

DIFFUSION MR IMAGE SEGMENTATION: TOWARDS GLOBAL BRAIN CONNECTIVITY ANALYSIS

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ABSTRACT

The exploration of the human connectome, a term denoting the global structural connectivity of the brain, is accessible to MRI at millimeter and centimeter scales. In this paper, we propose a methodology to map the connectome by constructing normalized whole-brain structural connection matrices derived from diffusion spectrum MRI tractography. Using a template-based approach, we propose a robust method that allows a) the selection of identical cortical regions of interest in different subjects with identification of the associated fiber tracts, b) a straightforward construction and interpretation of anatomically organized whole-brain connection matrices, and c) a statistical inter-subject comparison of brain connectivity.

Keywords: brain, diffusion MRI, tractography, connectivity.

INTRODUCTION

Due to its ability to probe the tissue microstructure, Diffusion MRI is known to be a very powerful tool to infer brain anatomical connectivity (LeBihan, 2003). Diffusion Tensor Imaging (DTI) (Basser *et al.*, 1994), which models the diffusion as a first-order tensor, is probably the most used technique to study brain neuronal circuitry. However, due to the limited angular resolution of DTI the interest towards higher angular resolution diffusion MRI methodologies is increasing. One of these methodologies is the Diffusion Spectrum Imaging (DSI) (Wedeen *et al.*, 2005; Hagmann *et al.*, 2006), which allows to map the diffusion of water molecules by reconstructing the spectrum of the spin displacement. The increased interest in Diffusion MRI has led to the development of various tractography algorithms, whose aim consists in inferring from the diffusion measurement the trajectories of the axonal bundles in the brain, allowing the study of the fiber tract architecture.

However, beyond the aim of characterizing individual fiber bundles, there is an increased interest from the neuro-scientific community towards the whole-brain connectivity profile. In this paper, we present a methodology that allows us to map the whole-brain connectivity from a DSI experiment. We proceed by generating fibers in the brain using a classical tractography algorithm, and then building a connection matrix in which each row and column corresponds to a small region of interest (ROI) of the white matter-gray matter (WM-GM) interface, i.e. the cortex for simplification. The information contained in

the matrix allows us to analyze the connectivity of the entire brain.

MATERIAL AND METHODS

This research was conducted in agreement with the ethics comity for clinical research of the University of Lausanne and informed written consent was obtained from the subjects before performing the study, in accordance with institutional guidelines. The proposed method consists of four steps (Hagmann *et al.*, 2008), as described in Figure 1 and presented in what follows.

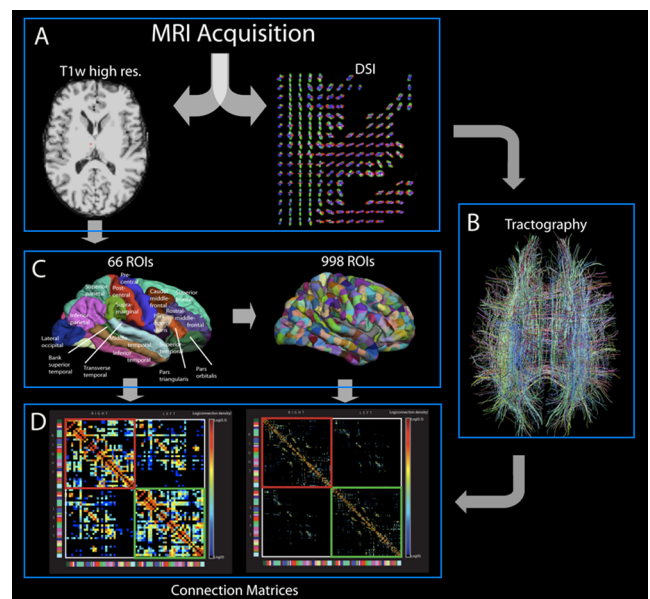


Fig. 1. Overview of the proposed method. (A) Acquisition of the diffusion MR images. (B) Tractography in the brain WM. (C) Partitioning of the WM-GM interface into small ROIs. (D) Creation of the connection matrices using the results of steps B and C.

A. A data set is acquired with an Achieva 3T Philips scanner. We use a diffusion weighted single shot EPI spin echo sequence with the following timing parameters: $TR/TE/\Delta/\delta = 4200/89/43.5/32.5$ ms, where Δ is the diffusion time interval and δ the diffusion gradient duration (Callaghan, 1991). With maximal diffusion gradient intensities of 80mT/m this yields a maximal b-value of 9000 s/mm². Q-space is sampled over a hemisphere using 129 different encoding gradients, and the data are reconstructed following a classical DSI scheme (Wedeen *et al.*, 2005), producing a 3D diffusion probability density function (PDF) in every voxel. The acquisition block is made of 36 slices of a 112 x 112 matrix, with a spatial resolution of 2 x 2 x 3 mm³. The acquisition time is approximately 18 minutes. Next, we compute for each voxel the orientation distribution function (ODF) by projection of the PDF in the radial direction. The ODF $\Phi(\mathbf{u})$ (\mathbf{u} being a 3D vector) is a function defined on a discrete sphere which captures the diffusion intensity in every direction. Moreover, a high resolution T1-weighted (MP-RAGE) MRI is performed on the same volunteer. This acquisition is then registered on the diffusion images using the affine registration method based on maximization of mutual information of Maes *et al.* (Maes *et al.*, 1997), and used to identify both the WM and GM with a T1w-based segmentation algorithm (Leemput *et al.*, 1999b;a), which allows us to define the WM-GM interface.

B. DSI tractography is performed in WM using an algorithm especially designed for DSI data (Hagmann *et al.*, 2007) and summarized below:

1. At each voxel, we define a set of directions of maximum diffusion as local maxima of $\Phi(\mathbf{u})$ (i.e., vectors \mathbf{u}_i such that $\Phi(\mathbf{u}_j) < \Phi(\mathbf{u}_i)$ for all \mathbf{u}_j adjacent to \mathbf{u}_i in the sampled tessellated sphere.
2. We choose a set of initialization points uniformly distributed in each brain WM voxel. The number of points is proportional to the number of direction vectors in the corresponding voxel. Next, from each of these points a fiber starts growing with a fixed step size (arbitrarily chosen to be 1 mm) in two opposite directions, locally following the direction of the vector \mathbf{u}_i whose orientation is the closest to the current direction of the fiber. If this results in a change of direction sharper than 0.25 rad/mm, the fiber is stopped. The growth process

ends when the end-points of the fiber reach the WM-GM interface. Fibers that do not reach the WM-GM interface are eliminated. Approximately 1 million fibers are generated in the brain WM with this algorithm.

C. The WM-GM interface partitioning is an important part of the processing, with several constraints. First, we want the ROIs to be as small and as compact as possible. Second, we want the ROIs to be placed in such a way that the anatomical location stays constant among the different subjects. The proposed procedure is based on an atlas-based cortical registration method using the curvature information, i.e. sulcus and gyrus (Cammoun *et al.*, 2007; Fischl *et al.*, 2004; Desikan *et al.*, 2006). This method was implemented in the Freesurfer software (<http://surfer.nmr.mgh.harvard.edu>), which provides an automatic labelling of the cortex into 66 gyral-based parcels, which are defined using curvature-based information on 40 manually labelled brains. The proposed procedure consists of three steps summarized below:

1. We use Freesurfer to register a labelled mesh from an average brain onto the brain of each subject, where each label corresponds to one of the 66 anatomical regions, providing for every subject a standardized partition of the cortex into 66 anatomical cortical regions.
2. We subdivide each gyral-based parcel of the atlas into many small ROIs, in order to build a new atlas containing approximately one thousand ROIs.
3. We register the obtained subdivision on the brain of each subject using the same transformation as for the 66 regional areas, thus maintaining the topological constraints of mapping.

Using this procedure, the cortex is divided into 998 ROIs, compact and of similar size, and with a surface of about 140mm².

D. We build the whole-brain connection matrix by combining the output of the two previous steps (B and C). Each row and column of the matrix corresponds to a particular ROI. The value of the connection matrix cell M_{ij} represents the fiber density of the bundle B_{ij} connecting the ROIs i and j and is defined as follows:

$$M_{ij} = \frac{\sum_{f \in B_{ij}} \frac{1}{l_f}}{0.5(S_i + S_j)}, \quad (1)$$

with l_f the length of the fiber f , and S_i, S_j the surface of the ROIs i and j respectively. l_f is a correction term needed to suppress the linear bias towards longer fibers introduced by the tractography algorithm (Hagmann

et al., 2007). To facilitate the visual interpretation of the connection matrix, it is organized by taking into account as much as possible the ROI neighborhood. Inspired by the brain development, the 33 parcels of each hemisphere are arranged in a fronto-caudal order.

RESULTS

Figure 2A represents the connection matrix of a healthy subject at low resolution (66 ROIs). The connection matrix is organized such that the upper left quadrant represents the connections in the right hemisphere and the lower right quadrant represents the left hemispheric connectivity. This matrix is symmetric since the measured connectivity is not oriented. The off-diagonal quadrants map the inter-hemispheric connections. The color bars at the left and bottom of the matrix help making the correspondence between the matrix entries and the 66 cortical parcels as displayed in Figure 2B. The color bar on the right codes the connection density seen in the matrix itself in logarithmic scale.

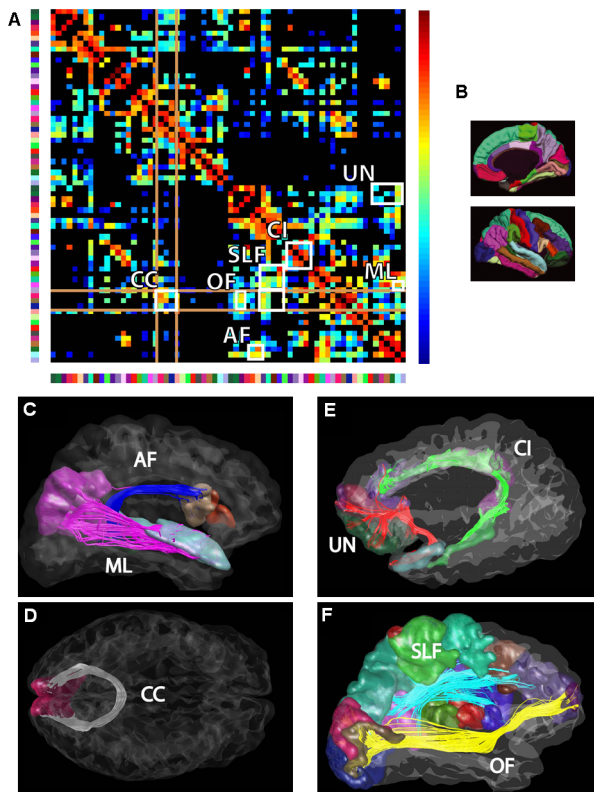


Fig. 2. Identification of different fiber bundles on the low resolution connection matrix. (C) Arcuate Fasciculus (AF) and Middle Longitudinal (ML); (D) Cuneus homotopic connection (CC); (E) Cingular

(CI) and Uncinate (UN); (F) Superior Longitudinal Fasciculus (SLF) and Occipito-frontal (OF).

It is possible to identify known bundles from the connection matrix. In Figure 2 we give several examples. We have selected groups of ROIs that are expected to correspond to language areas (Wernickes and Brocas Area). The connections between these areas can easily be identified on the matrix and correspond to the arcuate fasciculus. The latter with the uncinata, the occipito-frontal, the middle longitudinal and the superior longitudinal fasciculi form long distance connections, which are accordingly far from the diagonal of the matrix. The cingular bundle, which is made up mainly of sets of alternating short connections, is located close to the diagonal of the matrix. Another example is the pathways connecting the homotopic primary visual cortices, which are represented in the off-diagonal blocs. The occipito-frontal connection is represented by two squares in the matrix because not all the ROIs belonging to the frontal cortical area are neighbors in an arbitrary linear arrangement of the matrix entries.

It is worthwhile analyzing the empty part of the matrix located in the off-diagonal bloc. As expected from current anatomical knowledge, the inter-hemispheric fronto-temporal, temporo-temporal as well as the fronto-occipital and fronto-parietal connections are not mapped.

DISCUSSION

Over the last years it has become clear that MR based connectomic techniques are of highest interest for the neuroscience community (Bullmore and Sporns, 2009; Gross, 2008). The presented method is an answer to this growing interest. We step by step showed how to partition the cortex in a standard way such that ROIs are identically placed across subjects, enabling the construction of whole-brain normalized connection matrix at multiple scales, which can be averaged and compared over population of subjects. It is worth noting that defining a connection matrix as presented here with a connection density measure, is only one way to characterize the connectivity. Other tract properties can be computed and used to construct the matrix, such as the Fractional Anisotropy, the Mean Diffusion or other values measured by MRI or fMRI.

It has been shown that this whole-brain connection matrix has the capacity to be at the source of powerful analyzes (Hagmann *et al.*, 2008; Honey *et al.*, 2009). More than that, it opens up a whole range of clinical studies; either for longitudinal healthy development analysis, such as the development of

connectivity with age, or for the investigation of connectional disturbances in disease. Indeed, in many pathologies such as schizophrenia or epilepsy, the connectivity is suspected to be affected in some specific bundles, whereas inflammatory processes may affect connectivity more globally. The connection matrix, allowing us to perform group versus group comparisons, turns out to be a promising tool to investigate this kind of pathologies.

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