Published in final edited form as:

Neuroimage. 2016 February 15; 127: 277–286. doi:10.1016/j.neuroimage.2015.12.003.

Joint reconstruction of white-matter pathways from longitudinal diffusion MRI data with anatomical priors

Anastasia Yendiki^{a,*}, Martin Reuter^a, Paul Wilkens^b, H. Diana Rosas^b, and Bruce Fischl^{a,c}

^aAthinoula A. Martinos Center for Biomedical Imaging, Department of Radiology, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA

^bDepartment of Neurology, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA

^cComputer Science and Artificial Intelligence Laboratory, Massachusetts Institute of Technology, Cambridge, MA, USA

Abstract

We consider the problem of reconstructing white-matter pathways in a longitudinal study, where diffusion-weighted and T_1 -weighted MR images have been acquired at multiple time points for the same subject. We propose a method for joint reconstruction of a subject's pathways at all time points given the subject's entire set of longitudinal data. We apply a method for unbiased within-subject registration to generate a within-subject template from the T_1 -weighted images of the subject at all time points. We follow a global probabilistic tractography approach, where the unknown pathway is represented in the space of this within-subject template and propagated to the native space of the diffusion-weighted images at all time points to compute its posterior probability given the images. This ensures spatial correspondence of the reconstructed pathway among time points, which in turn allows longitudinal changes in diffusion measures to be estimated consistently along the pathway. We evaluate the reliability of the proposed method on data from healthy controls scanned twice within a month, where no changes in white-matter microstructure are expected between scans. We evaluate the sensitivity of the method on data from Huntington's disease patients scanned repeatedly over the course of several months, where changes are expected between scans. We show that reconstructing white-matter pathways jointly using the data from all time points leads to improved reliability and sensitivity, when compared to reconstructing the pathways at each time point independently.

Keywords

diffusion MRI; tractography; longitudinal data analysis

*Corresponding author ayendiki@nmr.mgh.harvard.edu (Anastasia Yendiki).

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

1. Introduction

Neuroimaging studies often aim to measure and localize progressive changes in brain structure over certain periods in the human life span, *e.g.*, during brain development or aging, and to compare these changes between populations, *e.g.*, subjects with a neurodegenerative or psychiatric disorder vs. healthy subjects. This can be done with a cross-sectional study, where each subject is selected to represent a given age or disease stage and scanned only once. However, the anatomical differences between individuals, even individuals that belong to the same diseased or healthy population, are often much greater than the within-subject changes that occur due to the biological process under investigation. If these within-subject changes, which constitute the signal of interest, are subtler than the inter-individual differences, which are confounding factors, sensitivity is reduced.

Longitudinal studies have many advantages, but they require specialized image analysis methods to take full advantage of their potential for increased sensitivity without introducing bias. This is especially the case if the progressive changes of interest are such that the conventional, cross-sectional analysis tools perform better on data from earlier than later time points (*e.g.*, due to degeneration) or vice versa (*e.g.*, due to treatment). To date most development on longitudinal MRI analysis has focused on anatomical data. Recent work has sought to exploit the knowledge that within-subject anatomical changes are usually much smaller than between-subject morphological variability, and to eliminate the bias that can result from asymmetric analysis of time points (Yushkevich et al., 2010; Thompson et al., 2011; Reuter and Fischl, 2011), *i.e.*, from performing different image-processing operations on the images from each time point. An example of asymmetric analysis is the interpolation asymmetry that occurs when follow-up images are resampled to the baseline image, thus smoothing the former and leaving the latter unsmoothed. This can lead to overestimation of longitudinal changes. The use of an unbiased within-subject template space has been proposed to avoid such asymmetries (Reuter et al., 2012). A similar approach has been applied to diffusion-weighted (DW) MRI and combined with tensor-based registration to align images within and across subjects for region-of-interest (ROI) analyses of diffusion measures (Keihaninejad et al., 2013). This approach can also be used to transfer ROIs from an atlas with the purpose of labeling tractography streamlines (Aarnink et al., 2013).

In the present work we propose a Bayesian framework for inferring white-matter (WM) pathways given a set of longitudinal diffusion MRI data from first principles. The problem of reconstructing WM pathways from longitudinally acquired images is relevant to a variety of neurodegenerative disorders, where changes in WM microstructure can be an important disease mechanism, as is cortical atrophy. Tract-based longitudinal studies are hampered by the difficulty in segmenting the pathways consistently across time points in the presence of progressive changes in WM anisotropy. This stems from the fact that, in general, tractography methods are designed to traverse areas of high anisotropy and avoid areas of low anisotropy. For example, in a study of a condition characterized by progressive degeneration of a WM pathway, this would cause fewer and fewer voxels to be included in that pathway at successive time points. On the one hand, this can be exploited by using the number of voxels traversed by the tractography solutions as the measure to be studied longitudinally. On the other hand, if anisotropy is the measure to be studied longitudinally,

this effect will lead to underestimation of the changes in average anisotropy in the pathway between time points. That is because at each time point the anisotropy will be averaged only over parts of the pathway that have high enough anisotropy to be included in the tractography solutions in the first place. This can also be a problem for studying anisotropy changes as a function of the position along the pathway's trajectory, as it makes point-to-point correspondence along the tractography solutions difficult to establish between time points.

We propose to address these issues with a longitudinal tractography framework for reconstructing a subject's WM pathways by using the data from all time points simultaneously. This yields tractography solutions in the native space of each time point that are consistent among time points, ensuring that the same part of the WM is compared between time points, whether the comparison is done on the basis of average measures over an entire WM pathway or on the basis of measures sampled at specific locations along the arc of the WM pathway. The proposed framework uses an unbiased within-subject template obtained from the subject's anatomical data (Reuter et al., 2012) to establish spatial correspondence between time points. We incorporate this into an algorithm for global probabilistic tractography with anatomical priors to estimate the posterior probability of WM pathways jointly from a subject's full set of longitudinal data. This is an extension to our automated tractography tool, TRActs Constrained by UnderLying Anatomy (TRACULA; Yendiki et al. (2011)), which heretofore could process data from a single time point only. The extension proposed in this work allows TRACULA to handle data from an arbitrary number of time points at once and to reconstruct pathways jointly given the data at all time points. We show that this joint reconstruction approach leads to improved test-retest reliability and sensitivity to WM changes when compared to reconstructing the pathways from the data of each time point independently.

2. Materials and methods

2.1. Within-subject registration and template generation

2.1.1. T_1 -weighted time point to within-subject template—For each subject we generate a within-subject template by combining the T_1 -weighted images at different time points via the longitudinal processing framework described in Reuter et al. (2012). In that work, an unbiased within-subject template is generated by iteratively aligning all input images to a median image using a symmetric robust registration method (Reuter et al., 2010). This can be applied to an arbitrary number of time points and treats all the input T_1 -weighted images equally, eliminating temporal bias. The median image, which functions as a robust within-subject template, is then used to initialize further processing of each time point's T_1 -weighted image, including a cortical parcellation and subcortical segmentation procedure (Fischl et al., 2002, 2004b,a). After initializing it with the segmentation of the within-subject template, the segmentation of each time point is refined based on the data from that time point, by iterating further without constraining the label estimates to match those in the within-subject template. This avoids the over-regularization that could result if temporal smoothness constraints were enforced, and allows the recovery of large temporal

deviations. This approach has been shown to improve robustness and sensitivity in the longitudinal analysis of T_1 -weighted images (Reuter et al., 2012).

2.1.2. DW time point to T_1 -weighted time point—As a pre-processing step for each time point, we align all images in the DW scan to the first non-DW image using affine registration (Jenkinson et al., 2002) and reorient the corresponding diffusion-weighting gradient vectors accordingly (Rohde et al., 2004; Leemans and Jones, 2009). We align the DW and T_1 -weighted volumes from the same time point using a surface-based method for within-subject, across-modality registration (Greve and Fischl, 2009). This method uses the surface of the cortical gray/white matter boundary that is reconstructed by FreeSurfer from the T_1 -weighted image. It then computes the mapping from the non-DW ($b=0$) image to the T_1 -weighted image that maximizes the intensity contrast of the non-DW image across the T_1 -derived surface.

2.2. Longitudinal tractography

Let $\mathbf{F}$ be a WM pathway of interest, which for our purposes will be represented in the space of the anatomical within-subject template described above. Our goal is to estimate the posterior distribution of $\mathbf{F}$ given the observed data for all time points, $k = 1, \dots, n_T$. The observations at the k -th time point include the DW images, $\mathbf{Y}_k$, the anatomical segmentation, $\mathbf{A}_k$, and the transformation $\mathbf{X}_k$ from the within-subject template space, where $\mathbf{F}$ is represented, to the native space of the DW images. We write the posterior distribution as:

$$P(\mathbf{F} | \mathbf{Y}_1, \dots, \mathbf{Y}_{n_T}, \mathbf{X}_1, \dots, \mathbf{X}_{n_T}, \mathbf{A}_1, \dots, \mathbf{A}_{n_T}) \propto \prod_{k=1, \dots, n_T} P(\mathbf{Y}_k | \mathbf{F}, \mathbf{X}_k) \cdot P(\mathbf{F} | \mathbf{A}_k). \quad (1)$$

The transformation $\mathbf{X}_k$ is the composition of the median-to- T_1 and T_1 -to-DW transformations for the k -th time point. For $n_T = 1$ and $\mathbf{X}_1 = \mathbf{I}$, (1) reduces to the model described in Yendiki et al. (2011) for the case of a single time point. The right-hand side of (1) involves the likelihood of the DW images at each time point given the pathway and its transformation to the DW image space, as well as the prior probability of the pathway given the anatomical segmentation that is derived from the T_1 -weighted image at each time point.

2.2.1. Data likelihood term—For the k -th time point, once the transformation $\mathbf{X}_k$ has been applied to map the path $\mathbf{F}$ from the within-subject template space to that time point's native DW image space, the global model of Jbabdi et al. (2007) for the conditional likelihood of the DW images $\mathbf{Y}_k$ given the path can be used. Under this model the DW image intensities, given the path, are assumed to be independent samples of a Gaussian distribution,

$$P(\mathbf{Y}_k | \mathbf{F}, \mathbf{X}_k) \sim \mathcal{N}(\mu; \Sigma), \quad (2)$$

where the unknown covariance Σ can be integrated out of the posterior as described in Jbabdi et al. (2007) and the mean μ involves a multi-compartment forward model of the diffusion process at each voxel (Behrens et al., 2007).

This “ball-and-stick” model of diffusion expresses μ_{ij} , the mean intensity at the j th voxel in the DW image acquired with the i th diffusion-encoding direction, as

$$\mu_{ij} = s_{0j} \left\{ \left(1 - \sum_{l=1}^{n_F} f_j^l \right) \exp(-b_i d_j) + \sum_{l=1}^{n_F} f_j^l \exp(-b_i d_j |\mathbf{g}_i' \cdot \mathbf{t}_j^l|^2) \right\}, \quad (3)$$

where the first summand inside the braces represents an isotropic diffusion compartment and the remaining n_F summands represent anisotropic compartments, *i.e.*, WM fiber bundles, with orientation vectors $\mathbf{t}_j^l$. The diffusion-encoding weights and gradient directions, b_i and $\mathbf{g}_i$ respectively, are known acquisition parameters. The non-DW image intensity s_{0j} , the diffusivity d_j , the anisotropic compartment volume fractions f_j^l , $l = 1, \dots, n_F$, and the anisotropic compartment orientations $\mathbf{t}_j^l$, $l = 1, \dots, n_F$, are unknown parameters to be fit to the data at each voxel j .

An aspect of this model that is important for our longitudinal tractography framework is that the only term involving the tangent vectors $\mathbf{t}_j^l$, through which the orientation of the unknown path is fit to the DW images at each voxel, is weighed by the volume fraction f_j^l of the anisotropic compartment in that voxel. Consider a voxel where the volume of an anisotropic compartment changes over time. The volume could be decreasing, *e.g.*, as a patient progresses to more advanced stages of neurodegeneration, or increasing, *e.g.*, after administration of an effective treatment. For the time points where the volume fraction is smaller, the term involving $\mathbf{t}_j^l$ will have a lesser contribution to (3), making the likelihood at those time points flatter with respect to orientation. However, the joint posterior (1) will compensate for this by giving more weight to those time points where the pathway is less compromised and orientation is easier to resolve. This will make it possible for parts of a pathway that are compromised, *e.g.*, by a disease, to be included in the estimated path posterior, even if they have lower anisotropy in some time points and could thus pose a challenge for conventional streamline tractography.

2.2.2. Anatomical prior term—Our goal in this work is to reconstruct major WM pathways, whose trajectories through the human brain are considered relatively well-characterized by neuroanatomists. Thus, unlike exploratory tractography analyses that aim to discover which brain region is connected to which, we can take advantage of prior anatomical knowledge on the pathways that we want to reconstruct. Specifically, we use the training data set described in Yendiki et al. (2011), which contains manually labeled streamlines for 18 major WM pathways in 33 subjects, as well as anatomical segmentations for the same subjects. The pathways are: corticospinal tract (CST), uncinate fasciculus (UNC), inferior longitudinal fasciculus (ILF), anterior thalamic radiations (ATR), cingulum - cingulate gyrus bundle (CCG), cingulum - angular bundle (CAB), superior longitudinal fasciculus - parietal branch (SLFP), superior longitudinal fasciculus - temporal branch (SLFT), corpus callosum - forceps major (FMAJ), and corpus callosum - forceps minor (FMIN). Other than the corpus callosum, all other pathways are reconstructed for the left (L) and right (R) hemisphere.

We use this training data to obtain the prior probability of the path $\mathbf{F}$ given its neighboring anatomical labels from the segmentation map $\mathbf{A}_k$ at each point along the trajectory of the path. This anatomical path prior can be written as:

$$p(\mathbf{F}|\mathbf{A}_k) = \prod_{j \in \mathbf{F}} \frac{n_{j\mathbf{A}_k(j)} + 1}{n_{j\mathbf{A}_k(j)} + \bar{n}_{j\mathbf{A}_k(j)} + 2}, \quad (4)$$

where $n_{j\mathbf{A}_k(j)}$ and $\bar{n}_{j\mathbf{A}_k(j)}$ are the numbers of streamlines in the training set that do or do not neighbor, respectively, label $\mathbf{A}_k(j)$ at position j . The position j is parameterized by arc length along the one-dimensional path, where arc lengths of 0 and 1 correspond, respectively, to the first and last point on the path. For example, to estimate the prior probability of a path belonging to the CST given its neighboring anatomical structures in the anterior direction, we identify, for each point along the path, the segmentation label that is the nearest anterior neighbor of the path. We then find how often we encounter the same segmentation label as the nearest anterior neighbor of the CST training streamlines at the same arc lengths along those streamlines. This is repeated for the segmentation labels that the path intersects at each point along its trajectory and for the labels that the path neighbors in the left, right, posterior, anterior, inferior, and superior direction at each point along its trajectory. These priors constrain the solution space of the tractography problem in a way that is robust to misregistrations between the subject being analyzed and the training subjects. That is because the information included in the priors is not the exact spatial *location* of the pathway in some template space but only the *identity* of the anatomical labels that the pathway intersects or neighbors at each part of its trajectory.

2.2.3. Algorithm—We estimate the posterior distribution in (1) by a Markov chain Monte Carlo (MCMC) sampling method. We model the path $\mathbf{F}$ as a Catmull-Rom spline. The training data from Yendiki et al. (2011) is used not only to compute the anatomical priors of (4), but also to inform the MCMC algorithm in the following ways:

- The number of control points of the spline is chosen based on prior knowledge of the shape of each pathway (more control points for higher-curvature pathways, such as the forceps major of the corpus callosum, than for lower-curvature ones, such as the inferior longitudinal fasciculus).
- The median of the training streamlines (or a streamline close to the median that is well-aligned with the WM of the test subject, if that is not the case for the median) is used to initialize the MCMC algorithm.
- The spread of the training streamlines around their median at the initial location of each control point is used to tune the standard deviation of the MCMC proposal distribution for that control point. This means, for example, that the end points of a pathway near the cortex will be perturbed more aggressively during the MCMC jumps than intermediate control points deeper in the WM, if the training data indicates that the end points of the pathway are more spread out than the midpoints. This improves the MCMC acceptance rate and thus speeds up convergence.

After the control points of the spline have been initialized and mapped from the training data to the anatomical within-subject template of the test subject, the following steps are repeated at the m -th MCMC iteration:

1. Choose one of the control points of the current path, F_m , at random and perturb it (in the within-subject template space) by drawing a random perturbation from the respective proposal distribution. Interpolate the new path, F_{m+1} , from the perturbed set of control points.
2. Map the path F_{m+1} from the within-subject template to the native DW image space of each of the n_T time points by applying the transformations X_k , $k = 1, \dots, n_T$. Typically this implies downsampling the path, as the DW image space is usually lower-resolution than the anatomical space.
3. In the native DW image space of each time point, compute the tangent orientation of the path at each point along its trajectory and compute the fit of the path orientations to the DW image data Y_k of that time point, as expressed by the likelihood term of (2)–(3).
4. Map the path F_{m+1} to the common template space of the training data, and compute its prior probability given the neighboring labels in the anatomical segmentation A_k of each time point and the training data, as given in (4).
5. Compute the log-posterior of the path F_{m+1} by summing the log of the likelihood and prior terms from all n_T time points.
6. Determine if F_{m+1} will be accepted or rejected by comparing its posterior probability to that of F_m .
7. If F_{m+1} is accepted, replace F_m with F_{m+1} .
8. Go to step 1 and repeat.

In the end, all accepted paths, which are shared among all time points but have also been mapped to the native DW image space of each time point, are summed to obtain the posterior distribution of the path. This yields a volumetric distribution of the pathway that is consistent among all time points but also exists in the native space of each DW scan and can be used in that space to sample diffusion measures of interest for this pathway at each time point.

In the following, we will compare the longitudinal tractography described above to the conventional cross-sectional tractography approach, where the pathways are reconstructed independently from the data at each time point, as if it were a cross-sectional data point. The longitudinal and cross-sectional processing streams are illustrated, respectively, in Figures 1 and 2.

2.3. Evaluation

In the following, we quantify the improvement in terms of test-retest reliability and sensitivity that can be achieved by analyzing data with the longitudinal tractography approach described above, where WM pathways are reconstructed from the data at all time

points jointly, in comparison to the cross-sectional tractography approach, where WM pathways are reconstructed from the data at each time point independently. We evaluate test-retest reliability using data from healthy volunteers scanned twice, where no WM changes are expected between scans. We evaluate sensitivity using data from Huntington's disease (HD) patients scanned repeatedly, where progressive WM degeneration is expected between scans. Both evaluations are performed on data that was acquired using widely available DW-MRI sequences and hardware.

2.3.1. Test-retest reliability—We use data from a set of 9 healthy volunteers (aged 45.9 ± 10.6 , 4 female) who were scanned twice. Each subject's sessions were separated by less than a month, and therefore no significant brain changes between sessions were expected at the group level. In each session, DW and T_1 -weighted images were collected by a 1.5T Siemens scanner with an 8-channel head coil. The DW images were acquired using a spin-echo echo-planar imaging (EPI) sequence with axial in-plane isotropic resolution 2 mm, slice thickness 2 mm, $128 \times 128 \times 60$ image matrix, $TR=8900$ ms, $TE=80$ ms, $NEX=1$, $BW=1860$ Hz/pixel, GRAPPA acceleration factor 2. The series included images acquired with diffusion weighting along 60 non-collinear directions ($b = 700 \text{ s m}^{-2}$), and 10 images acquired without diffusion weighting ($b = 0$). The T_1 -weighted images were acquired using an oblique axial gradient recalled echo (GRE) sequence with in-plane isotropic resolution 0.625 mm, slice thickness 1.5 mm, $256 \times 256 \times 144$ image matrix, $TR=12$ ms, $TE=4.76$ ms, $BW=110$ Hz/pixel, flip angle 20° .

We reconstruct the 18 WM pathways for each subject in two ways: (i) Using the DW and T_1 -weighted images from both sessions jointly, *i.e.*, $n_T = 2$ in (1), and (ii) Using the DW and T_1 -weighted images from each session independently, *i.e.*, $n_T = 1$ in (1). In both cases, TRACULA estimates the posterior probability distribution of each pathway in the native DW image space of each time point and finds the maximum *a posteriori* (MAP) path, which is a 1D curve in that space. A fractional anisotropy (FA) map is computed after fitting the diffusion tensor model to the DW images. (Note that tensors are used only in the voxel-wise FA calculation and not in the tractography itself, which uses the ball-and-stick model instead.) It then calculates the expected value of FA as a function of position along the pathway by performing a weighted average of FA values at each cross-section of the posterior distribution, where the cross-sections are defined at each voxel along the MAP path. This yields a 1D sequence of expected FA values, computed in the native space of each time point. These sequences can be used for point-wise analyses of the FA along the trajectory of a pathway, similar to those done for cross-sectional studies with streamline tractography elsewhere (Jones et al., 2005; Corouge et al., 2006; Maddah et al., 2008; O'Donnell et al., 2009; Colby et al., 2012).

Here we quantify test-retest reliability by computing the error $e \triangleq 100 \cdot |x_1 - x_2| / [0.5(x_1 + x_2)]$, where x_1 and x_2 the FA values extracted from the test and retest scan, respectively. This error is averaged over all positions along the pathway and over all subjects. In the case of longitudinal tractography, the correspondence of points along the pathways reconstructed from the test and retest scan is already known, as the paths have been mapped between the within-subject template and each scan by design. In the case of cross-sectional tractography, we establish correspondence of points by mapping the paths to the within-subject template

as a post-processing step. (This allows us to take advantage of the reliability afforded by the within-subject template space even in the cross-sectional case, although in a *post hoc* manner.) In both cases, however, the sequences of FA values are extracted in the native DW image space of each time point.

2.3.2. Sensitivity to WM changes—We compare the sensitivity of the longitudinal and cross-sectional tractography approaches by analyzing data from a set of HD patients. HD is an inherited neurodegenerative disorder, characterized by progressive motor dysfunction, emotional disturbances, and dementia. Carriers of the genetic mutation that causes HD develop symptoms early and survive for 15-25 years (Hersch and Rosas, 2008). Changes in WM measures derived from DW images in HD have been shown cross-sectionally (Reading et al., 2005; Rosas et al., 2006; Seppi et al., 2006; Bohanna et al., 2008; Magnotta et al., 2009; Rosas et al., 2010; Matsui et al., 2013) and longitudinally (Weaver et al., 2009). A widely reported finding, including from cross-sectional studies on our own data (Rosas et al., 2006, 2010), is progressive reduction of FA in the corpus callosum. Consequently we expect to be able to detect such changes in our longitudinal HD data as well, and we use the FMAJ and FMIN pathways here to evaluate the sensitivity of our longitudinal tractography to WM degeneration.

We analyze data from 46 early-stage HD patients (aged 53.3 ± 12.9 at baseline, 22 female) who were scanned at multiple time points. The minimum/median/maximum number of time points available per patient is 2/4/5. The interval between consecutive time points was 9.6 ± 4.2 months. At each time point, DW and T_1 -weighted images were collected by a 3T Siemens scanner with a 12-channel head coil. The DW images were acquired using a spinecho EPI sequence with axial in-plane isotropic resolution 2 mm, slice thickness 2 mm, $128 \times 128 \times 64$ image matrix, $TR=7980$ ms, $TE=83$ ms, $NEX=1$, $BW=1396$ Hz/pixel, GRAPPA acceleration factor 2. The series included images acquired with diffusion weighting along 60 non-collinear directions ($b = 700 \text{ s m}^{-2}$), and 10 images acquired without diffusion weighting ($b = 0$). The T_1 -weighted images were acquired using a multi-echo magnetization-prepared gradient echo (MP-RAGE) sequence with 1mm isotropic resolution, $256 \times 256 \times 176$ image matrix, 4 uniformly spaced echos with minimum $TE=1.64$ msec and maximum $TE=7.22$ msec, $TR=2.53$ sec, $TI=1.2$ sec, $BW=651$ Hz/pixel, flip angle 7° , GRAPPA acceleration factor 2.

Similarly to the previous experiment, we reconstruct the FMAJ and FMIN pathways for each subject in two ways: (i) Using the DW and T_1 -weighted images from all time points available for that subject jointly, *i.e.*, $n_T = 2$ in (1), and (ii) Using the DW and T_1 -weighted images from each time point independently, *i.e.*, $n_T = 1$ in (1). We obtain a sequence of expected FA values as a function of position along the pathway from each scan, as described in the previous section. We estimate the linear slope of FA values vs. time for each patient, as a function of position along the pathway, using the FA values from all time points available for a given patient. This yields a 1D sequence of slopes for each patient, showing the rate of change in the patient's FA values at different positions on each pathway. We establish spatial correspondence of these 1D sequences between different subjects by mapping the coordinates of each position to the MNI template space. This needs to be done

because the sequences will have a different lengths for different subjects in their native space.

Subject motion may also deteriorate progressively, thus confounding our results. To account for this, we compute the total motion index (TMI), a measure that we have shown previously to be effective in reducing spurious findings due to head motion when used as nuisance regressor in statistical analyses of FA (Yendiki et al., 2013). We perform linear regressions on the mean FA slope over all patients, using the slope of TMI vs. time as a nuisance regressor. We then compute *T*-tests on the mean FA slope for different positions along a pathway and we use the *p*-values of these tests to quantify the sensitivity of the longitudinal and cross-sectional tractography approaches.

3. Results

3.1. Test-retest reliability

Figure 3 shows the test-retest error in FA values for each of the 18 WM pathways reconstructed by TRACULA, averaged over all positions along the pathway and over all subjects, with standard error bars. The longitudinal tractography method, where pathways were reconstructed jointly from the test and retest scan, led to much lower error, *i.e.*, higher reliability, than the cross-sectional tractography method, where the reconstruction was performed independently in the test and retest scan. The difference in the average error between the two analysis methods was statistically significant at the $p < 0.05$ level for all pathways, based on paired *T*-tests.

Across all pathways, the average error was for $\epsilon = 5\%$ for longitudinal tractography and $\epsilon = 11\%$ for cross-sectional tractography. For reference, we also computed the average test-retest error for some ROI-based and voxel-based FA comparisons:

1. ROI-based

1.a *Whole-WM ROI*. Computing the average FA over the entire WM in the native space of each time point, based on a WM mask derived from each time point's structural segmentation, and averaging the test-retest error over all subjects: $\epsilon = 2\%$.

1.b *Atlas-based ROIs*. Computing the average FA over each of the 48 volumetric WM labels in the JHU atlas, which we mapped to each individual using the non-linear registration for FA maps from Smith et al. (2006), and averaging the test-retest error over all subjects: $\epsilon = 1\%/3\%/8\%$ (min/mean/max over the 48 WM labels).

1.c *Tract-based ROIs*. Performing deterministic tractography in each time point's DW data, labeling the 18 WM pathways listed in the Methods section with the two-ROI approach of Wakana et al. (2007), computing the average FA over an entire pathway, and averaging the FA test-retest error over all subjects: $\epsilon = 3\%/5\%/7\%$ (min/mean/max over the 18 WM pathways).

2. *Point-wise tract-based.* Labeling the 18 WM pathways with deterministic tractography and the two-ROI approach as above, but extracting point-wise FA values along each pathway rather than average FA over the entire pathway, and averaging the FA test-retest error over all subjects: $\epsilon = 9\%/16\%/25\%$ (min/mean/max over the 18 WM pathways).
3. *Skeleton-based.* Following the approach of Smith et al. (2006) and averaging the test-retest FA error over all voxels on the skeleton in template space and over all subjects: $\epsilon = 10\%$.
4. *Voxel-based.* Using the same non-linear registration for FA maps as in Smith et al. (2006) but without skeletonization, and averaging the test-retest FA error over all voxels in the brain in template space and over all subjects: $\epsilon = 18\%$.

Conceptually, our tractography approach, whether with the cross-sectional or with the longitudinal stream of TRACULA, is between an ROI-based and a voxel-based approach. On the one hand, we extract our FA statistics in the native DW image space and not in a template space. On the other hand, we do not compute a single average FA value for an entire pathway, but one for each cross-section along the pathway. That is, we neither average the FA over a large number of voxels (ROI-based approach), nor sample it at a single voxel (voxel-based approach). Therefore, it is reasonable for the test-retest error of our tractography approach without consideration for longitudinal analysis (11%) to be between the purely ROI-based error (2% for the entire WM and higher for smaller ROIs) and the purely voxel-based error (18%). When we also took into account the longitudinal nature of the data, by reconstructing the pathways jointly from the two time points, we were able to half the test-retest error of our tractography approach to 5%. Thus, our longitudinal tractography method achieved similar reliability as some of the ROI-based averages, while offering the ability to localize where along a pathway an effect is present, which would not be possible with the ROI-based averages.

As seen in figure 3, the longitudinal analysis approach not only reduced the mean values of the FA error, but also reduced the standard error bars on these values. An implication of this reduced error variance is that a smaller sample size would be needed to achieve the same statistical power with longitudinal tractography compared to cross-sectional tractography. Indeed, we follow Diggle et al. (2002), as was done by Reuter et al. (2012) for our anatomical analysis stream, to estimate the ratio of the sample sizes that would be required by the longitudinal and cross-sectional tractography to achieve the same power: $r_{SS} = 100(\sigma_L/\sigma_C)^2(1 - \rho_L)/(1 - \rho_C)$, where σ_L , σ_C the variance in the measurements obtained, respectively, with the longitudinal and cross-sectional tractography, and ρ_L , ρ_C the correlation coefficient between the test and retest measurements obtained, respectively, with the longitudinal and cross-sectional tractography. The average and standard error of this sample size ratio over all 18 pathways was $r_{SS} = 0.11 \pm 0.02$. That is, for the same effect size, the sample size required when the data is analyzed with longitudinal tractography is only about 11% of the sample size required when the data is analyzed with cross-sectional tractography.

We did not find a systematic bias towards including higher- or lower-FA areas in the pathways when using our longitudinal or cross-sectional tractography approach. A paired T -test on the mean FA difference between the longitudinal and cross-sectional methods in each subject, across both time points and all 18 pathways, did not find a statistically significant difference between the FA values extracted with the two methods ($p = 0.29$).

3.1.1. Sensitivity to WM changes—Figure 4 shows plots of the linear slopes of FA vs. time, estimated point-wise along the trajectory of the FMAJ and FMIN with cross-sectional and longitudinal tractography in HD patients. Each position along the x-axis represents a different point along these two pathways. At each position, there is a grouping of plots that was obtained from fitting linear slopes to the FA values of all time points at that position. Every black line represents a different patient. The red lines represent the average slope across all patients. An asterisk indicates a statistically significant group mean slope ($p < 0.05$) and a disk indicates a trend towards significance ($p < 0.1$). The estimated slopes of FA vs. time were mostly negative. When the data was analyzed with longitudinal tractography, these slopes were statistically significant at many more positions along the FMAJ and FMIN, indicating improved statistical power to detect subtle longitudinal changes. Small negative slopes were seen at several positions with cross-sectional tractography as well but without reaching statistical significance.

Here we focused on the FMAJ and FMIN because the corpus callosum has been found by other studies to be affected in HD patients and to be affected early (see, for example, Rosas et al. (2010)). Therefore, we had a specific hypothesis that we would be able to detect longitudinal changes in FMAJ and FMIN in the patient cohort examined above. Looking across the set of 18 WM pathways in an exploratory manner, we found 9.8% of the positions along all pathways to have statistically significant slopes with cross-sectional tractography, and 22.3% with longitudinal tractography. A one-sample T -test on the slopes estimated with longitudinal tractography across all subjects and all pathways found a significant mean slope ($p < 10^{-12}$). The same test on the slopes estimated with cross-sectional tractography did not find a significant mean slope ($p = 0.67$). Finally, a paired T -test on the difference between the FA slopes estimated with longitudinal and cross-sectional tractography at all positions along all 18 pathways, found the slopes estimated with longitudinal tractography to be significantly steeper ($p < 10^{-5}$).

4. Discussion

We have proposed a method for reconstructing WM pathways from longitudinally acquired DW images. Our method follows a Bayesian approach, estimating the posterior probability of a pathway given a subject's DW images and anatomical segmentations from all time points. This is achieved by representing the pathway in the space of an anatomical within-subject template and then transferring it to each of the time points to compute its likelihood given the DW image data at all time points, and its anatomical prior given the segmentation labels at all time points. We have shown that this can improve both reliability and sensitivity, when compared to the approach of reconstructing the pathway in each time point independently. As a result of the reduction in noise achieved by pooling the data from all time points, longitudinal tractography requires a substantially decreased sample size,

compared to cross-sectional tractography, to detect an effect of the same size. Our method is applicable to any number of time points and makes no assumptions on the direction of change (*e.g.*, decreasing or increasing WM integrity over time).

The proposed algorithm is the longitudinal extension of our previously developed method for automated global probabilistic tractography, TRAC-ULA (Yendiki et al., 2011). In global tractography, a path is modeled as a curve in 3D space and its shape is fit to the diffusion orientations over the entire brain. This is in contrast to local (“streamline”) tractography, where the shape of the path is fit step-by-step, using the diffusion orientation from one voxel at a time. The feature of local tractography, where streamlines may stop prematurely before reaching their destination, does not occur with global tractography. However, the latter involves searching over a massive solution space and therefore can benefit from constraining this space by incorporating prior information. In TRACULA this is done by using an atlas to learn how likely each pathway is to go through or adjacent to each anatomical segmentation label. That is, we do not use the atlas to determine the exact spatial coordinates of the pathway, and therefore we do not rely on perfect spatial alignment between the individual and the atlas. There is no assumption that the pathways have the same shape, size, or integrity in the study subjects as in the atlas subjects; only that they go through the same broad areas of anatomy.

In the longitudinal extension proposed here, we take into account the additional information that multiple data sets correspond to the same individual. Our joint reconstruction approach pools all the data available from an individual, therefore reducing noise. By using the data from all time points at once, we (*a*) avoid bias towards any of the time points and (*b*) ensure spatial correspondence of tracts between time points. Practically, this means that we avoid the scenario where we get the whole pathway at one time point and only part of the pathway in another time point, so we are always comparing equivalent structures. This is particularly important for point-wise analysis of diffusion measures along a pathway.

The algorithm that we have used for obtaining a within-subject template relies on a robust rigid registration method for aligning T_1 -weighted images across time points to a median space (Reuter et al., 2012). The use of rigid registration assumes that there is no change in intra-cranial volume across time points. This can be suboptimal in some applications, such as those involving developmental populations. We plan to address this limitation in the future by extending our method to non-linear within-subject registration, which would be more appropriate if large changes in the shape of the pathways were expected during the course of a longitudinal study. In addition, if the spatial extent of the probability distribution of the pathway were the measure of interest, instead of the point-wise FA along the pathway, it might be beneficial to allow the probability distribution in each time point to evolve independently, after initializing it with the jointly estimated distribution. However, we have shown that, even with the present registration and estimation approach, our longitudinal tractography can improve sensitivity to subtle changes in point-wise FA along a pathway in a patient population, when compared to cross-sectional tractography.

It would also be possible to generate a within-subject template based on the DW image data, by aligning the FA and/or diffusion orientation maps across a subject’s time points. In our

case, because we use the anatomical segmentations generated from the T_1 -weighted images by the longitudinal FreeSurfer stream, and we also use the T_1 -weighted images for registration to the TRACULA atlas, using a within-subject template generated from the T_1 -weighted images was a natural choice. In the future, however, we plan to investigate incorporating within-subject templates based on the DW image data into our longitudinal tractography method.

We used an affine registration method for mapping between the DW and T_1 -weighted images at each time point. This assumes that the images have been corrected for gradient non-linearity distortions. Note, however, that such distortions would confound our tractography method only if they were so severe that they changed the relative position (left, right, anterior, posterior, superior, or inferior) of major WM pathways with respect to their surrounding anatomical structures. Although a non-linear method for cross-modal registration could mitigate the effects of gradient non-linearities, it is important to ensure that such non-linearities and any online corrections for them do not change during the course of a longitudinal study, *e.g.*, due to a scanner upgrade. Such changes could confound any analysis approach, as they would amount to asymmetric processing of data from different time points.

For the experiments presented here, we used existing data that had been collected with acquisition protocols used routinely by prior neuroimaging studies at MGH. It is reasonable to expect longitudinal analysis methods to have an advantage over cross-sectional analysis methods when it comes to processing longitudinal data, regardless of data acquisition parameters. However, it is of interest to evaluate the impact that different acquisition parameters, such as the spatial and angular resolution of the DW images, have on the reliability and sensitivity of longitudinal study designs. Our analysis methods make use of T_1 -weighted images, so it is possible that the acquisition parameters of those images have an effect as well. Note, however, that we only use the cortical parcellation and subcortical segmentation labels from the T_1 -weighted image analysis, and we use them in the context of the much lower-resolution DW images. Hence, we do not expect the acquisition parameters of the T_1 -weighted images to affect our analysis as much as they would affect, say, a longitudinal study of cortical thickness estimates.

The statistical analysis that we performed on the HD patient data assumed a linear slope of FA vs. time and treated all subjects equally, even though each subject had a different number of time points. In the future, modeling non-linear time trajectories and taking into account the variable numbers of time points and inter-scan intervals could further improve inference. It would also allow us to incorporate time-varying regressors, such as the TMI (Yendiki et al., 2013), which we used here as a measure of motion in the DW images, or other measures that quantify motion in the T_1 -weighted images (Reuter et al., 2015). Furthermore, cluster-based correction and cluster enhancement could be used to address the multiple comparisons performed in the point-wise statistical analysis along the pathways. Although our statistical analysis of the point-wise diffusion measures was simplified, our goal here was to compare the relative merits of obtaining these measures by processing the images from all time points jointly rather than independently. We expect that longitudinal tractography will have an advantage over cross-sectional tractography, all else being equal,

even after the aforementioned downstream improvements to the statistical analysis methods. This will be a topic for future investigation.

Several methods have been proposed for combining data across subjects for point-wise analysis of diffusion measures along WM bundles (Jones et al., 2005; Corouge et al., 2006; Maddah et al., 2008; O'Donnell et al., 2009; Colby et al., 2012). This type of analysis allows the detection of localized effects that may be lost when averaging diffusion measures over the entire bundle. Of course, some localized effects in tensor-based diffusion measures may be related to confounds such as their dependence on pathway crossings. However, more generally, localized effects are supported by WM anatomy. That is, the large WM pathways that are typically studied with tractography are not monolithic structures. Each of them is composed of multiple smaller bundles that merge on and off the main pathway at different points along its trajectory. For example, the uncinate fasciculus contains both frontotemporal and frontolimbic connections. Therefore, disease effects cannot be expected to manifest uniformly along a WM pathway, and point-wise analyses can provide important information for localizing and interpreting these effects.

5. Conclusions

We have proposed an algorithm designed from first principles to reconstruct a WM pathway jointly from a series of longitudinally acquired DW images. The novelty of our approach consists in using the structural and DW images from all time points at once, rather than analyzing the data from each time point independently. In particular, we estimate the posterior probability distribution of a subject's pathways given the full series of longitudinal data. The algorithm is fully automated and therefore suitable for processing large sets of longitudinal data in an operator-independent manner. The joint reconstruction approach can improve reliability and sensitivity, leading to a substantial decrease in the sample size needed to detect subtle longitudinal changes in WM microstructure. This can be important to investigations of regional selectivity in age- or disease-related WM degeneration, as well as clinical trials where decreasing the required sample size would allow more treatments to be tested in parallel. Our results underline the importance of using image analysis methods that take into account the longitudinal nature of the data, rather than analyzing the data from each time point independently as if it were a cross-sectional data point.

Acknowledgements

Support for this research was provided in part by the National Institute for Biomedical Imaging and Bioengineering (*Pathway to Independence* award K99/R00-EB008129, R01-EB006758), the National Cancer Institute (K25-CA181632), the National Center for Research Resources (P41-RR14075, U24-RR021382), the National Institute on Aging (AG022381, 5R01-AG008122-22), the National Center for Alternative Medicine (RC1-AT005728-01), the National Institute for Neurological Disorders and Stroke (R01-NS052585-01, 1R21-NS072652-01, 1R01-NS070963), and was made possible by the resources provided by Shared Instrumentation Grants 1S10RR023401, 1S10RR019307, and 1S10RR023043. Additional support was provided by the National Institutes of Health Blueprint for Neuroscience Research (5U01-MH093765), part of the multi-institutional Human Connectome Project. In addition, B.F. has a financial interest in CorticoMetrics, a company whose medical pursuits focus on brain imaging and measurement technologies. B.F.'s interests were reviewed and are managed by Massachusetts General Hospital and Partners HealthCare in accordance with their conflict of interest policies.

References

- Aarnink SH, Vos SB, Leemans A, Jernigan TL, Madsen KS, Baaré WFC. Automated longitudinal intra-subject analysis (ALISA) for diffusion MRI tractography. *NeuroImage*. Oct.2013
- Behrens TEJ, Berg HJ, Jbabdi S, Rushworth MFS, Woolrich MW. Probabilistic diffusion tractography with multiple fibre orientations: What can we gain? *NeuroImage*. Jan; 2007 34(1):144–55. [PubMed: 17070705]
- Bohanna I, Georgiou-Karistianis N, Hannan A, Egan G. Magnetic resonance imaging as an approach towards identifying neuropathological biomarkers for Huntington's disease. *Brain Research Reviews*. 2008; 58(1):209. [PubMed: 18486229]
- Colby JB, Soderberg L, Lebel C, Dinov ID, Thompson PM, Sowell ER. Along-tract statistics allow for enhanced tractography analysis. *NeuroImage*. Feb; 2012 59(4):3227–3242. [PubMed: 22094644]
- Corouge I, Fletcher PT, Joshi S, Gouttard S, Gerig G. Fiber tract-oriented statistics for quantitative diffusion tensor MRI analysis. *Medical image analysis*. Oct; 2006 10(5):786–798. [PubMed: 16926104]
- Diggle, P.; Heagerty, P.; Liang, KY.; Zeger, S. *Analysis of longitudinal data*. 2nd. Oxford University Press; 2002.
- Fischl B, Salat DH, Busa E, Albert M, Dieterich M, Haselgrove C, van der Kouwe A, Killiany R, Kennedy D, Klaveness S, Montillo A, Makris N, Rosen B, Dale AM. Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. *Neuron*. Jan; 2002 33(3):341–55. [PubMed: 11832223]
- Fischl B, Salat DH, van der Kouwe AJW, Makris N, Ségonne F, Quinn BT, Dale AM. Sequence-independent segmentation of magnetic resonance images. *Neuroimage*. Jan; 2004a 23(Suppl 1):S69–84. [PubMed: 15501102]
- Fischl B, van der Kouwe A, Destrieux C, Halgren E, Ségonne F, Salat DH, Busa E, Seidman LJ, Goldstein J, Kennedy D, Caviness V, Makris N, Rosen B, Dale AM. Automatically parcellating the human cerebral cortex. *Cereb Cortex*. Jan; 2004b 14(1):11–22. [PubMed: 14654453]
- Greve DN, Fischl B. Accurate and robust brain image alignment using boundary-based registration. *NeuroImage*. Oct; 2009 48(1):63–72. [PubMed: 19573611]
- Hersch SM, Rosas HD. Neuroprotection for Huntington's disease: ready, set, slow. *Neurotherapeutics : the journal of the American Society for Experimental NeuroTherapeutics*. Apr; 2008 5(2):226–236. [PubMed: 18394565]
- Jbabdi S, Woolrich MW, Andersson JLR, Behrens TEJ. A Bayesian framework for global tractography. *NeuroImage*. Aug; 2007 37(1):116–29. [PubMed: 17543543]
- Jenkinson M, Bannister P, Brady M, Smith S. Improved optimization for the robust and accurate linear registration and motion correction of brain images. *Neuroimage*. Oct; 2002 17(2):825–41. [PubMed: 12377157]
- Jones DK, Travis AR, Eden G, Pierpaoli C, Basser PJ. PASTA: pointwise assessment of streamline tractography attributes. *Magnetic resonance in medicine : official journal of the Society of Magnetic Resonance in Medicine / Society of Magnetic Resonance in Medicine*. Jun; 2005 53(6):1462–1467.
- Keihaninejad S, Zhang H, Ryan NS, Malone IB, Modat M, Cardoso MJ, Cash DM, Fox NC, Ourselin S. An unbiased longitudinal analysis framework for tracking white matter changes using diffusion tensor imaging with application to Alzheimer's disease. *NeuroImage*. May.2013 72:153–163. [PubMed: 23370057]
- Leemans A, Jones DK. The B-matrix must be rotated when correcting for subject motion in DTI data. *Magn Reson Med*. Jun; 2009 61(6):1336–49. [PubMed: 19319973]
- Maddah M, Grimson WEL, Warfield SK, Wells WM. A unified framework for clustering and quantitative analysis of white matter fiber tracts. *Med Image Anal*. Apr; 2008 12(2):191–202. [PubMed: 18180197]
- Magnotta VA, Kim J, Kosciuk T, Beglinger LJ, Espino D, Langbehn D, Nopoulos P, Paulsen JS. Diffusion Tensor Imaging in Preclinical Huntington's Disease. *Brain imaging and behavior*. Mar; 2009 3(1):77–84. [PubMed: 21415933]

- Matsui JT, Vaidya JG, Johnson HJ, Magnotta VA, Long JD, Mills JA, Lowe MJ, Sakaie KE, Rao SM, Smith MM, Paulsen JS. Diffusion weighted imaging of prefrontal cortex in prodromal huntington's disease. *Human Brain Mapping*. Apr.2013
- O'Donnell LJ, Westin C-F, Golby AJ. Tract-based morphometry for white matter group analysis. *NeuroImage*. Apr; 2009 45(3):832–844. [PubMed: 19154790]
- Reading SAJ, Yassa MA, Bakker A, Dziorny AC, Gourley LM, Yallapragada V, Rosenblatt A, Margolis RL, Aylward EH, Brandt J, Mori S, van Zijl P, Bassett SS, Ross CA. Regional white matter change in pre-symptomatic Huntington's disease: a diffusion tensor imaging study. *Psychiatry research*. Oct; 2005 140(1):55–62. [PubMed: 16199141]
- Reuter M, Fischl B. Avoiding asymmetry-induced bias in longitudinal image processing. *NeuroImage*. Jul; 2011 57(1):19–21. [PubMed: 21376812]
- Reuter M, Rosas HD, Fischl B. Highly accurate inverse consistent registration: a robust approach. *NeuroImage*. Dec; 2010 53(4):1181–1196. [PubMed: 20637289]
- Reuter M, Schmansky NJ, Rosas HD, Fischl B. Within-subject template estimation for unbiased longitudinal image analysis. *NeuroImage*. Jul; 2012 61(4):1402–1418. [PubMed: 22430496]
- Reuter M, Tisdall MD, Qureshi A, Buckner RL, van der Kouwe AJW, Fischl B. Head motion during MRI acquisition reduces gray matter volume and thickness estimates. *NeuroImage*. Feb.2015 107:107–115. [PubMed: 25498430]
- Rohde GKG, Barnett ASA, Basser PJP, Marengo SS, Pierpaoli CC. Comprehensive approach for correction of motion and distortion in diffusion-weighted MRI. *Magnetic resonance in medicine*. Jan; 2004 51(1):103–114. [PubMed: 14705050]
- Rosas HD, Lee SY, Bender AC, Zaleta AK, Vangel M, Yu P, Fischl B, Pappu V, Onorato C, Cha J-H, Salat DH, Hersch SM. Altered white matter microstructure in the corpus callosum in Huntington's disease: implications for cortical "disconnection". *NeuroImage*. Feb; 2010 49(4):2995–3004. [PubMed: 19850138]
- Rosas HD, Tuch DS, Hevelone ND, Zaleta AK, Vangel M, Hersch SM, Salat DH. Diffusion tensor imaging in presymptomatic and early Huntington's disease: selective white matter pathology and its relationship to clinical measures. *Movement Disorders*. 2006; 21(9):1317–1325. [PubMed: 16755582]
- Seppi K, Schocke MFH, Mair KJ, Esterhammer R, Weirich-Schwaiger H, Utermann B, Egger K, Brenneis C, Granata R, Boesch S, Poewe W, Wenning GK. Diffusion-weighted imaging in Huntington's disease. *Movement disorders : official journal of the Movement Disorder Society*. Jul; 2006 21(7):1043–1047. [PubMed: 16570300]
- Smith SM, Jenkinson M, Johansen-Berg H, Rueckert D, Nichols TE, Mackay CE, Watkins KE, Ciccarelli O, Cader MZ, Matthews PM, Behrens TEJ. Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. *NeuroImage*. Jul; 2006 31(4):1487–1505. [PubMed: 16624579]
- Thompson WK, Holland D, Alzheimer's Disease Neuroimaging Initiative. Bias in tensor based morphometry Stat-ROI measures may result in unrealistic power estimates. *NeuroImage*. Jul; 2011 57(1):1–4. [PubMed: 21349340]
- Wakana S, Caprihan A, Panzenboeck MM, Fallon JH, Perry M, Gollub RL, Hua K, Zhang J, Jiang H, Dubey P, Blitz A, van Zijl P, Mori S. Reproducibility of quantitative tractography methods applied to cerebral white matter. *NeuroImage*. Jul; 2007 36(3):630–44. [PubMed: 17481925]
- Weaver KE, Richards TL, Liang O, Laurino MY, Samii A, Aylward EH. Longitudinal diffusion tensor imaging in Huntington's Disease. *Experimental neurology*. Apr; 2009 216(2):525–529. [PubMed: 19320010]
- Yendiki A, Koldewyn K, Kakunoori S, Kanwisher N, Fischl B. Spurious group differences due to head motion in a diffusion MRI study. *NeuroImage*. Nov.2013 88C:79–90. [PubMed: 24269273]
- Yendiki A, Panneck P, Srinivasan P, Stevens A, Zöllei L, Augustinack J, Wang R, Salat D, Ehrlich S, Behrens T, Jbabdi S, Gollub R, Fischl B. Automated probabilistic reconstruction of white-matter pathways in health and disease using an atlas of the underlying anatomy. *Frontiers in neuroinformatics*. 2011; 5:23. [PubMed: 22016733]
- Yushkevich PA, Avants BB, Das SR, Pluta J, Altinay M, Craige C, Alzheimer's Disease Neuroimaging Initiative. Bias in estimation of hippocampal atrophy using deformation-based

morphometry arises from asymmetric global normalization: an illustration in ADNI 3 T MRI data. *NeuroImage*. Apr; 2010 50(2):434–445. [PubMed: 20005963]

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Highlights

- A method for reconstructing white-matter pathways in longitudinal diffusion MRI data
- We reconstruct pathways using a subject's data from all time points jointly
- We represent a path in the space of a robust within-subject template We compute the posterior probability of the path given each time point's image data
- More reliable and more sensitive than analyzing each time point independently

Figure 1. Cross-sectional tractography

In the cross-sectional analysis approach, we process the data from each time point independently. The subject's T_1 -weighted image from each time point (a) is processed with FreeSurfer to yield a cortical parcellation and subcortical segmentation (b). The path of interest is represented as a spline in each time point's native DW image space independently (yellow curve for time point 1, magenta curve for time point N here). For each time point, the diffusion orientations (c) are estimated from the DW images and used to compute the likelihood of the path, whereas the cortical parcellation and subcortical segmentation labels are aligned with the DW images (d) and used to compute the prior probability of the path. The control points of the path are perturbed repeatedly and all the accepted paths are accumulated to estimate the posterior distribution of the path at each time point (e). This is repeated for each of the 18 pathways. Their posterior distributions are shown in (f) as isosurfaces thresholded at 20% of the maximum probability for each pathway.

Figure 2. Longitudinal tractography

In the cross-longitudinal analysis approach, we process the data from all time points jointly. The subject's T_1 -weighted images from all time points (a) are processed with the longitudinal FreeSurfer stream to compute a within-subject template (a1). This is used to initialize the reconstruction of the cortical parcellations and subcortical segmentations at all time points (b). The path of interest is represented as a spline in the space of the within-subject template, from which it is mapped to all time points (yellow curve for all time points). The diffusion orientations (c) are estimated from the DW images and used to compute the likelihood of the path given all time points jointly, whereas the cortical parcellation and subcortical segmentation labels are aligned with the DW images (d) and used to compute the prior probability of the path given all time points jointly. The control points of the path are perturbed repeatedly in the within-subject template space and all the accepted paths are accumulated to estimate the posterior distribution of the path given the images from all time points (e). This is repeated for each of the 18 pathways. Their posterior distributions are shown in (f) as isosurfaces thresholded at 20% of the maximum probability for each pathway.

Figure 3. Test-retest reliability

Percent error between FA along each of the 18 pathways reconstructed by TRACULA, as estimated from the test and retest scans of healthy controls with cross-sectional tractography (cyan) and longitudinal tractography (magenta). Errors are computed as $100 \cdot |x_1 - x_2| / [0.5(x_1 + x_2)]$, where x_1 and x_2 are the corresponding FA values from the test and retest scans, and averaged over all positions along a pathway and over all subjects. Longitudinal tractography increases test-retest reliability, when compared to cross-sectional tractography.

Figure 4. Sensitivity to WM changes

Slopes of the mean FA vs. time at each cross-section of the FMAJ and FMIN, plotted for each of the HD patients (black lines) and for the group on average (red lines). An asterisk indicates a statistically significant group mean slope ($p < 0.05$) and a disk indicates a trend towards significance ($p < 0.1$), based on a T -test. Longitudinal tractography increases power to detect changes, when compared to cross-sectional tractography.