Functional-anatomical validation of diffusion tractography-based segmentation of the human thalamus

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Synopsis

Parcellation of the human thalamus based on cortical connectivity information inferred from non-invasive diffusion-weighted images (DWI) identifies sub-regions that we have proposed correspond to thalamic nuclei. Here we test the functional and anatomical validity of this proposal by comparing data from DWI tractography, cytoarchitectonic measurements and functional imaging. The relative volumes of connectivity-defined sub-regions correlate well with volumes based on a histological atlas. Previously reported centres of functional thalamic activation during motor or executive tasks co-localise within regions showing high probabilities of connection to motor or prefrontal cortices, respectively. This work provides a powerful validation of quantitative grey matter segmentation using diffusion tractography in humans.

Introduction

The ability to parcellate the human thalamus into meaningful subdivisions *in vivo* would have significant implications for the study of normal brain function and of disorders associated with thalamic pathology. Activation of the thalamus is observed in functional imaging studies involving sensory, motor and cognitive tasks, but lack of detailed anatomical information in the thalamus has limited structure-function correlations. Thalamic lesions have wide-ranging effects on sensory, executive and memory functions and thalamo-cortical circuitry is implicated in certain neurological and psychiatric disorders. Currently, boundaries between thalamic subregions can only reliably be identified post-mortem. However, each nucleus has a distinct pattern of cortical connectivity. We have previously used DWI tractography [1] to parcellate the human thalamus on the basis of its cortical connectivity [2]. This results in parcellation of the thalamus into distinct subregions that we hypothesise correspond to thalamic nuclei or nuclear groups. Here, we test the anatomical and functional validity of this correspondence.

Methods

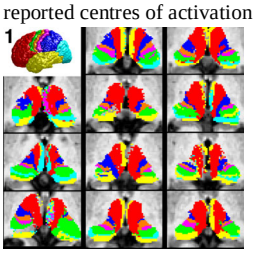
Image acquisition and analysis: Diffusion-weighted data were acquired in 11 healthy subjects with an optimised method [3]. A T1-weighted image also was acquired and used to manually define borders of the thalamus and 7 cortical zones corresponding to known thalamic connection sites. Tissue-type segmentation, skull stripping and registration were performed using FSL (www.fmrib.ox.ac.uk/fsl). From each thalamic voxel, we generated probabilistic connectivity distributions [1], and recorded the probability of connection to each cortical mask.

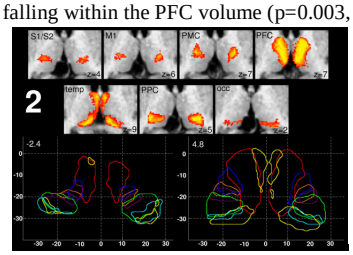
Volumetric validation: Thalamic voxels were classified according to their probability of connection to cortical areas and group probability maps of thalamic subregions were defined and used to directly calculate DWI-based volumetric measurements. In order to derive relative cytoarchitectonically-defined volumes of thalamic subregions we manually measured the cross-sectional area of major nuclei delineated in a cytoarchitectonic atlas of the human thalamus [4] and multiplied by slice thickness to calculate nuclear volumes which we combined to give total volumes for the region of the thalamus projecting to each of the seven cortical target regions.

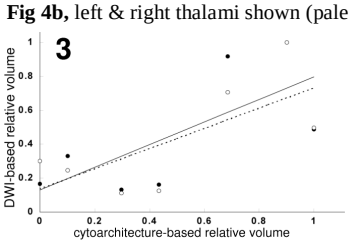
Functional validation: We compared the locations of DWI-based group probability maps to centres of thalamic activations from functional imaging studies of motor and executive tasks. The number of activation centres falling inside the connectivity-defined volume was counted and the probability of this number (or more) falling within the volume was computed using a cumulative binomial distribution.

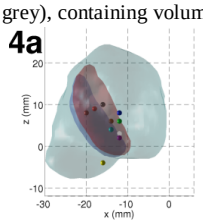
Results

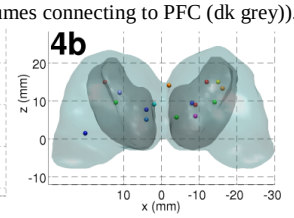
Classification of thalamic voxels based on the cortical region with which they showed the highest connection probability resulted in reproducible clusters of commonly-connected voxels whose locations correspond well to major thalamic nuclei (**Fig 1,** axial slices through thalamus for 11 subjects. voxels colour-coded according to cortical regions, top left). To characterise voxel-wise correspondence in thalamic connections across subjects quantitatively, we co-registered binarised thalamic regions showing greater than 25% probability of connection to each of the defined cortical areas (**Fig 2,** top two rows show group probability maps for connectivity to each cortical region. The edges of these were used to generate a probabilistic atlas (example slices below)). We propose that these connectivity-defined subregions correspond to thalamic nuclei or nuclear groups. In support of this, we found a strong correlation between relative volumes defined using DWI and those based on cytoarchitecture (**Fig 3**, left hemisphere (filled circles): r=0.7, p=0.04; right hemisphere (open circles): r=0.7, p=0.04). To test the functional validity of boundaries defined by our group maps, we assessed the correspondence between group maps and previously reported centres of functional activations localised to the thalamus. Previously reported activation centres for motor tasks co-localised well with thalamic regions connecting to motor and premotor cortices (**Fig 4a,** outer surface (pale grey) is whole left thalamus, surfaces within thalamus represent (overlapping) volumes where >4/11 subjects showed >25% probability of connection to M1 (dk grey) and PMC (red), spheres represent functional activations). Nine out of ten previously reported centres of motor activation fell within our M1/PMC volume ($p=8.4 \times 10^{-5}$). Similarly, activation centres for executive tasks co-localised with the thalamic region connecting to the prefrontal cortex, with fourteen out of sixteen previously reported centres of activation falling within the PFC volume (p=0.003, **Fig 4b,** left & right thalami shown (pale grey), containing volumes connecting to PFC (dk grey)).











Discussion

It has been difficult to directly validate diffusion tractography due to a lack of alternative methods providing similar data in humans, as well as the relative paucity of animal imaging data. Here we took two approaches to validation of a connectivity-based thalamic parcellation: first by comparison to cytoarchitectonic atlases and second by comparison to functional activations. We found good agreement between volumes of DWI-based thalamic sub-regions and comparable sub-regions from previous cytoarchitectonic data. Second, the locations of the individual regions correspond well with data from prior functional imaging experiments. The ability to perform probabilistic grey matter parcellation *in vivo* raises new possibilities for the study of the brain in disease. The fact that connectivity-based segmentation of the thalamus is reproducible across a group of healthy individuals demonstrates the feasibility of this approach for study of disorders with putative thalamic pathology. Connectivity between the thalamus and prefrontal cortex is hypothesised to play a role in schizophrenia, for example [5]. The relative size and location of the thalamic sub-region with a high probability of connection to prefrontal cortex could be directly compared between schizophrenic subjects and healthy controls. Lesions of the thalamus itself can cause a variety of cognitive impairments and it has been suggested that particular impairments relate to specific nuclear damage, e.g., lesions to the mediodorsal nucleus are associated with executive dysfunction whereas lesions involving the intralamina nuclei lead to impairments in attention [6]. Localising lesion sites on the group probability maps presented here would enable the generation of hypotheses concerning the likely thalamo-cortical pathways affected and enable more precise clinico-anatomical correlations to be made.

References 1. Behrens et al (2003) *Magn Reson Med* 50 1077-1088; 2. Behrens et al (2003) *Nat Neurosci* 6 750-757;3.Wheeler-Kingshott (2002) *Proc Intl Soc Mag Reson Med* 1118; 4. Schaltenbrand & Wahren, W (1977); 5. Andreasen et al (1996) *Proc Natl Acad Sci U S A* 93 9985-9990; 6. Van der Werf et al (2003) *Neuropsychologia* 41 1330-1344. **Acknowledgements**: The Wellcome Trust, EPSRC, MRC, The Multiple Sclerosis Society of Great Britain