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Research article

Age-related changes in structural connectivity are improved using subject-specific thresholding

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HIGHLIGHTS

- Diffusion tractography using HARDI is significantly affected by quantitative anisotropy (QA) threshold values.
- Tractography of specific fasciculi can be inadvertently influenced by QA threshold.
- Network-based analyses are also susceptible to the effects of QA threshold.
- Subject-specific QA thresholds are recommended to provide meaningful results.

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ABSTRACT

Background: Deterministic diffusion tractography obtained from high angular resolution diffusion imaging (HARDI) requires user-defined quantitative anisotropy (QA) thresholds. Most studies employ a common threshold across all subjects even though there is a strong degree of individual variation within groups. We sought to explore whether it would be beneficial to use individual thresholds in order to accommodate individual variance. To do this, we conducted two independent experiments.
Method: First, tractography of the arcuate fasciculus and network connectivity measures were examined in a sample of 14 healthy participants. Second, we assessed the effects of QA threshold on group differences in network connectivity measures between healthy young (n = 19) and old (n = 14) individuals.
Results: The results of both experiments were significantly influenced by QA threshold. Common thresholds set too high failed to produce sufficient reconstructions in most subjects, thus decreasing the likelihood of detecting meaningful group differences. On the other hand, common thresholds set too low resulted in spurious reconstructions, providing deleterious results.
Comparison with existing methods: Subject specific thresholds acquired using our QA threshold selection method (QATS) appeared to provide the most meaningful networks while ensuring that data from all subjects contributed to the analyses.
Conclusions: Together, these results support the use of a subject-specific threshold to ensure that data from all subjects are included in the analyses being conducted.

1. Introduction

Diffusion MRI can be used to assess the movement of water molecules within the brain, making it possible to infer structural properties of underlying neural tissue. Deterministic fiber tracking methods provide the ability to reconstruct models of white matter pathways obtained from diffusion MRI data. High angular resolution diffusion imaging (HARDI) and diffusion spectrum imaging (DSI) are becoming popular because of their ability to model pathways through the complicated geometry imposed by crossing, kissing, or other complex fiber orientations found in the brain (Wedeen et al., 2008). HARDI samples the diffusion MR signal at

Abbreviations: HARDI, high angular resolution diffusion imaging; ODF, orientation distribution function; QA, quantitative anisotropy; QATS, quantitative anisotropy threshold selection; ROI, region(s) of interest.

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a set of points on the surface of a sphere at a high b-value and is sensitive to the microstructural differences in the underlying tissue (Nagy et al., 2013). HARDI, as a single B-shell sequence, offers image acquisition times that are amenable for scanning clinical populations (Rodrigues et al., 2013).

In HARDI, the orientation distribution function (ODF) characterizes the relative likelihood of diffusion along any given direction within a voxel and is based on the spin density function (Yeh et al., 2010). For each reconstructed fiber within a voxel, a quantitative anisotropy (QA) value is calculated. QA is defined for each peak of the spin distribution function, making this technique rather insensitive to partial voluming. Because of this, QA provides a useful index for filtering fiber populations and for defining track termination in deterministic tractography (Yeh et al., 2013).

A critical step in the reconstruction of white matter projections with deterministic tractography is choosing the appropriate threshold parameters. These include anisotropy threshold (e.g. QA, FA), termination angle, step size, smoothing, and length constraints. The anisotropy threshold plays an important role in determining when tracts end. When the anisotropy value within a voxel falls below the threshold, the tracking algorithms terminate. Thus, anisotropy threshold ultimately determines which voxels are included in a tract and the choice of this value can significantly alter fiber trajectory (Mukherjee et al., 2008). One of the biggest challenges faced is in determining the optimal QA threshold. For example, setting the value too high can deflate the number of connections found, producing false negative results (Kunimatsu et al., 2004), while setting the QA threshold too low can result in spurious connections and cause false-positive results (Seehaus et al., 2012). Despite the importance of this parameter, finding a way to objectively determine the optimal QA value has received little attention in the literature. Furthermore, because the scaling of QA is different from FA (Yeh et al., 2010), previously determined FA thresholds (Domin et al., 2014; Kunimatsu et al., 2004; Parizel et al., 2007; Seehaus et al., 2012; Taoka et al., 2009) cannot be directly applied in studies using HARDI forms of imaging.

The impact that anisotropy threshold parameters can have on the resultant tractography models has not been studied within the context of ODF-based approaches, such as HARDI. This is concerning given the growing number of studies that are using ODF-based techniques to study a wide array of disorders such as neurological conditions (Abhinav et al., 2014; Dennis et al., 2011; Muhlert et al., 2013) or normal aging and development (Dennis et al., 2013; Lee et al., 2015). Moreover, the impact that these thresholds have on the fiber tract models generated has not been examined in the context of network-based connectivity (Rubinov and Sporns, 2010), which is also becoming increasingly popular. In the realm of network-based connectivity, there is evidence that early processing steps can significantly influence the outcome of network-based models. For example, studies have investigated the influence of different parcellation schemes with respect to a variety of network properties (Cammoun et al., 2012; Cheng et al., 2012b) and weighting schemes (Cheng et al., 2012a). Further, the specific tractography algorithm used has also been shown to impact network characteristics (Bastiani et al., 2012). However, it is unknown how QA threshold influences these measures.

Most studies being conducted today employ a common anisotropy threshold across all subjects even though there is a strong degree of individual variation in anisotropy values. In doing this, there is the potential for individual subjects to offer little to the analysis because their fiber reconstruction models have few to no connections. In this study, we sought to explore whether it would be beneficial to accommodate individual variation through the use of individual thresholds. To do this, we conducted two separate experiments. First, the effect of varying QA threshold in the reconstruction and anatomical properties of the arcuate fasciculus was examined. The arcuate fasciculus has been characterized extensively *in-vivo* using diffusion based imaging tractography (Catani and Thiebaut de Schotten, 2008) and *ex-vivo* using the Klinger dissection technique (Fernández-Miranda et al., 2015). Thus, there exists an anatomical/true "gold standard" that can be compared to the fiber reconstruction models that we generate. Second, the role of QA threshold on the network-based properties of clustering coefficient, node strength, nodal efficiency, network global efficiency, network density, and number of network hubs (Rubinov and Sporns, 2010) was investigated in two phases. The first phase involved a network-based exploration of the overall effects of QA threshold; independent of any clinical application. The second phase involved a network-based study on the effect of QA threshold on the ability to detect meaningful differences between healthy young and healthy aged participants.

2. Materials and methods

2.1. Subjects

For the first experiment, data were collected from fourteen healthy subjects (mean = 26.46 years, range = 15–44, 6 females). The second experiment consisted of a completely separate cohort of 19 young (mean = 24.9 years, range = 19–32, 8 females) and 14 aged individuals without subjective cognitive complaints (mean = 72.4 years, range = 65–84, 7 females). All subjects were free of any neurological or psychiatric disorders and had normal structural MRI scans. Written informed consent was obtained from all subjects (and/or their guardians where appropriate) prior to participation. The experimental procedures were approved by the Institutional Review Board at the Massachusetts Eye and Ear Infirmary, Boston, MA, USA or the Institutional Review Board at Boston University School of Medicine, Boston, MA as appropriate.

2.2. MRI acquisition parameters

All MRI scanning was performed using a 3T Philips Achieva system (Best, the Netherlands) with an eight-channel phased array head coil. In the first experiment, two T1-weighted structural images were acquired using a FFE pulse sequence (TE 3.1 ms, TR 6.8 ms, flip angle 9°, $1 \times 1 \times 1.2$ mm voxel size) and one high angular diffusion imaging (HARDI) scan using a single shot EPI sequence (TE 73 ms, TR 17844 ms, 64 directions, b_{max} 3000 s/mm^2, a single b0, $2 \times 2 \times 2$ mm voxel size, 80 mT/m, slew rate 100 mT/m/ms, diffusion time 36.3 ms, diffusion gradient duration 19.1 ms), and field map (TE 2.3 and 4.6 ms, TR 20 ms, flip angle 10°, $3 \times 3 \times 3$ mm voxel size). For the second experiment, data were obtained as part of the Healthy Outreach Program for the Elderly (HOPE) study using a 32 channel phased array head coil. The T1 w parameters were identical though only one scan was acquired and the single shot EPI HARDI parameters were as follows: TE 100 ms, TR 8789 ms, 64 directions, b_{max} 3000 s/mm^2, a single b0, $2 \times 2 \times 2$ mm voxel size, 40 mT/m, slew rate 200 mT/m/ms, diffusion time 50.3 ms, diffusion gradient duration 33.4 ms. Dynamic stabilization was used during all HARDI scans to adjust for B0 drift (Benner et al., 2006). Because of the differences in acquisition parameters, datasets for each experiment were assessed completely separately and the results of each analysis were independent.

2.3. Processing of T1-weighted data

T1-weighted data was processed using FreeSurfer 5.3.0 (https://surfer.nmr.mgh.harvard.edu/), which has been described in detail elsewhere (Dale et al., 1999; Fischl et al., 1999, 2002, 2004). Briefly, the T1-weighted images were skull stripping, intensity normalization, and Talairach registration. Grey matter was parcellated into 68