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Assessment of functional and structural connectivity between motor cortex and thalamus using fMRI and DWI

A. H. Jaberzadeh Ansari, M. A. Oghabian, G. A. Hossein-Zadeh

Abstract— **Connectivity evaluations have been performed in a noninvasive manner by examining resting state fMRI alongside diffusion-weighted images (DWI). The spatial structures of coherent spontaneous BOLD fluctuations provided the most convincing preliminary evidence that the BOLD signal was predominantly of neuronal origin rather than non-neuronal, artifactual noise. In this study we have shown that in thalamocortical network, the results of functional connectivity analysis and DWI correspond well with each other, thereby providing cross-validation of the two techniques. We have used the resting state fMRI data of 3 subjects with 10 minute resting state functional images via a 3T Siemens scanner. we used cross correlation for functional analysis and reported thalamocortical results with pvalue=0.01and cluster size=100, Then showed corresponding tracts connecting premotor cortex and thalamus. In addition, both techniques correspond well to histological delineation and invasive tract tracing, which provides a 'gold standard' validation of the two techniques. The degree of structural connectivity has been shown to correlate with the strength of functional connectivity, thereby providing a potentially straightforward structural explanation for many of the changes in functional connectivity in disease states.**

I. Introduction

The difference between resting state and task-related activation is about 1–5% of the total BOLD signal. so, by comparing the resting state brain activity, only a small percentage is needed to respond to an external stimulus. However, the function of this vast amount of baseline activity remains unclear [1]. Recently, however, a great deal of attention has been focused on the patterns of connectivity between multiple ROIs within spatially distributed, large-scale networks, characterised via both model-driven (e.g., seed-based correlation analysis; [2],[3],[4] and data-driven analyses (e.g., independent component analysis; [5],[6],[7]). These patterns have been variously termed 'intrinsic connectivity networks' [8], or 'resting-state networks' (RSNs; [3],[7],[9]). They are purported to reflect the intrinsic energy requirements of neurons that, via firing together with a common functional purpose, have subsequently wired together through synaptic plasticity [10]. RSNs can be reliably and reproducibly detected at individual subject and group levels across a range of analysis techniques [1],[11]. A characteristic set of co-activating functional systems is found consistently across subjects [1], [7],[9],[12],[13].

Connectivity comparisons have also been performed in a noninvasive manner by examining fcMRI alongside diffusion-weighted images (DWI). This latter imaging technique reconstructs anatomical pathways on the basis of the restricted Brownian motion of water molecules, which preferentially move parallel to the fiber tracts [14].

Functionally correlated networks demonstrate a high degree of correspondence with DWI-reconstructed anatomy in a variety of networks[15],[16]. The advantage of combining fcMRI with DWI is that together these techniques can provide a comprehensive characterization of connectivity in all areas of the brain.

The data from such analyses are invaluable for creating structural and functional 'connectomes' of brain architecture[17].

The need for both types of connectomes originated from the observation that these two measures of brain architecture do not always agree. This is often because functional connectivity reflects activity generated across multiple synaptic connections, whereas polysynaptic structural connectivity, determined on a large scale throughout the brain, cannot be imaged with high fidelity with currently available tools[18],[19],[20].

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II. Materials and Methods

A. fMRI and DWI data

Intrinsic brain activity was assessed with BOLD fMRI in a group of 3 healthy subjects (3T Siemens MR scanner [Imam Khomeini hospital], 3.44*3.44*3-mm voxels, time echo TE = 30 ms, time repetition TR = 2 s, 300 frames per subject). The subjects were instructed to fixate on a cross-hair, remain aware and still during the experiment.

Structural fiber tracks were assessed using diffusion-weighted MRI (DWI) acquired in a group of 3 subjects using the same scanner after functional imaging. Diffusion was measured in 30 directions plus 1 b zero volume (1.72*1.72*2.5-mm voxels, TE = 90 ms, TR = 9s, b value = 1000 s/mm2). 2 DTI data sets were acquired in each individual and averaged in reconstruction step.

B. Cortical Regions Definition

To follow our hypothesis we have made a thalamus mask using oxford-subcortical atlas available in FSL package with the dimensions of 2*2*2 mm. For our functional connectivity MRI (fcMRI) study, BOLD data were first registered to our standard atlas space which ensured correct alignment with our thalamus mask. Also, the anatomic

Amir Hossein Jaberzadeh Ansari (Corresponding Author) is with the Physics and Biomedical Engineering Department, Tehran University of Medical Sciences, Iran, E-mail: Jaberzadeh@razi.tums.ac.ir.

Mohammad Ali Oghabian is with the Physics and Biomedical Engineering Department, Tehran University of Medical Sciences, Iran, E-mail: Oghabian@sina.tums.ac.ir.

Gholam-Ali Hossein-Zadeh is with the school of ECE, College of Engineering, University of Tehran, Iran, Email: ghzadeh@ut.ac.ir

mprage 3D data was resliced to MNI space using FLIRT and then segmented for its white and grey matter and CSF using SPM8. We used these masks to find corresponding nuisance variables in next step.For our DWI study, data was normalized to MNI152 space 2mm using FLIRT.

C. Processing of Resting state fMRI data

Preprocessing included compensation for slice timing correction due to upward acquisition, rigid body correction for head motion within and across runs using SPM8, coregistration and normalization of the images across each run using FLIRT.

Linear trends across runs were removed voxelwise and the data were low-passed to retain frequencies below 0.1 Hz. Several sources of spurious variance were removed by regression of the following nuisance variables:

1) mean time course of global gray matter; 2) five representative signals from white matter by performing PCA on the masked images; and 3) five representative signals from CSF by performing PCA on the masked images. To map correlations in intrinsic brain activity between the cortex and the thalamus, the following analysis was performed. First, three representative BOLD time course was extracted from thalamus masked image. Then, cross correlation was computed between each of these time courses and whole brain time courses. For purposes of calculating statistical significance, we used False Discovery Rate(FDR) in a Matlab code with pvalue=0.01 and cluster size=100. Final maps were combined across subjects using a fixed-effects analysis using FSL.

D. Processing of DWI data

All DWI scans were upsampled to MNI standard space 2mm in order to overlay functional masks on them in the tractography step. Then, eddy current correction was applied using FDT in FSL package and the final images were analyzed using ExploreDTI software. In tractography step, the needed seeds were prepared from functional results which previously discussed. Streamline algorithms was used for tractography. Finally, the results were showed visually in order to evaluate the relationship between resting state functional and structural connectivity.

III. Results

For our functional study, three representative signals were extracted from thalamus region using PCA algorithms which finds orthogonal vectors inside the data and compared with the BOLD signal at each voxel in whole brain using correlation method. Fig 1 demonstrates corresponding region for every signal.

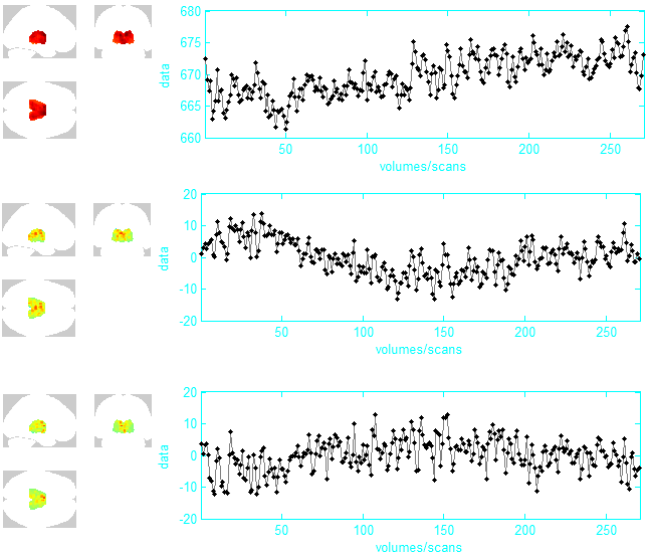

Fig 1: Three principal components extracted as the representative time courses of thalamus region, and their corresponding anatomical map(red means high connectivity and yellow means low connectivity, green is the thalamus mask)

connected regions for all three signals were evaluated and signal two was elected to show our hypothesis so, the result of signal two is shown in Fig 2.

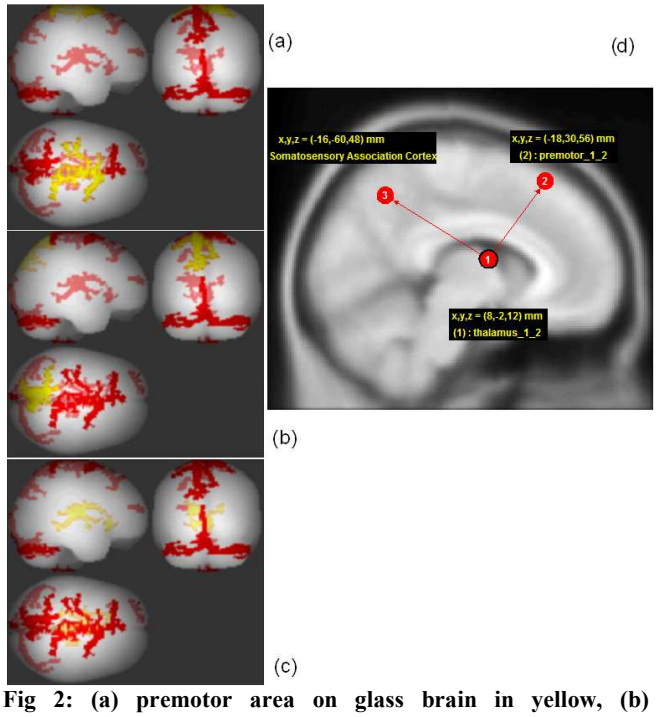

Fig 2: (a) premotor area on glass brain in yellow, (b) somatosensory area as yellow and (c) thalamus related regions, (d) sagittal view of these three regions showing the connectivity in motor and thalamus areas

There are many regions connected to thalamus but we are interested in motor areas. In Fig 2(a) premotor area is shown on glass brain with yellow color as indicator, in Fig 2(b) somatosensory area is shown as yellow and in Fig 2(c)

thalamus related regions are demonstrated. In Fig 2(d) we have shown in a sagittal view that our hypothesis was true and thalamus is functionally connected with motor areas. For demonstration purposes, REX and CONN toolboxes were applied. To validate our data we used Juelich atlas in FSL and made different functional masks. Table 1 shows the number of voxels in each functional mask.

Table 1: Number of voxels reported in each functional area

Functional Area	# of voxels
Premotor	768
Visual	205
Thalamus	251
Secondary somatosensory	230
Primary somatosensory	223
Primary motor	177
Hippocampus	33
Amygdala	4
Primary auditory	1
Sum of above	1892
Total Voxels	2926

For our DTI study, we need seed points which were transformed from fcMRI results of interconnection between thalamus and motor areas to DTI seeds. this step was done with Matlab to prepare compatible seeds and in the end tractography was done using streamline algorithm in ExploreDTI software. Fig 3 demonstrates the fiber tracts between thalamus and premotor area.

IV. Conclusion and discussion

In this study we used resting state fMRI data to demonstrate the connection between thalamus and motor area. As in the results, thalamus was correlated extensively with some functional areas in the brain like motor and visual areas which is predictable from anatomic and histological studies. By masking data with Jelich atlas and counting the voxels inside masks, it is portrayed that motor and thalamus has dominant functional connection. next hypothesis was a proof for fiber tract existence between these functional ROIs. Indeed, in the thalamocortical network, the results of fcMRI and DWI have been shown to correspond well with each other, thereby providing cross-validation of the two techniques. In addition, both techniques correspond well to histological delineation and invasive tract tracing, thereby providing a 'gold standard' validation of the two techniques [21].

it is a good theory that functional connectivity reflects the brain's structural connectivity (i.e. the anatomical connections between brain regions) but the exact relationship between structure and function is not so easy to interpretable. Several measures are used to quantify white matter integrity using DTI, the most common being fractional anisotropy (FA), mean diffusivity (MD), fiber count and probabilistic tractography. FA is a scalar measure of the degree of anisotropy (direction selectivity) and MD is a scalar measure of the total diffusivity. These two measures are calculated within a voxel. The remaining two measures, fiber count and probabilistic tractography, result from tracking the principle diffusion direction of every voxel between ROIs. Fiber count results in a total number of fibers connecting a seed region with a target region and probabilistic tractography produces a measure of the likelihood that two regions are connected. In this study we just demonstrated the tracts visually which is a qualitative method for results but regarding the quantitative methods which described above, there is open topic to work on in next papers.

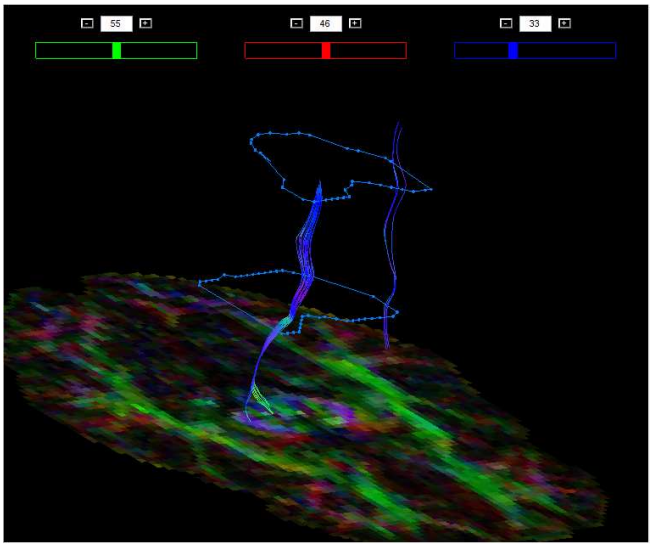

Fig 3: Final tracts showing structural connection between premotor and thalamus areas(blue means up-down direction of fibers and green means posterier-anterior)

However, one should be aware that DWI is prone to missing connections and also establishing false connections where fibers cross and where fibers diverge from 'bottleneck' regions of the brain The search for solutions to these problems is an active area of investigation[22],[23].

The degree of structural connectivity has been shown to correlate with the strength of functional connectivity,[24] thereby providing a potentially straightforward structural explanation for many of the changes in functional connectivity in disease states.

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