Motor and non-motor territories of the human dentate nucleus: Mapping the topographical connectivity of the cerebellar cortex with in-vivo sub-millimeter diffusion imaging

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Target Audience: cognitive neuroscientists, anatomists, motor learning/motor control, clinicians

Purpose: The reciprocal cortico-cerebellar loops that underlie cerebellar contributions to behaviour form one of the largest systems in the primate brain, yet we have virtually no knowledge about cerebellar anatomical connectivity in humans. Tract-tracing work in non-human primates has shown that not only do the dentate nuclei, the output nuclei of the cerebellum, project to non-motor regions of the cortex, but they also exhibit a topographical connectivity pattern that distinguishes between territories projecting to motor (rostro-dorsal dentate) and non-motor cortex (latero-ventral dentate) [1]. However, while we are only now beginning to understand how the cerebellum contributes to higher cognitive function, our inferences are fundamentally restricted by a lack of knowledge of anatomical connectivity. In fact, there is absolutely no knowledge of the structural connectivity between the cerebellar cortex and dentate nucleus in humans [2]. Understanding this fundamental component of the cortico-cerebellar loop will allow us to understand the relative influence of putative rostro-dorsal motor and ventro-lateral non-motor dentate nuclear territories on the rest of the brain. This, in turn, provides insight into how the cerebellum contributes to higher cognitive behaviour, and how its role may have developed through evolution. However, until now, the complex and tightly packed nature of cerebellar white-matter has made it extremely difficult to accurately represent cerebellar connectivity in humans at conventional diffusion imaging resolutions (3T, 1.7-3.0 mm isometric voxels). To address this, we acquired sub-mm resolution diffusion images in live subjects on a 7T MRI scanner and employed a fibre tracking technique that is able to resolve complex fibre arrangements.

Method: We collected four 0.8 mm isotropic acquisitions for each subject, concatenated them, and performed highly specific probabilistic tractography with constrained spherical deconvolution [3]. We segmented the grey matter of the dominant motor (HIV, V, VI) and non-motor (Crus I, II) lobules and modulated the number of streamlines from each lobule by the proportion of the cortical volume taken up by that lobule. We then performed tract-based classification of the dentate nucleus in 0.2 mm isotropic streamline space to both identify the topographical organisation of lobular connectivity and quantify the projections of motor and non-motor lobules to the surface.

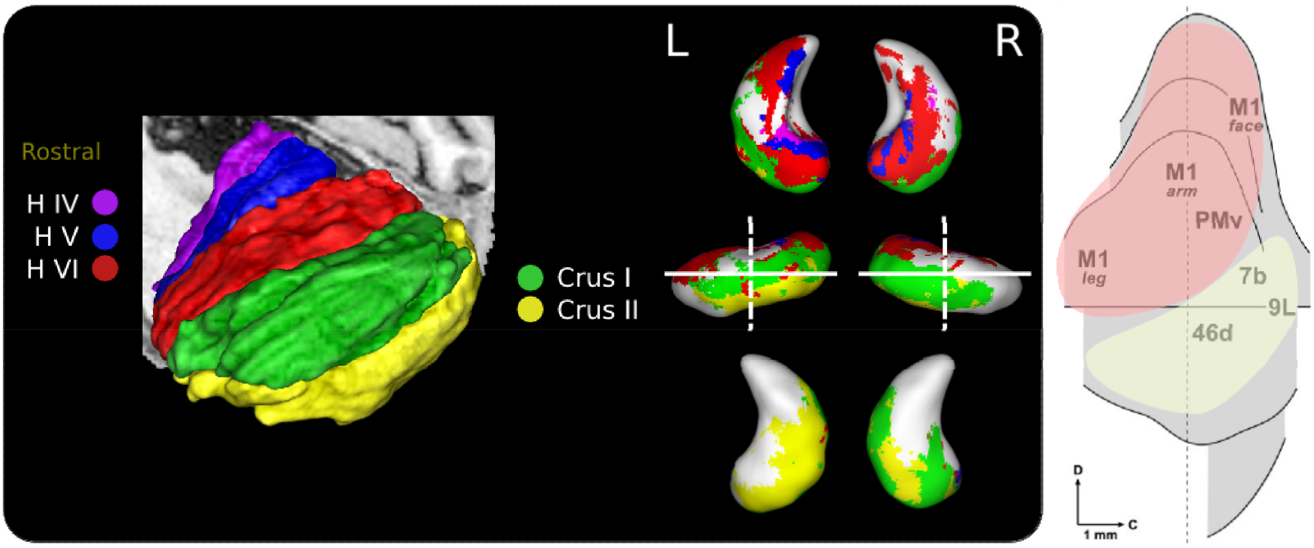

Figure 1. Relative dominance of non-motor connectivity (Crus I, II) in the human dentate nucleus. Left: colour-coded cortical segmentation and classified images of the dentate nucleus of the left (L) and right (R) hemispheres. Dividing lines correspond to the surface separation along the dorsal-ventral (solid) and rostral-caudal dimensions (dotted), as in the image on the right. Right: unfolded map of the projections of the dentate nucleus in non-human primates. Red depicts the approximate rostro-dorsal motor and green the latero-ventral zones of the dentate nucleus (Strick et al., 2009).

Results: Tractography revealed overlapping but distinct projections among lobules HIV, V, and VI (motor lobules) and topographic separation from Crus I and II (non-motor lobules). The motor lobules projected primarily to the rostro-dorsal surface of the dentate nucleus, while the non-motor lobules dominated the projections to the lateral and ventral surfaces. Tract-based classification of the dentate nucleus revealed the first structural evidence that the human dentate nucleus contains a rostro-dorsal motor and latero-ventral non-motor connectivity topography similar to that proposed by animal work (Figure 1). Crucially, we also found that non-motor lobules formed the primary projections to significantly more of the dentate nucleus than lobules H IV, V, and VI (non-motor – 34.2% +/- 4.9% of total surface; motor – 20.3% +/- 3.7%; $p<.001$).

Discussion and Conclusion: Our findings provide first structural evidence that the human dentate nucleus exhibits a topographical pattern of connectivity broadly similar to that of non-human primates. However, beyond these similarities, we also present initial evidence that the relative proportion of non-motor to motor connectivity of the cerebellum has increased relative to our primate cousins – reflecting a more prominent role for the cerebellum in human higher cognitive function.

References:

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