

Robust segmentation of white matter tracts in the aging brain

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Introduction: Understanding how normal aging affects brain function and structure is one of the most important challenges facing medical science. By allowing segmentation of tracts of interest from diffusion MRI (dMRI) data, tractography provides a potentially promising tool for assessing 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. This problem can be addressed using the multiple region-of-interest (ROI) approach where the tractography algorithm is initiated from a seed ROI within the fasciculus-of-interest and constrained by one or more ‘waypoint’ ROIs through which the resulting streamlines must pass. While this method can generate reproducible tracts [1], it does require the user to define waypoint ROIs, a condition that imposes a strong *a priori* restriction on the tractography output. It also implicitly assumes that single seed points are insufficient to segment tracts reproducibly.

We have shown, however, that it is possible to segment the same fasciculus in groups of subjects from single seed point tractography output, if that 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 [2]. Recently, we have developed a formal probabilistic tract-matching model to determine general length and shape similarity characteristics between groups of candidate tracts using separate training data [3]. While this new probabilistic NT approach has been shown to reliably segment different tracts in young healthy brains, to be clinically useful, its performance needs to be evaluated in a wide range of different populations, a process we begin here in the brains of aging subjects.

Methods: Thirty non-demented volunteers aged over 65 years without history of stroke were recruited from the community. Using a 1.5T GE Signa MRI scanner, these subjects underwent a whole brain dMRI examination (acquisition voxel dimension $2.5 \times 2.5 \times 2.5$ mm), based on single-shot spin-echo echo-planar imaging, which consisted of 7 T_2 -weighted and 64 diffusion-weighted ($b = 1000$ s/mm²) volumes. To provide reference and training data for the tract-matching model, 11 young healthy volunteers of mean age 33.6 (6.8) years were also recruited and imaged with 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 underlying connectivity data.

For this study, the fasciculi-of-interest were the genu of the corpus callosum, and the left and right cingulum bundles (MNI seed points [0, 27, 1], [-5, -2, 37] and [7, -3, 37]). A reference tract and training data 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 using maximum likelihood [3]. Once the model had been trained, the probabilistic NT algorithm was run over a neighborhood of $7 \times 7 \times 7$ voxel for the 30 aging subjects.

To assess the performance of probabilistic NT, its ‘best match’ tracts and those segmented by transferring single seed points directly from standard to native space, 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. Finally, tract-averaged values of MD and FA were determined for each fasciculus in every subject and the coefficients of variation (CV) determined for the cohort for the registration and probabilistic NT methods.

Results: The mean (SD) age of the 30 subjects was 74.8 (3.8) years. In the vast majority of cases for the three fasciculi studied, probabilistic NT provided more anatomically plausible representations of tracts than did the registration method (*cf.* Table 1 and Figure 1). This improvement is translated into a significant reduction, in some cases by half, in the CV of tract-averaged MD and FA over this aging population (*cf.* Table 2). This results from a significant reduction in the SD of the MD and FA measurements with probabilistic NT, coupled with a decrease in MD and an increase in FA as the tract profile more faithfully follows the underlying white matter fasciculi.

% Acceptable	Genu		Left cingulum bundle		Right cingulum bundle	
	Number	%	Number	%	Number	%
Registration method acceptable	19	63.3	9	30.0	5	16.7
Probabilistic NT acceptable	27	90.0	24	80.0	20	66.6
Either acceptable	28	93.3	27	90.0	20	66.6
Neither acceptable	3	6.7	3	10.0	10	33.3

Table 1: Tracts generated by the registration and probabilistic NT methods which were considered acceptable.

Metric	Method	Genu		Left cingulum bundle		Right cingulum bundle	
		Mean (SD)	CV (%)	Mean (SD)	CV (%)	Mean (SD)	CV (%)
MD ($\times 10^{-6}$ mm ² /s)	Registration	1055 (136)	12.9	1006 (225)	22.4	930 (217)	23.4
	Probabilistic NT	1002 (87)	8.7	859 (67)	7.8	821 (50)	6.0
FA	Registration	0.32 (0.03)	10.9	0.26 (0.07)	26.9	0.28 (0.08)	27.9
	Probabilistic NT	0.33 (0.03)	9.5	0.31 (0.04)	12.0	0.31 (0.04)	13.3

Table 2: Mean (SD) and CV for MD and FA for each fasciculus using registration and probabilistic NT methods.

Discussion: The probabilistic NT data show that it is possible automatically to segment comparable tracts in the brains of older subjects with atrophy and white matter lesions using single seed point tractography. Furthermore, even given the wide age range of our elderly cohort (67 to 81 years), the above CVs approach those reported by Heiervang *et al.* [1] for their multiple ROI method in eight healthy adults aged 21–34 years (genu: MD 4.9%, FA 6.9%; left cingulum: MD 3.1%, FA 8.3%; right cingulum: MD 2.8%, FA 9.3%). However, NT has the advantage that no complicated target, termination or exclusion masks are required, thereby removing observer constraints from the tractography process. The ability to measure tract-specific diffusion parameters accurately in older subjects will facilitate further studies that aim to investigate the biological bases of cognitive aging.

References:

1. Heiervang E, et al. *Neuroimage* 2006;**33**:867-877. 2. Clayden J, et al. *Neuroimage* 2006;**33**:482-492. 3. Clayden J, et al. *IEEE TMI* 2007;**26**:1555-1561.

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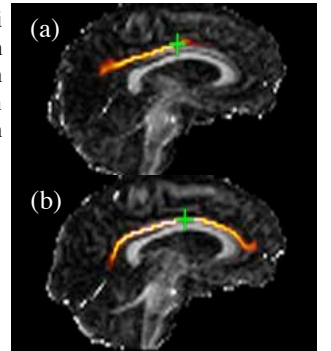


Figure 1: 2D sagittal projections of the left cingulum bundle in a 73 year old male subject obtained using the registration (a) and probabilistic NT (b) methods. Note how the tract is truncated in (a), but is more completely reconstructed in (b).