NeuroImage 88 (2014) 271–281

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

Knowledge-based automated reconstruction of human brain white matter tracts using a path-finding approach with dynamic programming

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ARTICLE INFO

Article history:
Accepted 7 October 2013
Available online 14 October 2013

ABSTRACT

It has been shown that the anatomy of major white matter tracts can be delineated using diffusion tensor imaging (DTI) data. Tract reconstruction, however, often suffers from a large number of false-negative results when a simple line propagation algorithm is used. This limits the application of this technique to only the core of prominent white matter tracts. By employing probabilistic path-generation algorithms, connectivity between a larger number of anatomical regions can be studied, but an increase in the number of false-positive results is inevitable. One of the causes of the inaccuracy is the complex axonal anatomy within a voxel; however, high-angular resolution (HAR) methods have been proposed to ameliorate this limitation. However, HAR data are relatively rare due to the long scan times required and the low signal-to-noise ratio. In this study, we tested a probabilistic path-finding method in which two anatomical regions with known connectivity were pre-defined and a path that maximized agreement with the DTI data was searched. To increase the accuracy of the trajectories, knowledge-based anatomical constraints were applied. The reconstruction protocols were tested using DTI data from 19 normal subjects to examine test–retest reproducibility and cross-subject variability. Fifty-two tracts were found to be reliably reconstructed using this approach, which can be viewed on our website.

Introduction

White matter tract reconstruction based on diffusion tensor imaging (DTI) was introduced more than 10 years ago (Basser et al., 2000; Conturo et al., 1999; Mori et al., 1999; Poupon et al., 2001). This technique, called tractography, is capable of faithfully reconstructing the macroscopic architecture of major white matter bundles, but its limitations are also widely known (see, e.g., Tournier et al., 2011). The DTI data, in which the neuroanatomy in each pixel is reduced to a mere six parameters, is only an approximation of the tract orientation, assuming all fibers within a voxel are aligned along one orientation. With 2–3 mm resolution, many axons could merge, diverge, or cross within one voxel. In addition, partial voluming occurs in all voxels that are located between two major bundles. As a result, the tractography results are known to have false-positive and false-negative results. To complicate the situation even further, the very notion of various "white matter tracts" was established based on macroscopic visual assessment of postmortem samples (e.g., Dejerine, 1895; Krieg, 1963) and their definitions on a microscopic scale, for instance, of the connectivity by axons, are often vague. This ambiguous anatomical definition has led to a lack of gold standards, which makes validation of tractography difficult.

There are several approaches, postulated in the past, to achieve more accurate tractography results. First, we can extract more information from each voxel by not reducing the diffusion information to the six-element tensor model (Frank, 2001, 2002; Tournier et al., 2004; Tuch et al., 2003; Wedeen et al., 2005; Wiegell et al., 2000). These methods usually require two conditions when acquiring data: a large number of diffusion orientation measurements (typically more than 60); and heavy diffusion weighting (typically more than 3000 s/mm^2). From these measurements, the fiber angles of multiple tract populations within a voxel can be estimated. These approaches, however, often sacrifice SNR and higher sensitivity to measurement artifacts, such as subject motion and eddy current. The low SNR of raw images, in particular, makes quality control challenging (Ben-Amitay et al., 2012). The second approach is to improve the tractography method. The simplest approach is deterministic line propagation, which simply follows the principal eigenvector in each voxel (see, e.g., Mori and Van Zijl, 2002). This approach has, however, been criticized for its high sensitivity to noise, because it accumulates errors from noise along the path. More elegant probabilistic approaches to incorporate the path

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http://dx.doi.org/10.1016/j.neuroimage.2013.10.011

uncertainty have also been postulated, in which path generation is repeated under different conditions, leading to multiple potential paths from one seed voxel (Behrens et al., 2003; Jeurissen et al., 2011; Jones, 2003; Jones and Pierpaoli, 2005; Lazar and Alexander, 2003, 2005; Lori et al., 2002; Parker et al., 2002; Richter et al., 2013; Tournier et al., 2002). While these methods can be considered "path generation" approaches, there is another class of "path-finding" approaches, in which the start and end points are prefixed and the most probable path that agrees most with the DTI results is sought. Namely, posing the problem as an optimization problem enables computation of a "shortest path" between chosen initial and terminal points that globally minimizes a sequentially additive energy constraint defined by the tensor in the spirit of the classical Djikstra's algorithm (Everts et al., 2009; Fout et al., 2005; Iturria-Medina et al., 2007; Lal, 2004; Lifshits et al., 2009; Merhof et al., 2006a, 2006b; Poynton et al., 2005; Richter et al., 2013; Tuch et al., 2001; Vorburger et al., 2012; Zalesky, 2008; Zalesky and Fornito, 2009). These assign a probability distribution to the local orientation of fibers at each voxel, and use path finding methods to compute the optimal path between two regions. Our method described in this paper is an extension of these efforts and uses dynamic programming to minimize a quadratic function based on the Gaussian form of the full DTI tensor.

This "path-finding" approach poses a challenging question: "what defines the ground truth where two points are connected?" One can argue that if there is one axon between two points, they are connected. However, we cannot expect that the MRI-based approach can faithfully reconstruct the pathway of a single axon. We could also argue that this approach attempts to reconstruct the large white matter bundles already well-described by classic anatomy literature (Dejerine, 1895; Krieg, 1963). However, visual identification of the long sweep of an axonal bundle from points A to B does not automatically guarantee that these two points are actually connected; many axons can merge and exit along the pathway and there could be no single axon that travels the entire length of the described tract. These arguments might suggest that tractography is not a tool with which to investigate connectivity based on cellular level structure, but to reconstruct macroscopic white matter architectures or a region-growing tool, which can cluster anatomically related pixels based on DTI data.

Although it is still vague, we could then define our gold standards as those large bundles that have been described by neuroanatomists. Some of the large tracts actually have well-known trajectories because their anatomy is homologous to animals, in which invasive studies are possible. These include the corticospinal tract, the visual pathway, the fornix, and many tracts in the brainstem. However, detailed trajectory patterns of many association tracts remain ambiguous because they are much less developed in animals, and our knowledge derived from this method remains at a lobar-level scale. Cortico-thalamic/thalamo-cortical projection fibers, as well as commissural fibers, are subject to the same limitations. A subset of their connectivity patterns is known from animal studies, but our knowledge of the human brain remains at a macroscopic scale; for example, the projection from or to the medial–dorsal thalamic nuclei penetrates the anterior limb of the internal capsule, the frontal corona radiata, and reaches the frontal lobe. Assuming that we can use these types of macroscopic knowledge as the gold standards, knowledge-based tractography can effectively increase the precision (reproducibility) of the results, while it also supports the accuracy (validity) of the employed knowledge. Specifically, knowledge-based tractography is usually performed using multiple regions of interest (ROIs) that define at least the two target regions, as well as waypoints along the path (Conturo et al., 1999; Huang et al., 2004). We can use these ROIs as anatomical constraints, retrieving only results that penetrate all the ROIs. Previous analysis has suggested that this approach can reduce false-positives (thus, results are specific), while the false-negatives remain stable (thus, sensitivity is unchanged) when a deterministic approach is used (Huang et al., 2004). In other words, if two target regions, which are known to be a part of a large fiber bundle, are defined in the brain, the reconstructed trajectory, if any, is likely to agree with the known trajectory, but it often returns no result. For example, it is widely known that the projections of the corpus callosum and the projection fibers (e.g., the corticospinal tracts and thalamic radiations) tend to miss large portions of projections to the lateral cortical areas with the tensor model and deterministic approaches.

In this paper, we extended these previous observations by combining a knowledge-based approach with path-finding algorithms. Because path-finding algorithms always generate a path, the false-negatives become zero. If the knowledge-based guidance, as a form of ROIs, ensures removal of false-positives, we expect a highly useful tool with which to study white matter architecture. Of course, the limitation of this logic is that the accuracy is defined by the qualitative anatomical knowledge about the white matter architecture. If we place a large number of ROIs to eliminate all potential false-positive results, it becomes the hand-segmented white matter tract defined by an anatomist and the tractography is not needed. In this study, therefore, we explored the following questions:

1) Can a path-finding algorithm reconstruct known tract trajectories through ROI guidance? If so, how many ROIs are needed?
2) How does this method compare to conventional deterministic approaches?
3) What is the level of precision in terms of test–retest and cross-subject reproducibility?
4) Can we automate the process of the ROI placement steps?

In this study, we employed the dynamic programming algorithm and tested a pipeline for automated trajectory reconstructions of well-described large white matter bundles to investigate the four questions posed above.

Methods

MRI data

Nineteen healthy volunteers with no history of neurological conditions (10 males, 9 females, 22–61 years old; mean, 31 years old) participated in this study. Local Institutional Review Board approval and written, informed consent were obtained prior to the examination. The details of the protocol can be found elsewhere (Landman et al., 2011). Briefly, the subjects were scanned twice using a 3 T MR scanner (Achieva, Philips Healthcare, Best, The Netherlands). The DTI dataset was acquired with a multi-slice, single-shot, echo-planar imaging (EPI), spin-echo sequence (TR/TE = 6281/67 ms, SENSE factor = 2.5). Sixty-five transverse slices were acquired parallel to the line connecting the anterior commissure (AC) to the posterior commissure (PC), with no slice gap and 2.2 mm nominal isotropic resolution (FOV = 212 × 212, data matrix = 96 × 96, reconstructed to 256 × 256). Diffusion weighting was applied along 32 directions (Philips parameters: gradient overplus = no, directional resolution = high, gradient mode = enhanced) with a b-value of 700 s/mm^2. Five minimally weighted images (five b0 with b ≈ 33 s/mm^2) were acquired and averaged on the scanner as part of each DTI dataset. The total scan time to acquire the DTI dataset was 4 min 11 s. No cardiac or respiratory gating was employed.

The raw diffusion-weighted images (DWIs) were first co-registered to one of the b0 images and corrected for eddy current and subject motion with affine transformation using automated image registration (AIR) (Woods et al., 1998). The six elements of the diffusion tensor were calculated for each pixel with multivariate linear fitting using DtiStudio (Jiang et al., 2006). After diagonalization, three eigenvalues and eigenvectors were obtained. For the anisotropy map, fractional anisotropy (FA) was used (Pierpaoli et al., 1996).

LDDMM-based parcellation

We used a single-subject white matter atlas (JHU-MNI-ss, www.mristudio.org) in the ICBM-152/ICBM-DTI-81 space. A detailed