Impact of DTI Smoothing on the Study of Brain Aging

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Abstract— **Diffusion tensor magnetic resonance imaging (DTI), a method for measuring the integrity of axon fiber tracts in the brain, plays an important role in clarifying brain changes that accompany aging and aging-associated neurodegenerative disease. While DTI smoothing methods theoretically have the potential to enhance such studies by reducing noise, it is unclear whether DTI smoothing has any practical impact on computed associations between fiber tract integrity and scientific variables of interest. Therefore we smoothed DTI images from 154 older adults using three kernel smoothing methods hypothesized to have differing strengths (the affine and log-Euclidean smoothers were hypothesized to enhance highly organized tracts better than the Euclidean smoother). Smoothing increased the strengths of expected associations between DTI and age, cognitive function, and the diagnosis of dementia. However, no particular smoothing method was uniformly superior in strengthening these associations. This data suggests that DTI smoothing enhances the sensitivity of studies of brain aging, but further research is needed to determine which smoothing technique is optimal.**

I. INTRODUCTION

Diffusion tensor magnetic resonance imaging (DTI) is a widely used brain imaging method that measures the integrity of axon fiber tracts that connect brain regions into distributed cognitive networks. DTI is currently used to study fiber tract integrity in Alzheimer's disease, multiple sclerosis, Huntington's disease, and other neurodegenerative disorders. Although DTI is non-invasive, broadly tolerated, and has the potential to provide important information to neuroscience researchers and clinicians, its signal to noise ratio (SNR) is known to be relatively low, possibly due to head motion, short T2 values [6], and the inherently low MR signal provided by diffusion of water molecules. Because this low SNR makes the extraction of anatomically meaningful brain connectivity information from DTI difficult, a variety of DTI smoothing algorithms have been developed that are applied after acquisition in an attempt to increase SNR (*e.g.*, [1][3][10]).

While numerous smoothing methods with distinct theoretical advantages have been presented, there exists no conventional wisdom about whether DTI smoothing has any meaningful impact on studies that relate DTI-based brain connectivity measurements to scientific variables of interest such as numerical measures of cognitive function. To our knowledge, no study to date has compared the effects of differing smoothing techniques on such studies that include large sets of real elderly human subjects. Performance comparisons on simulated DTI scans have been presented [3][4][10], and these have the advantage of a known gold standard to compare smoothing results to. However, it is unclear how the results of simulation studies generalize to real-world DTI scans. For individuals whose fiber tracts have been compromised by aging and neurodegenerative diseases in particular, it is unclear what constitutes a compelling simulated DTI scan. Therefore, it is imperative that the impact of DTI smoothing be assessed on large databases of real scans of individuals across a range from health to disease to better understand best practices for DTI research studies.

This study compares the performance of a set of DTI smoothing methods by determining how well they accentuate known associations between DTI summary variables and scientific variables of interest. There is a large literature showing that fractional anisotropy (FA), a voxel-level univariate DTI summary measure of local white matter tract integrity, is associated with a variety of clinical variables including age, vascular risk factors, and cognitive test scores in elderly individuals [2]. Building on this literature, we compare associations between FA and these clinical variables across a large set of images that are either in their raw form or smoothed using various methods. Smoothing methods that enhance the strength of expected associations between FA and the clinical variables are considered advantageous for application to studies that collect DTI data.

We smoothed a set of 154 DTI scans of elderly adults using three different smoothing methods that fall under the general category of kernel smoothers, with affine, Euclidean, and log-Euclidean kernels respectively. Raw DTI images and the outputs of DTI smoothers were summarized using voxel-level FA maps, and FA at each voxel was associated with twelve relevant clinical variables for which a particular association with FA was expected based on prior reports. We then conducted voxel-based and cluster-based significance tests to determine which smoothing method produced the most significant associations over the largest anatomical zones. We predicted that DTI smoothing would significantly enhance the strength of associations between FA and scientific variables, and that the affine and log-Euclidean

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smoothers would better enhance associations in areas containing complex-shaped fiber tracts.

II. METHODS

A. Data

All study participants were elderly volunteers in the UC Davis Alzheimer's Disease Center (UCD ADC) Longitudinal Cohort. Imaging was performed at the UCD Imaging Research Center on a 1.5T GE Signa Horizon LX Echospeed system. A single-shot spin-echo echo planar imaging DTI sequence was used to estimate diffusion tensors. Relevant DTI acquisition parameters include: TE: 94 ms, TR: 8000 ms, Flip angle: 90 degrees, Slice thickness: 5 mm, slice spacing: 0.0 mm, FOV: 22 cm x 22 cm, Matrix: 128 x 128, B-value: 1000 s/mm^2. Each acquisition included collection of 2 B0 images and 4 diffusion-weighted images acquired along each of 6 gradient directions. The raw DTI data was pre-processed as described previously to correct for head motion and eddy current artifacts, and to estimate a diffusion tensor at each voxel [7].

B. DTI smoothing

DTI provides, at each spatial position s in $\Re^3$, a 3x3 positive definite matrix Y such that the magnitude of water diffusion along 3D direction b is proportional to $\exp(-cb^T Y b + \xi)$, for random noise ξ and a constant c. Various univariate summary measures derived from the eigenvalues $\{\lambda_1, \lambda_2, \lambda_3\}$ and eigenvectors $\{v_1, v_2, v_3\}$ of Y are commonly used to quantify the amount and directionality of local water diffusion, and these in turn are used as proxy measures of axon tract integrity. Fractional anisotropy (FA), for example, quantifies the degree to which water diffusion is concentrated along one spatial direction:

$$ FA = \sqrt{\frac{3}{2}} \frac{\sqrt{(\lambda_1 - \hat{\lambda})^2 + (\lambda_2 - \hat{\lambda})^2 + (\lambda_3 - \hat{\lambda})^2}}{\sqrt{\lambda_1^2 + \lambda_2^2 + \lambda_3^2}} \tag{1} $$

Here, $\hat{\lambda}$ is the mean of $\{\lambda_1, \lambda_2, \lambda_3\}$. DTI smoothing amounts to removing fluctuations in Y between neighboring s positions, while insuring that the resulting Y remain positive definite. Weighted averaging is one prominent approach to removing such fluctuations. Specifically, for each location s, we provide the following smoothed estimate $\hat{Y}$ based on the positive definite matrices X_i located at locations s_i

$$ \hat{Y} = \text{argmin}_{Y \in M} \sum_{i=1}^{n} \omega_i(s) d_M^2(X_i, Y) \tag{2} $$

Here, $\omega_i(s) = K(\|s - s_i\|)$ is a weighting function, based on a non-negative integrable kernel K that provides decreasing values with increasing distance $\|s-s_i\|$ between s and s_i. The distance measure $d_M(X_i, Y)$ provides increased values with decreasing similarity between X_i and Y. M is the manifold of positive definite 3x3 matrices. Thus, we seek the Y that maximizes similarity to all other X_i while discounting the influence of X_i that are spatially distant.

The behavior of this approach, termed weighted Karcher averaging [5], critically depends on the distance measure d_M.

If d_M is Euclidean, $e.g.$ $d_M(X,Y) = \{trace(X-Y)^2\}^{1/2}$, $\hat{Y}$ can be calculated in closed form:

$$ \hat{Y} = \sum_{i=1}^{n} \omega_i(s) X_i \Big/ \sum_{i=1}^{n} \omega_i(s) \tag{5} $$

However, the resulting $\hat{Y}$ are prone to swelling artifacts, $i.e.$, increases in the determinant of $\hat{Y}$ that give an inflated sense of the amount of water diffusion locally [1]. To overcome this limitation, a log-Euclidean distance measure has been proposed: $d_M(X,Y) = \|\log X - \log Y\|$ where $\| \ \|$ is the Euclidean norm [1]. For this distance measure, $\hat{Y}$ can be calculated in closed form as well:

$$ \hat{Y} = \exp\left(\sum_{i=1}^{n} \omega_i(s) \log(X_i) \Big/ \sum_{i=1}^{n} \omega_i(s) \right). \tag{4} $$

An alternative to the log-Euclidean distance is the affine-invariant distance:

$$ d_M(X,Y) = \left[trace\left(\log(X^{-1/2} Y X^{-1/2}) \right)^2 \right]^{1/2}. \tag{5} $$

Its key advantage is that it is affine-invariant: for any affine transformation g, $d_M(gXg^T, gYg^T) = d_M(X,Y)$. This property may be advantageous for reproducibility across scans given that the absolute orientations of v_1, v_2, and v_3 are usually arbitrary and can vary from scan to scan. There is no closed form solution for $\hat{Y}$; iterative, recursive estimation approaches are used instead. While the log-Euclidean and affine distance measures have theoretical advantages suggesting that they will be better able to preserve geometric structures in the data, it is unclear whether these algorithmic differences have any practical effect on studies that relate DTI to relevant scientific variables.

C. Statistical analysis

FA associations with age and various cognitive functions and vascular measures reflect the damaging effects of aging-related biological processes on axonal integrity [2]. We used voxel-level statistical tests to determine the degree to which the DTI smoothers enhanced the strengths of these expected associations. The steps involved in these tests are as follows:

1) Image registration to common template: We selected a Gaussian kernel K and performed Euclidean, log-Euclidean, and affine-invariant smoothing on 154 DTI data sets. For each raw and smoothed data set we calculated FA at each voxel. All FA maps were co-registered to the same template space through a series of steps [7] including linear alignment to a corresponding T1-weighted image, nonlinear deformation of the T1-weighted image to a minimum deformation template (MDT), and transformation of the FA maps to the MDT space via the linear alignment and nonlinear deformation.

2) Tests of association between FA and clinical variables: At each voxel in the MDT space, we performed statistical tests that related FA to scientific variables that are relevant to studies of brain aging. Greater age and greater burden of
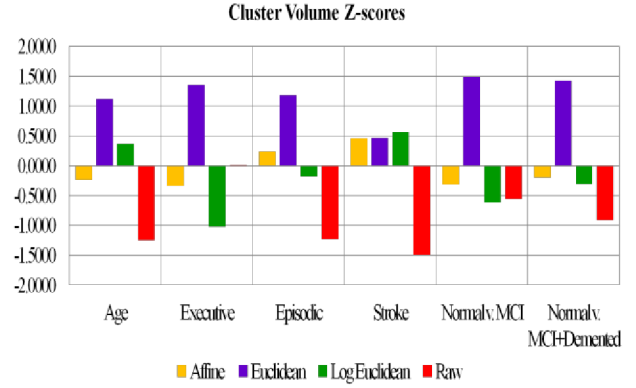
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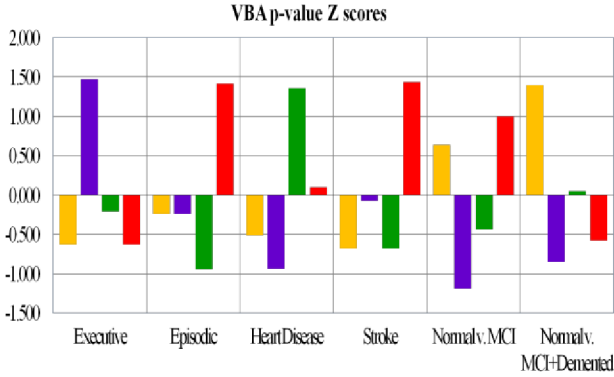
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Fig 1: (A) Z-scores of p-values between smoothing methods for parameters that correlate significantly ($p<0.05$) with FA when VBA is used. Lower z-scores implied stronger associations. Age correlated significantly ($p=0.002$) with FA and displayed z=0 for all smoothing methods. It was therefore removed. (B) Z-scores of volumes of significant clusters ($p<0.05$) in associations between FA and clinical variables. Greater z-scores indicate larger clusters of significantly-associated voxels. Z-scores for a particular smoothing method within a parameter are calculated with respect to all other smoothing methods within that parameter.

vascular disease are generally acknowledged to be associated with lesser FA, reflecting the damaging effects of aging-related and vascular-related biological processes on the brain [2]. Poorer cognitive function, measured by lower scores on cognitive tests and clinical diagnoses of mild cognitive impairment (MCI) or dementia, is generally understood to be associated with lesser FA. We used voxel-level statistical tests to determine the degree to which the DTI smoothers enhanced the strengths of these expected associations. At each voxel a set of linear regression models with FA as the outcome variable was estimated. Separate models included age, a vascular risk summary variable, a heart disease burden summary variable, or composite measures of episodic memory or executive function as the lone predictor. T tests at each voxel compared FA between cognitively normal individuals and those clinically diagnosed with MCI, or those with either MCI or dementia; and between individuals who did and did not have a clinical history of stroke. These tests were limited to voxels within a cerebral white matter mask, which encompassed white matter voxels common to all subjects.

3) Corrections for multiple comparisons: Each voxel-level statistical test provides a map of the *t* statistic indicating the strength of the association throughout the white matter mask. We used two common approaches to guard against spurious associations emerging from the large number of statistical tests performed. First, non-parametric permutation testing at each voxel was applied using $p<0.05$ as a voxel-level significance threshold [8]. Second, all voxels whose *t* statistic passed a predetermined threshold of 3 were entered into nonparametric significance testing (1000 permutations) for significant-sized clusters of correlations [8]. All clusters with a cluster significance value of $p<0.05$ in this cluster level permutation analysis were deemed statistically significant.

D. Comparison of smoothers

Using these statistical tests, we compared the raw FA maps and the FA maps generated by each of the smoothers in terms of the strengths of associations between FA and the

clinical variables. Specifically, for each permutation-corrected voxel-level statistical test we evaluated the minimum *p* value for the test across all voxels for which the test results were statistically significant, i.e. $p<0.05$. We also evaluated the volume of voxel clusters that were significant under cluster-level permutation tests. Because they provided stronger expected associations between FA and the clinical variables, FA maps that produced minimum significant voxel *p* values closer to 0 or larger clusters of significant voxels were considered advantageous.

III. RESULTS

A. Voxel-Based Analysis

Voxel-based analysis showed significant ($p<0.05$), expected associations between greater FA values and greater executive function, greater episodic memory, lesser burden of heart disease, absence of stroke, and a cognitively normal clinical diagnosis (Figure 1a). No single smoothing method provided the smallest minimum significant *p* values in these associations: the Euclidean smoother provided the lowest *p* values for associations with heart disease and clinical diagnosis, while the log-Euclidean and affine smoothers provided lower *p* values for associations with executive function, episodic memory, and stroke. Although the raw DTI data provided a minimum significant *p* value that is roughly equal to that of the affine smoother for associations with executive function, there were no clinical variables for which the raw data provided substantially lower *p* values than the smoothed data, implying that DTI smoothing is advantageous in a general sense.

B. Cluster-Based Analysis

In the cluster-based analysis, greater FA was significantly associated with lesser age, greater executive function, greater episodic memory, absence of stroke, and cognitively normal clinical diagnosis (Figure 1b). For most of these associations, Euclidean smoothing provided the largest clusters of significantly associated voxels, and the raw data provided the smallest clusters. The log-Euclidean and affine smoothers generally provided cluster sizes that
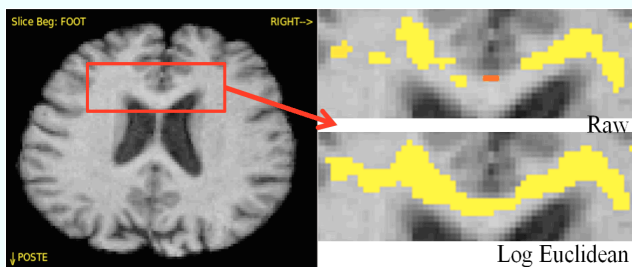
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Figure 2: Larger significance volume and more defined white matter tract are visible when log-Euclidean smoothing is used. Cluster of the significant correlation between FA and age (p=0.00) is overlaid on a standard MDT image.

were intermediate between the high and low extremes provided by Euclidean-smoothed and raw data, with the exception being the association between FA and a clinical diagnosis of normal vs. MCI. An example of a difference in significant voxel cluster size between raw and log-Euclidean smoothed DTI data is shown in Figure 2, for an association between FA and age.

IV. DISCUSSION

The goal of this study was to determine whether DTI smoothing exerts a significant impact on studies that associate DTI summary parameters with scientific variables that are relevant to brain aging. The key finding is that the strengths of expected associations between a DTI summary parameter (FA) and a variety of associated variables, including vascular risk factors and measures of cognitive function, increased substantially by applying DTI smoothing. Associations are measured by the magnitude of voxel p values and the volumes of significant voxel clusters. This strongly suggests that neuroscience practitioners should apply smoothing methods to their DTI data to best enhance the information about the natural course of brain aging that DTI can provide.

However, among the three smoothers, the results did not uniformly support the view that techniques which appeared more mathematically attractive (*i.e.*, the affine and log-Euclidean smoothers) best enhanced the expected associations. Euclidean smoothing generally led to larger significantly associated brain regions. However, for some clinical variables (episodic memory and stroke) the strengths of significant associations at a voxel level (as measured by voxel p values) were relatively stronger for log-Euclidean and affine smoothers. One interpretation for this finding could be that the Euclidean smoother more effectively forces a greater degree of homogeneity over larger local regions, that is, it removes geometric structure from anatomical zones rather than preserving it, as affine and log-Euclidean smoothers do. This results in larger image regions with significant associations; however, because the other smoothers more accurately preserve the white matter tract structure, their associations over smaller neighborhoods are stronger. Further study is required to better understand this phenomenon.

This study is one of the few that compares the performance of multiple DTI smoothers from the point of view of the scientific end user and not from the perspective of the theoretical mathematical advantages. However, the study is not without limitations. First, we did not have ground-truth information about which white matter voxels are and are not associated with the scientific variables; we only had strong hypotheses about these associations gleaned from a large body of prior DTI studies. Second, we only compared three kernel smoothing methods and didn't consider entirely different DTI smoothing techniques that do not fit into the kernel smoothing framework. Third, our experiments were applied to diffusion tensor data, and it is not clear how they generalize to High Angular Resolution Diffusion Imaging (HARDI), a more advanced and increasingly widespread extension of DTI that allows a much richer representation of local water diffusion properties [9].

In summary, DTI smoothing has a substantial positive impact on studies of brain aging, but the tradeoffs among diverse smoothers in this setting may be complex.

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