Quantitative Tractography Metrics of White Matter Integrity in Diffusion-Tensor MRI Using Diffusivity Scalars

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Introduction

We introduce and evaluate six quantitative tractography metrics for assessing white matter integrity. These metrics build on earlier work by Correia et al. [1]. Our new metrics not only distinguish between healthy and diseased populations, but also complement the previously introduced metrics by potentially exposing the nature of axonal damage. Brain tractography models derived from DTI data can yield valuable insights about the topography and overall structural integrity of white matter. Quantitative measures of tractography models, however, are necessary to characterize changes of white matter integrity caused by aging and disease. Several studies have examined quantitative tractography. DTIStudio [2], a recent software tool that generates tractography models, lets users select tracts of interest and display their lengths and number. Similar approaches by different research groups have successfully combined tract generating software packages [3] with diffusion scalar maps [4], but these efforts extend no further than the projection of neural tracts into scalar maps. Correia et al. introduced and evaluated several metrics that weighted the lengths of neural tracts by scalar measures of diffusivity, such as linear and fractional anisotropy. We propose to weigh the lengths of neural tracts by other diffusivity scalars, such as the reciprocals of mean, axial, and radial diffusivity. We use the reciprocals of these diffusion scalars because they correlate negatively with atrophy.

Methods

MRI data for 12 participants with vascular cognitive impairment (VCI) and 15 healthy controls (HC) (group-matched for age) were acquired on a 1.5T Siemens Symphony scanner. Three co-registered double spin-echo, echo-planar diffusion-weighted volumes of the brain were collected. The parameters for subsequent acquisitions were: thickness=5mm, inter-slice spacing=.1mm, slices/acquisition = 30, matrix = 128 × 128, FOV = 21.7cm × 21.7cm, TR = 7200ms, TE = 156ms, NEX = 3, bipolar diffusion encoding gradients were applied in 12 directions. The total time for the three acquisitions was slightly under 15mins. Tractography models were generated using a fiber tracking algorithm that carefully covers the entire brain with fibers that capture all features while minimizing redundancy. This careful seeding and calling is central to the calculation of the metrics and is described in detail in [5]. We evaluated our metrics for whole brain models as well as three specific regions of interest: transcallosal fibers, right and left cingulum bundles. To eliminate artifacts resulting from variations in intracranial volumes, metrics were normalized by intracranial volume. To adjust for multiple comparisons the significance threshold of 0.01 was used.

Table 1 summarizes the metrics, with abbreviations and definitions. We used ANOVA to evaluate our metrics and Levene's and Shapiro-Wilkins tests to confirm homogeneity of variance between groups and normality across the metrics.

Table 1 *Metrics and definitions*

Abbreviation	Definition
TWL*rd*	Total Weighted Length: The total summed length of all streamtubes in tract of interest after weighting each streamtube by the reciprocal of its average radial diffusivity
TWL*ad*	Total Weighted Length: The total summed length of all streamtubes in tract of interest after weighting each streamtube by the reciprocal of its average axial diffusivity
TWL*md*	Total Weighted Length: The total summed length of all streamtubes in tract of interest after weighting each streamtube by the reciprocal of its average mean diffusivity
NTWL*rd*	Normalized Total Weighted Length: TWLrd normalized by intracranial volume
NTWL*ad*	Normalized Total Weighted Length: TWLad normalized by intracranial volume
NTWL*md*	Normalized Total Weighted Length: TWLmd normalized by intracranial volume

Results

The average age was 62±10.7 years for the healthy control group and 63±15.0 years for the VCI group. A *t*-test revealed no significant effect of age (p=.07) among groups. There was a high correlation between age and TWL*ad*, TWL*rd*, and TWL*md*, in healthy subjects (r=-.57, p<.01). The correlation was not significant for the metrics normalized by intracranial volume. In VCI patients there was no significant correlation between age and any of the metrics. A Pearson bivariate coefficient matrix revealed a strong correlation among all metrics (r >.93, p<.01). ANOVA results showed that these metrics were not statistically significant (F<5.93, p>.02) in whole brain models. In transcallosal fibers, however, there was a significant group difference for all metrics (F>8.75, p<.01). All six metrics had a strong effect size (g=.81 to 1.45), with TWL*rd* having the largest effect size. The effect sizes for these metrics were somewhat stronger than for the metrics reported by Coreia et al. [1], which used linear and fractional anisotropy as weighting factors (g=.79 to 1.42, p<.01). In both left and right cingulum bundles, the ANOVA model revealed no significant difference between subjects (F<3.90, p>.06).

Discussion and Conclusion

The correlation between the metrics and age, in healthy controls, supports the validity of the metrics, since white matter deteriorates with aging. The results suggest that normalizing our metrics for intracranial volume attenuates their association with age in the healthy control group. This is in agreement with previous findings by Correia et al. [1].The intercorrelation among the metrics was expected, since they all derive from the total length of the streamtubes and are weighted by similar measures. Radial diffusivity increases with demyelination whereas axial diffusivity increases with axonal loss [6]. Although white matter atrophy in VCI is characterized by both types of axonal damage, our results suggest that demyelination may have a slightly greater impact. Since mean diffusivity depends on both radial and axial diffusivity, the effect size of the metrics using this measure should lie between those of the metrics using *ad* and *rd*. We retain the *md*- and *ad*- based metrics as being equally important to *rd*-based metrics, despite the lower effect size, because use of all three metrics could potentially reveal more about the type of axonal damage than one type of metric alone. Overall, these new metrics provide some insight into the pathological characteristics of white matter injury in VCI. As such, they complement the previously introduced metrics that use linear and fractional anisotropy. The absence of a significant group difference in the left and right cingulum bundles is consistent with previous findings by Correia et al. [1]

In general, the results showing that patients with known white matter injury differ significantly on our metrics, supports the potential utility of these metrics for quantifying and characterizing changes in white matter integrity. These new metrics may provide new insights into the pathological processes underlying changes in white matter integrity throughout the lifespan, in both health and disease.

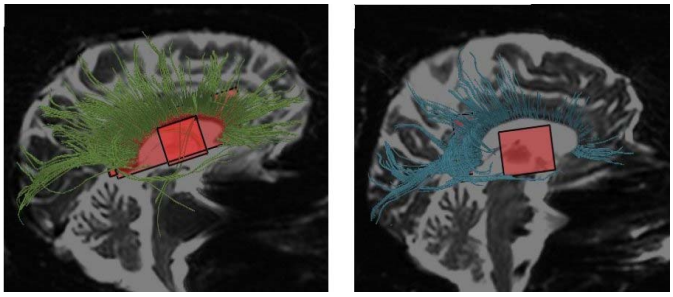

Fig. 1 Transcallosal fibers of a 45 year old healthy subject and a 45 year old VCI patient. The density of streamtubes decreases significantly in the VCI patient. Our metr ics quantify this decrease and shed light on the nature of damage.

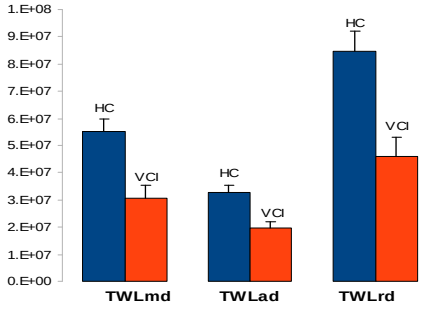

Fig. 2 Average Total Weighted Lengths (mm) of streamtubes in the corpus callosum of healthy and VCI subjects. This graphical representation shows the drastic decrease of the metrics in VCI subjects.

References: **[1]** S. Correia et al. NeuroImage. 2008 **[2]** H. Jiang et al. Comput. Methods Programs Biomed. 2006 **[3]** MedINRIA, PRIDE **[4]** M. Ashtari et al. Arch. Gen Psychiatry. 2007 **[5]** S. Zhang et al. IEEE Trans. Vis. Comput. Graph. 2003 **[6]** S. Song et al. NeuroImage. 2002