Editor's Pick

Quantitative TOI metrics for white-matter integrity based on diffusion tensor MRI data

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Introduction

DTI (diffusion tensor imaging)-based tractography can be used to generate curves in space that show the direction of fastest water diffusion. Such curves tend to be related to white-matter structure. One of the challenges with tractographic result is to quantify the curves in a way that can be used for scientific and medical inquiry.

We present several new tractography metrics for quantifying the structural integrity of cerebral white-matter fiber pathways. Our hypotheses were 1) that the metrics would inversely correlate with age, 2) that they would have lower values in patients with vascular white-matter injury compared to controls, 3) that they would correlate significantly with performance on tests of executive cognitive function [i.e., Trail Making Test parts A and B (TMT-A and TMT-B)[1)]] thought to be related to white-matter integrity, and 4) that they would not correlate significantly with performance on a task thought to be more sensitive to cortical than white-matter impairment [i.e., Boston Naming Test (BNT)[2)]].

The remainder of this short article will present our methods for calculating tractography results, describe how we calculate the particular measures we introduce, and demonstrate correlations with pathology, age, and cognitive task performance.

Tractography methods

As we describe in the article of Zhang et al,[3)] we calculate a set of curves in 3-space that represent a diffusion imaging dataset. Each curve is a path of fastest diffusion through the dataset. The curves tend to be correlated with coherent white-matter structures. We calculate the set as follows: first, we produce a set of seed points that are spaced every 0.85 mm on a regular Cartesian grid. Second, we jitter each point randomly within a diameter of 0.85 mm to remove any structure related to the grid. Third, we calculate a path through each seed point that moves always in the direction of fastest diffusion. We use a tri-cubic b-spline interpolation of the tensor coefficients at each pixel to evaluate the image between sample points. The path is calculated using second-order Runge-Kutta integration.[4)] We terminate the integration if the linear anisotropy[5)] drops below 10%. Fourth, we cull paths shorter than 10 mm as well as redundant paths. Redundancy is identified by comparing each new path with those already present; the shorter path of any similar pair (as described in the article of Zhang et al[3)]) is removed. After this culling step we have a set of paths that are representative of the connectivity information in the diffusion imaging dataset.

New white-matter measures

Our new white-matter measures are calculated from the representative set of curves. First, a subset of the curves is selected interactively using software similar to that described in the article of Akers et al.[6)] We call such a subset of curves a "tract of interest" or TOI. For that tract we define the following five measures.

First, the number of streamtubes (NS) is the count of curves. We posit that this measure provides information about the bandwidth of the tract or the variability across a section. It is likely to decrease with pathology or age, in general, although it may also increase if long paths have been broken.

Second, the total length (TL) is the sum of the lengths of all the curves in the TOI. This measure is likely to capture a sense of the size of a tract. It, too, should tend to decrease with pathology or age as paths shrink away from the end or are cut at a lesion.

Third, the total weighted length (TWL) is the sum of the lengths weighted by the average linear anisotropy. As with other measures, it should tend to decrease with pathology or age. It is likely to be more sensitive to subtle changes in white-matter integrity that cause local reductions in anisotropy that are insufficient to alter the number or length of the calculated paths.

The measures described so far would increase and decrease with brain size. While that might be useful in some cases, we have also defined measures that are normalized by the relative intracranial volume. These measures are: fourth, normalized total length (NTL) and fifth, normalized total weighted length (NTWL).

Correlates of measures with pathology, age, and cognition

We tested these five measures on healthy controls (HC) and on patients with vascular cognitive impairment (VCI). These patients have cognitive impairment that is thought to be related to subcortical ischemic vascular disease but the level of impairment is insufficient to warrant a diagnosis of dementia.[7] We interactively chose four TOIs for each subject: whole brain, interhemispheric paths, and the left and right cingulum bundles (Fig. 1).

Diffusion imaging was performed on a Siemens scanner using an interleaved double-spin-echo protocol producing datasets with 1.7 mm^3 samples. The datasets were zero filled to produce 0.85 mm^3 voxels. We imaged eighteen HC and fifteen patients with VCI.

After controlling for age, all five measures were significantly lower ($p < 0.01$) for the VCI group in whole brain and interhemispheric fibers but not in either left or right cingulum bundles (e.g., Fig. 2). Almost all measures were significantly correlated with age in the HC group (except $p = 0.052$ in one metric of one TOI). The measures were not correlated with age in the VCI group possibly due to a masking of aging effects by the vascular pathology.

Subjects also underwent cognitive testing, including TMT-

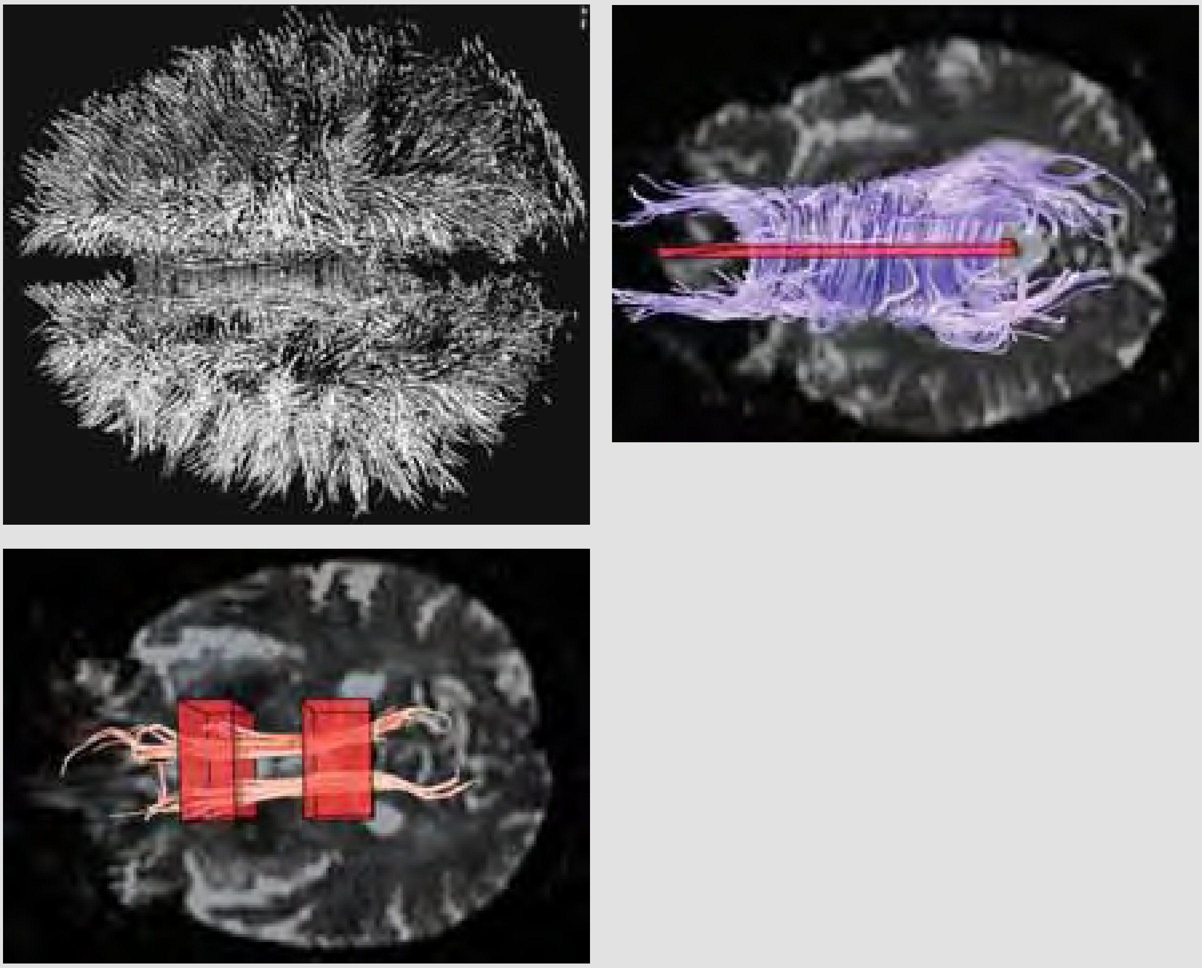

Fig. 1 TOIs used in our study
a: Whole brain model
b: Interhemispheric fibers
c: Cingulum bundle

a	b
c	

A and TMT-B and BNT. The normalized TOI measures are robustly and significantly correlated with both TMT-A and TMT-B, which are known to be linked to white-matter injury. None of the measures correlated with BNT, which is known to be linked to cortical abnormalities. These results are consistent with the hypothesis that our measures can quantify clinically-relevant white-matter changes.

Conclusion

In conclusion, we have demonstrated a set of new diffusion-derived measures for quantifying white-matter changes. Our results show that the measures correlate with disease, age, and cognitive testing as hypothesized. Taken together, these results suggest that the new measures quantitatively capture clinically relevant white-matter changes and may be useful for quantifying such changes to study and manage many diseases.

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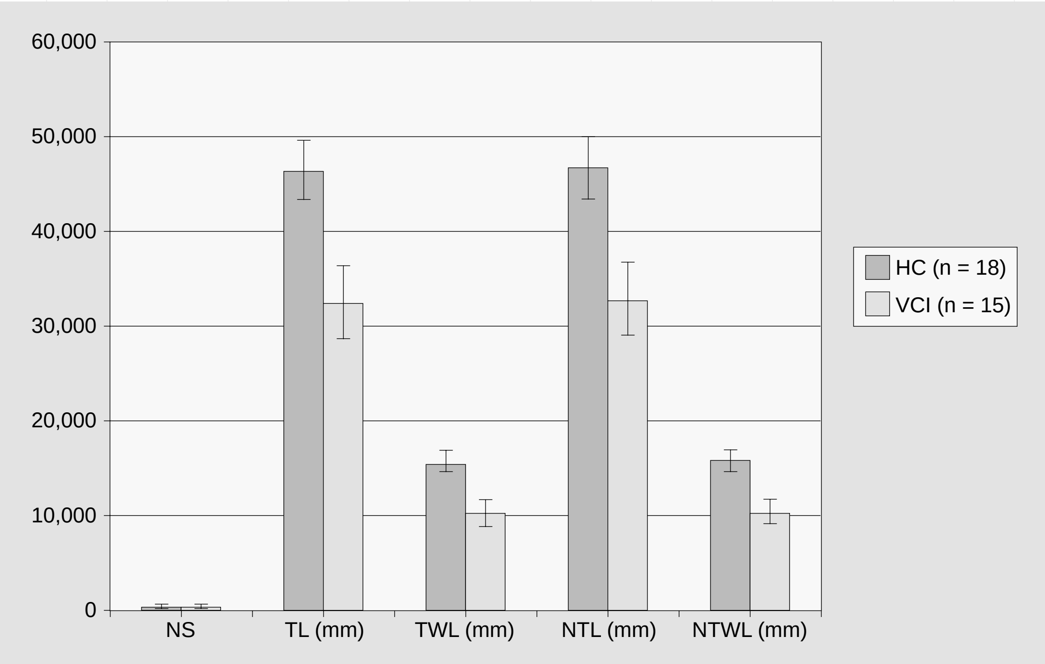

Fig. 2 Differences between HC and VCI groups for interhemispheric fibers passing through the corpus callosum: results were similar in whole brain white matter

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