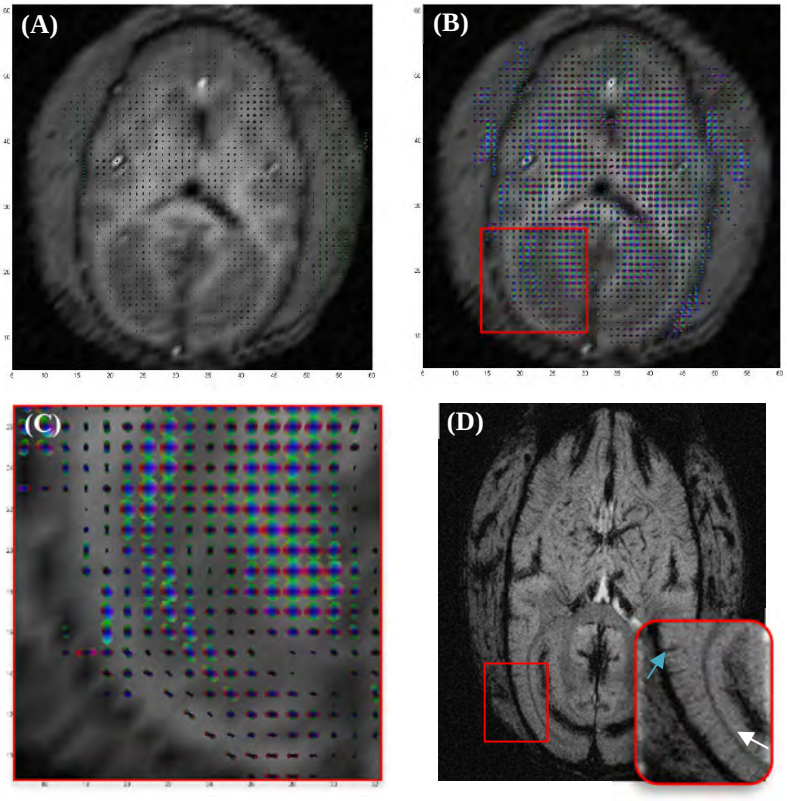


**Figure 1**. Spatio-Temporal Correlation Tensors overlaid on T1-weighted anatomical images (A) BOLD (B) CBV-weighted (C) zoomed in section of CBV-weighted indicated by the red square (D) contrast agent enhanced T2*-weighted anatomical image; bottom right hand is a zoomed image of the red square with arrows pointing to major vasculature (blue) and white matter tract (white)

**Methods:** Resting state T2* and CBV-weighted fMRI images were acquired on a 9.4T magnet using a customized quadrature birdcage coil (diameter = 85mm). Squirrel monkeys were anesthetized (isoflurane 0.5-1.5%) and ventilated, and continuously monitored for physiological signs. $T_1$-weighted images were collected using a fast gradient echo sequence (TR/TE=3000/2.78 ms, ETL=4, Ti=600 ms, flip angle=80). Resting state BOLD-sensitive images were acquired using T2*-weighted GE-EPI sequence (TR/TE=750/16ms, 4 shots, resolution of 1x1x1 $mm^3$, 24 slices, 3s/volume, 300 volumes). CBV-weighted images were acquired using the same sequence (but with TE=10 ms) 10 minutes following a slow i.v. bolus of monocrystalline iron oxide nanocolloid contrast agent (MION, 12 mg/kg). The resting state data were first corrected for head motion and smoothed with the standard spm12 tools. The corrected data were then coregistered with the anatomical $T_1$-weighted images before a bandpass filter of 0.01 - 0.08Hz was applied to the time series. Spatio-temporal correlation tensors were subsequently constructed using the method reported in [1]. Briefly, each voxel in the fMRI signal contains a series of small amplitude fluctuations. Each voxel has 26 nearest neighbors, and so 26 cross-correlation coefficients can be estimated that describe the degree of synchronous but anisotropic covariations with neighboring voxels. Using these values for each voxel, the detailed construction of 3x3 spatio-temporal correlation tensors is analogous to that for diffusion tensor computations [3]. Moreover, the principal eigenvectors and tensor terms can be used for tractography exactly as the case for DTI.

**Results and Discussion:** Maps of the spatio-temporal correlation tensors from T2* and CBV-weighted data are shown in Figs. 1A-B respectively, which demonstrate the effects of MION administration in a squirrel monkey. Specifically, we observe an enhancement in temporal correlations between neighboring voxels, as indicated by overall greater tensor sizes across Fig. 1B; orientations of the tensors are also more consistent among neighboring voxels and dominant directions of the tensors agree better with local macroscopic tissue structure, as can be appreciated in Fig. 1C. These findings suggest that the spatio-temporal correlation patterns observed in white matter are driven by local vascular changes as opposed to other potential effects. Moreover, close inspection of the CBV-weighted anatomical image in Fig. 1(D) reveals that the dominant directions of vascular structures (blue arrow) are not associated with the white matter tract (white arrow) in general. This tends to imply that the greater temporal correlation (tensor dominant direction) observed along white matter tracts reflect intrinsic signal correlations that are not dominated by macroscopic vascular structures.

**Conclusion:** The concept of spatio-temporal correlation tensors provides an attractive means for revealing intrinsic synchronizations of neural activity, and holds the potential of mapping functional architecture and directly integrating structure and functions in the brain. Our *in vivo* MION experiments on a squirrel monkey suggest that the spatio-temporal correlations in white matter may be driven by local hemodynamic effects related to neural activity, consistent with BOLD effects rather than some other potential mechanisms.

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**References:** [1] Ding Z et al. (2013) Spatio-temporal correlation tensors reveal functional structure in human brain. *PLoS One* 8(12): e82107.
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