Comparison of neighborhood tractography methods for segmenting white matter tracts in the ageing brain

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Introduction: There is increasing evidence that the brain's white matter is deleteriously affected by normal ageing. By allowing segmentation of tracts-of-interest from diffusion MRI (dMRI) data, tractography provides a promising tool for assessing changes in white matter connectivity in old age. However, the output from tractography algorithms is usually strongly dependent on the potentially subjective location of user-specified 'seed points', with the result that it can be both difficult and time consuming to identify reliably the same tract from subject to subject. We have shown, however, that it is possible to segment the same fasciculus in groups of subjects using single seed point tractography, if the seed point is carefully chosen. In this generic method, which we term neighborhood tractography (NT), seed points are automatically placed in a neighborhood surrounding a seed point transferred from standard space, with the tract that best matches a predefined reference tract in terms of both length and shape chosen from this group of 'candidate' tracts [1]. In addition to this original 'heuristic' NT approach, we have recently developed two new methods for creating formal probabilistic tract-matching models to determine general length and shape similarity characteristics between groups of candidate tracts using supervised and unsupervised learning techniques [2,3]. These methods differ in that the former requires tract-training data, i.e. a small number of hand picked training tracts, to generate matching and non-matching tract models while the latter determines these models iteratively using the whole dataset. These probabilistic NT methods have the advantage that they provide a measure of the absolute goodness-of-fit, the log-ratio *R*, of the best match tract to the reference in each subject [4]. Here we investigate which of these three NT methods performs best in segmenting tracts in the brains of a cohort of elderly subjects.

Methods: Sixty non-demented volunteers aged over 65 years without history of stroke were recruited from the community. Using a GE Signa 1.5T MRI scanner, these subjects underwent a whole brain dMRI exam (acquisition voxel dimension $2.5 \times 2.5 \times 2.5$ mm), based on single-shot spin-echo EPI, which consisted of 7 T_2- and 64 diffusion-weighted (b = 1000 s/mm^2) volumes. To provide reference tracts and training data (supervised NT only), 11 young healthy volunteers of mean age 33.6 (6.8) years were also recruited and imaged using the same protocol. The dMRI data were then preprocessed to remove skull data and eddy current distortions using FSL tools (FMRIB, Oxford, UK), and maps of mean diffusivity (MD) and fractional anisotropy (FA) generated. The BEDPOST/ProbTrack algorithm was used to generate the connectivity data.

For this study, the fasciculi-of-interest were the genu and splenium of corpus callosum, and left and right cingulum cingulate gyri (CCG). A reference tract and training data (supervised NT only) were generated for each fasciculus from the 11 young volunteers (one reference and ten training subjects), and the tract-matching model parameters fitted to these datasets [2-4]. All three NT algorithms were run over a neighborhood of $7 \times 7 \times 7$ voxel for each fasciculus in the 60 ageing subjects, and tract-averaged values of MD and FA determined for the 'best match' tract.

To assess the performance of the three NT methods, their best match tracts and those segmented by transferring single seed points directly from standard to native space using affine registration, the 'registration method', were visually inspected to establish whether or not they were anatomically plausible representations of the tracts-of-interest. Specifically, tracts were deemed not to be acceptable if they were heavily truncated or deviated from their known anatomical orientation [4].

Finally, to explore whether white matter structure is affected by normal ageing, tract-averaged values of MD and FA measured using the four tractography methods for each fasciculus were correlated with age (Pearson's *r*). We also used the log-ratio parameter *R* derived from the tract shape models provided by supervised and unsupervised NT to investigate whether topological change is associated with ageing (Spearman's ρ).

Results: The mean (SD) age of the 60 subjects was 75.4 (4.8) years. For all four fasciculi, the three NT methods provided significantly more anatomically plausible representations of the tracts than did the registration method (Table 1 and Fig. 1). Unsupervised NT provided the largest number of anatomically acceptable tracts (~ 90 %) closely followed by supervised NT (~ 85 %). In genu, heuristic NT performed well, but in the other three fasciculi it provided the smallest number of acceptable tracts of the three NT methods (~ 65 %).

%	Genu	Splenium	Left CCG	Right CCG
Registration method	66.7	41.7	18.3	16.7
Heuristic NT	91.7	50.0	68.3	55.0
Supervised NT	83.3	91.7	85.0	71.7
Unsupervised NT	91.7	93.3	85.0	81.7

Table 1: Percentage of subjects in whom tracts were anatomically acceptable.

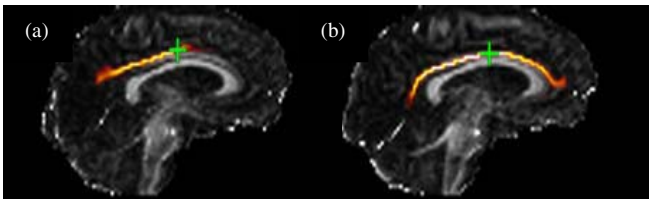

Fig. 1: 2D sagittal projections of the left CCG in a 73 year old male subject obtained using the registration (a) and unsupervised NT (b) methods. Note how the tract is truncated in (a), but is more completely reconstructed in (b).

Significant correlations and trends between FA and age were measured in genu with heuristic NT (r = -0.30, p = 0.02), and unsupervised NT (r = -0.25, p = 0.05). MD significantly correlated with age in splenium (r = 0.30, p = 0.02) with unsupervised NT. No significant correlations were seen between tract-averaged diffusion parameters and age using the registration method.

Significant correlations and trends between *R* and age were seen in genu with supervised (ρ = -0.29, p = 0.03) and unsupervised NT (ρ = -0.25, p = 0.05), and right CCG with supervised (ρ = -0.26, p = 0.04) and unsupervised NT (ρ = -0.30, p = 0.02). (Heuristic NT does not provide *R*).

Discussion: These data show that of the four automatic single seed point tractography methods investigated, unsupervised NT was able to segment the highest proportion of anatomically acceptable tracts in this ageing cohort, followed by supervised and then heuristic NT.

The increasing improvement in tract segmentation provided by these NT methods is also reflected in the number of significant correlations seen between diffusion parameters and age. Thus, while no significant correlations were seen between MD or FA with age using the registration method, correlations were found between MD and age in splenium using unsupervised NT, and FA and age in genu using both heuristic and unsupervised NT; in each case where more than 90 % of best match tracts were considered anatomically acceptable.

For genu, in addition to the negative correlation between FA and age, there was also a significant negative correlation between probabilistic model-based measures of tract shape similarity to a young brain reference tract (*R*) and age. This result showing topological change as well as loss of integrity with age is consistent with previous dMRI studies which indicate that frontal areas may be most affected by normal ageing [5].

In conclusion, these data show that it is possible automatically to segment comparable tracts in the brains of older subjects using NT-based single seed point tractography. The ability to measure tract-specific diffusion parameters accurately and automatically in older subjects will facilitate further studies that aim to investigate the biological bases of cognitive ageing.

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