Multi-scale brain connectivity with diffusion MRI

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Chapter 6

Summary and future directions
The studies reported and discussed in this thesis investigate the structural architecture and the anatomical connectivity of the human brain at different spatial scales. The macroscopic, mesoscopic and microscopic organization of brain connectivity and anatomy is probed with diffusion Magnetic Resonance Imaging (dMRI) and tractography techniques combined with histological staining approaches and mathematical network analysis. The described research contributes both to dMRI and tractography methodology and basic knowledge of human neuroanatomy.

**Macroscopic brain organization**

Given the large variety of dMRI-based tractography algorithms available (Basser et al., 2000; Behrens et al., 2007; Iturria-Medina et al., 2007; Parker et al., 2003; Sotiropoulos et al., 2010; Wedeen et al., 2008), chapter 2 aims at evaluating their differences when reconstructing graph representations of the human macroscale connectome. We reconstruct the whole cortico-cortical connectivity matrix using a variety of tractography parameters, such as angular and fractional anisotropy thresholds, seeding strategies and six different algorithmic classes. We evaluate the effects of these variations on scalar graph theoretical indices (for a review, see: Rubinov and Sporns, 2010). We show that density and other indices such as small-worldness are greatly affected by the choice of tractography algorithm and the value of its user-set parameters. Furthermore, we address the issue of quality control of the whole connectivity matrix (Cammoun et al., 2012; Owen et al., 2013) by introducing the tract specific density coefficient (TSDC). This index provides a reliable quantitative measure of the quality of reconstruction of a known tract, assessing the sensitivity of a tractography approach. Moreover, we show it can be used to detect false negative results within the entire connectivity matrix, assessing its specificity. Finally we show that assessing the trade-off between sensitivity and specificity can assist in objectively setting probabilistic thresholds in tractography. Based on
TSDC assessment we conclude that more sophisticated diffusion models, capable of reconstructing multiple fiber directions, and probabilistic or global tractography approaches should be preferred when performing structural connectomics. This is an important recommendation since connectomes are currently mostly obtained from diffusion tensor imaging (DTI) and deterministic streamline tractography. By applying the TSDC method developed in the chapter, newly developed fiber tracking algorithms can be evaluated with respect to both their sensitivity and specificity. Finally, quality control of connectomes obtained from large population studies can also be implemented using the proposed TSDC framework.

Diffusion MRI data quality keeps improving very rapidly and is currently moving towards mesoscopic resolutions. Voxel resolutions of 1 mm$^3$ are achievable using a clinical 3T machine as illustrated in figure 1, while data at sub-millimeter resolution can be acquired using ultra-high field MRI scanners (Heidemann et al., 2012). Tractography approaches will need to be carefully validated and possibly improved before being applied to mesoscale dMRI data. Future work can aim at using the TSDC framework in assessing the improvements in connectome reconstruction possible when using this much higher resolution.

In chapter 3 we used the methods and parameters for connectome mapping recommended in chapter 2 to compare the macroscale brain connectivity of two different species, namely human and macaque. We propose a rigorous and quantitative framework for anatomical comparative studies. This is based, on the one hand, on a database of whole brain tracer injection results for the macaque brain and, on the other hand, on in-vivo connectome mapping using dMRI tractography for the human brain. We directly compare the structural pattern and the topological properties of the two species using network analysis approaches. On the whole, the brain of humans and macaques show a very high degree of similarity in their macroscale connectome.
**Figure 1**: Major eigenvector from standard DTI analysis of 1mm³ isotropic data superimposed on an axial slice of fractional anisotropy. Data was acquired using a 3T MRI scanner and a b-value of 1000 s/mm². Blue arrows highlight radial cortical fiber insertions within gray matter, while the green arrow points at a short-association fiber connecting to adjacent gyri.

Specifically, a set of frontal, occipital and temporal regions exhibit a significant overlap of their whole brain connectivity across the species. The most important differences are present in the connectivity of parietal and cingulate regions. Furthermore, we identify a common structural backbone that could have been preserved during mammalian evolution. Our comparative analysis demonstrates that the regions forming a so-called rich club (van den Heuvel and Sporns, 2011) exhibit a high and significant overlap in 14 out of 20 regions. These mainly involve regions located in the frontal, parietal, cingulate and insular cortex. We conclude that the human and macaque brain as a whole are similarly wired. Moreover, we offer a rigorous and quantitative
translational bridge between macaque and human research. This framework will be very useful in the field of comparative neuroanatomy especially since recent developments have provided the scientific community with better tracers. The combination of our quantitative comparative approach with better tracing techniques capable of identifying weak and directed connections (Markov et al., 2014) and high-resolution dMRI data (Fig. 1) will help to further improve human-macaque brain connectivity comparisons and translation.

**Mesoscopic brain organization**

In chapter 4 we shift perspective from the macroscale organization of brain connectivity through white matter to the mesoscopic organization of the neocortex, focusing on its laminar organization. It has recently been shown that dMRI is capable of describing the intra and inter-laminar connectivity within post mortem tissue samples (Kleinnijenhuis et al., 2013; Leuze et al., 2014). We use dMRI of a human post mortem tissue sample containing motor and premotor cortex acquired at ultrahigh field (9.4T). The high spatial resolution (340 μm isotropic) and angular resolution (60 diffusion directions) of the acquired data enabled automatic delineation of several distinct cortical layers in the entire span of the sample. Our results and their validation based on histology show that dMRI can probe layer-specific intracortical fiber organization and classify architecturally distinct cortical areas. This work establishes methodological requirements on classification of gray matter architecture and microcircuitry by dMRI contrast and paves the way for non-invasive, in vivo human histology. As such it shows that high-resolution diffusion MRI not only reveals the edges (i.e. white matter projections) of the human macroscale connectome but also the respective nodes (i.e. architecturally distinct gray matter areas).
Figure 2: In vivo whole brain dMRI-based automatic cortical layer segmentation superimposed to a T1-weighted sagittal slice. Data was acquired using a 3T MRI scanner and a b-value of 2000 s/mm². Both dMRI and T1 data have a voxel resolution of 1mm³. Three relatively depth-specific clusters (red, green and light blue) are identified. CS: central sulcus.

The steadily increasing quality and resolution of dMRI data can be utilized not only in white matter, but also to probe the mesoscale organization within gray matter. Figure 2 shows results of applying the developed cortical layer classification technique to 1mm isotropic in-vivo dMRI data. Future work can continue to develop and apply the developed techniques to the study of larger expanses of cortex ex vivo and in vivo and help establish dMRI based histology approaches. Using modern neuroanatomical techniques it is possible to unravel the structural basis of brain functions such as language (Amunts et al., 2010) and motor control (Geyer et al., 1996). DMRI-based histology could be
capable of achieving similar results in vivo and in larger population studies.

**Microscopic brain organization**

In chapter 5 we focus on the microscopic organization of white matter. The estimation of the volume fraction of the hindered (extra-axonal) and restricted (intra-axonal) water compartments using the composite hindered and restricted model of diffusion (CHARMED; Assaf and Basser, 2005) usually requires very long acquisition times. This is because acquisitions with multiple high b-values and high angular resolution are needed. We combine protocol optimization, simultaneous multi-slice-multi-band imaging (SMS/MB; Moeller et al., 2010) and a high amplitude, gradient set to enable short-time high-resolution CHARMED acquisitions. We show that short-time high-resolution CHARMED acquisitions are feasible when using the three methods combined and provide optimized reference protocols. Furthermore, we evaluate resolution and partial volume effects for the microstructure-specific restricted fraction (FR) index. We show that at higher resolution the estimated FR will tend to be higher. These findings show that whole-brain microstructural mapping is feasible at high spatial resolution in clinically feasible times. Moreover, they highlight the issue of comparability between different studies performed at different resolutions. Our study should provide the basis to further objective quantification of microstructural indices and their dependency on data acquisition parameters (e.g. spatial resolution).

**Future directions**

Since dMRI data resolution keeps improving (Figs. 1-2) and both the accuracy and the precision of microstructural mapping techniques are constantly increasing, future studies will need to take into account the
different levels in which the brain is organized more explicitly. The work in this thesis illustrates how combination of acquisition modalities and analysis frameworks can support this endeavor. Macro-, meso- and microstructural organizational principles will need to be combined in the same models of the brain. Multimodal data acquired on the same subject or post mortem tissue at different scales (e.g. MRI and light microscopy) will need to be fused and interpreted together rather than kept as standalone findings. Further developments in this direction can deliver new MRI-based atlas resources with a high translation potential to in vivo MRI imaging. Furthermore, when combined with genetic, molecular, cyto- and myeloarchitectural information these new datasets could help the creation of detailed multimodal atlases (Amunts et al., 2014; Toga et al., 2006).

Technical advancements from the world of microscopy are constantly increasing both in the level of detail and the field of view which can be investigated. Recent efforts have already shown the potential of classical cytoarchitectonic staining of an entire brain at the very high resolution of 20 μm (Amunts et al., 2013) with more individual datasets currently underway. Combining such maps with observer independent techniques to demarcate architecturally different cortical areas (Schleicher et al., 1999) will allow identifying new common structural principles which are shared between individuals and which could not be described in earlier works based on single subjects (Brodmann, 1909; Talairach and Tournoux, 1988). Moreover, it has been shown that three-dimensional structural connections can be investigated in 3D in larger tissue samples after having made the tissue transparent with optical clearing techniques (Chung and Deisseroth, 2013).

On the other hand, validation of dMRI-based techniques is still an important issue. The combination of whole brain post mortem findings obtained from techniques such as polarized light imaging (PLI; Axer et al., 2011) with tractography results might represent a very good
way to address this. Both techniques in principle allow for a whole brain three-dimensional reconstruction of fiber tracts. Here it should be noted that both techniques, be it at different intrinsic resolutions, have the same basic tractography problem to solve, starting from local fiber directions. At the microstructural mapping side, there is also the need to improve the sensitivity and the specificity of estimated microstructural indices and reconstructed axonal pathways (Bells et al., 2011).

Finally, consortium projects including large population studies have recently started mapping structural and functional macroscale connectomes of adult human brains (Sotiropoulos et al., 2013; Van Essen and Ugurbil, 2012) and newborns (http://www.developingconnectome.org/) at the population level and at very high resolution. Making these data available to the whole scientific community must become a fundamental prior to any future study aimed at mapping the structural architecture of the brain.

We hope that the empirical work presented in this thesis will represent a step forward in the field of in vivo neuroanatomy and that it will constitute the basis on which the aforementioned future directions can be further developed.
References


Summary and future directions


