A PROBABILISTIC METHOD FOR UNBIASED LONGITUDINAL TRACTOGRAPHY WITH APPLICATION TO HUNTINGTON'S DISEASE

Anastasia Yendiki[1], Martin Reuter[1], Paul Wilkens[1], Herminia Diana Rosas[1], and Bruce Fischl[1,2]

[1]HMS/MGH/MIT Athinoula A. Martinos Center for Biomedical Imaging, Charlestown, MA, United States, [2]MIT Computer Science and Artificial Intelligence Laboratory, Cambridge, MA, United States

TARGET AUDIENCE: The proposed method is of interest to neuroimaging researchers working with longitudinal diffusion MRI (dMRI) data.

PURPOSE: Longitudinal population studies of brain structure allow us to measure within-subject changes but they require specialized analysis methods to make optimal use of these measurements. For example, the progressive changes of interest may be such that conventional, cross-sectional analysis tools perform better on data from earlier than later time points or vice versa. Recent work on analysis methods for longitudinal T1-weighted data has illustrated the importance of eliminating bias due to interpolation asymmetries[1-3]. Such bias can occur, for example, if follow-up images are resampled to the baseline image, thus smoothing the former and leaving the latter unsmoothed. Similar ideas have been applied to the unbiased within-subject alignment of longitudinal dMRI data for the purposes of ROI-based analysis[4]. Here we propose a method for unbiased reconstruction of white-matter (WM) pathways from multiple time points that can be used for tract-based longitudinal analyses. Our method is unbiased, as it does not treat any time point preferentially to transfer information from it to the other time points. Although it is possible to apply a conventional cross-sectional approach to longitudinal data by performing tractography in each time point independently, it is challenging to delineate WM pathways consistently across time points in the presence of progressive changes in anisotropy. This makes "along-the-tract" analyses of dMRI measures[5] particularly challenging to perform longitudinally, if different parts of the trajectory of a pathway are reconstructed for different time points. Our approach addresses this issue by reconstructing the pathways jointly from the dMRI data of all time points, thus ensuring point-to-point correspondence among time points.

METHODS: The proposed approach generalizes a framework for global probabilistic tractography with anatomical priors[6] to the case where images from multiple time points are available for the same subject. Within each time point, the subject's dMRI and T1 images are co-registered using boundary-based cross-modal registration[7]. A robust symmetric registration method is applied to the s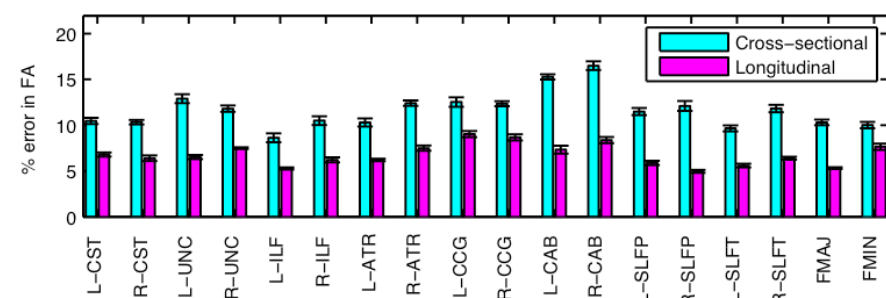ubject's T1 images from all time points to obtain an unbiased within-subject base template[8]. The white-matter pathway of interest is represented as a spline in the space of this base template and its posterior distribution is estimated by an MCMC algorithm. At each iteration, the control points of the spline are perturbed and the new spline is mapped from the base template to the dMRI data of every time point to compute its likelihood given the dMRI data, as well as its prior given its surrounding labels from an anatomical segmentation. The posterior probability of the pathway given the data from all time points is computed as the product of the likelihood and prior terms from all time points. We compare this longitudinal tractography, which reconstructs the pathway at all time points jointly, to the conventional cross-sectional approach[6], which reconstructs the pathway at each time point independently. We evaluate specificity on test-retest data from 9 healthy volunteers. We evaluate sensitivity on longitudinal data from 46 Huntington's disease (HD) patients, each of which had data from 2-5 time points, collected at 6-month intervals.

Figure 1. Test-retest reliability of FA, shown for longitudinal vs. cross-sectional tractography.

RESULTS: Fig. 1 shows, for 18 tracts, the % error between the FA values at corresponding positions along the tract between the test and retest data, averaged along the tract and over the 9 healthy volunteers. The lower this error, the greater the reliability of the along-the-tract FA estimates. Fig. 2 shows the estimated slopes of the longitudinal change in FA at different positions along the left anterior thalamic radiation
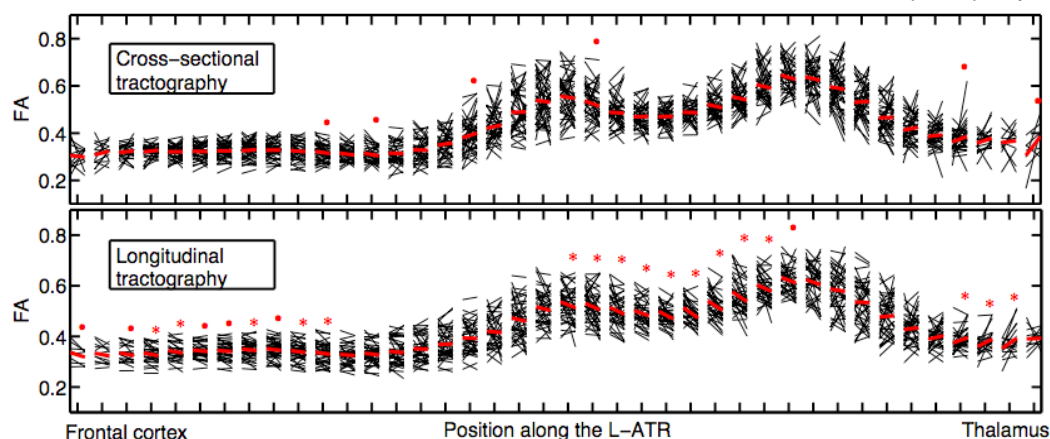

Figure 2. Slopes of longitudinal FA changes in HD patients, with longitudinal vs. cross-sectional tractography.

(ATR) for the HD patients. Each black line shows the slope for an individual patient. The red line shows the average slope. Slopes significantly different than zero based on a one-sample T-test ($p<0.05$) are marked with an asterisk. Slopes with a trend towards significance ($p<0.1$) are marked with a disk.

DISCUSSION: As seen in fig. 1, the longitudinal approach led to increased reliability (reduced error) in the test-retest estimates of FA along each tract, when compared to the cross-sectional approach. Differences in the errors between the longitudinal and cross-sectional methods were significant for all tracts based on paired T-tests. As seen in fig. 2, the longitudinal approach was able to detect significant longitudinal changes (mainly reductions) in FA in HD patients at more positions along the ATR, when compared to the cross-sectional approach. The same trend was seen in several other pathways and is consistent with the progressive degeneration of WM that is expected in these patients[9].

CONCLUSION: We have developed a probabilistic framework for joint reconstruction of white-matter pathways from multiple longitudinal time points. Our method is unbiased, treating all time points equally with no assumptions on the directionality of longitudinal changes. It is fully automated, facilitating the processing of large data sets. By reconstructing the pathways jointly for all time points, our method ensures that the pathway is delineated consistently among time points. This allows us to establish point-to-point correspondence along the trajectory of the pathway and perform along-the-tract longitudinal analyses. Our preliminary results indicate that, compared to the conventional approach of performing tractography in each time point independently, the proposed longitudinal tractography leads to improved test-retest reliability, as well as increased sensitivity to white-matter alterations in HD. This implies that the proposed method would require smaller sample sizes of longitudinal data to detect the same effect. In future work, we will perform power analyses to investigate this point further.

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