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Intra-subject reliability of the high-resolution whole-brain structural connectome

Pierre Besson [a,b,*], Renaud Lopes [b,c], Xavier Leclerc [b,c], Philippe Derambure [a,b], Louise Tyvaert [a,b]

[a] Department of Clinical Neurophysiology, Lille University Hospital, France
[b] UMR 1046, University of Lille, France
[c] In-vivo Imaging Core Facility, IMPRT-IFR114, Lille University Hospital, France

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ABSTRACT

Recent advances in diffusion weighted image acquisition and processing allow for the construction of anatomically highly precise structural connectomes. In this study, we introduce a method to compute high-resolution whole-brain structural connectome. Our method relies on cortical and subcortical triangulated surface models, and on a large number of fiber tracts generated using a probabilistic tractography algorithm. Each surface triangle is a node of the structural connectivity graph while edges are fiber tract densities across pairs of nodes. Surface-based registration and downsampling to a common surface space are introduced for group analysis whereas connectome surface smoothing aimed at improving whole-brain network estimate reliability.

Based on 10 datasets acquired from a single healthy subject, we evaluated the effects of repeated probabilistic tractography, surface smoothing, surface registration and downsampling to the common surface space. We show that, provided enough fiber tracts and surface smoothing, good to excellent intra-acquisition reliability could be achieved. Surface registration and downsampling efficiently established triangle-to-triangle correspondence across acquisitions and high inter-acquisition reliability was obtained. Computational time and disk/memory usages were monitored throughout the steps.

Although further testing on large cohort of subjects is required, our method presents the potential to accurately model whole-brain structural connectivity at high-resolution.

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Introduction

The structural connectome is a convenient and efficient way to describe the brain architecture in mathematical terms (Bullmore and Sporns, 2009; Bullmore and Bassett, 2011). The highly complex brain structure, involving billions of neurons (Murre and Sturdy, 1995), is represented by means of a mathematical graph where the nodes are brain regions and the edges are structural links across the nodes. Usually, a whole-brain structural connectome is obtained by defining a set of regions of interest based on brain anatomical images and modeling white matter fibers using diffusion-weighted imaging. The size and number of regions of interest are important parameters for constructing the structural connectome and have substantial influence on network topological characteristics (de Reus and Van den Heuvel, 2013; Zalesky et al., 2010). Currently, whole-brain structural connectome can be obtained using coarse cortical parcellation (ranging from about 1 cm^2 to several cm^2), possibly including subcortical structures, or using large cubic regions of interest covering the whole brain (Hagmann et al., 2008; Verstraete et al., 2011; Zalesky et al., 2012).

This macroscale description of the whole-brain structural connectivity (Sporns et al., 2005) shows good to excellent inter-subject, inter-scan and inter-site reliabilities (Owen et al., 2013) and offers the possibility to characterize small-worldness, rich club organization, motif/node degree distributions of the healthy brain (Bullmore and Sporns, 2009; Hagmann et al., 2008; Rubinov and Sporns, 2010; Sporns et al., 2004; van den Heuvel and Sporns, 2011). The overall structural brain organization relevantly parallels the functional segregation/integration brain organization, leading to the hypothesis that brain functioning could be in part driven by the underlying structural core (Bullmore and Sporns, 2009; Greicius et al., 2009; Honey et al., 2009). However, such whole-brain parcellation-based connectomes only provide a coarse description of brain structural connectivity and may not be suitable for precise whole-brain connectivity based segmentation (de Reus and Van den Heuvel, 2013).

One way to improve the anatomical accuracy of the whole-brain structural connectome is by significantly reducing the size of the regions of interest defining the nodes of the structural connectivity graph (Van Essen and Ugurbil, 2012). To this end, the notion of 'dense connectome' was introduced to provide as accurate as possible description of whole-brain structural connectivity. Rather than using all brain voxels as graph nodes, which would have yielded enormous datasets (about 220,000 nodes; 195 GB per subject), nodes of the structural connectivity graph

* Corresponding author at: Service de neuroradiologie, Hôpital Roger Salengro, Rue du Professeur Laine, 59037 Lille, France. Fax: +33 320446488.
E-mail address: besson.pierre@gmail.com (P. Besson).

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were the vertices of the cortical surfaces and voxels of subcortical structures and cerebellum (Glasser et al., 2013). The use of cortical vertices provides a compact representation of the cortical ribbon and considerably lightens generated datasets although 'dense connectomes' are still large (about 90,000 nodes; 31 GB per subject), resulting in considerable problems for data sharing, storage, processing and handling (Glasser et al., 2013; Marcus et al., 2011). Another difficulty arising from the 'dense connectome' is the definition of a network weighting taking into account the size of the regions of interest. Computing fiber densities across pairs of nodes would require additional processing as nodes of the network can be either volume elements (subcortical and cerebellar voxels) or surface elements (cortical vertices) whereas simpler weightings, such as the number of fiber tracts across pairs of nodes, would not correct for anatomical nodes' size.

In this paper, we present a method to extract the whole-brain high-resolution structural connectome (HRSC). The aim of our method is to define the structural connectome at a high spatial resolution, to provide the necessary tools for individual and group analysis keeping in mind computational time and memory usage constraints. For this purpose, we extended the surface-based compact representation of the cortical ribbon to the subcortical structures.

High-resolution triangulated cortical and subcortical surface models were extracted in native space and a large number of white matter fiber tracts were generated using whole-brain probabilistic tractography. Each surface triangle defined a node of the HRSC while fiber densities across every pair of nodes defined network weighting, therefore providing a unique and size corrected network weighting between any pair of nodes. Resulting structural connectomes constituted a spatially dense sampling of the brain connectivity, as HRSC relied on about 500,000 triangles whose area was on average 0.3 mm^2 in the cortex and 0.5 mm^2 for subcortical surface models. We defined surface-based registration of the structural connectome to a common surface template to allow group analysis to be performed. An iterative surface smoothing procedure of the structural connectome was introduced to reduce the variability induced by the stochastic nature of the tractography algorithm, mostly remarkable in native space, and to attenuate the effects of possible misalignments to common surface space. The spatial resolution of the common surface space may be adapted to the purpose of the study or to fulfill memory usage requirements.

Our method was tested on 10 acquisitions of a single healthy subject. First, we estimated the effects of processing parameters such as the number of generated fiber tracts, surface smoothing and surface registration and downsampling; we then calculated the inter-acquisition HRSC reliability on a common downsampled surface space. We also measured the time and memory usage required by the processing steps as well as the size of the output files.

Materials and methods

Participant and MR acquisition

Ten sets of images were obtained from a 32-year-old healthy female participant with no history of neurological disease. Data were acquired on ten scanning sessions spread over two weeks. Written consent was obtained and this study was approved by the local ethics committee.

MR images were acquired on a 3T scanner (Achieva Philips, Best, The Netherlands) at the In-vivo Imaging Platform, Lille University Hospital, France. The imaging protocol included a 3D T1 fast-field echo sequence (TR/TE = 9.8/4.6 ms, flip angle = 8°, matrix size = 256 × 256, FOV = 256 × 256, voxel size = 1 × 1 × 1 mm^3) and diffusion weighted images (DWI) using a single-shot EPI sequence (TR/TE = 12,000/55 ms) with 64 directions of the diffusion gradient (b = 1000 s/mm^2, 64 contiguous slices, voxel size = 2 × 2 × 2 mm^3). Two non-diffusion weighted images (b = 0 s/mm^2) with reversed phase-encoding polarity were also collected.

T1 processing

Cortical surface models

Repeated T1 images were processed independently, as in cross-sectional studies, using the software package Freesurfer (v5.0, http://surfer.nmr.mgh.harvard.edu/). This included the preprocessing steps of bias field correction, signal and spatial normalizations, skull stripping and brain tissues segmentation (Dale et al., 1999). Triangulated surface models of the inner and outer cortical surfaces were obtained for each repetition. After inflation, topological correction and parameterization, cortical surface models were registered to a common surface template (Freesurfer's *fsaverage*) using a multiscale non-rigid spherical registration procedure minimizing folding pattern differences across individuals (Fischl et al., 1999a,b).

Subcortical surface models

Labels of the subcortical regions were extracted from all T1 images by the automated whole brain segmentation of Freesurfer (Fischl et al., 2002). In this study, 7 regions of interest per hemisphere were included: accumbens nucleus, amygdala, caudate nucleus, hippocampus, pallidum, putamen and thalamus. All labels were visually inspected and none required manual adjustment.

Subcortical labels were converted to smooth surface meshes using spherical harmonics with point distribution model (SPHARM-PDM v1.12, http://www.nitrc.org/projects/spharm-pdm/) (Styner et al., 2006); thereafter meshes were inflated and parameterized, and the convexity was calculated at every surface point and mapped on the unit sphere (Fischl et al., 1999a).

Creation of the subcortical surface templates

As opposed to the procruste alignment proposed within the original SPHARM-PDM framework and widely used in literature (Gerardin et al., 2009; Morey et al., 2009; Styner et al., 2006), subcortical surface templates were created using an iterative multiscale non-linear registration procedure. First, for each subcortical region, a single surface picked at random was used as the initial template and all other surfaces were aligned with this initial template. Then, an updated template was obtained by averaging all registered surfaces (Fischl et al., 1999b). Further details about the creation of the subcortical surface templates are provided in Appendix A and final templates of the subcortical regions of interest are shown in Figure A1 of supplemental material.

Surfaces and transformations of interest

Eight surfaces of interest per hemisphere were previously defined. Seven are surface models of subcortical structures and one is the inner-cortical surface. For each acquisition repetition, spherical transformation was calculated to register each surface to the corresponding template surface, defining the common space across repetitions.

In the following, unless specified otherwise, "surface" refers to the concatenation of the surfaces of interest and "registration" to the registration of the concatenated surfaces or features of interest according to the corresponding spherical transformation.

DWI processing

Preprocessing and coregistration with T1

Each DWI was corrected for Eddy current artifacts using the eddy_correct FSL function (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/). Then the distortion field, inherent to EPI acquisition schemes and responsible for geometric and signal artifacts, was calculated using the forward and reversed phase-encoding polarity images and applied to correct all DW images (Holland et al., 2010).

T1 image was registered to corresponding DWI space using the rigid body registration provided by SPM8 (http://www.fil.ion.ucl.ac.uk/spm/). The obtained transformation matrix was then applied to other data

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