CONNECTIVITY-BASED ANALYSIS: APPLICATION TO WHITE MATTER MATURATION IN MOUSE BRAIN

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ABSTRACT

This paper presents a paradigm for population-based studies using geodesic connectivity maps computed from DTI (Diffusion Tensor Imaging) data. Geodesic connectivity maps provide a measure of connectivity characterization between different regions of the brain using a tensor-based measure that combines anisotropy and orientation information. A connectivity map is constructed relative to a given region in a template space. Population based statistical analysis is then undertaken on these connectivity maps, pertaining to regions of interest. Group-wise changes in these connectivity maps therefore indicate potential disruptions of pathways connecting the ROI with the rest of the brain. This general paradigm for connectivity-based analysis is applied herein to a specific problem, namely the study of white matter maturation in a developing mouse brain, by performing voxel-wise linear regression on connectivity maps computed from several white matter regions. The study shows a significant effect of age whereas no effect of sex is observed.

Index Terms— geodesic connectivity, statistics, diffusion tensor imaging, mouse, maturation

1. INTRODUCTION

In this paper, we present a paradigm for group-based statistical analysis of connectivity maps computed from Diffusion Tensor Imaging (DTI), that provides an insight into changes in "connectivity" between different regions of the brain. The term connectivity may have different connotations depending on the modality and context. Here we use it to describe structural connectivity that elucidates relationships between different regions using white matter (WM) fiber bundles as pathways. The framework we describe is generic and it can be applied to any population study to analyze pathology or growth related changes that alter the connectivity.

The increasing popularity of DTI in clinical studies is due to the extensive information that it provides about WM and structural connectivity and consequently pathology maturation induced axonal loss changes and demyelination. The methods available in the literature for studying structural connectivity can be divided into the following categories: (1) streamline; (2) probabilistic; (3) variational.

In this paper, we use geodesic connectivity maps for the purposes of subsequent population-based statistical analysis. We improve existing geodesic methods by incorporating the full tensor information (orientation and anisotropy) in the metric to obtain the connectivity maps. We propose a protocol for facilitating population-based analysis of geodesic connectivity maps. Population-based analysis of connectivity maps has been undertaken in several ways: (1) tract-based: in which streamline connectivity maps are used Regions of Interest (ROI) extracting and scalar measures of anisotropy (FA) or diffusivity (MD) are calculated and compared along the tracts across subjects ([Pagani et al.(2005)])); (2) connectivity-based: in which connectivity maps generated by using the same seed region, are statistically analyzed voxel by voxel ([Ciccarelli et al.(2003)]). Tract-wise analysis has been limited to studying streamline connectivity maps across different subjects using manually drawn ROIs, making them prone to human error in drawing comparable regions across subjects. In ([Ciccarelli et al.(2003)]), geodesic connectivity maps are used to study differences between patients affected by optic neuritis, and controls. The geodesic connectivity maps are obtained by using a metric that does not include anisotropy information. The fundamental difference between these two methods, is the information that they provide after statistical analysis. Tract-wise analysis will determine localized regions where scalar measures of anisotropy/diffusivity vary across the whole population. Analysis of geodesic maps will produce regions of population difference, which show that the entire tract from the seed to that region is affected, therefore providing realistic connectivity information.

We demonstrate the applicability of our method, by a regression-based analysis on aging mouse brains to study the effect of maturation on connectivity patterns. In the previous work see ([Verma et al.(2005), Baloch et al.(2008)]), maturation patterns were studied using voxel-based analysis. Our framework allows us to investigate not only changes in diffusion signal locally that affect connectivity, but also to examine its properties along paths connecting a voxel to other regions in the brain.

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The paper is organized as follows: in the Methods section, the proposed connectivity-based group analysis approach is presented; in the Results section, we apply our framework to study connectivity changes in mouse brains, followed by a discussion of the results.

2. METHODS

In this section, we present the method of computing geodesic connectivity maps (Section 2.1), and then establish the paradigm for population based studies on geodesic connectivity maps (Section 2.2).

2.1. Creating connectivity maps

For any two given points in the brain, we can generate a mathematical path connecting them. Therefore, it is crucial to define a criterion or measure of connectivity that allows to select paths that correspond most likely to fibers. In this context the following indices have been used: (1) dot product of the major diffusion direction with the tangent to the path ([Parker et al. (2002)]); (2) mean of the Euclidean length of paths ([O'Donnell et al.(2002), Prados et al.(2006)]); (3) product of the mean diffusivity along the path with mean FA along the path ([Jbabdi et al.(2008)]). In contrast to ([Parker et al. (2002)], [Jbabdi et al.(2008)]), the method proposed by [Prados et al.(2006)] does not require an extraction of the path to compute the connectivity, which reduces the computing time considerably. Indeed, the control optimal formulation of geodesic tracking allows a computation of the connectivity along geodesics by dynamics. The dynamics can be viewed in the Riemannian framework as the derivative of the geodesics which allows the computation of the Euclidean length of the path. However, the use of the FA or the principal diffusion direction ([Parker et al. (2002), Jbabdi et al.(2008)]) seems to be more meaningful physically than using only a geometric criterion such as the Euclidian length of the path. In this context we propose to take advantages of the two approaches. Our approach is more meaningful physically than these approaches as it includes the FA and main direction of the tensor. In addition, the computation time is in the order of seconds. We define the connectivity measure by the relation:

$$\mathcal{C}(\gamma) = \frac{1}{\tau} \int |\gamma'(t)|_E \left|\left\langle \gamma'(t), \mu(\gamma) \right\rangle\right| FA(\gamma(t)) \mathrm{d}t, \qquad (1)$$

where τ is the travel time from the source to the given point; γ and γ' are respectively the path and the tangential to the path; μ is the main direction of the tensor, see figure 1; FA is the fractional anisotropy [1] In the formulation (1) the Euclidean length of the paths is weighted with the FA and the dot product of the tangential to the path with the main direction of the diffusion tensor. The dot product focuses the direction of diffusion in the direction of the underlying fiber and the FA values help weight the connectivity towards higher anisotropy regions.

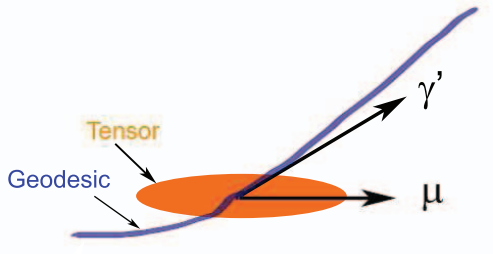


Fig. 1. Connectivity index.

Furthermore, we divide with τ to focus on paths that have large weighted euclidean lengths but also short travel times. τ (called also geodesic distance) is the solution of the eikonal equation which we solve using the Fast Marching algorithm.

2.2. Group analysis of connectivity maps

In order to perform group analysis on the connectivity maps, we spatially normalize the brains to a day 10 brain that is intermediate in the period of development being considered, using our well validated deformable registration algorithm DROID [Yang et al.(2008)]. An ROI of choice is identified on the atlas and connectivity maps are created for that ROI for each of the spatially normalized subject brains. We remind that the connectivity map computed by the relation (1) at each voxel of the brain is a distance from source voxels along minimal paths to the given voxel using a metric designed from the tensor (see Section 2.1), principal direction, and the FA map. Furthermore, the connectivity maps are generated after normalizing the subjects to the same template. Therefore the connectivity map computed are comparable across subjects for a given ROI. Consequently voxel-wise regression and group-wise t-test can be carried out on these aligned connectivity maps.

Our group analysis framework can be summarized in the following three steps. Namely 1) register subjects to the template space; 2) generate connectivity maps using ROIs in the normalized subjects; and 3) perform voxel-wise statistics on connectivity maps across subjects.

3. RESULTS

Connectivity maps generated with mouse data were used to study connectivity changes as a result of growth and maturation. We studied a population of 67 mice. DT images at different ages of development of these mice were acquired ex

[1] $FA = \sqrt{\frac{3}{2}} \sqrt{\frac{\sum_{i=1}^{3} (\lambda_i - \bar{\lambda})^2}{\sum_{i=1}^{3} \lambda_i^2}}$, where $\lambda_i,\ i = 1, ..., 3$ are the eigenvalues of the tensor and $\bar{\lambda}$ is the mean of the eigenvalues.

vivo. The following mice ages were studied: 2, 3, 5, 7, 10, 15, 20, 30, 40 and 80 days. The matrix size of the data is $300 \times 300 \times 200$ voxels with a resolution of $0.078 \times 0.125 \times 0.070 mm^3$.

3.1. Connectivity Analysis of Mouse Brains

We selected a Day 10 mouse as a template as it lay in the middle of the development period. All the mice brains were registered to the template. The ROIs were drawn manually on the template by the authors (as there is no electronic template available for mouse DTI images) in such way that each ROI is contained in the white matter and within only one tract. The ROIs that were investigated are: corpus callosum, right and left hippocampus, internal capsule, external capsule, and triangular septal nucleus. The ROI voxels were used as seed points to perform the Fast Marching propagation method and to simultaneously compute the connectivity maps. After generating all the connectivity maps in the template space, we performed linear regression with respect to age, and sex as a covariate to study the effect of the sex on the statistical model. The regression was achieved by the module 3dRegAna of the software AFNI[2].

3.2. Group-wise analysis on aging mouse brains

Using the data described above we create geodesic connectivity maps for different ROIs. Details are described in section 2.1. With a C++ implementation running on 7GHz GNU/Linux, computational costs is 39 seconds. Figure 2, shows changes of the geodesic connectivity maps at different ages, which were generated with the ROI on the corpus callosum. To evaluate the effect of age on the white matter of the mouse brain, a voxel-wise regression of connectivity maps with different ROIs was performed. The regression maps, which associate the slopes of regression curves with each voxel, characterize the evolution of the connectivity values with age. A positive value of the regression map corresponds to an increase of connectivity whereas a negative value corresponds to a decrease of connectivity. Figure 3-(right panel) shows regression maps that summarize the effect of age on the connectivity of the brain using all the 67 mice. Note that, in contrast to previous statistical studies of white matter maturation [Verma et al.(2005), Baloch et al.(2008)] where only local measurements, such as FA , are used on the voxel basis, our approach detects changes along the pathways between the source (where the tracts originate) and the rest of the brain. Voxel-wise regression performed by controlling for sex shows that sex does not have a pronounced affect on the white matter maturation in the brain. These effects were also observed with small ROIs within different tracts (corpus callosum, hippocampus, and internal capsule), which means that these results are independent of the position of the ROIs.

[2]http://afni.nimh.nih.gov/afni

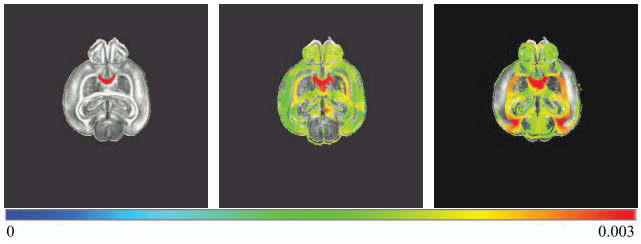


Fig. 2. Left panel shows in red the localization of the ROI on the corpus callosum (axial view of the brain); center and right panels show connectivity maps computed for mice from a young and adult groups respectively. The color bar at the bottom shows the connectivity values.

As we expect the age related changes to be non-linear, we study regression at different developmental stages of the mouse brain, we performed regression with age by dividing the data into three different groups: (1) young and teenager (mice aged 2 to 30 days); (2) teenager and adult (mice aged 15 to 80 days); (3) all subjects (mice aged 2 to 80 days). Figure 3 shows regression maps observed at $p < 0.01$ for the three groups. The changes in the connectivity values are most significant during the period 2-30 days, which is consistent with the results of [Verma et al.(2005), Baloch et al.(2008)] that the white matter anisotropy changes faster in the early stages, after which it slows down in the teenage-adult period.



Fig. 3. Group-wise analysis with the ROI on the corpus callosum, regression according to the age with different mouse population samples (axial view of the brain). The left panel shows the regression map for the age groups young and teenager observed at $p < 0.01$; The center panel shows a regression map for the age groups teenager and adult observed at $p < 0.01$; the right panel shows a regression map for the sample composed of all age groups, young, teenager, and adult, observed at $p < 0.01$. Red corresponds to an increase of connectivity whereas blue corresponds to a decrease of connectivity.

4. CONCLUSION

In this paper, we have presented a framework for group-wise statistical analysis of connectivity maps. This has been applied to a study of maturing mouse brains, regressing with

age. The same framework can be applied to any population with pathology and clinical variables can be used for regression. The normalized connectivity maps can be used for group-based analysis. While specific ROIs can be explored on the basis of a hypothesis, the framework facilitates systematic investigation of any ROI that can be drawn on the template, as all the subjects in the study have been normalized to the template.

Few studies have addressed the quantification of white matter maturation using the tractography ([Jones el al.(2006)]). These studies have investigated the change in FA, trace and other scalar indices computed along the tracts, and identified specific regions of difference. Our approach is connectivity based. Although in our approach, we perform a voxel-based analysis of the connectivity maps, the p-maps of region wise significance need to be interpreted differently than those produced by traditional voxel-based morphometry (VBM) of scalar maps of FA and trace computed from the tensors. The regions of difference produced by our framework indicates a systematic group-wise change along the whole pathway between the source (where the tracts originate) and the rest of the brain, between the two groups. In VBM, regions of significant change indicates a change in that region itself between the two groups. Unlike other connectivity indices [Parker et al. (2002)] employed by other studies that investigate geodesic connectivity differences in a population [Ciccarelli et al.(2003)], ours uses the full tensor information, the anisotropy and the orientation information. Furthermore, the computation of our connectivity index is achieved simultaneously within the Fast Marching propagation, which reduces the computation time considerably. In [Ciccarelli et al.(2003)] the connectivity maps are computed in the space of the subjects. This method makes incomplete use of the information obtained from the tensor and is more time consuming than our approach, and risks introducing interpolation errors due to normalization, as the analysis is done in the subject space prior to the normalization of maps.

In Figure 3, the regression maps show an increase in connectivity with age in the WM tracts and a decrease in connectivity in the cortex. This is in line with the physiology which indicates that WM becomes more organized, with age day 2 to day 80. The GM is the cortex, which is initially anisotropic, becomes more isotropic as glial structural changes take over. Using the proposed connectivity based group analysis we find significant changes of connectivity of the brain with age whereas no effect of sex is observed. These age effects are consistent with other studies that used other scalars measurements describing the anisotropy of the white matter, [Verma et al.(2005), Baloch et al.(2008)].

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