NeuroImage 142 (2016) 150–162

Contents lists available at ScienceDirect

NeuroImage

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

Correction for diffusion MRI fibre tracking biases: The consequences for structural connectomic metrics

Chun-Hung Yeh [a,*], Robert E. Smith [a], Xiaoyun Liang [a], Fernando Calamante [a,b,c], Alan Connelly [a,b,c]

[a] Florey Institute of Neuroscience and Mental Health, Melbourne, Victoria, Australia
[b] Florey Department of Neuroscience and Mental Health, University of Melbourne, Melbourne, Victoria, Australia
[c] Department of Medicine, Austin Health and Northern Health, University of Melbourne, Melbourne, Victoria, Australia

ARTICLE INFO

Article history:
Received 7 December 2015
Revised 27 April 2016
Accepted 18 May 2016
Available online 20 May 2016

Keywords:
Diffusion MRI
Fibre-tracking
Tractography
Structural connectome
Network metrics

ABSTRACT

Diffusion MRI streamlines tractography has become a major technique for inferring structural networks through reconstruction of brain connectome. However, quantification of structural connectivity based on the number of streamlines interconnecting brain grey matter regions is known to be problematic in a number of aspects, such as the ill-posed nature of streamlines terminations and the non-quantitative nature of streamline counts. This study investigates the effects of state-of-the-art connectome construction methods on the subsequent analyses of structural brain networks using graph theoretical approaches. Our results demonstrate that the characteristics of structural connectivity, including connectome variability, global network metrics, small-world attributes and network hubs, alter significantly following the improvement in biological accuracy of streamlines tractograms provided by anatomically-constrained tractography (ACT) and spherical-deconvolution informed filtering of tractograms (SIFT). Importantly, the commonly-used correction for connection density based on scaling the contribution of each streamline to the connectome by its inverse length is shown to provide incomplete correction, highlighting the necessity for the use of advanced tractogram reconstruction techniques in structural connectomics research.

Introduction

Diffusion MRI is an increasingly popular technique for exploring structural brain networks in the rapidly evolving field of human connectomics. This is achieved by using whole-brain tractography in conjunction with brain parcellation to provide quantitative measures of white matter (WM) connections between pairwise grey matter (GM) regions, thereby enabling the construction of a connectivity matrix (i.e. the connectome). Subsequent graph theoretical analysis of brain network characteristics (Bullmore and Sporns, 2009; Hagmann et al., 2008; Iturria-Medina et al., 2008; Sporns et al., 2005) provides opportunities for understanding topology and physical properties of structural brain networks in healthy and disordered states (see (Sporns, 2014; Stam, 2014) for review).

Despite promising applications of this analysis approach, a number of problems associated with quantification of the structural connectome based on streamlines tractograms are well-recognised (see for example (Jones et al., 2013)). In particular, (a) the termination criteria of tractography algorithms often cause streamlines to end erroneously within WM or cerebrospinal fluid (CSF), which is not biologically reasonable (Smith et al., 2012), and (b) the number of streamlines interconnecting brain regions (nodes) is known to be an unreliable quantitative marker of fibre connectivity (edges) due to multiple confounding factors in the process of tractogram reconstruction. Thus, it is inadvisable to infer structural networks based on raw streamline count, as the validity of any conclusions drawn from this approach regarding brain network properties remains uncertain.

One of the recurrent issues relating to connectome quantification is the over-reconstruction of streamline density for longer fibre pathways; this problem is induced by homogeneously initiating (i.e. seeding) streamlines throughout WM, yet this is the most commonly used seeding strategy. In order to compensate for such fibre-tracking bias in streamline density, a pioneer study on structural network analysis suggested scaling the contribution of each streamline to the connectome by its inverse length (Hagmann et al., 2008). This mechanism has been frequently adopted for structural connectome studies (e.g. (Buchanan et al., 2014; Griffa et al., 2014)); however, since it addresses primarily only one of the potential biases in the tractogram (see the synthetic example in Methods for expansion of this argument), such an approach is likely to provide incomplete correction. An alternative way for bypassing this source of bias can be achieved by seeding from the

* Corresponding author at: Florey Institute of Neuroscience and Mental Health, Melbourne Brain Centre, 245 Burgundy Street, Heidelberg, Victoria 3084, Australia.
E-mail addresses: chun-hung.yeh@florey.edu.au, jimmy.chyeh@gmail.com (C.-H. Yeh).

http://dx.doi.org/10.1016/j.neuroimage.2016.05.047
1053-8119/

interface between GM and WM (abbreviated as GMWMI) (Girard et al., 2014; Smith et al., 2012), however this method is possibly limited to deal with this specific type of bias that arises from using WM seeding (see also the synthetic example in Methods).

Since raw streamlines tractograms are quantitatively untrustworthy, there is considerable diversity in how structural connectomes have been analysed. Some studies have adopted 'unweighted' structural networks where connections were represented in a binary fashion (Gong et al., 2009; Zalesky et al., 2010). While this approach does avoid the problems associated with using 'track counts' as a measure of connectivity, it does introduce other limitations in that such a 'binarisation' process discards the known biological heterogeneity of connection density (Markov et al., 2011). Some studies have maintained the structural connectomes weighted by streamline count while introducing an arbitrary threshold value of connection number or probability to filter out the weakest connections (Buchanan et al., 2014; Li et al., 2009; Owen et al., 2013); however, this may unfavourably alter the characteristics of structural connectivity being investigated. Other studies, instead of using streamline count, have employed some quantitative parameter of diffusion (e.g. fractional anisotropy) within the volume of the connecting pathways (Hagmann et al., 2010; van den Heuvel and Sporns, 2011); however, such metrics become unreliable themselves in regions of so-called 'crossing fibres', which are widespread throughout the brain (up to ~90% of WM voxels (Jeurissen et al., 2013)). Importantly, therefore, none of the analysis strategies described above have provided a solution to the problem of underlying tractogram biases.

These important issues related to tractogram reconstruction potentially can be addressed through application of more comprehensive correction methods. There are several state-of-the-art tractography techniques that are designed to address different aspects of the required correction. These include particle filtering tractography (Girard et al., 2014) and anatomically-constrained tractography (ACT) (Smith et al., 2012), which use anatomical information from high-resolution T1-weighted images (T1WIs) to control the evolution and termination of fibre tracking; and convex optimisation modelling for micro-structure informed tractography (COMMIT) (Daducci et al., 2014) and spherical-deconvolution informed filtering of tractograms (SIFT) (Smith et al., 2013), which improve tractogram reconstruction with quantitative and biologically-plausible features. Although differing in algorithms, these approaches potentially correct for similar types of errors or biases, respectively.

To investigate the effects of more comprehensive tracking correction, the present study focuses on the effects of ACT and SIFT. The ACT framework can effectively prevent biologically unrealistic connections caused by the tractography algorithm termination criteria (Smith et al., 2012), while the application of SIFT has been shown to effectively reduce known biases in streamline density (Smith et al., 2013), and to improve overall biological accuracy of the structural connectome (Smith et al., 2015a). In addition, SIFT has been shown to improve the reproducibility of some basic connectomic measures (Smith et al., 2015a). Unlike the heuristic inverse length scaling method that deals with one specific type of fibre-tracking bias, SIFT provides a tractogram with streamlines densities that are consistent with the underlying fibre densities, and may therefore address a wider range of potential reconstruction biases. Altogether, it is reasonable therefore to expect that the characteristics of the resultant structural connectome will be more biologically accurate and interpretable following the application of ACT and SIFT (Smith et al., 2015a), as compared to those without tractogram bias correction or with partial correction using inverse length scaling. However, statistical evaluations of the practical consequences for structural connectome analyses at different levels of tractogram bias corrections have not yet been determined. Hence, the main purpose of this study is to investigate whether correction of the tractogram using ACT and SIFT has a statistically significant effect on brain network properties derived from graph theoretical analyses, including a more comprehensive range of connectomic metrics and higher-order brain network analyses than previously addressed (Smith et al., 2015a). In addition, we also assess whether scaling the contribution of each streamline by its inverse length is sufficient in practise, or if more comprehensive tractogram correction using SIFT has additional effects on connectomic metrics.

Methods

Synthetic example

To illustrate the effect of fibre-tracking bias correction on quantification of structural connectome, we generate synthetic fibre orientation distributions (FODs) of two simulated fibre bundles that have an identical cross-section and length but different microscopic fibre densities (Fig. 1). The FODs reflect the apparent fibre density as a function of orientation (Raffelt et al., 2012), i.e. the bundle with higher fibre density yields greater FOD amplitude. Fig. 1(a) and (b) show the ground-truth connectivity underlying this FOD field and the relevant streamline connection densities in the structural connectome, respectively.

In this example, most fibre-tracking algorithms would likely reconstruct an equal number of streamlines for the two pathways (Fig. 1(c)), no matter whether streamlines are initiated uniformly from the image (akin to WM seeding) or from the extremities of the fibre bundles (akin to GMWMI seeding). Accordingly, a structural connectome generated using either streamline count (Fig. 1(d)) or inverse length scaling (Fig. 1(e)) as edge weight will erroneously produce an equal connection density for the two pathways. Since both methods neglect the quantitative nature of the underlying FODs, the information relating to connection densities reflected in the FODs (Fig. 1(a)) is entirely lost in the connectome. By contrast, SIFT uses the sizes of the FODs to guide a tractogram reconstruction, and hence the streamline density in each pathway corresponds to the actual fibre density up to a global scaling factor (Fig. 1(f–g)). This simple scenario suggests that the connectome quantification may remain biased despite using the inverse length correction, whereas SIFT enhances the consistency of the streamlines tractogram with the underlying fibre densities, and can therefore improve the overall accuracy of connectome quantification.

MRI acquisition

Twenty-two healthy volunteers were recruited in this study (number of females/males = 11/11; 32.5 ± 6.5 years old; all right-handed). All participants provided written informed consent, and all protocols were approved by the local Institutional Review Board. MRI data were acquired using a Siemens 3T Tim Trio system (Erlangen, Germany). Anatomical T1WIs were acquired using the three-dimensional magnetization-prepared rapid gradient echo sequence (MPRAGE) sequence (Mugler and Brookeman, 1990) as follows: TR/TE/TI = 1900/2.6/900 ms, flip angle = 9°, field-of-view (FOV) = 230 × 230 mm^2, matrix size = 256 × 256, 192 sagittal slices, 0.9 mm isotropic resolution. Diffusion-weighted images (DWIs) were acquired using a twice-refocused spin-echo echo-planar imaging sequence (Reese et al., 2003) with the following parameters: TR/TE = 8400/110 ms, parallel acceleration factor = 2, phase partial Fourier = 6/8, FOV = 240 × 240 mm^2, matrix size = 96 × 96, 60 axial slices, 2.5 mm isotropic voxel dimension, 60 diffusion sensitization directions with b = 3000 s/mm^2, and 8 b=0 images. An additional pair of b=0 images with opposing phase encoding polarity was acquired for B_0 inhomogeneity field estimation.

Overview of data analysis

Fig. 2 illustrates a global workflow of MRI data analysis. The following subsections describe the procedures for connectome construction, and for all steps in which the relevant software is not explicitly stated, processing was performed using MRtrix3 (http://www.mrtrix.org).