Combining structural and funcional connectivity techniques to characterize the thalamo-cortical networks in vivo

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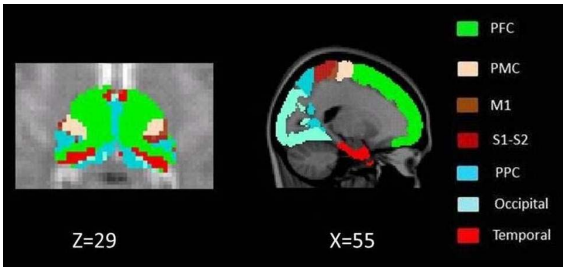
TARGET AUDIENCE: Basic scientists and clinicians with an interest in thalamo-cortical connections.

PURPOSE Thalamo-cortical networks are organized topographically into parallel pathways linking distinct cortical areas to specific thalamic nuclei well characterized for primates (1, 2). Previous studies based on diffusion tensor (DT) MRI and tractography demonstrated a reliable inference of anatomical connectivity between cortical grey matter and specific thalamic nuclei (3), effectively enabling a segmentation of the thalamus based on this connectivity pattern. The aim of the present study is to validate this approach by comparing structural (as measured by DTI) and functional (as measured by resting-state [RS] fMRI) connectivity between the thalamus and the cerebral cortex in a group of healthy participants. We used DTI tractography to define distinct thalamic regions structurally connected to different cortical areas. Seed-based RS-fMRI was then performed to identify the cortical areas more strongly connected, from a functional point of view, with each specific thalamic nucleus identified by DTI connectivity segmentation. The results were visually compared to cross-validate these 2 commonly used approaches to assess anatomical and functional connectivity.

MATERIAL AND METHODS MRI**:** We recruited 30 healthy subjects [M/F=16/15; mean (SD) age=50.51(13.33) years], who underwent an MRI examination at 3.0 T. The acquisition protocol included: 1) MDEFT (TR=1338 ms, TE=2.4 ms) 2) Diffusion weighted EPI (TR= 7 s, TE=85 ms, number of diffusion directions=61; max b factor=1000 smm^{-2}); 3) T2-weighted EPI sensitized to BOLD contrast (TR=2080 ms, TE=30 ms, 32 axial slices parallel to AC-PC line). BOLD EPIs were collected during rest for 7'and 20", resulting in a total of 220 volumes. During this acquisition, subjects were instructed to keep their eyes closed, not to think of anything in particular, and not to fall asleep. DTI analysis: A mask of the thalamus in MNI coordinates was obtained by binarizing the Oxford Thalamic Connectivity Atlas (http://www.fmrib.ox.ac.uk/connect/), while the target areas were defined on the MNI T1-weighted template provided with FSL as in ref (3), identifying 7 exclusive cortical regions: prefrontal (PFC), primary motor (M1), premotor (lateral and medial) (PMC), temporal, posterior parietal (PPC), primary and secondary somatosensory (S1/S2) and occipital cortices (See Fig 1). After the correction for eddy current distortions, DTI images were processed using the Camino toolkit (www.camino.org.uk). The diffusion tensor was estimated in every voxel, and maps of FA were obtained for each subject. The transformation matching the seed and target masks to every subject's DTI data was obtained by first co-registering the template with each participant's T1-weighted volume, and then registering the T1-weighted volume with their FA map. All registrations were performed using FLIRT (http://fsl.fmrib.ox.ac.uk/fsl/). Thalamic parcellation was obtained by running the probabilistic index of connectivity (PICo,) (4) from each voxel in the thalamic mask, and labelling each voxel based on the most likely cortical region it was connected to, as described in (3). The parcellated thalamic masks were transformed into standard space and averaged across subjects (see Fig 1). fMRI analysis: The RS-fMRI data were preprocessed in SPM8, including correction for motion and slice-timing, and normalisation. In-house software was used to remove the global temporal drift using a 3rd order polynomial fit, the realignment parameters, and the signal averaged over whole brain voxels. Data were band-pass filtered to remove high frequency variations. The mean time series from each thalamic nucleus were extracted for every subject and used as regressors in a first-level analysis in SPM8, in order to identify areas of correlation, adding the motion parameters as nuisance variables. The contrast images were fed into a 2nd level analysis using a one-sample T-Test. Results were considered significant for $p<0.05$ FWE corrected at voxel level, and masked to retain only cortical activations.

Fig.1 Group averaged thalamic parcellated mask and colour-correspondent cortical areas from MNI T1-weighted template.



RESULTS The DTI tractography segmentation (Fig1) yielded results comparable with those reported in (3). The RS fMRI data showed significant patterns of connectivity for all the thalamic nuclei considered. In some cases the functional connectivity pattern was partially overlapping with the target regions used for DTI segmentation (see Fig 2), while no correspondence was found for parietal and occipital areas.

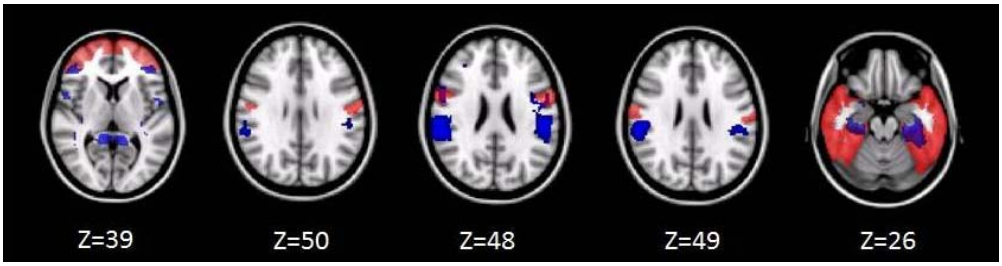


Fig. 2 Partial overlap of structural (red) and functional (blue) connectivity with specific thalamic nuclei was found in prefrontal (PFC), primary motor (M1), premotor (PMC), primary and secondary somatosensory (S1/S2) and temporal cortex.

DISCUSSION This study confirms the reproducibility of thalamic parcellation based on probabilistic tractography. Additionally, it attempts for the first time to compare structural (based on DTI) and functional (based on RS-fMRI) thalamo-cortical connectivity in the same subjects. Our results show that these two methods yield partially consistent results, within the limitations of the experimental design (e.g., different image resolution). Unsurprisingly, the largest overlap is found for the thalamic regions connected to PMC, M1 and S1/S2. These cortical areas are small, and their expected anatomical connections (sensory-motor networks) relatively simple. Some connections between specific thalamic nuclei and the sensory-motor cortex are indeed known to be monosynaptic. Future work should combine DTI segmentation with effective connectivity measurements to better identify the connectivity patterns with respect to PFC, temporal, and occipital cortex.

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