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The average pathlength map: A diffusion MRI tractography-derived index for studying brain pathology

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ABSTRACT

Magnetic resonance diffusion tractography provides a powerful tool for the assessment of white matter architecture *in vivo*. Quantitative tractography metrics, such as streamline length, have successfully been used in the study of brain pathology. To date, these studies have relied on *a priori* knowledge of which tracts are affected by injury or pathology and manual delineation of regions of interest (ROIs) for use as waypoints in tractography. This limits the analyses to specific tracts under investigation and relies on the accurate and consistent placement of ROIs. We present a fully automated technique for the voxel-wise analysis of streamline length within the entire brain, the Average Pathlength Map (APM). We highlight the precision and reproducibility of voxel-wise average streamline length over time, and assess normal variability of pathlength values in a cohort of 43 healthy participants. Additionally, we demonstrate the utility of this approach by performing voxel-wise comparison between pathlength values obtained from a patient with a severe traumatic brain injury (TBI, Glasgow Coma Scale Score = 7) and those from control participants. Our analysis shows that voxel-wise average pathlength values are comparable to fractional anisotropy (FA) in terms of reproducibility and variability. For the TBI patient, we observed a significant reduction in streamline pathlength in the genu of the corpus callosum and its projections into the frontal lobe. This study demonstrates that the average pathlength map can be used for voxel-based analysis of a quantitative tractography metric within the whole brain, removing both the dependence on *a priori* knowledge of affected pathways and time-consuming manual delineation of ROIs.

Introduction

Diffusion Magnetic Resonance Imaging (dMRI) is a non-invasive imaging technique that enables the investigation of the structure and architecture of white matter (WM) *in vivo*. With respect to pathology, WM integrity is often assessed locally using diffusion tensor derived metrics which describe the anisotropic nature of water diffusion in the brain (e.g. fractional anisotropy (FA); Basser and Pierpaoli, 1996; Bodini and Ciccarelli, 2009). Using step-wise tracking of the direction of the principal eigenvector of the diffusion tensor, it is possible to delineate WM pathways in three dimensions, a technique known as diffusion tractography (Behrens and Jbabdi, 2009). However, diffusion tractography based on the diffusion tensor has often resulted in false positive streamlines following a physiologically implausible course or false negative streamlines (i.e. failure to delineate known pathways; Jones 2008). These streamline propagation errors often arise in areas where fibres cross and are caused by the inability of the diffusion tensor to resolve complex WM networks. With the development of higher-order models of diffusion which are capable of resolving complex WM architecture in the brain, such as DSI (diffusion spectrum imaging; Wedeen et al., 1999), q-ball (Tuch et al., 2003) and constrained spherical deconvolution (Tournier et al., 2007), the accuracy of diffusion tractography has been greatly improved.

Although diffusion tractography may be used to visualise the anatomical pathways of specific WM tracts, the technique can also be employed to assess WM integrity within a tract by using the delineated volume as a region of interest (ROI) to extract FA or mean diffusivity (MD) measures (Johansen-Berg and Behrens, 2006). Quantitative metrics can also be derived from the tractograms directly (Correia et al., 2008). The metrics proposed by Correia et al. (2008)

Abbreviations: APM, average pathlength map; FA, fractional anisotropy; MD, mean diffusivity; CoV, coefficient of variation; TBI, traumatic brain injury; SD, standard deviation; ROI, region of interest; TOI, tract of interest; VOI, volume of interest; HARDI, high angular resolution diffusion imaging; FOD, fibre orientation distribution; VBA, voxel-based analysis; TPM, total pathlength map; TDI, track density imaging.

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include the total length of streamlines, the total weighted length (where each streamline is weighted by its average fractional anisotropy FA or average linear anisotropy C_L), the total number of streamlines, and the average length of streamlines.

As the local diffusion properties are assessed at each step of the tracking process, streamline propagation is terminated when predefined conditions are not met. Typical termination criteria include the radius of curvature, FA (for tensor-based tractography), or fibre orientation density (FOD) amplitude (for high angular resolution diffusion imaging (HARDI) based tractography). Thus, changes in the local diffusion properties incurred by brain injury or disease may cause a streamline to terminate prematurely, resulting in a shorter length of streamlines within a tract of interest.

The average length of streamlines has successfully been employed in studies of autism in children (Kumar et al., 2009), HIV (Tate et al., 2010), agenesis of the corpus callosum (Nakata et al., 2009), and young adults, where correlations have been calculated between connection length and connectivity (Lewis et al., 2009). To date, these studies have relied on the assessment of all streamlines generated either within the whole brain or within tracts of interest that are extracted using manually outlined ROIs. The assessment of all streamlines simultaneously within the whole brain is not ideal in terms of sensitivity, as it may be difficult to detect subtle injury to a single WM pathway. Extracting tracts of interest, on the other hand, increases sensitivity, however placement of waypoint ROIs for tractography is time-consuming and operator-dependent, and requires expert knowledge.

Alternatively, voxel-based analysis (VBA; Ashburner and Friston, 2000) is an operator-independent technique that is often used in the analysis of diffusion MRI. VBA is normally performed by registering every participant's FA and/or MD map with a common brain template (Smith and Kindlmann, 2009). Group analysis of FA and/or MD values can then be achieved on a voxel-wise basis, and clusters of voxels exhibiting a statistically significant correlation with (for example) injury severity can be identified in a fully automated fashion.

In this study, we extend the work of Correia et al. (2008) by creating a map of a quantitative tractography metric, namely the average length of streamlines for the entire brain, which can in turn be used to perform VBA. We call this the *average pathlength map* (APM). An APM voxel value reports the average length of all streamlines traversing this particular voxel. The resolution of the APM is not restricted to the resolution of the diffusion scan, equivalent to the recently introduced Track-Density Images (Calamante et al., 2010), such that super-resolution can be achieved. Our primary objectives were to i) assess the precision of APMs, given the noisy nature of the diffusion data; ii) address the problem of adjusting for differences in brain size; iii) examine pathlength variability across the population; iv) demonstrate the utility of APMs in a case of traumatic brain injury (TBI); and v) discuss the factors that affect APMs and how they relate to the clinical interpretation of the new measure.

Methods

Participants

Data from forty-four healthy participants (27 males; aged 18–73, average 40, SD 14, 5 left-handed) and one patient who had sustained a severe traumatic brain injury (motor vehicle accident; age 20, male, right-handed) were included in the study. The patient's lowest Glasgow Coma Scale (GCS) score was 7, which was recorded by ambulance officers at the accident scene. The patient had no prior history of TBI, neurological disorder, or alcohol or drug abuse. Imaging data was obtained 197 days post injury. Control participants included controls who had sustained an orthopaedic injury not involving the face or head. All participants were recruited as part of a larger study of TBI.

The local ethics committee approved the study and informed consent was obtained from each participant. No participant reported having a history indicating any developmental, psychiatric or neurologic disorders that might affect brain structure or function.

Image acquisition

MRI data were acquired at the Royal Adelaide (RAH) and Royal Melbourne (RMH) Hospitals using a 3 T Siemens TimTrio (Siemens, Erlangen, Germany) scanner with TQ gradients (45 mT/m, SR 200 T/m/s), using commercial sequences from VB15 Neuro applications and Diffusion Tensor Imaging options.

Diffusion images were acquired using an optimised diffusion sequence. The imaging parameters were: 60 axial slices, FOV 25×25 cm, TR/TE 9400/116 ms, 2.5 mm slice thickness and acquisition matrix 100×100 with a 2.5 mm^3 isotropic resolution. Sixty-five diffusion-weighted images were acquired at each location consisting of 1 low ($b=0$) and 64 high ($b=3000$ s mm^{-2}) diffusion-weighted images, in which the encoding gradients were uniformly distributed in space using the electrostatic approach (Jones et al., 1999). The acquisition time for the diffusion scan was 10:41 min.

A field map was acquired using two 2D gradient recalled echo images (TE1/TE2 4.76/7.22 ms) to assist the correction for distortion due to susceptibility inhomogeneities.

To enable segmentation into white matter (WM), grey matter (GM) and CSF, high-resolution structural images were also acquired for each participant using a 1 mm^3 isotropic 3D T1 MPRAGE sequence based on the ADNI protocol (http://www.loni.ucla.edu/ADNI/Research/Cores/ADNI_Siemens_Human_3TVB15_Trio.pdf). The imaging parameters were: FOV $24\times25.6\times17.6$ cm, TR/TE/TI 2300/2.26/900 ms, flip angle 9. The imaging time was 9:14 min.

One participant was scanned on two occasions at the RAH, and on a third occasion at the RMH using the same scanner model and sequences in order to assess within-subject reproducibility. All three scans were acquired within 2.5 months. MRI data of all other participants was acquired at the RAH.

Data pre-processing

Pre-processing of diffusion data was performed as described previously (Pannek et al., 2010). Briefly, diffusion-weighted images were corrected for eddy current distortions using tools provided with FMRIB's Diffusion Toolbox (FDT, part of FMRIB Software Library FSL (Smith et al., 2004, http://www.fmrib.ox.ac.uk/fsl). Susceptibility distortions were corrected using the field map, employing FUGUE (Jenkinson, 2003) and PRELUDE (Jenkinson, 2004; both part of FSL). Skull stripping was performed using BET (FSL, Smith, 2002).

The fibre orientation distribution (FOD) was estimated using the constrained spherical deconvolution method with default parameters implemented in the MRtrix package (http://www.brain.org.au/software; Tournier et al., 2007). Fibre tracking was performed using MRtrix. Every voxel of the brain volume was seeded with 50 probabilistic streamlines. The following tracking parameters were employed: step size 0.2 mm, FOD amplitude threshold 0.1, minimum curvature radius 2 mm, minimum streamline length 10 mm.

Average pathlength maps in native space

The length of every probabilistic streamline of the whole brain tractogram (WBT) was determined. For every voxel on a predefined grid (here 1 mm^3 isotropic), the sum of the length of all streamlines passing through each voxel was calculated, giving a total pathlength map (TPM). Additionally, the number of streamlines traversing each voxel was recorded, rendering a track-density image (TDI; Calamante et al., 2010). The average pathlength map (APM) was then