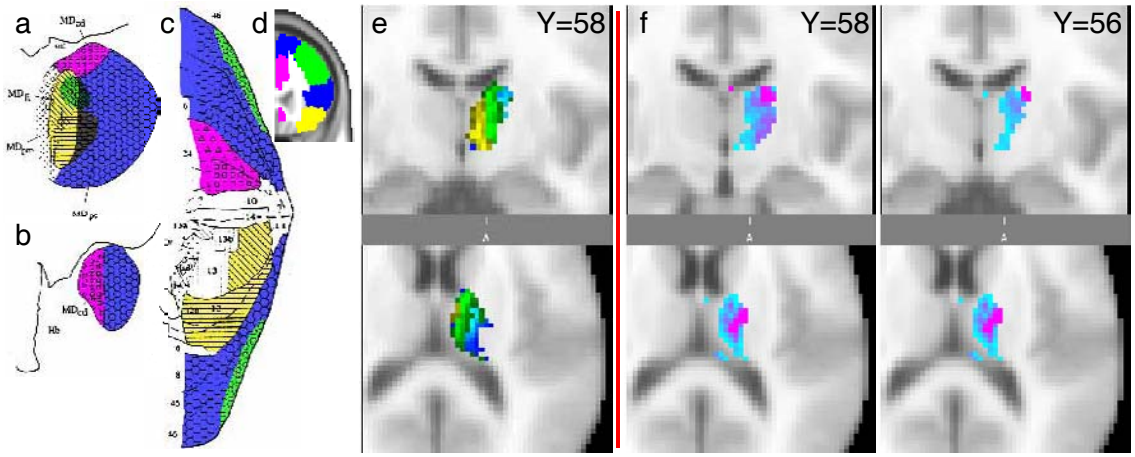
Fine-grained topography of human thalamo-prefrontal connectivity revealed by multi-fibre probabilistic tractography

J. C. Klein[1], T. E. Behrens[1], C. E. Mackay[2,3], M. D. Robson[2], M. F. Rushworth[4], and H. Johansen-Berg[1]

[1]FMRIB Centre, University of Oxford, Oxford, Oxon, United Kingdom, [2]Centre for Clinical Magnetic Resonance Research, University of Oxford, Oxford, Oxon, United Kingdom, [3]University Department of Psychiatry, University of Oxford, Oxford, Oxon, United Kingdom, [4]Department of Experimental Psychology, University of Oxford, Oxford, Oxon, United Kingdom

Introduction Parcellation of deep grey matter into functionally meaningful sub-regions has been a topic of animal research for many years(1-3). Histological studies demonstrated partition of thalamus into individual nuclei whose projections to cortex were later established using lesional and tracer injection approaches, and it emerged that there is a fine-grained topography of projections to different regions of cortex within individual thalamic nuclei. Prefrontal cortex has undergone immense expansion in the development of man when compared to other primates, with mediodorsal nucleus (MD) being its main thalamic target(4). Due to reciprocal connectivity, this change in cortical organisation between species is expected to be reflected in the layout of the thalamus. Only limited data on MD are available in studies on human brain injury and deep brain electrical stimulation, as these data are either random in nature or severely invasive. Furthermore, applicability of animal findings in MD to humans is not clear.

Recent advances in neuroimaging, such as diffusion tensor imaging and absolute mapping of relaxivity(5, 6), now allow for differentiation of thalamic nuclei in vivo using non-invasive magnetic resonance imaging. With the advent of multi-fibre diffusion tractography(7), we can now aim to subdivide thalamus at an even more fine-grained level. Here, we test suitability of multi-fibre DTI to subdivide human MD into projectional subsets, mimicking macaque retrograde tracer labelling studies by Ray and Price(3).



Methods Eight volunteers underwent DTI scanning on a 1.5T Sonata scanner (4 men, 4 women, age range 21-34 years). Diffusion was measured in 60 isotropically distributed directions using echo-planar imaging (SE-EPI, TE 97 ms, TR 10.1 s, 72 axial slices, voxel size 2 mm·2 mm·2 mm) at a b-value of 1000 s·mm-2. Measurement was repeated three times to increase SNR. In a separate set of 10 controls, prefrontal cortex was subdivided into reliable anatomical subregions on T1-weighted MRI using gross anatomical landmarks(8). These were then grouped (Fig. 1d) following injection targets defined by Ray and Price (Fig. 1a-c). Masks and diffusion data were registered to MNI152 standard space to allow for group processing, and DTI results were averaged in standard space across subjects. All data were processed using FMRIB's FSL toolbox, including prototype multi-fibre diffusion tractography methods.

Results The topography of prefrontal connections with the MD nucleus of the human thalamus was similar to the previously described topography in the non-human primate. Parvicellular part of MD (MDpv) has projections (Fig. 1e) distributed to dorsal prefrontal and ventrolateral prefrontal cortex (Brodmann's macaque areas 6, 8, 44, 45, blue hues). Orbitofrontal cortex (areas 11, 12, yellow) is represented mesially in MD's fibrous part (MDfi). The representation of Brodmann's area 46 (green) in MD is bilaterally enclosed by both these regions, and projections to dorsal/ventrolateral prefrontal cortex encircle it. Projections to cingulate cortex appear caudally and dorsally from the afore-mentioned projections (magenta, Fig. 1f) in caudodorsal MD (MDcd), its centre of mass being located more laterally.

Discussion Multi-fibre DTI reveals the internal organisation of human MD at a level unattainable with other non-invasive methods so far. This organisation is closely related to macaque findings, with connexions to MDfi and MDpv showing the same principal layout as in macaque. However, projections to area 46 have expanded in humans. This phylogenetically young area is not present in rodents and has expanded significantly in man relative to macaque, explaining its larger representation in human thalamus. As the integrative demand placed on MD rises between species, interconnection of previously separate areas in rat conflate in macaque and seem to do so even more in humans, an evolutionary trend that was previously established in other deep brain structures, such as nucleus accumbens. Projections to cingulate cortex are detected in caudodorsal MD, as expected, but more laterally than macaque findings would suggest.

In summary, multi-fibre DTI establishes MD connectivity in concordance with monkey findings. This organisation cannot be explained by simple geometric relationships between MD locations and cortical targets. Importantly, expansion of area 46 in humans is also reflected in expansion of its representation in MD. All these findings suggest that current DTI methodology is suitable for the study of sub-nuclear organisation in MD, and further studies will need to establish applicability of this approach in other nuclei of thalamus.

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