Distinct Components of the Cingulum Bundle Revealed by Diffusion MRI

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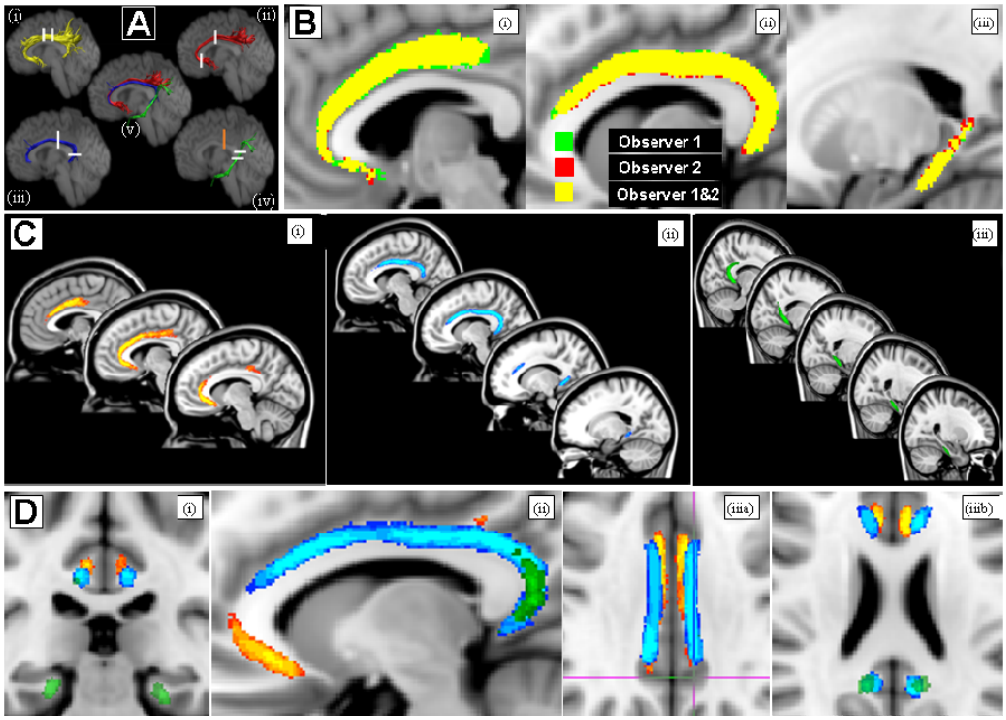
INTRODUCTION: The cingulum bundle is a prominent white matter tract extending longitudinally above the callosum. Its descriptions have a long history[1-3], and it has been appreciated for over a century that it contains many short association fibres, as well as longer fibres that potentially link the frontal and temporal lobes. The fibres include connections with sites such as the anterior and dorsal thalamic nuclei and dorsolateral prefrontal cortex, while others are assumed to connect to structures in the temporal lobe, including the parahippocampal and subicular cortices, and amygdala. Thus, the cingulum bundle is a complex tract comprised of many different connections with trajectories of different lengths[3]. However, this complex composition is rarely reflected in published diffusion tractography images, which most often show a continuous band of white matter that seemingly links (uninterrupted) the caudal medial temporal lobe with retrosplenial, cingulate, prefrontal, and subgenual areas. We suggest that this discrepancy arises from the common practice of placing regions of interest (ROIs) dorsal to the body of the corpus callosum and identifying all white matter linking them. Our concern is that that the cingulum bundle may comprise several distinct subregions that only appear united due to the numerous short association fibres within the tract and the resulting overlap in their trajectories. This work examined the unity of the cingulum bundle using tractography by comparing results from ROIs at different points along the tract and reveals a set of overlapping, but largely separate, connections within what is often visualised as a unified bundle.

METHODS: Diffusion weighted data (cardiac-gated, b = 1200 s mm^{-2}, 60 directions, 6 b=0s; 2.4 mm isotropic resolution) were collected from 20 healthy individuals (dextral males, age range 25-40 years). After motion/ distortion correction, fibre orientational density functions (fODFs) were derived in each voxel using constrained spherical harmonic decovolution[4]. Streamline tracking – following peaks in the fODF- was performed from all voxels in the brain. First the 'standard' approach of placing two 'AND' ROIs above the body of the corpus callosum, one caudal and rostral to its midpoint (Figure A(i) below) was used. The reconstructed tract covered much of the entire extent of the cingulum bundle. Three other reconstructions were then visualised: 1) the **'subgenual cingulum' (SGC)**– 2 'AND' ROIs were placed in the subgenual cingulum and above the rostral part of the body of the corpus callosum; 2) the **'retrosplenial cingulum' (RSC)** – 2 'AND' ROIs were placed at the most inferior level of the splenium and above the more caudal part of the body of the corpus callosum; 3) the **'parahippocampal cingulum' (PHC)**- 2 'AND' ROIs were placed at the most inferior level of the splenium and within the temporal lobe. These three subregions were selected as tract tracing studies suggest that each subregion might contain a preponderance of fibres that arise from different sources[5].For each subject, the tracking result was binarized – so that if a voxel is intersected by a streamline, it is assigned a value of one, (zero otherwise). Each subject's FA map was then nonlinearly normalized to the FMRIB58 MNI FA template using FNIRT (*www.fmrib.ox.ac.uk/fsl)* and the transformations applied to the tracking results. The 20 tract maps for a given segment were then summed to give an overlap-map – which was thresholded at 70% (i.e., $\geq$ 14 of the 20 subjects have a streamline passing through a voxel). The analysis was repeated by 2 independent observers to derive inter-observer reliability. Finally, the mean FA and radial diffusivity (RD) in each of the three tracts were compared with one another using paired t-tests.

RESULT: Panel A shows the ROI's used to dissect the three parts of the cingulum (single subject). (i) shows the 'standard' 2 ROI approach that results in an apparently continuous cingulum. (ii), (iii) and (iv) show the SGC, RSC and PHC respectively, while (v) shows the bundles together. **B** shows the inter-observer consistency in tract reconstructions for (i) SGC; (ii) RSC; & (iii) PHC, showing a high overlap; **C** shows the thresholded overlap maps (in MNI space) for 20 subjects, for (i) SGC; (ii) RSC; and (iii) PHC; Note the lack of restrosplenial voxels in (i) and subgenual voxels in (ii). **D** shows superimposed overlap maps from the 3 bundles in (i) coronal; (ii) sagittal; and (iii) axial planes & clearly shows the separate bundle locations with the SGC and PHC being most medial and lateral respectively. Importantly, the SGC had significantly different FA & RD from the RSC - in both hemispheres ($p<.05$), and the RSC and PHC had significantly different FA and RD again in both hemispheres. However, SGC and PHC did not differ. There were no hemispheric differences in FA/RD for any subregion. High intraclass correlations were found for all metrics (df = 19 $p<0.01$) ranging from .789 (left SGC) to .920 (right SGC).



DISCUSSION: Our results strongly suggest that the 'standard' tractography cingulum reconstruction is misleading. Rather, we found that the three cingulum subregions largely occupy different space and this was true even when the subregions overlapped, i.e., the tract is topographically arranged so the fibres from these subregions are partially segregated (Panel D). Further evidence for distinct bundles comes from the finding that the SGC and PHC have FA / RD measures that differ from the RSC. There are clear implications for the growing number of studies that quantify the status of the cingulum bundle, (with diffusion MRI) in health and disease. If the cingulum is not a unitary tract and contains distinct fibre populations at different levels, the study results may differ appreciably depending on where/how the tract is reconstructed. Any reconstruction that aims to encompass as much of the tract as possible, i.e., like the 'standard' cingulum (Panel A(i)), is potentially insensitive to change if a disease process preferentially targets one particular subregion. Conversely, any reconstruction targeted at just one of the subregions identified here runs the risk of not selecting the most sensitive part of the cingulum. The present findings reinforce the value of isolating specific parts of the cingulum, and highlight the benefit of comparing findings with those from other parts of the cingulum in order to determine the specificity of any observed neurological correlations. By subdividing the tract in this way, it should prove easier to link any disease-related changes in the cingulum to the disruption of particular connections.

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