ExTracT: extracting tract terminations using diffusion imaging

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Target Audience: Researchers who wish to investigate the terminations of white matter tracts, researchers who wish to use tract termination maps as a basis to carry out further functional connectivity studies and researchers with an interest in tractography methods.

Purpose: Since the development of probabilistic tractography in the early 2000s[1], the method has been used as a pseudo-dissection technique to delineate major white matter tracts *in vivo*. We propose a novel technique to investigate the end points of major white matter fibre tracts on the cortex. Fibre terminations are problematic for two reasons: Firstly, in order to investigate a fibre termination, an investigator must know where the main fibre bundle is. Due to variations in individuals' neuroanatomy, the task of identifying a fibre bundle *a priori* is not a simple one. Although white matter atlases are available, these do not necessarily reflect the anatomy of your group of subjects (particularly if the individuals have some form of pathology). Secondly, errors in fibre estimation tend to accumulate as the tracking process moves away from the seed region, making the end point of the estimated tract the least reliable part of the estimation. We propose a technique that helps to address these two research challenges.

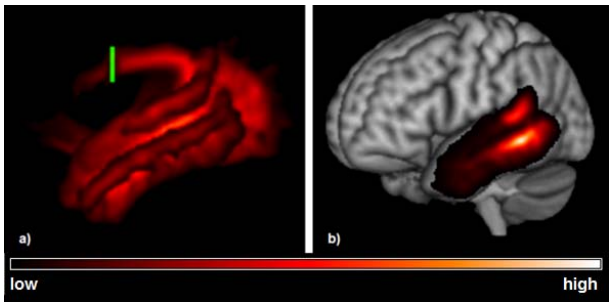

Figure 1: a) Average tractogram with ROI drawn around the Arcuate Fasciculus. b) unthresholded termination map in the temporal lobe.

Methods: *Imaging:* High resolution T1 structural scans followed by diffusion images were obtained for 24 participants (11F, mean age 25.9 years, range 19 – 47 years) on a 3 T Philips Achieva scanner (Philips Healthcare, Best, The Netherlands) using an 8 element SENSE head coil. T1: 3D turbo field echo inversion recovery, TR ≈ 2000 ms, TE = 3.9 ms, TI = 1150 ms, flip angle 8°, 256×205 image matrix reconstructed to 256×256, reconstructed in-plane voxel resolution 0.938 mm × 0.938 mm, slice thickness 0.9 mm, 160 slices, SENSE factor = 2.5. Diffusion: PGSE EPI, TE = 59 ms, TR ≈ 11884ms, G_{max} = 62 mT/m, half scan factor = 0.679, 112×112 image matrix reconstructed to 128×128, reconstructed in-plane voxel resolution 1.875×1.875 mm^2, slice thickness 2.1 mm, 60 contiguous slices, 61 non-collinear diffusion sensitization directions at b = 1200 s/mm^2 (Δ = 29.8 ms, δ = 13.1 ms), 1 at b = 0, SENSE acceleration factor = 2.5, corrected for susceptibility-related image distortions[2]. *ExTracT:* A large area of cortex (e.g., in this example, the entire temporal lobe) was chosen in each individual's native space. Probabilistic tractography was run from all voxels in the interface between the grey and white matter, in native space using the Probability Index of Connectivity (PICo) algorithm[1] (bootstrap spherical deconvolution-derived PDFs, unconstrained tracking, Monte Carlo streamlines: 10,000, step size: 0.5mm, curvature threshold: 180°). The output was non-linearly transformed into MNI space using FMRIB's FSL (www.fmrib.ox.ac.uk/fsl) FNIRT[3]. The average output of the tracking was computed and the tractogram (see Figure 1(a)) was used as a 'localiser map' to identify the main fibre bundles. Regions of interest were drawn in each tract at the point where they were clearly visible and separated. An in-house algorithm was used to assess which of the original seeds from the grey-white interface contributed to the streamlines in the ROI. Two sets of maps were generated: unthresholded mean termination maps and statistically thresholded maps. For the mean maps, raw individual maps were smoothed (5mm FWHM) and averaged across participants (see Figure 1(b)). The thresholded maps were created in three steps: 1) each raw map was binarised keeping the voxels that were in the top 5% voxel intensity, with the binarised maps then averaged across participants; 2) significance testing was carried out on unbinarised maps (voxels below the mean were removed to remove noise) in order to determine which voxels were significantly more likely to have tract A terminate there than tract B (e.g. which voxels were more likely to have the arcuate fasciculus terminate there over the uncinate fasciculus) using FSL randomise[4] ($p < 0.05$ TFCE corrected within the temporal lobe volume, Bonferroni corrected for the multiple tests); 3) the significant voxels from (2) were used to mask the corresponding binarised average maps from (1) (e.g. voxels that were significantly more likely to be arcuate terminations over uncinate terminations were used to mask the arcuate fasciculus binarised average map). Finally, the results were group averaged across each tract termination. For example, Figure 2(a) shows consistent areas were the anterior commissure termination frequency is greater than any other tract across all individuals.

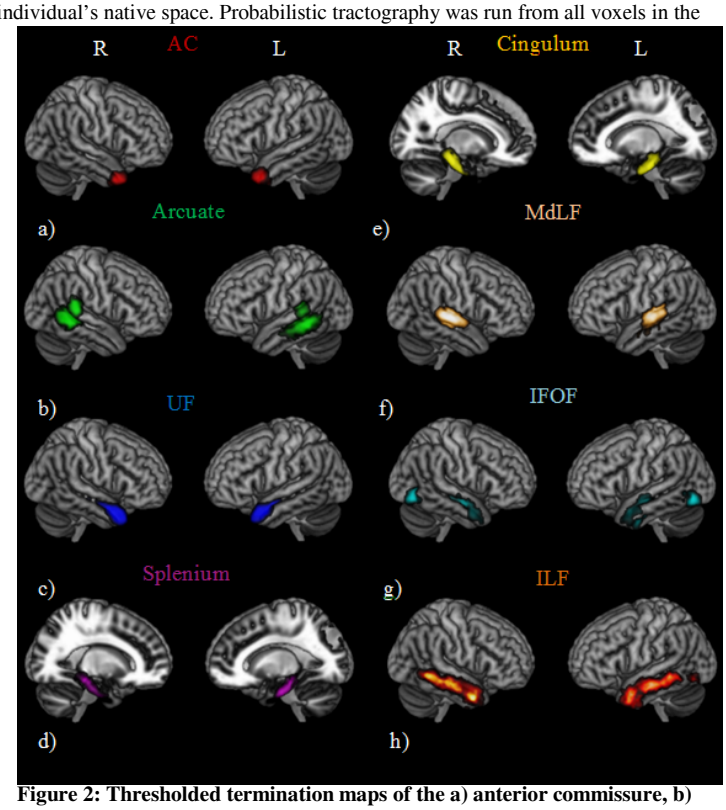

Figure 2: Thresholded termination maps of the a) anterior commissure, b) arcuate fasciculus, c) uncinate fasciculus, d) splenium of the corpus callosum, e) cingulum, f) middle longitudinal fasciculus, g) inferior fronto-occipital fasciculus, h) inferior longitudinal fasciculus

Results: We present here an example of ExTracT being applied to the temporal lobe to identify the terminations of eight major white matter tracts. Figure 2 shows the thresholded ($p < 0.05$) summary maps for each tract, overlaid on a 3D-rendered T1-weighted brain (see figure legend for further details).

Discussion: While ExTracT requires minimal prior anatomical knowledge from the researcher, it produces results that are plausible and largely consistent with our current knowledge of tract terminations gained by gross dissection methods. The maps provide a multi-subject atlas of tract terminations. These can be used alongside current cortical parcellation atlases to allow researchers, who do not have the time or experience with tractography, to relate their findings to the potential structural underpinnings and to improve models of functional/effective connectivity.

Conclusion: This technique may have implications both for gathering basic knowledge about the structure of the brain and could also aid researchers in interpreting functional imaging data. While we have presented results for the temporal terminations of major white matter tracts here, we plan to use this technique to map tract terminations across the whole brain. Future work could also include using ExTracT to compare tract termination profiles of neurotypical individuals to ones with neuro- and psychopathologies.

References: [1] Parker G. J. M. *et al, J Magn Reson Imaging* **18**, 242-254, 2003. [2] Embleton, K. V. *et al*, *Human brain mapping* **31**, 1570-1587, 2010. [3] Andersson, J. L. *et al*, FMRIB technical report TR07JA2. 2010. [4] Nichols, T. E. & Holmes, A. P., *Human Brain Mapping* **15**, 1-25, 2002.

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