Iterative Co-linearity Filtering and Parameterization of Fiber Tracts in the Entire Cingulum

Marius de Groot¹, Meike W. Vernooij^{2,3}, Stefan Klein¹, Alexander Leemans^{4,5},
Renske de Boer^{1,2}, Aad van der Lugt³, Monique M.B. Breteler²,
and Wiro J. Niessen^{1,6}

¹ Biomedical Imaging Group Rotterdam, Departments of Radiology and
Medical Informatics, Erasmus MC, Rotterdam, the Netherlands
marius.degroot@erasmusmc.nl

² Department of Epidemiology, Erasmus MC, Rotterdam, the Netherlands

³ Department of Radiology, Erasmus MC, Rotterdam, the Netherlands

⁴ Image Sciences Institute, University Medical Center Utrecht, the Netherlands

⁵ CUBRIC, School of Psychology, Cardiff University, United Kingdom

⁶ Imaging Science and Technology, Faculty of Applied Sciences,
Delft University of Technology, the Netherlands

Abstract. We present a method for the fully automated extraction of the cingulum using diffusion tensor imaging (DTI) data. We perform whole-brain tractography and initialize tract selection in the cingulum with a registered DTI atlas. Tracts are parameterized from which tract co-linearity is derived. The tract set, filtered on the basis of co-linearity with the cingulum shape, yields an improved segmentation of the cingulum and is subsequently optimized in an iterative fashion to further improve the tract selection. We evaluate the method using a large DTI database of 500 subjects from the general population and show robust extraction of tracts in the entire cingulate bundle in both hemispheres. We demonstrate the use of the extracted fiber-tracts to compare left and right cingulate bundles. Our asymmetry analysis shows a higher fractional anisotropy in the left anterior part of the cingulum compared to the right side, and the opposite effect in the posterior part.

1 Introduction

The use of diffusion tensor magnetic resonance imaging (DTI) for analyzing brain microstructure is well established [1]. The diffusion tensor, estimated from multiple diffusion weighted image volumes, captures the local organization of the brain. The fractional anisotropy (FA), derived from this tensor, describes the microstructural tissue organization in terms of the degree of diffusion directionality [2]. Comparing differences between neuroanatomical structures across subjects requires one to establish correspondence between these subjects. This may involve a common white matter skeleton [3], or the identification of separating manifolds between white matter structures [4] for the projection of individual measures onto a reference frame. Compared to FA extraction, streamline tractography in the tensor field provides a richer description of the local white matter structure. Tractography based comparison between subjects will therefore be more sensitive to subtle differences, provided, of course, that the abundance of data in the tracts can be interpreted.

In this paper, we develop a method to automatically analyze the cingulum in a large cohort using streamline tractography.

The Cingulum. The cingulum is a tube-like structure that courses from the hippocampal formation and bends around the ventricles and the corpus callosum (cc) up to the genu of the cc. The anterior cingulate is thought to be primarily involved in executive functioning, whereas the posterior cingulate is assumed to play a role in memory processes. Its role in cognitive functioning has generated a large interest in the analysis of various aspects of the cingulum. Due to high curvature in its local anatomy, the cingulum is difficult to reconstruct with streamline tractography past the bending point around the splenium of the cc [5]. This may explain why most previous research focused on tracking only the anterior part of the cingulum. Research aiming to study the cingulum with the use of tractography in multiple subjects, has often relied on manual ROI definition to allow tract selection (e.g. [6-8]). O'Donnell et al. use a spectral embedding function to identify tracts similar to a template tract [9]. Their 'tract based morphometry' can robustly capture tracts in the anterior cingulate bundle, but has not been able to identify tracts when every tract only overlaps partly with the anatomical structure of interest. Depending on DTI data quality, the high curvature in the cingulum may pose a particular challenge for tractography. We propose an automated method that does not rely on individual tracts coinciding with the entire cingulum, but rather on extracting the parts of all tracts that describe at least some part of the cingulum. The complete filtered set of all (partial) tracts then has more power to capture the actual cingulum anatomy, in particular the posterior part.

2 Methods

In short, after performing whole-brain tractography, we propose to identify partial tracts that make up the cingulate bundle with the use of a registered anatomical atlas. We derive a parameterization, which allows for a more accurate selection of tracts that belong to the cingulum and facilitates inter-subject comparison. The iterative approach, outlined in Fig. 1, consists of the following steps: tract selection, derivation of the parameterization, projection of tracts and co-linearity filtering. In the methods description, all parameters that need to be set are printed in *italic*.

Tractography and Atlas Registration. Deterministic streamline tractography is performed using the 'ExploreDTI' package (www.exploredti.com) [10]. Tracts are described by cubic B-splines, and stored as equally spaced points. We adopted the neuroanatomical ICBM-DTI-81 atlas of Mori et al. [11] for the initial tract selection. This atlas is created by manual segmentation of 50 neuroanatomical structures. We nonrigidly registered the atlas' FA image towards all subjects' FA image using 'elastix', a publicly available software package that uses an efficient stochastic gradient descent optimization method [12]. The registration is used to transform the atlas' labels to each subject's native space, resulting in an initial three-dimensional segmentation of the cingulate bundle. In following iterations, an improved segmentation is used, which is derived after filtering for co-linearity.

Tract Selection. The cingulate template is used to identify tracts running inside the cingulum. Owing to the absence of nearby co-linear structures, we assume that fiber tracts which are partially within the cingulum before they divert due to, e.g., partial voluming effects, can be included in the analysis [9]. Tracts are cut off when leaving the segmented region unless they reenter the segmentation within a maximum distance (*maxDist*). In this case they are considered part of the cingulum and included in the filtered tract set. A tract-density map is generated from the identified tracts at a 1mm cubic grid, indicating the number of cingulum tracts visiting each voxel.

Derivation of the Centerline and Projection of Tracts. By extracting the centerline of the cingulum, we establish a parameterization axis for the tract set. We achieve this by treating the tract-density map as a reciprocal cost image, and find the minimum cost centerline from one end of the cingulum to the other. To bridge potential gaps in the tract sets, we allow background voxels to be part of the centerline, but only at high costs (*backgroundWeight*). The parameterization should permit direct inter-subject comparison and should therefore not depend on individual performance of the fiber tracking. Especially at the far ends of the cingulum, tracts are often hard to reconstruct, leading to decreased tract density, which in turn could lead to problems in establishing correspondence across subjects. We therefore add the registered atlas mask to the tract density map with a fixed weight (*atlasWeight*), prior to converting it to the cost image. In dense regions, this has little effect, but in sparse regions, this allows to find the centerline aided by the registered atlas. The centerline is smoothed by fitting a B-spline with a fixed number of control points (*controlPoints*). The parameterization is then super sampled using *parSegments* equally spaced segments.

We then use the planes normal to the parameterized centerline to associate every tract segment to one of the parameterization segments.

Co-linearity Filtering. Because of the linear structure of the cingulum, it is safe to assume tracts running inside the cingulum are to a certain extent co-linear. Therefore, for every tract segment, we use the local direction to calculate co-linearity defined as the absolute dot product of the tract and parameterization segment direction vectors. A filtering step is then applied to exclude tract segments that are not co-linear (less than *minColin*) with the parameterization for a prolonged segment length (*maxDist*). After filtering, we construct a binary segmentation of all voxels containing tract(s).

Iterative Approach. The binary tract mask can be regarded as an improved segmentation of the cingulate bundle. It has been allowed to expand, by tracts locally exiting and re-entering the previous segmentation. And it has been allowed to shrink, by the local absence of co-linear tract segments. The mask is used as an updated segmentation for the entire procedure. The whole procedure is performed iteratively, until either follow-up iteration masks disagree on less than a fixed number of voxels (*maxVoxels*), or when a maximum number of iterations (*maxIt*) has been performed.

Statistical Analysis. Measures describing tracts and tract locations, such as FA, tract curvature etc, are at this point associated with a single linear parameterization and can thus be compared across subjects. In our application study, we chose to study hemispheric asymmetry in FA of the cingulum. The FA is a well-established measure and allows comparison of our results with previously published findings.

Fig. 1. Schematic overview of the tract selection procedure

3 Experiments and Results

DTI data from the population based Rotterdam Scan Study is used [13]. From this prospective cohort study, a random subset of 500 datasets was selected. Mean age of participants was 54.9 years, with an SD of 5.52; 52 percent of participants was female. All subjects were scanned on a 1.5 Tesla GE MRI system, with the following DTI acquisition parameters: 25 diffusion gradient directions, FOV= 210x210 mm², scan matrix= 96x64 (zero padded in k-space to 256x256), slice thickness 3.5 mm, 35 contiguous slices, TR= 8000 ms, TE= 68.7 ms, b-value= 1000 s/mm² and 3 volumes acquired without diffusion weighting. Datasets were preprocessed using the FDT toolbox in FSL [14] to correct for head motion and Eddy currents and to calculate FA images for the atlas registration. Atlas registration was performed using a 10 mm B-spline control point spacing with mutual information as similarity measure and took 8 minutes per subject on a single standard CPU. Streamline tractography was performed seeding tracts in a 2 mm cubic grid; and ending tracts when FA dropped below 0.2, taking 2 minutes per subject to compute.

Fig. 2. (a) Histogram showing the number of missing segments per subject. (b) Most problematic tract set identified in histogram. The dotted line indicates the centerline; parameterization position is indicated by color, parameterization legend in Fig. 3(b).

Fig. 3. (a) Typical tract set. The dotted line indicates the centerline; parameterization position is indicated by color. (b) Mean parameterization of the left and right cingulate bundles, serving as parameterization legend for Fig. 2(b), 3(a), 4 and 5. Thin lines indicate projections.

The applied setpoints have been determined empirically by visual inspection of resulting tract sets. The *maxDist* length of a tract part that is allowed outside the segmentation, as well as the maximum non-collinear length has been set to 3mm. The *backgroundWeight*, allowing the parameterization to cross over gaps, is set to 5 times the maximum costs encountered in the individual cost image. The *atlasWeight* is set to 1. The number of *controlPoints* of the parameterization is 15, later super sampled to 200 *parSegments*. Tract segments need to have a *minColin* of 0.8 to be considered co-linear with the parameterization. Iteration stops once the tract mask changes at most *maxVoxels*, 10, in a single iteration, or after reaching *maxIt*, 5, iterations. Iterative filtering took 9 minutes to compute; per subject per hemisphere.

The tract selection method does not require a tract to be mapped at every parameterization segment. Fig. 2(a) shows a histogram of the number of associated parameterization segments per subject. Ideally, all subjects should have no missing segments, this is however not the case. For the worst performing subject, the rightmost element in Fig. 2(a), the tract set is shown in Fig. 2(b). The procedure identified a very limited

number of tract segments; yet it did not make any apparent mistakes in corresponding the tract set. A typical tract set is shown in Fig. 3(a).

The FA is compared between the left and right cingulum for every segment of the parameterization, using a two-tailed paired t-test. Subjects therefore need to have a mean FA value associated with a particular segment on both their left and right cingulum. Failure in either or both hemispheres leads to exclusion of that subject from the analysis at that particular parameterization segment. Fig. 4(a) shows the number of subjects included for every tract segment. Resulting $\log(p)$ -values, shown in Fig. 4(b), show highly significant differences in both the anterior and posterior part of the cingulum. Mean parameterization coordinates are presented in Fig. 3(b) for reference, the mean FA along the left and right cingulate bundles is presented in Fig. 5(a).

As we are studying hemispheric asymmetry, it is important to rule out asymmetric influence of the atlas. To verify our findings, we flipped the atlas over the sagittal plane and repeated the registrations to the subjects' FA images. These new registrations were used to again measure FA profiles in cingulate bundles for all subjects. The blue lines in Fig. 5(a) present the mean FA profiles for left and right cingulate bundles, extracted with the flipped atlas, where left means subject-left. The profiles appear nearly identical to the original results, ruling out a bias by the atlas.

To investigate robustness of our findings, we evaluated the mean left – right FA in a subset of 50 subjects, repeatedly drawn random from the full set; shown in Fig. 5(b).

Fig. 4. (a) Number of complete cases, i.e. subjects with FA measurements in both left and right cingulate bundle, tested per parameterization segment. (b) Significance per tract segment, reported in $\log(p)$ -values.

Fig. 5. (a) Mean FA in left and right cingulate bundles, compared to mean FA obtained using a flipped atlas. (b) Robustness of left-right FA difference, measured by 200 random draws of 50 subjects from the total set of 500 subjects.

4 Discussion

We have developed a novel method for selecting tracts of interest from a whole brain tract set. The approach is especially useful in large datasets and is aimed at investigating tracts that are difficult to follow with more conventional region of interest tract selection approaches. The present work allows tracking of tube-like structures such as the cingulate bundle or the fornix. We acknowledge that the method contains a number of thresholds, albeit most of them having a physical, intuitive meaning, which have to be pre-defined. These thresholds were determined by qualitative evaluation of the resulting tract selections. To validate our method we compare our analysis results with published findings. To this extent we have studied inter-hemispheric differences in cingulate FA using a large sample of 500 subjects from the general population. We have shown that our findings are not caused by a bias in the initial atlas segmentation. In the anterior part of the cingulum, we observe a very significant difference with the FA being higher left than right. This is in agreement with results from other analyses that also used some form of tract selection [6, 7, 9]. Less is known, however, for the posterior cingulate. Malykhin et al. [7] selected tracts in this region in 24 healthy subjects. They found no significant difference between left and right tracts, possibly lacking statistical power. As the anterior and posterior cingulate are involved in different processes, the left/right difference in FA between the anterior and posterior cingulum might be hypothesized to reflect a difference in function between left and right hemispheric processes.

We tested for differences using a paired t-test on the parameterization-segment level, and reported p-values for every segment. To correct p-values for the number of tests performed (we tested on 200 segments), a permutation based correction method would have been appropriate [15]. Applying a Bonferroni correction results in an overly conservative upper bound to the multiple comparison correction, but still leaves our findings highly significant, as indicated by the green threshold in Fig. 4(b).

The method allows capturing the difficult connection between the posterior and anterior cingulate, but it does so with varying success along the pathway. For the most problematic segment, about half of the subjects give problems in either or both of the cingulate bundles, as shown in Fig. 4(a).

5 Conclusion

We have developed a fully automated method for the robust extraction and parameterization of the cingulum including the posterior cingulate. As an example application, we studied asymmetry of FA in the cingulum. Our findings in the anterior part, where FA was found to be higher left than right, are in agreement with previous research. Our analysis also found right higher than left FA in the posterior part.

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