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# Spatial coherence of oriented white matter microstructure: Applications to white matter regions associated with genetic similarity

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ABSTRACT

We present a method to discover differences between populations with respect to the *spatial coherence* of their oriented white matter microstructure in arbitrarily shaped white matter regions. This method is applied to diffusion MRI scans of a subset of the Human Connectome Project dataset: 57 pairs of monozygotic and 52 pairs of dizygotic twins. After controlling for morphological similarity between twins, we identify 3.7% of all white matter as being associated with genetic similarity (35.1 k voxels, $p < 10^{-4}$, false discovery rate 1.5%), 75% of which spatially clusters into twenty-two contiguous white matter regions. Furthermore, we show that the orientation similarity within these regions generalizes to a subset of 47 pairs of non-twin siblings, and show that these siblings are on average as similar as dizygotic twins. The regions are located in deep white matter including the superior longitudinal fasciculus, the optic radiations, the middle cerebellar peduncle, the corticospinal tract, and within the anterior temporal lobe, as well as the cerebellum, brain stem, and amygdalae.

These results extend previous work using undirected fractional anisotrophy for measuring putative heritable influences in white matter. Our multidirectional extension better accounts for crossing fiber connections within voxels. This bottom up approach has at its basis a novel measurement of coherence within neighboring voxel dyads between subjects, and avoids some of the fundamental ambiguities encountered with tractographic approaches to white matter analysis that estimate global connectivity.

## Introduction

Structural connectomics of the human brain is increasingly recognized as an essential complement to functional imaging. Imaging the physical connectivity in the brain is primarily based on diffusion-weighted MRI (dMRI). While this imaging continues to improve in angular resolution of diffusion signals, there remain significant challenges in image reconstruction, representation of diffusion features, and statistical analysis of white matter structures across populations of subjects.

There is an abundance of methods for analyzing dMRI, many of which show promise in diagnosing brain abnormalities such as strokes (Yeh et al., 2013) and discovering correlates of many cognitive processes including metacognition (Baird et al., 2015). Current approaches generally fall into one of two categories: *Brain Graph* methods (Bullmore and Sporns, 2009) use dMRI to estimate "connection strength" between pairs of cortical regions while *Scalar-based* methods calculate a single value at each voxel that is interpreted as reflecting "white matter integrity" (Jones et al., 2013).

Brain Graphs succinctly represent long-range connectivity between non-overlapping parcels of gray matter. The analyst chooses a gray matter parcellation, then uses a tractography algorithm to trace paths across white matter voxels. There are many approaches to tractography, but they all utilize diffusion orientation information to grow streamlines through space. Tractography results therefore depend on the accuracy of the voxel-wise estimates of white matter orientation, which can be complicated in structures such as crossing fibers (Jbabdi and Johansen-Berg, 2011) with Maier-Hein et al. (2016) suggesting these tractography methods are readily dominated by false positive streamlines. Brain Graphs represent cortical regions as nodes and use a property of streamlines (such as their count) to weight edges, resulting in a connectivity matrix. These connectivity matrices are the basis for numerous

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network-based approaches (Bullmore and Bassett, 2011) that have shown promise in understanding the development of large-scale brain connectivity (Hagmann et al., 2010) and processes such as aging, disease, and cognition (Deary et al., 2006; Poudel et al., 2014).

Scalar-based methods typically reduce the 6-dimensional dMRI data, a 3D oriented diffusion field measured in a 3D space, into a 3D volume. These scalar-valued volumes can easily be spatially normalized and statistically compared across individuals. The most common example of this is the analysis of Fractional Anisotropy (FA) derived from diffusion tensor imaging (DTI). FA is a function of the eigenvalues of a fitted diffusion tensor, with higher values reflecting a large degree of diffusion along a single orientation while lower values can reflect white matter damage (Papadakis et al., 1999; Wieshmann et al., 1999; Filippi et al., 2001; Kanaan et al., 2005; Werring et al., 2000; Witwer et al., 2002) or the presence of fiber populations projecting in multiple orientations (Jones et al., 2013; Volz et al., 2017). The inability of tensors to represent multiple directions has been addressed by methods that use higher angular-resolution dMRI to calculate an orientation distribution function (ODF) in each voxel where multiple fiber populations appear as "lobes" (Wedeen et al., 2005), as seen in Fig. 2a. Although ODFs can represent multiple fiber orientations, popular ODF-based scalars such as generalized fractional anisotropy (GFA) (Tuch, 2004) and multi-directional anisotrophy (MDA) (Tan et al., 2015) are still heavily reduced in voxels with fiber crossings (Volz et al., 2017). A major benefit to scalar-based techniques is that 3D interpolation can be performed accurately during spatial normalization, whereas interpolating 6D ODFs has been shown to systemically affect tractography (Greene et al., 2017); this normalization is important to be able to compare the same spatial regions of the brain between subjects that, in general, have different brain shapes and sizes.

Although the resampling of entire ODFs after applying a spatially-normalizing displacement field can produce undesirable results (Christiaens et al., 2012), 3D vector fields are generally well-behaved when spatially warped. We can take advantage of this by extracting directional maxima from each ODF and treating them as vectors. One vector is produced from each lobe of each ODF and warped to a group template where they can be compared across subjects. We calculate a similarity measure between each voxel and its neighbors instead of performing tractography on this spatially-normalized vector field. Where tractography seeks to determine whether axons *project into* a neighboring voxel, similarity scores reflect whether two voxels *are part of the same white matter structure*; this can be considered a generalization of tractography, capturing both the projections and cross-sections of a single white matter structure.

Fig. 1 shows how this approach compares to other current methods. Consider two fascicles in the brain that have been spatially normalized to overlap in space (top row). Two groups have different projections even though scalar based measures and tractography (middle row) would look identical. The bottom row shows the fascicles from both groups superimposed on one another. Distance measures between neighboring voxels would reveal four areas that are *coherent* both between and across groups. In contrast, the vectors in the center crossing region are coherent within each group but differ across groups. The output of this pipeline is a set of regions like the red outlined area of crossings in Fig. 1, where directed ODF maxima are similar within groups but differ across groups.

Directional ODF maxima tend to vary smoothly in space albeit with large discontinuities around anatomical features, as seen in Fig. 2. We can measure the similarity of neighboring voxels by defining a distance between two ODFs that takes into account both magnitude and direction of each peak. Fig. 3 shows an example of *incoherence*, or dissimilarity, between ODFs from all dyads of neighboring white matter voxels within a single subject. Most dyads exhibit very low dissimilarity, with a long

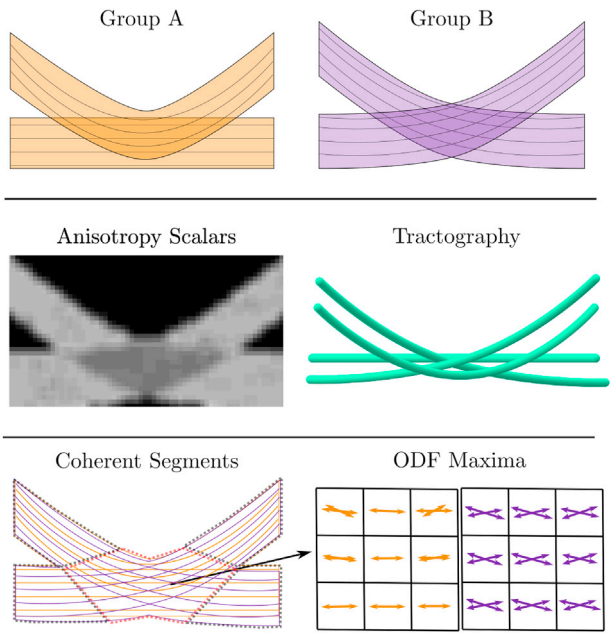


**Fig. 1.** Two fascicles from two hypothetical groups of individuals (top row). These fascicles would generate very similar anisotropy images and tractograms (middle row). Coherent regions can be identified that agree across groups (bottom left, gray outlined) and that are dissimilar across groups (red outline in center). A sample of the MDA vectors of each population from the dissimilar region is shown on the bottom right.

tail of voxel dyads with large dissimilarities. *Dyadic distances form the basis for the method proposed here. These distances are used to build a lattice network, which expands the comparison from neighboring voxels to large white matter regions. Region-based distances are then used to compare between groups.*

To demonstrate the validity and usefulness of the dyad approach, we consider the problem of finding spatially contiguous regions of white matter that are associated with a population of interest as compared to some control population. This problem mirrors the approach taken to subdivide the gray matter of the brain into functional regions (Glasser et al., 2016; Zhu et al., 2011). We develop a non-parametric method for discovering arbitrarily shaped white matter regions that are significantly more similar with the population of interest, not on the basis of their connectivity to gray matter regions but instead on a group-wise local consistency in oriented white matter microstructure. This is accomplished by discovering spatially contiguous white matter voxels that are significantly more coherent within the population than would be expected from a matched control group. (Alternatively, especially in the context of neurological disorders and/or injuries, one could additionally search for regions that are *less* coherent in the population of interest.) In contrast to previous studies (Yeh et al., 2016a), we measure coherence simultaneously across both subjects *and* neighboring voxels.

We apply this method to diffusion scans from the Human Connectome Project on a population of monozygotic (MZ) and dizygotic (DZ) twins to discover white matter regions that are associated with genetic similarity and/or a common upbringing. We hypothesize that in this situation, there should be significantly more coherence in the MZ twins than DZ twins, and DZ twins than unrelated individuals. The discovered regions are more similar within MZ and DZ twins than as compared to a control population of strangers. We also test the robustness of the discovered