Resting-state Functional Connectivity, Probabilistic Diffusion Tensor Tractography, and Histological Delineation in the Human Thalamus

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Introduction: Recently, two radically dissimilar approaches that start at opposite ends of the structure/function spectrum have been used to characterize connectivity of the human thalamocortical system. Resting-state functional connectivity MRI (fcMRI) is able to directly measure intrinsic functional interactions but not the underlying anatomical pathway that led to the observed synchrony [1]. Diffusion tensor imaging and tractography (DTI/DTT) uses diffusion-weighted anisotropy to reconstruct fiber tracts on which inferences of functional interactions are possible [2]. Therefore, an obvious complement exists between the two approaches toward understanding of physiologically important functional interactions. Here, we compare the results of the two methods within the human thalamocortical system.
Methods: *Subjects/Data Acquisition*: Resting-state BOLD sensitized fMRI data were acquired in 17 subjects (4x4x4mm voxels, 28min per subject) [1]. Diffusion-weighted MR data were acquired in 11 subjects (separate population). *Functional connectivity preprocessing and analysis*: fcMRI analysis is described in [1]. Briefly, low-pass filtering was performed to retain frequencies less than 0.1Hz. Five cortical ROIs corresponding to prefrontal, parietal/occipital, motor/premotor, somatosensory, and temporal cortices were drawn and used as "seeds" for a partial correlation analysis: the correlation coefficient was computed between each voxel in the thalamus and a cortical seed, after eliminating shared variance from all other seed regions. Thus, 5 thalamus maps were computed corresponding to the 5 cortical seeds. *Diffusion-weighted preprocessing, tensor calculation, tractography:* Initial data preprocessing was performed according to [3]. At the voxel level, the principal eigenvector from a diffusion tensor model was represented in the form of a probability density function according to the methods of [2,4] analyzed using the FSL/FDT package [4]. Probabilistic tracking was performed at a global level starting from each voxel in the thalamus and tracked to its ipsilateral cortex using the above set of 5 cortical ROIs. The probability of connectivity from a seed to a cortical ROI was calculated to be the number of successful tracts to the ROI divided by the total number of tracts to all cortical ROIs. Group level probability maps were calculated using a random effects model. *Mai Histological Atlas 3D Reconstruction:* The Atlas of the Human Brain in Stereotaxic Space by Mai, Paxinos, Voxx is derived from serial coronal sections of a 24 year old male [5]. Histological, morphometric and immunohistochemical studies were performed to generate a detailed delineation of subcortical as well as cortical structures. From the 2D coronal slices of labeled structures derived from the histological sections, we reconstructed the 3D volume and registered this volume to our standard anatomical atlas to facilitate comparison with functional and diffusion-weighted imaging registered to the same space.
Results/Discussion: The overlay of fcMRI and probabilistic DTI/DTT results are presented in the top row of Figure 1. Correspondence between the two methods is remarkably similar considering the dissimilar nature of the two measurements, one intended to measure correlations in neuronal activity and the other intended to measure disturbances in Brownian motion due to the presence of fiber tracts. Figure 1 rows 2 and 3 show the fcMRI and DTT tracings on top of our "gold standard" histological atlas. Alignment with the atlas is consistent with predictions based on anatomy to the extent that our cortical ROIs capture the rough connectional division in the thalamic nuclei. For example, fMRI and DTI connectivity from motor/premotor areas match well to VA/VL/VLP nuclei but also extends into mediodorsal nucleus, which predominantly connects with prefrontal cortex (Column 3, Figure 1). However, the frontal eye fields (BA6 in humans) which are included in our motor/premotor ROI has been argued to be a transitional area between prefrontal and premotor cortex. Therefore, our results may not be expected to strictly follow classically defined thalamic boundaries due to our cortical ROI definitions and due to distributed patterns of anatomical connectivity within the thalamocortical system.

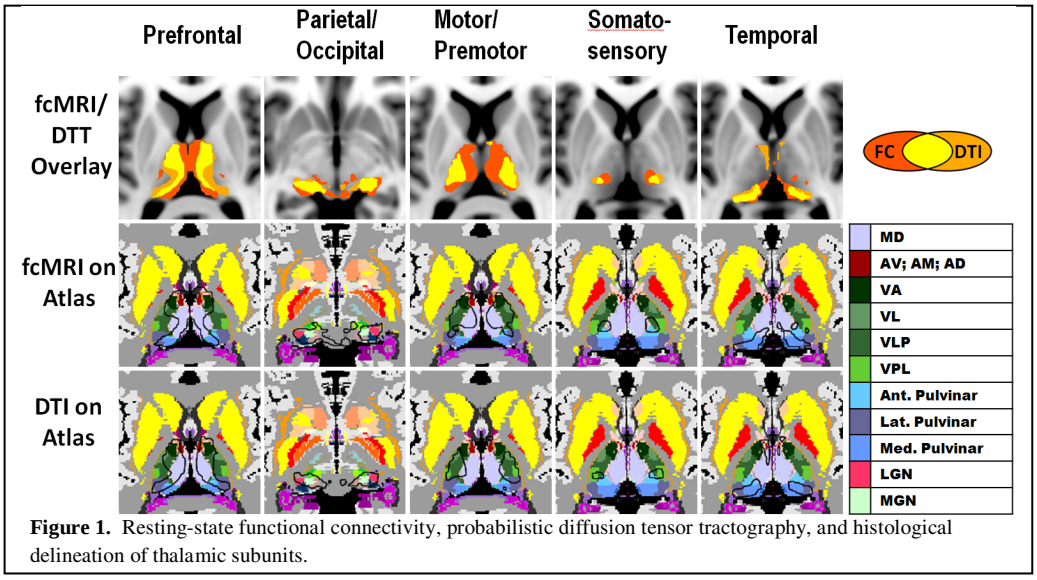

Figure 1. Resting-state functional connectivity, probabilistic diffusion tensor tractography, and histological delineation of thalamic subunits.

At a global level, structural and functional connectivity measures are expected to correspond. However, this correspondence is not expected to be perfect. Functional measures at the resolution of fMRI describe aggregate population activity that are based on neuronal interactions that occur through *multiple synapses* at local and global scales, much of which are not captured by the currently observed structural connectivity of the system. *Distinct synaptic properties* at neuronal junctions shape the functional interaction of the system including terminal arbor morphology, neurotransmitter type, probability of transmitter release, ionotropic vs. metabotropic receptor activation. These parameters have been investigated in certain model systems but this level of detail is currently difficult/impossible to characterize globally in the human brain. Differences between our structural and functional measures can also exist for technical reasons. The resolution of our fMRI acquisition is coarse compared with histology. Partial volume effects tend to further decrease the effective spatial resolution. Tractography based on DTI can successfully label major fiber bundles in the brain but tends to generate false negatives due to loss of anisotropy in voxels that encompass multiple fibers orientations.
Conclusions: Resting-state functional connectivity and DTI/DTT offer complementary views of thalamocortical connectivity from the perspective of neuronal activity and physical connectivity. The results of the two approaches are remarkably similar given the dissimilar nature of their measurements. As we move forward, it is important to appreciate differences between measured structural and functional connectivity, keeping in mind possible confounds generated by differences in technique.
References:

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