Published in final edited form as:

Magn Reson Med. 2019 March ; 81(3): 2011–2024. doi:10.1002/mrm.27512.

Functional Tractography of White Matter by High Angular Resolution Functional-correlation Imaging (HARFI)

Kurt G Schilling^{1,2}, Yurui Gao^{1,2}, Muwei Li^{1,3}, Tung-Lin Wu^{1,2}, Justin Blaber⁴, Bennett A Landman^{1,2,3,4}, Adam W Anderson^{1,2,3}, Zhaohua Ding^{1,3,4}, and John C Gore^{1,2,3}

¹Vanderbilt University Institute of Imaging Science, Vanderbilt University, Nashville, TN, USA

²Department of Biomedical Engineering, Vanderbilt University, Nashville, TN, USA

³Radiology and Radiological Sciences, Vanderbilt University, Nashville, TN, USA

⁴Department of Electrical Engineering, Vanderbilt University, Nashville, TN, USA

Abstract

Purpose: Functional magnetic resonance imaging with blood oxygenation level dependent (BOLD) contrast is widely used for detecting brain activity in the cortex. Recently, several studies have described anisotropic correlations of resting-state BOLD signals between voxels in white matter (WM). These local WM correlations have been modeled as functional-correlation tensors (FCTs), are largely consistent with underlying WM fiber orientations derived from diffusion MRI, and appear to change during functional activity. However, FCTs have several limitations. The use of only nearest-neighbor voxels makes FCTs sensitive to noise. Furthermore, adjacent voxels tend to have higher correlations than diagonal voxels, resulting in orientation-related biases. Finally, the tensor model restricts functional correlations to an ellipsoidal bipolar-symmetric shape, and precludes the ability to detect complex functional orientation distributions (FODs).

Methods: We introduce High-Angular-Resolution Functional-correlation Imaging (HARFI) to address these limitations. In the same way that high-angular-resolution diffusion imaging (HARDI) techniques provide more information than diffusion tensors, we show that the HARFI model is capable of characterizing complex FODs expected to be present in WM.

Results: We demonstrate that the unique radial and angular sampling strategy eliminates orientation biases present in tensor models. We further show that HARFI FODs are able to reconstruct known WM pathways. Finally, we show that HARFI allows asymmetric “bending” and “fanning” distributions, and propose asymmetric and functional indices which may increase fiber tracking specificity, or highlight boundaries between functional regions.

Conclusions: The results suggest the HARFI model could be a robust, new way to evaluate anisotropic BOLD signal changes in WM.

Keywords

Functional magnetic resonance imaging; functional connectivity; functional pathways; high angular resolution

Introduction

Functional magnetic resonance imaging (fMRI) detects hemodynamic changes associated with neural activity on the basis of blood oxygenation level dependent (BOLD) contrast (1). Task or stimulus driven fMRI has been widely used in the neuroscience community to study cognitive and sensory processes in development, aging, and pathological disorders (2). Alternatively, fMRI acquisitions in the absence of explicit stimuli – resting-state fMRI (rsfMRI) – are commonly used to infer functional connectivity by investigating the temporal correlations of resting state BOLD signals between voxels or brain regions (3,4).

To date, a majority of fMRI studies have focused on brain gray matter (GM) (2,5) and reliable detection of BOLD changes in white matter (WM) has proven elusive. Recently, however, it has been suggested that BOLD signals in WM may arise in similar manner as those in GM. For example, several reports have demonstrated task-based BOLD signal changes in the corpus callosum (6,7), internal capsule (8,9), and optic radiations (10), while statistical analysis of WM resting-state signals has yielded distinct clusters, or functional networks, which closely resemble known WM pathways (10–12). Of particular interest here, it has been shown that neighborhood correlations of WM rsfMRI signals display distinct anisotropy in many regions (13). These directional variations of temporal correlations are largely consistent with the orientation of expected WM pathways and those derived using diffusion tensors, and persist over long distances within these structures. To evaluate these anisotropic correlations, Ding et al. (13) introduced the functional correlation tensor (FCT). Much like the diffusion tensor with diffusion weighted contrast, the FCT uses a 3×3 symmetric tensor formalism to characterize correlations from BOLD contrast. The orientation estimates from the FCT principal eigenvectors can be followed using techniques borrowed from diffusion fiber tractography (14) to reconstruct “functional” pathways (15). Together, these techniques offer unique possibilities to map the functional structure and properties of neural networks, and the potential to integrate structural and functional relationships in the brain.

There are several limitations inherent in the use of the functional correlation tensor. First, the use of nearest-neighbor voxels (in combination with a limited SNR of WM BOLD effects) makes FCTs sensitive to noise (16). Second, adjacent neighboring voxels tend to have higher correlations than diagonal neighbors – possibly caused by the decreased distance from the voxel-of-interest (i.e. 1 voxel versus 2 voxel distances) – which can result in orientation-related biases. Third, the use of a 2nd-order tensor model restricts functional correlations to an ellipsoidal shape. This precludes the ability to detect complex *functional* orientation distributions (FODs), in much the same way that the diffusion tensor has been shown to fail to characterize complex *fiber* orientation distributions such as crossing, kissing, and fanning axonal geometries (17). Finally, the tensor forces bipolar symmetry, meaning that the

measures in opposite directions are equal. While this is appropriate for diffusion tensor imaging (in that diffusion in one direction cannot be distinguished from that in the opposite direction), this does not have to be true of functional correlations, which may well be asymmetric.

Here, we present a new way to evaluate rsfMRI BOLD signal changes in WM. In the same way that high angular resolution diffusion imaging (HARDI) techniques (18,19) were introduced to overcome diffusion tensor imaging limitations, we introduce high angular resolution functional imaging (HARFI). This technique presents a novel sampling and fitting strategy that addresses limitations of FCTs. Because correlation anisotropy has been shown to extend over relatively long distances, the use of extended neighborhoods can improve robustness to noise, while sampling at uniform radial distances reduces orientation biases. Similarly, a higher angular sampling (compared to 26 neighboring orientations) allows reconstruction of complex FODs. These FODs are represented using a set of basis functions that can describe both symmetric and asymmetric functions on a sphere.

The manuscript is organized as follows. We first describe the HARFI fitting strategy, and show that correlation biases from nearest neighbor sampling are reduced or eliminated. We then show that HARFI is capable of characterizing complex FODs, and is able to reconstruct expected WM functional pathways. We then demonstrate the ability to characterize asymmetric distributions and introduce metrics that may be useful to identify unique functional geometries or to identify boundaries between functional regions.

Methods

MRI Acquisition

The protocol used in this study was approved by Vanderbilt University Institutional Review Board. Prior to experiments, written informed consent was obtained from each participant.

Sixteen healthy volunteers participated in this study. All imaging was performed on a 3T Philips Achieva scanner (Best, Netherlands) installed in the Vanderbilt University Institute of Imaging Science, using a 32-channel head coil. For each subject, a set of anatomical and fMRI scans were acquired. One dataset was not used due to the presence of abnormally enlarged ventricles. Functional MRI with BOLD contrast was acquired using a single shot T2*-weighted gradient echo, echo planar imaging sequence with TR=3s, TE=45ms, SENSE factor of 2, matrix size=80×80, field of view=240×240mm, 43 axial slices, 3mm thick with zero gap, and 200 dynamic image volumes. To provide anatomical references, T1-weighted images were also acquired using a multi-shot 3D gradient echo (GE) sequence with TR=8.9ms, TE=4.6ms, matrix size=256×256×170, and voxel size = 1×1×1mm.

Image Preprocessing

BOLD images were preprocessed using the statistical parametric mapping software package SPM12 (www.fil.ion.ucl.ac.uk/spm/software). First, images were corrected for slice timing and head motion. Second, T1-weighted images were registered to the mean BOLD image after the motion correction procedure. Third, BOLD images were normalized into the Montreal Neurological Institute (MNI) space, along with the co-registered T1-weighted

images. Next, BOLD images underwent removal of linear trends from the signals to correct for signal drift and temporal low pass filtering to retain frequencies below 0.1 Hz. Finally, time series in the BOLD images was normalized to unit variance voxel-wise.

HARFI calculation

Ding et al. (13) described functional correlations using the tensor formalism. Briefly, for each voxel, a set of unit vectors that point to the 26 nearest voxels in its neighborhood is defined, and the temporal correlation of BOLD signals along each of the directions is computed (Figure 1, A). The correlation tensor, T , is computed from

$$C_i = n_i \cdot T \cdot n_i^t$$

where C_i is the correlation coefficient along the direction n_i . T can be represented using ellipsoidal contours (shown in 2D in Figure 1, B), and the major eigenvector represents the dominant direction of temporal correlation (Figure 1, B).

To remove the constraints of the tensor, a simple approach would be to fit the nearest neighbor correlations to a general function of a sphere, e.g., a linear combination of spherical harmonic functions (again, as is typical of diffusion orientation distributions) to approximate complex functions over a sphere (see Appendix A, Spherical Harmonics). However, because correlations generally decrease with distance, this would bias results towards the neighbors immediately adjacent to the voxel-of-interest (at a distance of 1 voxel), relative towards those at the edges (distance = 2 voxels) or diagonals (distance = 3 voxels) of the cubic lattice.

For HARFI, we take a more general approach, which involves spatial interpolation of the fMRI signals to points on a sphere of a given radius from the voxel of interest. Mathematically, the HARFI function F , at voxel x , in a direction r , can be formulated from the fMRI times series f as:

$$F(\vec{x}, \hat{r}) = \int_0^R \langle f(\vec{x}), f(\vec{x} + r \cdot \hat{r}) \rangle dr$$

A cartoon depiction of the processing is shown in Figure 1 (C-E). For any given direction (Figure 1, C), the BOLD signal is interpolated from a radius of 0, to a maximum value R (empirically set at $R = 9\text{mm}$), and correlation coefficients calculated for all distances (Figure 1, D). Next, integration over distance was performed, resulting in the final measure in each direction.

Traditional Fitting

The function values calculated over a set of directions were fit to spherical harmonic coefficients (Appendix A, Spherical Harmonics), resulting in a function defined over a sphere (Figure 1, E). From the diffusion MRI literature, it is traditional to fit to even order spherical harmonics, which forces antipodal symmetry. Thus, in our experiments we begin by using similar strategies and fit to only even order coefficients. The resulting HARFI

functions are visualized in a manner similar to that performed for diffusion HARDI approaches (20).

Fiber Tractography

Streamline fiber tractography was performed with the HARFI FODs using the methodology described in Wakana et al. (21). For each subject, a multi-region-of-interest (ROI) approach was used to reconstruct tracts of interest which exploited existing anatomical knowledge of tract trajectories. Tracking was performed from all voxels in the brain and results penetrating all manually defined ROIs (defined on the MNI template) were assigned to specific tracts associated with the ROIs. A selection of tracts from (21) was chosen to demonstrate functional tractography feasibility, including the cingulate gyrus (CGC), forceps minor (FMinor), inferior longitudinal fasciculus (ILF), and the uncinate fasciculus (UNC). Tractography was performed using MRTRix software (22) using the streamline propagation algorithm, with the *functional* spherical harmonic coefficients used directly as input (i.e. no diffusion MRI data were used in the functional tractography process).

Asymmetric distributions and indices

In addition to the even-order HARFI analysis, we also fit all FODs using the full complement of spherical harmonic coefficients (even and odd order), which allows asymmetric FODs. We propose a variety of measures and metrics to quantify the shape of the FOD including degree of asymmetry, homogeneity index, number of peaks, bending index, and fanning index.

First, in order to quantify the degree of asymmetry in the orientation distribution fit using our model, we used the power of the odd order coefficients. Overall power, P , of the spherical harmonic basis can be calculated as the sum-of-squares of the coefficients:

$$P = \sum_{l=1}^L \frac{1}{2l+1} \sum_{m=-l}^l |Y_{lm}|^2$$

where L is the maximum harmonic order, and Y_{lm} is the spherical harmonic coefficient of order l and degree m . We calculated and displayed the power of the odd order coefficients divided by the overall power of all coefficients (not including 0th order).

Second, we calculated a homogeneity index. Two distributions with similar shape will have a high angular correlation coefficient (ACC) (see Appendix B, Angular Correlation Coefficient). We computed the ACC of a voxel with its nearest neighbors, and averaged this for a homogeneity index. This measure describes how spatially consistent (or conversely, varying) the distributions are in a given region, and may highlight boundaries of regions sharing similar functional properties.

We next counted the number of local maxima, or peaks, in each FOD, using methods previously described in the diffusion literature (23). From the peaks, we computed both a measure of functional “bending” and functional “fanning”, described in detail in Appendices C and D, respectively. Briefly, for bending, we extracted the largest peak and calculated the

angle between its antipodal vector (i.e., where the peak would be if there was no bending) and all other peaks. The bending value, in degrees, is the minimum of these values (see Appendix C for qualitative illustration). For fanning, all peaks were fit to Von-Mises Fisher distributions - a spherical distribution with a mean direction, $\hat{u}$, and concentration parameter, κ :

$$VMF(\hat{r}; \hat{u}, \kappa) = A(\kappa) \exp(\kappa \hat{u}^T \hat{r})$$

Here, $A(\kappa)$ is a normalization constant. The greater the value of κ , the higher the concentration of the distribution around the mean direction. It is desirable to characterize this spread as a more intuitive measure, the peak opening angle:

$$\alpha(\kappa) = \cos^{-1} \left(\frac{\kappa - \frac{1}{2}}{\kappa} \right)$$

which describes the distance from the main direction at which the FOD has dropped to $\exp(-1/2)$ its maximum value. This measure of functional spread was calculated for all peaks. The amount of fanning then, is simply the absolute value of the difference in spread between the largest peak and its nearest antipodal peak. A larger value indicates that fibers are concentrated at one hemisphere, and more spread at the other, while a value of 0 degrees indicates equal spread at both hemispheres (see Appendix D for illustrations).

All measures were calculated for all subjects, and results are displayed below for a representative subject as well as the population average in MNI space.

Results

Nearest Neighbor Bias

We evaluated potential biases in the correlation coefficients between voxels in the nearest neighborhood (Figure 2). We calculated the correlation coefficients between all voxels in the WM and their nearest neighbors, and found that adjacent WM voxels (those that share a voxel face) consistently had a higher correlation than neighbors that share only one edge, which have a higher correlation than the diagonals (which share only a corner point) (Figure 2, A). Fitting just the neighborhood correlations *directly* with spherical harmonic coefficients shows clear biases in three orthogonal imaging orientations (Figure 2, B), with nearly every voxel containing local maxima in the anterior/posterior, superior/inferior, and left/right directions.

These results motivated the need to sample on spheres of uniform radius from the voxel of interest. Figure 2, C shows that, using the proposed HARFI sampling, which samples on concentric spheres, there are no obvious biases in any direction with glyph orientations following largely the directions of known WM pathways.

Complex Functional Orientation Distributions

Figure 3 shows the HARFI FODs for a single subject in two regions of interest, in both an axial and coronal slice of the brain. In both cases, the glyphs are qualitatively similar to those expected when using diffusion MRI HARDI reconstruction techniques (24,25). For example, the axial slice (Figure 3, A) shows the expected left/right orientation of the corpus callosum, merging and/or crossing with those of the superior longitudinal fasciculus (SLF) oriented anterior/posterior – a well-known “crossing fiber” region of the brain (red arrows). The coronal slice (Figure 3, B) shows another region with fibers of the posterior thalamic radiation, SLF, and WM (arrows) near the middle temporal gyrus (MTG). Thus, the HARFI methodology is able to characterize complex FODs. For comparison, the previous tensor method to detect local anisotropic correlation - FCT (13) - is also shown in both regions. Because the FCT describes these FODs using the tensor formalism, they are restricted to ellipsoidal shapes and cannot characterize complex or crossing functional distributions.

Reconstruction of WM Pathways

Figure 4 shows a visualization of 4 *functional* pathways (CGC, FMinor, ILF, and UNC) in a single subject (Figure 4, top panel). All pathways show the same general location, orientation, and shape as known white matter *structural* pathways (21,26) created using diffusion MRI tractography on the same subject (Figure 4, bottom panel) (Diffusion MRI was acquired on the same subject with a single-shot, spin echo EPI sequence with $b=1000$ s/mm², 32 diffusion-sensitizing directions, TR=10s, TE=60ms, SENSE=3, matrix size=128×128×60, and field of view=256×256×170mm³). However, qualitatively, the functional pathways are generally thinner, or more sparse, than those reconstructed using the diffusion MRI data (see also Wakana et al. (21) figures 2, 11, 7, and 9, for comparison). Functional pathways were successfully visualized in all subjects (with the exception of the ILF in a single subject), using the same MNI-space ROIs for all subjects.

Asymmetric Functional Correlation Distributions

Figure 5 demonstrates that implementing the spherical harmonic fitting strategy with estimates of odd-order coefficients results in unique, asymmetric, functional distributions. For example, fibers (or rather, functional distributions) show evidence of fanning, or spreading out, as they leave the tightly fasciculated genu of the corpus callosum (Figure 5, A) or splenium of the corpus callosum (Figure 5, B) and merge with adjacent pathways. In addition, a 3-way, non-symmetric, crossing region is apparent in the area of the angular gyrus (Figure 5, C). Finally, bending, U-shaped, distributions are clearly visible in WM adjacent to the cortex near sulcal banks (Figure 5, D), areas known to contain short association fibers (i.e. “U-fibers”). Qualitatively, HARFI is able to capture fanning, crossing, and bending distributions of functional correlations.

Quantitative metric maps are shown in Figures 6, 7, 8, and 9 for both a single individual, and the population (N=15) of study individuals, as well as a T1-weighted anatomical reference image (Figure 6, A; Figure 8, A). The individual asymmetry map (Figure 6, B), while noisy, highlights many regions of high asymmetry, which could be indicative of either fanning or bending-type configurations. For the population-averaged map (Figure 8, B), there is a clear WM core (blue arrows) with stronger symmetry (lower asymmetry). For homogeneity

(Figure 6, C; Figure 8, C), some parts of corpus callosum (red arrows) show lower values, indicating quickly changing orientations. Again, the WM coincides in general with regions of lower homogeneity, indicating that there is stronger contrast, or change, in FOD from voxel to voxel than in the GM where FODs are largely isotropic. There is generally a larger number of FOD peaks (Figure 7, A; Figure 9, A) in the gray matter. This, again could be due to the isotropic GM voxels, where any angular difference (for example, due to noise) could introduce additional local maxima. Most WM contains voxels that have 2 or 3 FOD peaks (we note that the individual map is shown using discrete values, while the population-average is a continuous distribution). Functional bending is shown in Figure 7 and 9, B. In the individual, high bending is observed in superficial white matter regions near sulcal fundi (yellow arrows) where U-fibers are expected (see Figure 5, D). In the population average, a similar line of high intensity near these areas is also observed (yellow arrows). Finally, functional fanning (Figure 7, C; Figure 9, C), tends to be higher near the WM/GM interface, where there may be a broad correlation with GM but a more concentrated correlation with specific white matter tracts, or where fibers are expected to fan into the cortex (i.e. at gyral crowns (27,28)).

Discussion

Analysis of functional connectivity in the brain is traditionally based on characterizing changes in fMRI signals from cortical regions (2). However, a number of studies reporting reliable detection of BOLD signals in WM have appeared in recent years. For example, fMRI activations have been reported in the corpus callosum (6,7), internal capsule (8,9), and optic radiations (10). Furthermore, Ding et. al. (13) reported WM spatiotemporal correlation patterns which exhibit orientations similar to those found with diffusion MRI. In this work, we present a new method to characterize and evaluate these anisotropic BOLD signal changes in WM. With this approach, we are able to characterize complex functional orientation distributions, as well as depict functional structures that are consistent with known structural pathways.

The HARFI orientation distributions are reminiscent of the results from Q-ball Imaging (QBI) (24) or Diffusion Spectrum Imaging (DSI) (25), both of which are high angular resolution diffusion techniques intended to address known limitations of estimating structural connectivity using DTI. The HARFI reconstruction technique is motivated in part by DSI - rather than the radial integral of the diffusion propagator (29), we have chosen to take the radial integral of the correlation coefficients over a large number of orientations. This unique angular and radial sampling strategy removes orientation biases associated with using nearest neighbor voxels (Figure 2), and is able to capture functional crossing (Figure 3), bending (Figure 5), and fanning (Figure 5) distributions.

The ultimate significance and potential applications of HARFI results remain to be established but it is already clear that resting state signals in white matter represent a level of neural activity that has been largely ignored and which represent functional variations that are closely coupled with corresponding activities in cortical regions to which they connect. As such HARFI tractography provides a unique and novel way to identify functional connectivity in white matter that differs from but may complement structural connectivity

from diffusion data. The ability to detect and quantify correlated functional signals in white matter is a crucial aspect of delineating functional circuits in the brain that is currently unavailable from other fMRI methods, and it is highly plausible that aberrant HARFI patterns may be biomarkers of functional changes in white matter disorders.

Towards Functional and Structural Connectivity

Unlike traditional fMRI analyses, our approach attempts to characterize the directional preference of temporal BOLD signal correlations. Given a 3D functional (principal eigen)vector field, it is natural to use streamline tractography (14) in an attempt to reconstruct functional pathways. Using HARFI, we show that we are able to reconstruct streamlines that show features similar to known WM pathways in the brain (Figure 4). It is important to emphasize that these reconstructions do not represent structural connectivity by and of itself, though it seems natural to expect some geometric relationship between the functional and structural connectivities. Qualitatively, we find that HARFI generally resulted in thinner, sparser, pathways than would be obtained using diffusion MRI techniques. For example, the CGC, FMinor, and UNC appear thinner for HARFI tractography than diffusion tractography, while the ILF is quite similar, and possibly covers an even greater spatial extent using HARFI methods (for the subject shown in Figure 4). It is possible that the ROIs may not be optimized for subject or pathways, or that a completely different tracking logic or strategy is more appropriate to reconstruct functional pathways.

Of particular interest, it may be possible to quantify modulation of these functional pathways due to functional loading in task-based fMRI (30), or to quantify temporal modulation in resting state conditions. There is also potential to harmonize diffusion MRI structural data and fMRI functional data. For example, Zhang et al. (16) used machine learning to predict or inform functional anisotropy mapping from DTI data. We also envision the use of functional correlations to inform DTI tractography, possibly by weighting the streamline propagation step with the functional orientation, or filtering diffusion tractography streamlines (31) using functional information extracted from the HARFI FODs.

A related approach of estimating anisotropic spatial and temporal patterns in resting state data has been detailed by Frank and Galinsky (32). They introduced a method, entropy field decomposition (EFD), to characterize local interactions between neighboring voxels without an explicit signal model, and use these spatiotemporal correlations to construct functional pathways. In addition, the EFD approach has recently been extended to jointly analyze diffusion and functional data (33) in order to estimate modes of connectivity – both structural and functional - across a range of spatial scales. This approach has similar goals, and comparisons of results from the two methods could be valuable and lead to better insights into both techniques.

The asymmetric HARFI distributions derived here could also be used to improve fiber tracking specificity and sensitivity. It is currently not possible to distinguish the diffusion process in one direction from diffusion in the opposite direction. This leads to significant ambiguity in estimating the voxel-wise fiber geometries in each voxel. For example, it is not possible to estimate axonal configurations that contain a fanning, bending, or a 3-way asymmetric crossing, all of which are easily visualized using the HARFI model (Figure 5).

The ambiguity in diffusion data can lead to both false positive and false negative tractography results (17,34,35). Thus, future work could develop an appropriate tracking strategy that uses these asymmetric HARFI distributions, and evaluate the sensitivity and specificity of the resulting tractograms.

The motivation for the HARFI description of the local anisotropic functional correlations originated from two concerns. First, in the original description of the anisotropy, Ding et al. (13) use a tensor formalism to describe the local structure. While this was a compelling insight into the nature of BOLD signals in white matter, in the early 2000's, researchers realized that the *diffusion* tensor is restrictive (and sometimes inadequate) for describing structural anatomy. Much like Tuch et al. (18), Frank et al. (19), and others (25) chose to describe the diffusion signal with little to no constraints on the shape of the fiber geometry, and we similarly aim to provide as few restrictions on the shape of the functional geometries. Second, in the original implementation of FCT, only nearest neighbor voxels were utilized, whereas these correlations were shown to exist over distances as great as 10mm (or more) (13), meaning more information may be available if signal from additional, non-neighboring, voxels is queried. In our implementation, we empirically choose to incorporate information over a distance of 9mm (based on (13)) although smaller or larger radii may make the technique more or less sensitive to input from different sizes or lengths of pathways or functional regions. This choice comes at the expense of spatial resolution, for example HARFI may be able to detect input only from rather long tracts (or at least weighted more towards longer pathways) when functional correlations exist over these distances (in this case, 9mm).

Indices

In addition to reconstructing several WM pathways, HARFI allows extraction of several indices that highlight distinct features of the FOD (Figure 6–9), with potential applications towards functional tractography or functional segmentation. The bending and fanning metrics highlight regions in which we expect structural fiber arrangements with similar geometries (i.e. U-fibers and/or at cortical interfaces). Thus, it is feasible that fiber fanning can be included in probabilistic-type tractography algorithms to emphasize dispersion, or uncertainty, in reconstructed pathways. The bending (and associated lobes of the FOD) could be used to infer sub-voxel fiber (or functional) arrangements, again increasing tracking specificity. The homogeneity index could serve as a useful indicator of functional boundaries, highlighting locations where the temporal correlation anisotropy varies from voxel to voxel. This and other spatial agreement measures, in combination with diffusion MRI, could aid in establishing the relationship between regional boundaries based on structural differences (36,37) and functional boundaries based on temporal correlations of the BOLD signal. Finally, in addition to modulation of functional pathways, it may be possible to study modulation of these, or similar, descriptors of the FOD in a resting state or under functional loading.

Conclusion

We have presented a new way to evaluate anisotropic BOLD signal changes in WM, called high angular resolution functional imaging (HARFI). In the same way that high angular resolution diffusion imaging (HARDI) techniques improved upon tensor descriptions of diffusion, we show that the HARFI model improves upon current techniques to characterize BOLD signal correlations in WM. HARFI is capable of characterizing complex functional distributions and is able to reconstruct WM functional pathways that are structurally plausible. This technique could increase fiber tracking specificity, and/or provide a better understanding of the relationship between functional and structural connectivity in brain WM.

Acknowledgements

This work was supported by the National Institutes of Health under award numbers RO1NS058639, R01EB017230, R01NS093669, and T32EB001628. This project was supported in part by ViSE/VICTR VR3029 and the National Center for Research Resources, Grant UL1 RR024975-01. This work was conducted in part using the resources of the Advanced Computing Center for Research and Education at Vanderbilt University, Nashville, TN.

Appendix A. Spherical Harmonics

We use spherical harmonics to describe the HARFI function over a sphere. The spherical harmonic of order $l = 0, 1, 2, \dots$ and index $m = -l, \dots, 0, \dots, l$ is

$$Y_{lm}(\theta, \phi) = \left(\frac{(2l+1)(l-m)!}{4\pi(l+m)!} \right)^{\frac{1}{2}} P_{lm}(\cos \theta) \exp(im\phi)$$

where θ is the angle of colatitude, ϕ the angle of longitude, and P_{lm} is the associated Legendre polynomial with order l and index m . The functions are waves on a sphere with a frequency that increases with order l . Most complex-valued functions on a sphere may be expressed as a weighted sum of spherical harmonic functions:

$$f(\theta, \phi) = \sum_{l=0}^{\infty} \sum_{m=-l}^l c_{lm} Y_{lm}$$

where c_{lm} is a complex number. Series truncation at finite order gives a low-frequency approximation of the function analogous to truncations of other expansions.

For real-valued functions (as in both diffusion MRI signals and fMRI correlations), $c_{lm}^* = (-1)^m c_{l-m}$, so that the number of scalar parameters estimated for order l is $(l+1)^2$ rather than $2(l+1)^2$ for complex-valued functions. Diffusion MRI is both real-valued and has antipodal symmetry, i.e., $f(\hat{x}) = f(-\hat{x})$, and requires only even-order spherical harmonics (setting $c_{lm} = 0$ for odd l), so the total number of parameters for order l estimation is further reduced to $1/2(l+1)(l+2)$. This symmetry does not have to exist for HARFI data, so that we elected to fit to both even-order (forcing symmetry) and full-order spherical harmonic coefficients.

Appendix B. Angular Correlation Coefficient

A method for calculating the correlation of functions over a sphere given the SH expansions of both functions is given in (38). Given two spherical functions and their spherical harmonic expansions:

$$\begin{aligned} U(\theta, \varphi) &= \sum_{l=0}^{\infty} \sum_{m=-l}^l u_{lm} Y_{lm}(\theta, \varphi) \quad [\text{B.1}] \\ V(\theta, \varphi) &= \sum_{l=0}^{\infty} \sum_{m=-l}^l v_{lm} Y_{lm}(\theta, \varphi) \end{aligned}$$

The ACC of the functions is calculated as:

$$ACC = \frac{\sum_{l=1}^{\infty} \sum_{m=-l}^l u_{lm} v_{lm}^*}{\left[\sum_{l'=1}^{\infty} \sum_{m'=-l'}^{l'} |u_{l'm'}|^2 \right]^{1/2} \left[\sum_{l''=1}^{\infty} \sum_{m''=-l''}^{l''} |v_{l''m''}|^2 \right]^{1/2}} \quad [\text{B.2}]$$

The ACC is used to quantify the similarity between two FODs.

Appendix C. Bending

The functional “bending” is depicted in 2D in Figure A1a. Bending is calculated after extraction of local maxima from the FOD. The largest peak is selected, and the angular difference between its antipodal vector and all other peaks is calculated. The bending is then the minimum of these angles (i.e., angle β).

Appendix D. Fanning

All FODs are fit to a Von-Mises Fisher (or mixture of Von-Mises Fisher) distribution(s)

$$VMF(\hat{r}; \hat{u}, \kappa) = C(\kappa) \exp(\kappa \hat{u}^T \hat{r})$$

with concentration parameter κ . A smaller κ implies higher the angular spread, which we have chosen to describe using the peak opening angle:

$$\alpha(\kappa) = \cos^{-1} \left(\frac{\kappa - \frac{1}{2}}{\kappa} \right)$$

This angle describes the distance from the main direction in which the FOD has dropped to $\exp(-1/2)$ its maximum value, and is the angle at which the distribution reaches its first standard deviation level (analogous to a normal distribution standard deviation). Given a set of peak opening angles, the fanning is defined as the absolute difference in spread between the largest peak and its nearest antipodal peak. In Figure A1b, the opening angle of peak #1

(δ_1) is slightly larger than that of peak #2 (δ_2), thus there is a fanning. The fanning, then, is the absolute value of their angular difference (note that bending is also present in the FOD).

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Figure 1.

2D example of HARFI fitting. For traditional FCT fit, only neighborhood voxels (8 in 2D, 26 in 3D) are used to fit a tensor (A), from which the major eigenvector is extracted (B). In HARFI fitting, a large number of directions are evaluated (C), and the BOLD signal is integrated over a larger distance for correlation calculation (D), resulting in the HARFI signal defined over a sphere (E).

Figure 2.

Nearest Neighbor bias is removed using the HARFI fitting method. Correlation coefficients for all nearest-neighbor voxels are shown for adjacent voxels (light gray, distance = 1), cube side-diagonal voxels (medium gray, distance = 2), and cube corner-diagonal voxels (dark gray, distance = 3) for all voxels in the WM. Correlation coefficients are always higher for adjacent voxels, causing an orientation bias in three orthogonal directions when fitting spherical harmonic coefficients directly to nearest neighbors (C). The HARFI fit shows no apparent bias in the orientation distributions.

Figure 3. HARFI is capable of characterizing complex functional orientation distributions. HARFI fits are shown for an axial (A) and coronal (B) slice, with magnified views of crossing or complex distributions. Note that glyphs are shown min-max normalized (as is common in diffusion visualization) in order to highlight orientation contrast. For comparison, functional correlation tensor glyphs are shown, which are restricted to ellipsoidal distributions. Arrows highlight regions of complex orientation distributions.

Figure 4.

HARFI is able to reconstruct functional pathways (top) that are qualitatively similar to known structural pathways (bottom). Visualizations from left to right include the cingulate gyrus (CGC), forceps minor (FMinor), inferior longitudinal fasciculus (ILF), and the uncinate fasciculus (UNC). Structural pathways are created using DTI fiber tractography on the same subject from diffusion data acquired in the same scan session.

Figure 5. HARFI is able to capture complex, asymmetric functional distributions. Fiber fanning (A, B; red arrows), three-way crossings (C; blue arrows), and bending (D; black arrows) voxels are reconstructed in regions expected to contain complex distributions.

Figure 6. Individual HARFI indices. Tri-planar views are shown for an individual subject for T1 anatomical image, asymmetric index, and homogeneity index.

Figure 7. Individual HARFI indices. Tri-planar views are shown for an individual subject for number of peaks, bending index, and fanning index.

Figure 8. Subject averaged HARFI indices. Tri-planar views are shown averaged over all subjects (N=15) for T1 anatomical image, asymmetric index, and homogeneity index.

Figure 9. Subject averaged HARFI indices. Tri-planar views are shown averaged over all subjects (N=15) for number of peaks, bending index, and fanning index.

Figure A1.

Bending and Fanning Illustrations. (A) 2D Illustration of functional bending. Two peaks show an angular bend of β degrees. (B) 2D Illustration of functional fanning. Because the angular opening of peak #1 (red, δ_1) is slightly larger than that of peak #2 (blue, δ_2), the functional correlations “spread” from peak #2 to #1, or “converge” as we travel from #1 to #2.