Explorations in the Field of Brain Connectivity

Analysis and Visualization

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Chapter 1

Introduction

Brain imaging concerns the exploration, modeling, and analysis of data that come from brain measurements. It consists of the set of techniques that noninvasively produce images of the internal aspects of the brain (e.g., magnetic resonance imaging (MRI)), and also of the techniques related to the analysis of quantitative data that are not primarily designed to produce images (e.g., electroencephalography (EEG)).

In a research context, brain imaging deals with the investigation of brain anatomy and function, both in normal and pathological circumstances. In a clinical context, medical visualization plays a key role in the diagnostic process, by providing quantitative information on the pathological features of the patients.

In this thesis we apply brain imaging techniques and visualization methods to investigate connectivity properties of the human brain.

1.1 Basic anatomical background

In this section, a basic overview of the anatomy of the human brain is provided. This will guide the reader in the comprehension of the following sections.

The brain is divided in two major areas: gray matter and white matter. Gray matter is located in the outer portion of the brain (the cortex) and in the inner part of the brain (the deep nuclei, such as thalamus, hypothalamus, etc.). Gray matter is also located in the cerebellum, the brain stem and the spinal cord. The gray matter contains neural cell bodies (the neurons) and is responsible for the processing of stimuli and information that originate in sensory organs or in other gray matter regions. This information is conveyed via the white matter.

The white matter lies in the region between the cortex and the thalamus, and consists of neural fibers. Its function is to connect regions of the gray matter and transport neural signals to and from gray matter regions. Neural fibers in the white matter, also known as fiber tracts, are the transmission lines of the nervous system. Fibers consist of bundles of axons, which are protrusions of the neurons. An axon transmits nerve pulses from the cell body of a neuron to its synapses, where the receptors of another neuron can detect the pulse (cf. Figure 1.1). An axon is typically one micron thick and one millimeter long. Fiber tracts can reach much longer distances and can connect gray matter areas which are several centimeters apart from each other.
Axons are surrounded by a myelin layer, an insulating sheath that increases the speed at which the nerve pulse propagates along the fiber and that prevents dispersion of the signal. Another important feature of the myelin sheath is its water impermeability: water molecules inside the axon are constrained to follow the direction of the neural fiber because they cannot pass through its protective sheath. This peculiarity allows us to study how water diffuses throughout the white matter, a principle which is used in diffusion weighted imaging (DWI) to explore the location and the direction of the fiber tracts of the white matter.

Functional magnetic resonance imaging (fMRI), electroencephalography (EEG) and magnetoencephalography (MEG) allow instead the study of the functional activity in gray matter regions. In the following sections we will discuss how structure and function of the brain are related and how they can be investigated through DWI, fMRI, and EEG analysis.

1.2 Brain connectivity

In neuroscience, the concept of brain connectivity has multiple meanings and refers to several different and interrelated aspects of brain organization. A basic distinction concerns anatomical connectivity, functional connectivity and effective connectivity [78, 110]. A different distinction could be made on the basis of scale level. Structural, functional and effective connectivities occur in fact both at the microscopic level of individual neurons linked by synaptic connections,
at the level of populations of neurons (e.g., microcolumns and columns of the cortex), and at
the macroscopic level of large populations of neurons (neuronal systems) forming distinct brain
regions interconnected by fiber pathways.

1.2.1 Anatomical connectivity

Anatomical connectivity refers to a network of structural (physical) connections linking neurons
or neuronal systems in a network, and to the properties of this network. At a microscopic scale, only invasive methods are able to demonstrate anatomical connectivity. On a macroscopic scale, in vivo imaging techniques such as DWI are able to provide useful insights on connectivity patterns, although the limited spatial resolution restricts their use to the detection of major structural differences or temporal changes in fiber pathways. The patterns of structural connectivity appear in fact stable on short time scales, but dynamic on longer time scales (days), for instance during development and learning experiences. The exploration of anatomical connectivity is a key aspect of the definition of the connectivity space in which functional and effective connectivity may take place [130].

1.2.2 Functional connectivity

Functional connectivity is fundamentally the study of statistical properties of neuronal systems, and of the extent to which their interaction differs from statistical independence [172]. This analysis is often performed by studying correlation, covariance, coherence, or other statistical measures. Functional connectivity does not make any reference to causal effects and usually it does not take into account structural connectivity.

1.2.3 Effective connectivity

Effective connectivity describes the information flow, and thus the causal relations, between two neuronal systems [29]. It tries to explain how different neuronal systems communicate with each other by means of the influence that a neuronal system has over another, either directly and indirectly [61]. It usually takes into account both functional and structural aspects of the connectivity to create a causal model.

1.2.4 Relations among anatomical, functional and effective connectivity

A common ingredient of anatomical, functional and effective connectivities seems to be the structure of the connectivity network. All kinds of connectivity occur in fact both at the microscopic and the macroscopic level, such as when two complementary networks cooperate for performing cognitive tasks. At the microscopic level, interconnected populations of specialized neurons cooperate in single brain areas [162]. This yields the possibility to locate anatomical regions dedicated to certain brain processes or functions. Nevertheless, cognitive processes do not occur only in isolated brain regions [129]: at the macroscopic level, networks of large populations of neurons cooperate to perform cognitive tasks.
Although a comprehensive anatomical network of the human brain has not yet been completely mapped [172], the general assumption is that anatomical connectivity is essential to define functional dynamics, assessable either by functional or effective connectivity. Structure and function in the brain are strongly interdependent, and the study of their relations represents one of the major challenges of neuroscience.

In the following sections we discuss how DWI, fMRI and EEG analysis can provide insights on the function and structure of the brain and how these techniques can be used to assess brain connectivity.

1.3 Structural analysis with DWI

Diffusion weighted imaging is a MRI-modality that produces in vivo images of the structural organization of individual biological tissues. DWI images reflect the local microstructural characteristics of water diffusion in the tissue: each image voxel has an intensity that reflects the amount of water diffusion at that brain location.

1.3.1 Diffusion

Diffusion is the molecular process of matter spreading in a certain environment, a phenomenon called Brownian motion. Diffusion describes the spontaneous spread of particles (e.g., molecules) from regions of higher concentration to regions of lower concentration. The difference in concentration is called the gradient. In an environment where a concentration gradient is defined, the diffusion tends to be gradient-driven. In structured biological tissues, such as the white matter of the brain or the heart, water diffusion primarily occurs in a preferential direction along (neuron or muscle) fibers and it is restricted in directions transverse to the fibers. This phenomenon is called diffusion anisotropy and is caused by the presence of boundaries and membranes in the tissue. Changes in diffusion anisotropy in the white matter are caused by local directional coherence of the neural fibers, axon density, integrity of the axon membranes, and amount of myelination [19, 170].

1.3.2 DWI physics

Diffusion weighted imaging utilizes the properties of protons in water molecules to generate contrast in the brain images: in the presence of an external magnetic field, the spins of the protons in the hydrogen nuclei tend to align along the direction of the field. Since an exact alignment is not possible, they precess around the direction of the magnetic field. Figure 1.2 shows the principle of how a diffusion weighted spin echo is used to quantify diffusion along a certain direction. The top of the figure shows the series of radio frequency (RF) pulses and magnetic gradients applied in the MR scanner. Relevant time steps are labeled with letters. The central part of the figure shows the effects of RF pulses and magnetic gradients on the spin of the protons of hydrogen nuclei, and the bottom part of the figure shows the phase of the spin of a stationary proton (black) and of a proton in motion (red). At time step A, the spins are
aligned with the z-axis, which is the direction of the main magnetic field in the MR scanner. The first excitatory RF pulse (at time step B) tilts the spins to the plane transversal to the direction of the main magnetic field. Spins now precess in the x-y plane. This configuration produces the maximum nuclear magnetic resonance (NMR) signal, since all the spins are in phase (the detected NMR signal decreases proportionally to the amount of spins out of phase). During the application of the magnetic gradient labeled as “position encode”, the spins of the protons start to dephase (C). The precession speed is proportional to the strength of the magnetic field, so the magnetic gradient induces spins to dephase faster or slower according to their position with respect to the magnetic gradient. A maximum difference in phase is reached at the end of the application of the magnetic gradient (D). At this point, an inverse RF pulse (E) tilts the spins by 180 degrees. During the second magnetic gradient (F), which has the same strength and time length as the first magnetic gradient, the phases of the spins refocus until they reach a point where the scanner detects again the maximum NMR signal (G). The acquisition (“readout”) of the NMR signal is performed at this point.

The application of the two RF pulses and the two identical magnetic gradients is able to re-focus only the spins of those protons that did not move during the time interval between the RF pulses. Protons that have moved cannot properly refocus during the application of the second magnetic gradient, causing NMR signal loss at acquisition time. The bottom of Figure 1.2 shows the ideal phase change of a static proton (thick line), and the phase change of a proton that is moving (thin line) during the MRI pulse sequence.

The MRI sequence is repeated using gradients with different directions, each of them allowing the assessment of water diffusion along a single direction. Figure 1.3 shows an example of how the NMR signal is attenuated in brain regions with high directional diffusivity, when the reading is performed along certain directions. On the left, the image is acquired along the direction from front to back. Notice that the optic radiations (the areas in the white boxes) are darker than in the central and rightmost figure. This is due to the fact that the optic radiation runs parallel to the acquisition direction (illustrated by the arrow beneath the brain image), and water diffusion occurs more easily along the optic nerve than perpendicularly to it. Similarly, notice that the splenium of the corpus callosum in the central figure (the area in the white box) is darker than in the other two figures and that the cortico-spinal tracts in the rightmost figure (the areas in the white boxes) are darker than in the left and central figures.

There are several mathematical approaches to the modeling of water diffusion in the brain. DTI (diffusion tensor imaging) is the most common technique and consists of modeling water diffusion in a brain voxel by a second order diffusion tensor. Probabilistic tractography is a technique based on the statistical analysis of the DWI images. Diffusion imaging techniques such as HARDI (high angular resolution diffusion imaging), QBI (q-balls imaging), and DSI (diffusion spectrum imaging) are mathematical alternatives to DTI in which the diffusion is not restricted to a single tensor model.

1.3.3 DTI

In DTI, different permeability of brain tissue in varying directions is modeled through tensors. A diffusion tensor is defined as a two dimensional positive-definite symmetric matrix of the form:
Figure 1.2. Spin-echo sequence used to detect water diffusion in biological tissue. Top: sequence of RF pulses and magnetic gradients (courtesy Karla Miller, Oxford). Center: effects of the RF pulses and of the magnetic gradients on the spins of the hydrogen nuclei (source: www.medlibrary.org). Bottom: differences between the phases of the spins in case of motion (thin line) and no motion (thick line). See the text for a detailed explanation of the picture.

\[
D = \begin{pmatrix}
D_{xx} & D_{xy} & D_{xz} \\
D_{yx} & D_{yy} & D_{yz} \\
D_{zx} & D_{zy} & D_{zz}
\end{pmatrix}
\]

and describes the diffusion along a single direction (\(D_{xx}, D_{yy}, D_{zz}\)) and the diffusion along pairs of perpendicular directions (\(D_{xy}, D_{yz}, D_{xz}\)). Note that the matrix representing the tensor is symmetrical. In fact, DTI maps the diffusion properties along certain directions, and not the directionality of diffusion. Thus, to fully determine a diffusion tensor, at least 6 directions of acquisition are necessary. Usually more acquisition directions are used, to improve the signal-
to-noise ratio (SNR), by averaging the results of several scans. Given a diffusion tensor in each brain voxel, the next step is to determine the principal directions of diffusivity and the magnitude of diffusion associated to these directions.

This operation corresponds to building a local coordinate system for identifying the diffusion directions. The diagonalization of the diffusion tensor produces three real nonnegative diffusion coefficients, the eigenvalues of the tensor, and three corresponding eigenvectors. These eigenvectors define the three (orthogonal) principal directions of diffusivity: the eigenvector corresponding to the largest eigenvalue indicates the direction of major diffusivity; the other two eigenvectors point respectively at the medium and the minor diffusion directions [109]. In other words, the eigenvectors of each tensor define an orthogonal basis indicating the main directions of diffusion; by scaling the eigenvectors by the corresponding eigenvalues we obtain the major, medium and minor diffusion directions.

Ellipsoids [13,14] were introduced for visualizing the diffusion tensors. Ellipsoids are three-dimensional representations of the diffusion distance covered in space by water diffusion in a given time. Figure 1.4 shows an example of such an ellipsoid. The axes of the ellipsoid are labeled with the corresponding eigenvalues and eigenvectors.

The main axis of a diffusion ellipsoid gives the main diffusion direction in a voxel, while the eccentricity of the ellipsoid provides information about the degree of anisotropy. The size of the ellipsoid in any direction in space indicates the diffusion distance covered in this direction in a given amount of time.

The magnitude of the individual eigenvalues, their ratios and the overall eccentricity of the ellipsoid describe the behavior of water diffusion and the amount of diffusion anisotropy. Several scalar values are available in the literature for the quantification of diffusion properties [149, 190]. A key parameter is the fractional anisotropy (FA) index. FA characterizes the degree of anisotropic diffusion within a voxel as a function of the eigenvalues of the tensor associated to the voxel. A FA value of zero means that diffusion is isotropic, i.e., it is equally restricted in all directions. A value of one means that diffusion occurs only along one axis and is fully restricted.
Figure 1.4. Ellipsoid representing a diffusion tensor. The directions of the axes are determined by the three eigenvectors of the diffusion tensor. The length of each axis is determined by the corresponding eigenvalue.

along all other directions. FA is defined as:

$$FA = \frac{3\sqrt{(\lambda_1 - \tilde{\lambda})^2 + (\lambda_2 - \tilde{\lambda})^2 + (\lambda_3 - \tilde{\lambda})^2}}{2\sqrt{\lambda_1^2 + \lambda_2^2 + \lambda_3^2}}$$

where $\tilde{\lambda}$ is called the trace of the diffusion tensor and is defined as $\tilde{\lambda} = (\lambda_1 + \lambda_2 + \lambda_3)/3$. FA has the property to be rotationally invariant, thus it does not depend on the orientation of the MRI scanner. Several other scalar values have been introduced in the literature for quantifying the degree of anisotropy; however, FA is the most commonly used anisotropy index.

A more sophisticated mapping of diffusion properties is the barycentric coordinate system for anisotropy metrics [203], a subdivision of all possible shapes that an ellipsoid could have according to three coefficients $C_s$, $C_p$, and $C_l$, defined as:

$$C_l = \frac{\lambda_1 - \lambda_2}{3\lambda}$$
$$C_p = \frac{\lambda_2 - \lambda_3}{3\lambda}$$
$$C_s = \frac{\lambda_3}{\lambda}$$

These three anisotropy coefficients are designed so that their sum is always 1. For instance, in the case of linear anisotropy, $C_l$ is one, while $C_p$ and $C_s$ are zero. Figure 1.5 shows the barycentric space of the anisotropy coefficients.

1.3.4 Fiber tractography

An important application of DTI is the visualization of anatomic connections between different brain regions.

DTI tractography (also called fiber tracking or DTI streamline tracing) utilizes the vector field generated by the major eigenvectors of the tensors to infer a continuous fiber orientation from voxel to voxel within the white matter. Under the assumption that the major eigenvectors
of the tensors tend to be aligned with the fibers in the brain, DTI tractography proceeds in three main steps. The first step is defining a starting position. The second step is to compute the path by integrating the vector field of the main diffusion directions in the brain voxels. The third step is terminating the path computation when a stopping criterion is reached. The most common stopping criterion is a low FA value, since in voxels with low FA the major eigenvector is no longer a reliable indicator of the main diffusion direction.

Streamlining in the vector field induced by the major eigenvectors of the tensors is commonly used in white matter tractography studies, because it is easy to implement and because it can give excellent results. An example of DTI tractography is shown in Figure 1.6. In the figure, a green colour represents diffusion in the front-back direction, a blue colour represents diffusion in the up-down direction, and a red colour represents diffusion in the right-left direction.

1.3.5 DTI limitation

DTI tractography is affected by some limitations, related both to the diffusion tensor imaging technique per se and to the DWI acquisition methods.

A relatively low SNR ratio in DWI data acquisition is the principal cause of erroneous tractography results. Noise can effectively influence the vector field and because the fibers are computed via subsequent integration steps, the errors propagate and accumulate through the tracking. The resulting trajectories are smooth and accurate under the assumption that the SNR is sufficiently high to limit the deviation of the vector field of the main diffusion directions from reality and thus prevent instability.

Partial volume effects are another major problem. Axons are microscopic filaments whose size is in the order of microns (thickness) and millimeters (length), while DWI has a spatial resolution of ca. \(2\text{mm}^3\). The single tensor model is a simplistic description of the fibrous microstructure of the axon network, as it represents the average behaviour of millions of axon fibers with only six values. It has been estimated that only 30% of the brain voxels present a diffusion
1.3 Structural analysis with DWI

Figure 1.6. An example of DTI tractography. The image shows some of the major fiber bundles of the brain in a sagittal view. The green, blue and red colours represent diffusion in the front-back, up-down, and right-left directions, respectively. Source: www.wikipedia.org.

A further limitation of DTI tractography is that tracking errors in estimated tracts are difficult to detect. The stunning aesthetics of DTI visualization methods produce results that actually look as real white matter fiber pathways, and could instill false confidence on the part of the investigators [2].

Several strategies have been proposed for measuring and interpreting complex diffusion behaviours. Among others, there are DSI, QBI, and HARDI. These methods vary in acquisition and analysis approaches, and share the goal to overcome the limitations of the single tensor model by improving the angular resolution. They use spectral analysis of diffusion parameters [183] and higher order tensor analysis [15] for a more accurate description of the diffusion properties within the brain voxels.

1.3.6 Probabilistic tractography

Although DTI tractography is able to visualize fiber pathways and nice connectivity patterns, it is prone to tracking errors and provides little information on the reliability of the results. Probabilistic tractography ([23, 102, 141]) generalizes DTI tractography by using the whole tensor information available per voxel. Most of the algorithms based on probabilistic tractography use a Monte Carlo approach in which, for each voxel, possible directions of main diffusivity are generated and probabilistic distributions of tracts are used to estimate probabilities of connectivity between brain voxels.

Probabilistic tractography produces confidence values on the presence of a connectivity path-
way between any target voxel in the brain and a chosen source voxel (or group of voxels). Contrarily to DTI tracking, probabilistic tractography is able to analyze areas with low anisotropy, and thus to investigate voxels where two or more fiber bundles meet. This is a significant advantage over DTI tractography, since it also allows to explore gray matter regions, characterized by low FA values, and provides in this way the possibility to compare tracking results with functional analysis (which concerns brain activity in the gray matter).

Figure 1.7 shows an example of probabilistic tractography results. Confidence values on the presence of a connectivity pathway between the seed region (here, the Insula) and any voxel in the brain are represented using a colourmap ranging from red (low probability) to yellow (high probability). Voxels where no colour is used have probability zero.

![Figure 1.7](image)

**Figure 1.7.** An example of probabilistic tractography. Shown is a coronal slice of the brain where the colours (ranging from red to yellow) represent the probability of connectivity between any voxel in the brain and the Insula.

### 1.4 Functional analysis with fMRI

Functional magnetic resonance imaging is a MRI modality that measures changes of blood flow in the brain (the haemodynamic response) due to neuronal activity in the gray matter. fMRI does not directly measure activation, but local variations in oxygenation of the blood vessels running through the gray matter.

The blood supply in the brain is dynamically regulated to be able to provide energy, in the form of glucose and oxygen, to those areas with increased neural activity. Although the exact relationship between blood supply and neural activity is still under investigation, changes in oxygenation in the blood supply in a certain brain region correlates with increased neuronal activity in that region. As the delivered oxygen exceeds the local demand, the venous capillary bed fills with a larger ratio of oxygenated to deoxygenated haemoglobin, inducing a local change
of the magnetic properties of the blood. This is the blood oxygenation level dependent (BOLD) effect that can be observed using fMRI.

### 1.4.1 fMRI physics

During fMRI acquisition, as in the first step of DWI acquisition, a RF pulse is used to tilt the spins of the protons of hydrogen nuclei to a plane transverse to the constant magnetic field produced by the MR scanner. After the RF pulse, as they start to dephase, the spins slowly return to the initial position, i.e., parallel to the direction of the magnetic field. The dephasing, also called relaxation, is caused by two factors: the first factor is spin-spin interaction, the second is the inhomogeneity of the magnetic field. The interaction of individual spins generates a dispersion of the precession frequency that is characterized by a time constant $T_2^*$ called the spin-spin relaxation time. The dephasing effects of both spin-spin interactions and inhomogeneities of the magnetic field is characterized by a time constant $T_2$.

A substance present in the magnetic field alters the field to some extent, and undergoes a polarization called “magnetic susceptibility effect”. Oxygenated haemoglobin is diamagnetic and thus has a small magnetic susceptibility effect, comparable to that of the surrounding brain tissue. It does not significantly alter the regional magnetic field and therefore its presence in the vascular system does not greatly influence the local $T_2^*$ relaxation. Deoxygenated blood, on the contrary, is paramagnetic and it undergoes a stronger magnetic susceptibility effect: its presence significantly disturbs the local magnetic field and thus influences the local $T_2^*$ relaxation.

The changes in oxygenation of the blood in vessels passing through the gray matter influence the $T_2^*$ by causing fluctuations of magnetic susceptibility. An increase in oxygenation of venous blood, caused by metabolic overcompensation in the blood supply in a certain brain area, produces a longer $T_2^*$ relaxation time that is mapped by fMRI as an image intensity increase in the corresponding voxel.

### 1.4.2 Connectivity with fMRI

A fMRI sequence is a collection of functional brain data acquired one after the other for a certain period of time, that results in a time signal for each voxel of the brain. It is important to bear in mind that while neural activity usually occurs within milliseconds, the time scale of the haemodynamic response is in the order of seconds. Independent component analysis (ICA) [33, 127] and temporal correlation between time sequences of individual voxels or between mean time sequences in groups of voxels is often used as a means to assess functional connectivity and cooperation between brain regions for the processing of a certain cognitive task. Also when no cognitive task is performed (the so called resting state), functional connectivity assessed with fMRI time series reveals the presence of active physiological brain networks [26, 158]. fMRI time series can also be used to assess effective connectivity, for instance by using correlations of delayed time series, structural equation modelling [126], dynamical causal modelling [64], or Granger causality [155].
1.5 Functional analysis with EEG

Electroencephalography (EEG) is the recording of the spontaneous electrical brain activity by means of multiple electrodes positioned on the scalp. Neurons, like any other cell in biological tissues, maintain a voltage difference across their cell membrane. This charge difference is called membrane potential, and it is caused by the activity of enzymes that transfer ions through the cellular membrane. Action potentials are rapid changes in membrane potential, caused by the release of ions through the membranes of the neurons, that play a key role in neuronal communication. When an ion wave, propagating through the brain and the scalp (volume conduction), reaches a EEG electrode, this detects a difference in voltage with respect to the other electrodes. The recording of the voltage differences detected by the electrodes during a certain amount of time produces the EEG.

Electric potentials generated by individual neurons are too small to be detectable by electrodes on the scalp. Rhythmic activity and synchronous oscillations of large populations of neurons can give rise to macroscopic oscillatory electric fields that can be detected with EEG. Electrical activity on the scalp shows oscillations at a variety of frequencies, in whose terms brain activity is described. Different frequency bands are recognized, each with different biological significance.

Often EEG signals are recorded after a stimulus presentation. Stimuli can be external (sensory stimulation) or internal (mental activity). Electrical activity registered after the presentation of an external stimulus is called evoked potential (EP). Electrical activity related to higher level cognitive processes such as memory, attention, etc., is called event-related potential (ERP). EEG analysis can separate these potentials from the background normal brain activity to investigate brain activity in response to stimuli.

1.5.1 Connectivity with EEG

Synchronous oscillations of electrical activity in neuronal networks may be an important mechanism by which different brain regions cooperate to perform a certain cognitive task [164], and synchronization at certain frequency bands may correspond to different levels of cooperation [12]. A descriptor of synchronization of electrical activity in the brain is EEG coherence, that provides a measure of frequency-specific associations between two EEG signals in a certain frequency band. Figure 1.8 shows an example of coherence analysis. Here, Voronoi cells represent EEG electrodes projected on a horizontal plane. Neighbouring cells coloured with the same gray value represent groups of electrodes (functional units) that registered a highly coherent signal. Links connect the barycenters of functional units when the average recorded signals in the two functional units are highly coherent. Coherence is mapped to the edges by using colours, according to a chosen colourmap.

Compared to fMRI, EEG is able to detect faster changes in signals, in the order of milliseconds, but it has a poor spatial resolution. An interesting and relatively new field of research is the acquisition of EEG data in the MRI scanner while recording fMRI data. The procedure is difficult because of the electromagnetic interactions between the MR scanner and the EEG electrodes and wires, but allows simultaneous analysis of fMRI, EEG and DWI data from a single
The aim of this thesis is to investigate brain connectivity by means of DWI, fMRI, and EEG analysis. Because the amount of data generated by these scanning techniques is generally very large, and increases with improvements in acquisition technology, visualization can provide useful insights in the analysis of the functions and structures of the brain and allows both quantitative and qualitative interpretation of the experimental results.

In Chapter 2, structural connectivity within the auditory pathway and between auditory nuclei and the limbic system is investigated by means of probabilistic tractography. The study provides a method to summarize properties of fiber paths and applies it to the comparison of differences in connectivity between a group of patients affected by tinnitus and a control group. While interaction between the limbic system and the perception of tinnitus has been assessed in the literature using fMRI approaches, structural implications were only hypothesized. The analysis investigates the possibility that the perception of tinnitus could also be related to structural connectivity properties of the brain.

In Chapter 3, a method to enhance DTI tractography is proposed. In DTI tractography, low FA values are often used as stopping criteria for the tracking. With the new method, when DTI tractography enters a voxel with a low FA value, directional information is gathered by interpolation of tensor information in the neighbouring voxels so that the tracking can continue. Furthermore, this method investigates the possibility to detect and resolve the branching of fiber

**Figure 1.8.** An example of connectivity results computed using EEG analysis. Each Voronoi cell corresponds to an EEG electrode. For simplicity in visualizing the results, electrodes on the scalp were projected to a plane. Groups of cells coloured with the same gray value correspond to neighbouring EEG electrodes that registered highly coherent signals (called Functional Units, or FUs). Edges connecting the barycenters of the FUs represent the average coherence between the signals registered in the FUs.
tracts by studying the directions of main diffusivity in the neighbouring voxels. The method is successfully tested on synthetic datasets and applied to the tracking of fibers in the corpus callosum in a brain dataset.

In Chapter 4, the relations between structural and functional connectivity in the premotor cortex are investigated. The premotor cortex is divided into two areas, SMA (sensory-motor area) and pre-SMA, that are distinguishable via functional analysis and that injection animal studies confirmed to be distinguishable also via structural analysis. A visualization tool, based on techniques borrowed from graph theory, is proposed to investigate the structural connectivity properties of those regions and the comparison with functional classification. The method shows how individual variability can play a major role in the classification of connectivity results.

In Chapter 5, functional connectivity is investigated using EEG. A method is presented to quantify differences among multichannel EEG coherence networks represented by functional units (FUs). The method extends a tool for the detection of FUs proposed in the literature. It performs non-exact graph matching among coherence networks to produce average activation maps where group results as well as individual variations in EEG activity are intuitively assessable. The method is applied to the study of mental fatigue and neurodegenerative disease.

In Chapter 6, the method for the detection of FUs in EEG analysis that was extended in Chapter 5 is used for the analysis of functional connectivity with fMRI. The method allows data-driven functional analysis of the brain cortex and detects which areas are working in synchrony, by analyzing correlation of time sequences recorded in cortical areas. The method produces both a 3D and a 2D visualization of the cortex to ease the localization of the FUs and to support the investigation of the functional similarities between FUs.

In Chapter 7, summary and conclusions are presented, as well as directions for future research.
Chapter 2

A Diffusion Tensor Imaging Study on Auditory System and Tinnitus

Abstract

Tinnitus is an auditory percept in the absence of an external sound source. Mechanisms in the central nervous system are believed to be key in the pathophysiology of tinnitus. Diffusion tensor imaging (DTI) is an MR imaging technique that allows in vivo exploration of white matter tissue in the human brain. Using a probabilistic DTI approach, we determined the characteristics of fiber tracts from the inferior colliculus to the medial geniculate body up to the primary auditory cortex. We also investigated the connections between the auditory system and the amygdala, which may be involved in some forms of tinnitus. White matter tracts were characterized by three quantities: the mean field anisotropy, the weighted mean field anisotropy and the path strength. All these quantities are measures of the patency of white matter tracts. The most important finding is an increased patency of the white matter tracts between the auditory cortex and the amygdala in tinnitus patients as compared to healthy controls.

2.1 Introduction

2.1.1 Auditory System and Tinnitus

The central auditory system starts at the auditory nerve (AN) which conveys action potentials in response to neurotransmitters released by the hair cells in the cochlea. The cochlear nucleus (CN) is the first nucleus of the auditory system receiving information from the ipsilateral cochlea. A next step in the pathway is the superior olivary complex (SOC), in which input from the two cochlear nuclei converge. Neurons from the CN and SOC project to the inferior colliculus (IC) through axons that form the lateral lemniscus (LL). The next step is formed by connections between the inferior colliculus and the medial geniculate body (MGB) of the thalamus, a relay station of several types of information of which the auditory pathway is only one. Fibers leaving the MGB project to the primary auditory cortex (AC). For more detailed information we refer to Ehret and Romand [54]. In addition to this classical auditory pathway there are connections
between the auditory system and the limbic system [132]. The limbic system is involved in moti-
vation, mood and emotion [45] and consists of many subsystems, including the hippocampus,
the amyloid complex, the cingulate gyrus and the prefrontal cortex [133]. Typical complaints
attached to tinnitus such as anxiety, depression, and emotions such as fear indicate the asso-
ciation of the limbic system with tinnitus [82]. Cognitive therapies focus on the reduction of
alteration of the emotional content of the percept of tinnitus by habituation [83, 84]. Changes in
regional cerebral blood flow (rCBF) and blood oxygenation (BOLD) signal have been reported
in the limbic system by several studies [107]. The connection between the auditory system and
the limbic system may thus be of importance in the pathology of tinnitus.

In this paper we study the characteristics of white matter fiber tracts defining the (classical)
auditory pathway, especially the pathways from the IC to the MGB up to the primary auditory
cortex. We also investigate the connections between the auditory system and the limbic sys-
tem, especially the amygdala (AM). Both pathways were studied using diffusion tensor imaging
(DTI) methods. Additionally, we investigated possible differences in structural brain connec-
tivity between subjects affected by tinnitus and healthy subjects. Since hemispheric differences
have been reported in patients [48, 128, 169], also lateralization of DTI findings was investigated.

2.1.2 Diffusion Tensor Imaging

Diffusion tensor imaging (DTI) is a recently developed MR acquisition modality that enables
the measurement of structural organization of tissues [13, 149]. As a powerful and non-invasive
technique for in vivo exploration of human tissues, DTI is widely used in various medical fields,
especially in brain imaging [200, 201].

DTI is based on the diffusion properties of water molecules in white matter of the brain. The
diffusion is limited by the fibrous nature of white matter: the well-organized axon structure, axon
membranes, neurofilaments and overall the myelin coating surrounding the neurons induce the
displacement of water molecules to occur preferentially along the axon fibers rather than perpen-
dicular to them [19]. This anisotropic diffusion of water molecules can be measured by an MR
scanner, allowing us to infer information on white matter connectivity. Two interesting features
of DTI techniques are the ability to derive local information, such as the amount of anisotropy
and the principal water diffusion direction in a single brain voxel [97], and the possibility to track
fiber bundles from a selected brain area [16].

Although several imaging studies have examined the auditory system and tinnitus [106, 115,
128], only a few of them applied DTI techniques [112, 120, 209]. The main reason for the in-
frequent application of DTI in studies on the auditory system is the poor spatial resolution of
DTI images. Partial volume effects lead to underestimation of diffusion anisotropy, and mul-
tiple nerve fiber tracts crossing a single brain voxel may disturb the fiber tracking algorithm.
According to tracing studies on the macaque [160] using radioactive tracers, we know that the
fibers of the auditory pathway intersect motor bundles (in the CN-SOC-IC path) and are close
(within millimeter range) to the corticospinal tract (in the IC-MGB path) and do cross the internal
capsule [123] when connecting the MGB with the AC.

Standard deterministic fiber tracking techniques only consider the main diffusion direction
in each voxel, which is provided by the eigenvector corresponding to the largest eigenvalue of
the diffusion tensor in the voxel. This technique is incapable of resolving voxels with multiple fiber directions that occur when two fibers cross each other within a voxel, but also has problems in the presence of gray matter voxels. For this reason, we used probabilistic tractography with multiple fiber orientations [20]; this technique has been shown to provide significant advantages in sensitivity when tracking non-dominant fiber populations and allowed us to track the auditory paths, which are impossible to detect with deterministic tractography. Although probabilistic tractography does not allow the visualization of the actual fiber bundles, it outputs a whole-brain probabilistic connectivity map for localizing white matter tracts. Using this method, we investigated the connections of the auditory pathways and the connections between the auditory system and the limbic system in a focused per-subject analysis. We also studied differences in tractography results of these paths in subjects with and without subjective tinnitus.

2.1.3 Related Work on the Auditory System

The auditory system and tinnitus have been studied using functional imaging techniques [106, 115, 128]. DTI methods have been used in a few studies on the auditory system, but in most cases only scalar values derived from DTI analysis, such as the fractional anisotropy (FA) index, describing the amount of anisotropy per voxel, were considered. For instance, Lee et al. [112] performed a study where the FA index in several areas of the brain was determined. Reduced FA values in tinnitus patients were found in the left frontal Arcuate Fasciculus and the right parietal Arcuate Fasciculus. However, the classical auditory pathway was not studied. Lutz et al. [120] were able to detect changes in FA maps in cortical and subcortical auditory regions, in relation with the age of the subjects (although the study did not concern tinnitus): elder subjects showed bigger FA values in IC and lower FA values in the auditory radiation and in the temporal gyri. Moreover, Lee et al. [111] showed differences in FA values between subjects with conductive hearing loss and subjects with profound sensorineural hearing loss, reporting that DTI findings of subjects with profound sensorineural hearing loss revealed neural damages in the auditory pathway. De Groof et al. [70] used DTI to study the auditory and vocal system in birds. They discerned a number of song control and auditory nuclei, and discriminated the tracts running from and to these nuclei. Using DTI fiber tracking techniques, Upadhyay et al. [185] studied the connectivity patterns within the primary auditory cortex.

Different methods are available for exploring differences in brain structure between two groups. Using voxel-based morphometry (VBM), brain data from different subjects are aligned to a reference volume so that voxel-wise statistics can be computed [9]. This method has been used for comparing diffusion tensor data [90, 140] and provides a whole-brain picture of structural differences; the major drawback of this technique is that the results could be strongly influenced by the quality of the alignment among the brain data and by the spatial smoothing usually applied to the data [167]. Tract-based spatial statistics [167] is another tool for comparing DTI data among subjects. This technique seems to be very robust to misalignment of brain data; however, it only allows comparisons of high-FA white matter voxels and is not able to analyze a specific fiber bundle per se.
2.2 Materials

2.2.1 Subjects

DTI data were acquired from 25 subjects: 15 healthy subjects and 10 subjects with tinnitus. The group of healthy volunteers consisted of 12 men and 3 women; the age of these varied from 26 to 75, with a mean of 46 and a standard deviation of 16. The subjects affected by tinnitus (9 men and 1 woman) had ages varying from 30 to 70, with an average of 49 and a standard deviation of 12. All the subjects were right-handed. Six of the patients suffered from bilateral tinnitus. Four suffered from tinnitus in the left ear only. Figure 2.1A shows the hearing levels of the patients at different octave frequencies; Fig. 2.1B shows the severity of tinnitus as perceived by the patients during rest, according to a visual analogue scale (VAS) ranging from 1 to 10. The frequency and loudness level of tinnitus were determined by a matching procedure. Frequency matching was performed with an external tone presented at the non-tinnitus ear (unilateral tinnitus) or at both ears (bilateral tinnitus) at a comfortable level. The loudness level was then determined by adjusting the level of this tone to match the tinnitus loudness. All subjects gave written informed consent for their participation in the study.

2.2.2 Data acquisition

All the imaging experiments were performed on a 3T Philips Intera MRI scanner. DTI was performed using a diffusion weighted spin-echo, echo-planar imaging technique. The DTI parameters were as follows: field of view = 240 × 240 mm; matrix size = 128×128; no. of slices = 50; imaging resolution = 1.85×1.85×2 mm³; TR = 5485 ms; TE = 74 ms. In total, 61 volumes were acquired per subject, one without diffusion weighting (b = 0 s/mm²) and 60 volumes with diffusion weighting (b = 800 s/mm²) along 60 noncollinear directions. To correct for susceptibility artefacts, two acquisitions were used: one with fat-shift direction in the posterior direction (APP) and one in the anterior direction (APA).

An anatomical scan was acquired to serve as reference (T1-weighed fast-field echo scan, TR= 25 ms, TE = 4.5 ms, flip angle = 30°, imaging resolution = 0.94×0.94×1 mm³, matrix = 256×256×160 slices).

For the region of interest (ROI) selection, functional MRI data were acquired. These consisted of 2179 ms single shot T2*-sensitive echo planar imaging (EPI) sequences, 41 slices, 2 mm thickness, TR = 10 s, TE = 22 ms, flip angle 30°, matrix 128×128, field of view 224 mm, SENSE reduction factor 2.7, 51 acquisition per subject. The influence of acoustic scanner noise on fMRI data was reduced by using a sparse sampling strategy [72]. A TE of 22 ms was chosen for optimal SNR at areas close to air-tissue boundaries, like the temporal lobes, at the cost of a small SNR decrease in the BOLD signal (see e.g., the introduction of [47]).

Auditory stimuli were delivered by a MR-compatible electrodynamic system (MR Confon GmbH [18]). This system was driven by a PC equipped with a digital-analogue card (National Instruments 6052E) controlled by Labview 6.1 (National Instruments Corporation, Austin, TX). The auditory stimuli were generated off-line using Matlab © and consisted of temporally and spectrally modulated broadband “rippled” noise [104]. The stimuli had a frequency-range of
125 – 8000 Hz with a spectral modulation density of 1 cycle per octave, a temporal modulation frequency of 2 cycles per second and a modulation-amplitude of 80%.

Each of the three functional runs consisted of the acquisition of 61 volumes under 3 experimental conditions: (i) a condition in which bilateral rippled noise noise was presented at a level of 70 dB (SPL), (ii) a condition in which subjects were visually instructed to protrude their jaw, and (iii) a combination of these two conditions (jaw protrusion + sound stimuli). Each condition was presented 15 times per functional run.

**Figure 2.1.** A: Hearing levels (in dB HL) of the tinnitus patients at several frequencies. Circles represent the average levels for the right ear, crosses represent average levels for the left ear. The whiskers show standard deviations. B: Severity (VAS), frequency and loudness level (in dB SL) of tinnitus perceived by the patients. An “X” is used when data were not available.
2.3 Methods

First we investigated the auditory connections and the connections between the auditory and the limbic system using standard deterministic DTI tracking provided by TrackVis [194]. This method was inadequate and failed to reveal any connections. Therefore we reverted to probabilistic tracking [168]. While standard DTI tracking computes a single main diffusion direction per voxel, probabilistic DTI tries to determine the most probable diffusion direction in each voxel by computing voxel-wise probability distributions of the main diffusion direction. The technique consists of sampling these distributions in each voxel to find the probabilities to reach the neighboring voxels, and repeating the process in the voxels reached. In this way it is possible to compute the probability to reach any voxel, starting from a certain voxel (or group of voxels).

2.3.1 Preprocessing

Before DTI analysis, preprocessing of raw data is necessary. This preprocessing step includes susceptibility correction, as well as eddy current and gradient table correction, depending on the scanner used for the acquisition. Susceptibility correction, which requires two DTI acquisitions with different fat-shift directions, was performed using MatLab, combined with the Statistical Parametric Mapping toolbox [63], the FieldMap toolbox [86], and the MatLab routines created by Andersson et al. [6]. Correction for eddy currents was performed with the software package FSL [168], a library of analysis tools for fMRI, MRI and DTI data. The gradient table modification was achieved using a MatLab toolbox created by Farrell et al. [57]. The last step before tracking is skull stripping (i.e., disregarding all non-brain data) and it was performed using BET [165].

2.3.2 Region of Interest selection

We studied a number of brain areas involved in auditory processing and investigated how they are connected to each other. In particular, we determined the connectivity profiles between auditory cortex and inferior colliculus (AC-IC), auditory cortex and amygdala (AC-AM), inferior colliculus and amygdala (IC-AM) and all reverse connections. We disregarded the connections between inferior colliculus and cochlear nucleus (IC-CN), because a preliminary analysis showed that the motor fibers in the brain stem, running next to the acoustic fibers, have a strong influence on the results due to the poor spatial resolution of DTI. The selection of these ROIs (AC, IC, and AM) was done manually and for each individual patient, using the anatomical T1 scan as a primary reference. When possible (in 6 datasets), the location of the AC was checked by a comparison with BOLD activation maps (contrast: sound - baseline) provided by fMRI analysis. Location and size of the ROIs were checked by overlapping the drawn ROIs, normalized to the Montreal Neurological Institute (MNI-152) template brain [27], to the correspondent areas defined by the Juelich Histological Atlas, thresholded at 5% [4, 136]; ACs showed an average overlap of 70%, AMs showed an average overlap of 77%.

Following Anwander et al. [7], each ROI selection included both the gray matter and a part of the white matter directly beneath it. This was done to avoid dispersion of samples already at
the early stages of the tracking procedure, due to the low anisotropy of gray matter areas. In this way the first part of the axon bundles leaving from the concerned gray matter area was included in the ROI.

To prevent the tractography from finding connections passing through cortical regions or the cerebrospinal fluid (CSF), masks were defined where tracts could not enter. These were positioned in the CSF above the AC and along Reil’s Insula, and served as barriers to avoid tracts passing through these regions. Nevertheless, the usage of these masks was not sufficient and after the probabilistic tracking an additional filtering was necessary, i.e., fiber tracts leading to the cerebellum or to the motor cortex were manually removed.

### 2.3.3 Probabilistic Tractography

The BEDPOST tool [23], which runs a Markov Chain Monte Carlo sampler, was used for building distributions of parameters describing the diffusion direction in each voxel. Probabilistic tractography was accomplished using the FMRIB Diffusion Toolkit [23]. For each voxel in a ROI, 5000 samples were taken from the distribution.

The probabilistic tractography outputs a connectivity map depicting the voxel-wise probability to reach any given voxel starting from a user-defined ROI, and it is defined as the percentage of samples leaving from the starting ROI that pass through that voxel. The connectivity map was then filtered so that only those paths connecting two different ROIs, a seed and a target ROI, were considered. An intrinsic problem of the sampling is that regions nearby the starting ROI are reached by a large number of samples, whereas the further a region is from the starting ROI, the fewer samples are able to reach it. This is a well-known and still unsolved problem. We addressed it by computing the connections between two ROIs in both directions: first starting from a region and reaching the other one, and then the other way around. Statistics on the paths, as described in the next section, were computed independently on each single path.

### 2.3.4 Statistical Analysis

Although the voxel-wise FA value is the conventional statistical measure used in DTI analysis, we considered various novel statistics to compare the two groups. For each path between a seed ROI and a target ROI (and vice versa) the following three statistical values were computed. First, the mean FA value of a path was determined as the mean of the FA values of all voxels in the path. Second, the weighted mean FA value (wFA) of a path was determined, where the weighting was provided by the probability value of each voxel (i.e., the chance that a voxel is reached as determined by the probabilistic tracking). Voxels with a larger weight are more likely to represent the actual anatomical pathway. The third statistical value was the strength $S$ of a path, defined as the percentage of the samples leaving from the starting ROI that were able to reach the target ROI. We consider the strength of a path as a key feature that describes the relevance of that path with respect to any other path connecting the starting ROI to other brain areas. Additionally, hemispheric differences were determined for all three statistical values (features) for each subject.
2.3 Methods

Figure 2.2. Box & whisker plots of the distributions of FA, weighted FA and strength in the paths of tinnitus patients and controls. For each pair of box and whiskers, the left data set corresponds to control subjects and the right one to tinnitus patients. Panel (a) shows the statistical results computed on the tract AC-IC; panel (b) of the tract IC-AC; panel (c) of the tract AC-AM, panel (d) of the track AM-AC, panel (e) of the tract AM-IC, panel (f) of the tract IC-AM. Paths where a statistically significant difference between tinnitus patients and controls was found (see Table 2.1a)) are marked with an asterisk below the plot.

and path, using a lateralization index $L$ defined as:

$$L_{\text{feature}} = 2(\text{feature}_{\text{right}} - \text{feature}_{\text{left}})/(\text{feature}_{\text{right}} + \text{feature}_{\text{left}}).$$

These statistical values were used to compare the two groups, resulting in a distribution of statistical values for each group and path. Since a chi-square test revealed that the distributions were not normally distributed, we used the non-parametric Kruskal-Wallis test in which the equality of the medians of the distributions is assessed to test for differences between control subjects and tinnitus patients.
2.4 Results

The fiber tracts of the classical auditory system and of the connections between the auditory nuclei and the limbic system could be identified by the probabilistic tracking technique. These connections were consistent between the two directions of tracking. We also ascertained that standard deterministic DTI tracking is not able to reveal these connections. However, probabilistic tractography was not able to detect every path in a statistically significant way for every subject. The easiest path to track was the auditory path, which was detected in 50% (from AC to IC) and 35% (from IC to AC) of the subjects, respectively. The connection between IC and AM was found in 40% of the cases (50% from AM to IC), and the path AC-AM (and vice versa) was found in 40% of the subjects. We did not find any relation between the cases where it was impossible to find a path and the type of subject (control or tinnitus patient). It appears that the difficulties in tracking the paths are due only to the low imaging resolution or to the low signal-to-noise ratio. No significant differences were found between the positions of the paths in the control group and the tinnitus group: all subjects showed the same connectivity pattern. This was true both for the connections between the auditory nuclei (AC and IC) and for the connections between the auditory nuclei and the amygdala.

Table 2.1. Significance values (p-values) determined by the Kruskal-Wallis test of differences between tinnitus group and control group. (a): Differences in path indices between the groups for each hemisphere. (b): Differences in path lateralization between the groups. Significant p-values (0.05 threshold) are indicated in bold.

|         | AC-IC | AC-AM | IC-AC | IC-AM | AM-AC | AM-IC |
|---------|-------|-------|-------|-------|-------|-------|
| left hem. | FA    | wFA   | S     | FA    | wFA   | S     |
|         | 0.943 | 0.936 | 0.127 | 0.423 | 0.521 | 0.047 |
|         | 0.148 | 0.624 | 0.020 | 0.333 | 0.106 | 0.006 |
|         | 0.630 | 0.261 | 0.377 | 0.149 | 0.423 | 0.199 |
|         | 0.108 | 0.935 | 0.016 | 0.743 | 0.106 | 0.109 |
|         | 0.333 | 0.732 | 0.016 | 0.261 | 0.744 | 0.077 |
|         | 0.512 | 0.262 | 0.261 | 0.631 | 0.077 | 0.149 |
|         | 0.935 | 0.732 | 0.261 | 0.618 | 0.333 | 0.998 |
|         | 0.631 | 0.108 | 0.135 | 0.998 | 0.631 |       |

The results of the statistical analysis of differences between tinnitus patients and control subjects are summarized in Table 2.1 and in Figure 2.2. Statistics were computed on each single path connecting two different ROIs. Note that in this phase of the analysis, we consider the path from a ROI “A” to a ROI “B” different from the path from “B” to “A”. Table 2.1a) shows
the significance values (p-values) determined by the Kruskal-Wallis test of differences between tinnitus patients and control subjects in fractional anisotropy (of the detected paths), weighted fractional anisotropy (of the detected paths) and strength of all the paths. The test detects a number of significant differences between the paths of the two groups. Statistically significant differences (threshold 0.05) can be noted in the strength of the AC-AM connection: it is higher in the tinnitus group, as seen from Fig. 2.2, both for the right and the left hemisphere. Other significant differences are present in the FA values of the path AM-AC in the left hemisphere and in the strengths of the path AC-IC in the right hemisphere (stronger in the tinnitus group) and the path IC-AM in the left hemisphere (stronger in the control group).

Lateralization of FA, weighted FA and strength of the paths in the two groups is shown in Fig. 2.3. Table 2.1b) shows the significance values (p-values determined using the Kruskal-Wallis test) of the differences in these indices between the two groups. Statistically relevant differences (threshold 0.05) can be noted in the lateralization of FA and of weighted FA in the path AC-AM, and in the lateralization of weighted FA in the path IC-AC. In both cases the tinnitus group shows a right lateralization whereas the control group shows a left lateralization, as can be seen from Fig. 2.3.

So far, statistics on the paths were computed independently on each single path between ROIs. For the sole purpose of visualizing the auditory paths as found by the probabilistic tractography, we used the intersection of the two paths (A→B, B→A) between any pair (A,B) of ROIs to define the location of a connection. For this purpose we normalized all the paths to the MNI template brain [27] using FLIRT [85], and averaged the per-subject results to obtain a group-wise connectivity map. The result is shown in Fig. 2.4. The paths in Fig. 2.4(A) show connections between AC and IC. These paths also involve the MGB through which they pass. Note that the MGB was not used as a ROI. In Fig. 2.4(B) we show the connections between the amygdala and the inferior colliculus, overlapped with the connections between the amygdala and the auditory cortex. The two paths follow the same route from the AM to the MGB, where they split into two separate paths, one to the IC and one to the AC.

2.5 Discussion

In this study we extended the application of DTI of the brain to the study of auditory pathways in tinnitus patients and controls. We considered DTI tracks that connect the inferior colliculus, the auditory cortex and the amygdala and vice versa. In other words, we only considered tracks that connected these preselected seed and target ROIs. Obviously, such an approach will not identify new connections. Rather, it allows for the quantification of known connections in the brain.

The first interesting result is the ability to track the classical auditory pathway. The tracks that connect the AC and the IC all pass through the MGB. Thus, although the MGB was not preselected as a region of interest, these tracks follow the expected pathway of the classical auditory system. Hence, as in a recent validation study performed in the macaque [46], DTI identifies known neuronal tracks in the brain.

Based on earlier hypotheses [82, 132] we expected that an anatomical connection between the auditory system and the limbic system would exist and indeed, we found such a connection...
between the auditory cortex and the amygdala which also connected to the MGB. This suggests that DTI is able to detect an anatomical pathway which is part of the non-classical auditory pathway, e.g., the connection from the dorsal MGB to the limbic system (amygdala).

In order to summarize the track properties, we computed three quantities for each connection in each subject: the fractional anisotropy (FA), the weighted fractional anisotropy (wFA), and the connection strength (S). The anisotropy is a property of each voxel in the brain. It is a measure of the directionality of water diffusion in the voxel. If the water diffusion is primarily in a particular direction, the voxel is assumed to contain neural fibers that are oriented in that direction. A fiber track consists of a large number of neighboring voxels. The average FA of a track is thus assumed to be a measure of the patency of the track. We assumed that the wFA is an improved measure of this patency, as it takes the probability that a voxel is actually part of the track into account. Obviously, the wFA can only be computed when using probabilistic fiber tracking. Finally, the connection strength S is the fraction of samples in a seed region that actually reach the target region. A high strength S is again a measure of the patency of the track. Conversely, a low strength may indicate that the seed region is connected primarily to other end points. Although these three measures (FA, wFA and S) are the result of considerable data reduction, they provide measures that allow for straightforward comparisons between subjects and subject groups.

By quantifying the tracks that pairwise connect the IC, AC and AM, we were able to make comparisons between control subjects and tinnitus patients. These three ROIs were selected because they may play an important role in the mechanisms that lead to tinnitus. Tinnitus is an auditory percept that occurs in the absence of a known acoustical source outside the body. In many cases, tinnitus is presumably related to abnormal spontaneous neural activity in the brain. Such patterns may occur in cases of peripheral hearing loss, as reviewed in Eggermont and Roberts [53], apparently as a consequence of altered (often reduced) peripheral input to the central auditory system.

Despite the fact that a relation between tinnitus and peripheral hearing loss is present, it is not straightforward. For example, tinnitus may be present in the absence of any substantial hearing loss. Also, the presence of hearing loss is associated with tinnitus in only about 20% of the cases [114]. The mechanisms underlying the diffuse relation between hearing loss and tinnitus are unclear. It is possible that subtle characteristics of the functional or anatomical (structural) connectivity of the central auditory systems determine whether a subject develops tinnitus. In addition, non-auditory brain areas are believed to be involved in tinnitus. Specifically, the interaction between the limbic and the auditory system has been proposed in models that explain tinnitus [82, 115, 131].

Abnormal spontaneous brain rhythms in tinnitus patients are indicative of abnormal functional connectivity in such patients. These brain rhythms reflect the activity of forward and backward loops connecting brain areas, specifically of the cortical-thalamic connections [113]. In tinnitus patients, the alpha brain rhythm is reduced, while the delta rhythm is substantially enhanced [198]. These abnormal brain rhythms, which differentiate tinnitus patients from control subjects, could in part be due to differences in the anatomical connections.

Our study is an attempt to show possible anatomical differences between subject groups using DTI. The computation of FA, wFA and S allowed us to compute such differences. We found differences and similarities between tinnitus patients and healthy controls. For example,
the variability across subjects for FA and wFA of the paths was remarkably small within each group, and was also very similar between both groups.

Significant differences in path strength between tinnitus patients and healthy controls were found for the left IC-AM connection, the right AC-IC connection, and the AC-AM connection for both hemispheres (see Table 2.1a and Fig. 2.2(c)), which also resulted in a significant difference for the lateralization (see Table 2.1b and Fig. 2.3(c)). Tinnitus patients also showed a higher FA in the AM-AC connection.

Regarding lateralization, differences between tinnitus patients and controls were found for the FA of the AC-AM connection and the weighted FA of the AC-AM and IC-AC connections, cf. Fig. 2.3(b). This result may correspond to the abnormal lateralization in brain function observed in tinnitus patients in a PET study [105].

The difference in strength of the connection between auditory cortex and amygdala in subjects with tinnitus compared to controls indicates that the limbic system may indeed play a major role in tinnitus, especially concerning the emotional content of the percept of tinnitus. Although cognitive therapies, focused on treating tinnitus by habitation, have been used for many years [83, 84], no imaging study prior to the present one has shown a potential anatomical pathway that might function differently between tinnitus patients and normal hearing controls.

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Figure 2.3. Lateralization of the paths in the two groups. The black bars represent lateralization in the control group, the white bars represent lateralization in the tinnitus group. Positive values mean right lateralization, and negative values mean left lateralization (the range of the lateralization is [-2,2]). The Kruskal-Wallis test (see Table 2.1b) found significant differences (marked with an asterisk in the picture) in lateralization of fractional anisotropy (FA) and weighted fractional anisotropy (wFA) of the path leaving from the auditory cortex (AC) to the amygdala (AM), and in lateralization of wFA in the path leaving from the inferior colliculus (IC) to the auditory cortex.
Figure 2.4. A: Connections of the auditory pathways. Each path shown is the group average of the normalized (to the MNI standard template) paths of all the subjects. The intersection of two paths (A→B, B→A) between any pair (A,B) of ROIs was used to define the location of a connection. The image shows iso-probability surfaces, coded with color (the color scale ranges from yellow to red, where yellow indicates the highest probability to find the path in that brain region, and red indicates lower probabilities). Track endpoints are identified by numbers. 1: inferior colliculus, 2: auditory cortex, 3: amygdala. The iso-probability surfaces are semitransparent so that an exploration of all voxels is possible. B: the connections between the amygdala and the inferior colliculus, overlapped with the connections between the amygdala and the auditory cortex.
Chapter 3

Enhanced DTI tracking with Adaptive Tensor Interpolation

Abstract

A novel tensor interpolation method is introduced that allows Diffusion Tensor Imaging (DTI) streamlining to overcome low-anisotropy regions and permits branching of trajectories using information gathered from the neighbourhood of low-anisotropy voxels met during the tracking. The interpolation method is performed in Log-Euclidean space and collects directional information in a spherical neighbourhood of the voxel in order to reconstruct a tensor with a higher linear diffusion coefficient than the original. The weight of the contribution of a certain neighbouring voxel is proportional to its linear diffusion coefficient and inversely proportional to a power of the spatial Euclidean distance between the two voxels. This inverse power law provides our method with robustness against noise. In order to resolve multiple fiber orientations, we divide the neighbourhood of a low-anisotropy voxel in sectors, and compute an interpolated tensor in each sector. The tracking then continues along the main eigenvector of the reconstructed tensors.

We test our method on artificial, phantom and brain data, and compare it with (i) standard streamline tracking, (ii) the Tensorlines method, (iii) streamline tracking after an interpolation method based on bilateral filtering, and (iv) streamline tracking using moving least square regularisation. It is shown that the new method compares favourably with these methods in artificial datasets. The proposed approach gives the possibility to explore a DTI dataset to locate singularities as well as to enhance deterministic tractography techniques. In this way it allows to immediately obtain results more similar to those provided by more powerful but computationally much more demanding methods that are intrinsically able to solve crossing fibers, such as probabilistic tracking or high angular resolution diffusion imaging.

3.1 Introduction

Diffusion Tensor Imaging (DTI) is a Magnetic Resonance (MR) technique that allows quantitative measurement of three-dimensional diffusion of water molecules in biological tissues [13, 149]. DTI has found many applications in medicine and neuroscience [96, 193] and nowadays is the only method enabling in vivo and non-invasive exploration of architectonic organisation of
human brain (among other organs), particularly of the cerebral white matter. Self-diffusion of water molecules in white matter is more probable to occur along neural fibers than perpendicular to them [19], leading to anisotropic diffusion of water which reflects the fibrous structure and the directional arrangements of bundles of axons [17]. Although axon myelination seems not to be essential for diffusion anisotropy [205], it is widely assumed to be the major barrier to water diffusion in brain white matter.

The DTI method approximates the diffusion process in each voxel of a DTI dataset by modelling the probability density function of water displacement via a second order diffusion tensor that represents the covariance matrix of a Gaussian diffusion process. This tensor is expressed as a three-by-three symmetric non-negative definite matrix. For each voxel, the tensor’s eigensystem is used to describe the local diffusion process; in particular, the principal eigenvector (corresponding to the largest eigenvalue) shows the direction of main diffusivity.

DTI provides an estimation of anatomical connectivity patterns and reconstructs fiber pathways within the human brain [149]. Several techniques have been proposed in the literature: deterministic tractography (or fiber tracking) [10, 36, 93, 134] is one of the most commonly used techniques and relies on the assumption that the principal eigenvector of a tensor accurately describes the orientation of the underlying fiber bundles. This information is used to perform streamlining (or other line propagation techniques) in the vector field induced by the principal eigenvectors of all voxels in the dataset. Fiber tracking has been shown to be effective in many brain regions.

A major limitation of DTI is the fact that local diffusion information is not always sufficient to determine the underlying fiber direction. In the case of low anisotropy, i.e., when the two biggest eigenvalues (or even all three) have comparable magnitude, the principal eigenvector of the tensor does not necessarily correspond to the main diffusion direction. In this case a tensor representation can sometimes provide an approximated average of the multiple compartments present within a voxel [204] and thus the streamlining may suffer from cumulative tracking errors that could lead to erroneous results [108, 173].

Fractional anisotropy (FA) is a measure of the anisotropy of a tensor. Voxels with a small FA mainly occur because of partial volume effects at locations where fiber crossing, fiber branching, or fiber kissing occur when two fibers meet and depart from each other within a voxel [1, 91] (cf. Fig. 3.1). The presence of low-anisotropy voxels is also related to the resolution of DTI data (being roughly 2 × 2 × 2 mm³, while axons have a diameter in the order of µm) and to the high susceptibility of DTI to noise during data acquisition [149, 152]. The inability to deal with areas of low anisotropy and to distinguish among singularities (i.e., crossing, branching, or kissing fibers) is considered to be the biggest problem of DTI [16, 134, 195]. Thus a tensor representation may not always be adequate to describe the underlying white matter structure. Possible solutions are to perform MR acquisition with a large number of gradient directions, as in High Angular Resolution Diffusion Imaging (HARDI) [184] or Q-ball imaging [183], or process the data using probabilistic tractography with multiple fiber orientations [20]. However, these methods require longer scanning times and longer preprocessing steps (computing the directional probability distributions needed for probabilistic tractography is very time consuming) and are not always available in current clinical environments.

The method proposed in this paper aims to improve deterministic DTI tracking by adding the
ability to solve singularities without introducing a different diffusion model. We present a tensor interpolation method which can achieve noise reduction and resolve singularities to enhance subsequent streamline tractography in areas of low anisotropy. The method improves deterministic fiber tracking by interpolating voxels with low anisotropy reached during the tracking process. In such voxels directional information is gathered from the neighbourhood and the track is split to follow both crossing or kissing fibers. Our approach provides a good alternative when more involved approaches are not available or when the emphasis is more on speed than quality: while probabilistic tractography requires hours of preprocessing, our method detects and resolves fiber crossings in a few seconds.

3.2 Related Work

The issue of characterising fiber orientation in voxels with a population of more than one fiber has been addressed in several ways in the literature [92]. Model-based approaches include for instance multiple tensor fitting [24, 171, 184], probabilistic techniques [20, 23, 102, 125, 142], DTI tracking based on front propagation algorithms [143, 144, 161], and higher order tensor models [77]. Model free approaches include Diffusion Spectrum Imaging (DSI) [196], HARDI [184] and Q-ball Imaging [183]. For a review of tracking methods we refer to [3].

The importance of considering singularities in fiber tracking algorithms has been shown by Behrens et al. [20]. Nevertheless, depending on the quality of the data and the complexity of the tissue, model parsimony measures are required to determine when more complex models are justified [92]. For instance, probabilistic and front propagation algorithms can intrinsically resolve singularities but have the major drawback not to output a connection path but values describing the likelihood to find a connection between two brain regions. Hence the user has to heuristically set a threshold on these values and decide how reliable the result is.

The method proposed in this paper has been inspired by three different papers: Hamarneh & Hradsky’s bilateral filtering of tensors [74], the surface reconstruction method via Coulomb potentials [81], and the Tensorlines propagation method by Weinstein et al. [197]. Bilateral filtering of DTI data is a technique that tries to reduce noise by identifying and delineating areas with similar diffusion properties. Several papers on interpolation of tensor data or of expressions derived from tensors (such as eigenvalues, eigenvectors, or FA) have been published [41,71,151,182]. For instance, Westin and Knutson [202] have shown how normalised convolution can be used as regularisation of tensor fields. Welk et al. [199] proposed median filtering, and Castano-Moraga et al. [34] proposed anisotropic interpolation of DT-MRI data. Hamarneh’s method is the application of bilateral filtering to DTI images and seems to perform well in detecting edges in tensor fields. It can also handle, as a special case, tensor interpolation; see the Appendix for more information on this method.

The surface reconstruction method proposed in [81] is not related to DTI; it is an approach that tries to gather the necessary information from the whole dataset, weighting the contribution of each sample by its distance from the area to be interpolated. Using the whole dataset instead of only a certain neighbourhood of the surface gives this method a better resistance to noise. We incorporate an adapted version of this distance weighting in our method.
3.3 Methods

The Tensorlines method [197] does not address the issue of estimating a smooth tensor but it is a technique that adaptively interacts with streamline propagation using the whole local tensor information to deflect the incoming tracking direction. In this method the tracking direction in a voxel is defined by the collinearity between the local main eigenvector and the main eigenvector of the previously visited voxel. This method does not solve singularities but can perform tracking in low-anisotropy regions and can produce longer tracks than standard streamlining. A drawback of this method is that the integration step for tracking the fibers is equal to the voxel size, while standard streamlining usually uses smaller integration steps. Furthermore, this tracking technique seems to be very sensitive both to noise and to the parameters set by the user, who has to choose the relative weight of the incoming direction for the local tracking.

Another interpolation method that adaptively interpolates tensors along streamlines is the technique proposed by Zhukov et al. [210]. This method is based on a moving least square regularisation of the tensors along the streamline. After reconstructing a continuous tensor field in the volume through trilinear interpolation, the method finds a polynomial that fits the data, in a least square sense, in a region around the tensor to be interpolated. The fitting depends on the location, the orientation of the streamline at the point, and the history of motion along the streamline. This method was successfully applied to brain as well as heart diffusion data [210, 211].

3.3 Methods

Our method is meant to enhance deterministic tracking techniques by interpolating diffusion information from neighbourhoods of voxels with low anisotropy. Inspired by [197] and [210], we do not apply interpolation to every voxel of the dataset but only to those voxels reached during tracking. When a voxel with low anisotropy is reached, regional information is gathered from the surrounding voxels and this is used to find the direction, or directions, in which to continue the tracking. This prevents, in contrast to global interpolation, that the interpolation affects high anisotropy as well as low-anisotropy voxels.

The basic steps of our algorithm are the following:

1. Choose a starting voxel in the dataset and start tracking a fiber.
2. Continue the tracking until a voxel with low FA is reached (FA < 0.3).
3. If such a voxel is encountered, interpolate the neighbouring voxels to find an interpolated tensor with higher FA than the original. If this is possible, continue the tracking along the main eigenvector of this tensor.
4. Visualise the resulting fiber.

3.3.1 Tensor Interpolation

Diffusion tensors do not form a vector space and special attention must be paid when performing calculations on them [146] (cf. Fig. 3.6). The value of the determinant of a tensor is in fact a
measure of the dispersion of the diffusion process [8] and Euclidean averaging of tensors has been shown to lead tensor swelling effects [35, 58, 182]. This could lead to a decrease of FA and to a possible stopping of the tracking algorithm. Therefore tensor averaging is performed in Log-Euclidean space as proposed by Arsigny [8]. Performing computations in this space prevents the increase of the determinant of the averaged tensor [40].

We recall here that the logarithm of a tensor $T$ is defined as

$$\log_m(T) = R^T \log(D) R,$$

where $D$ is the diagonal matrix of the eigenvalues of $T$ and $R$ is the matrix of its eigenvectors. The formula for tensor exponentiation $\exp_m$ is analogous.

Given a (low-anisotropy) voxel at a certain position $x$, the corresponding tensor $T(x)$ is interpolated by gathering information from a neighbourhood of $x$ containing $N$ voxels. The weight of the contribution of a certain neighbouring voxel at position $\xi_i$ is set proportional to its linear diffusion coefficient $C_L(\xi_i)$ and, like in [81], inversely proportional to a power $n$ of the spatial Euclidean distance between the two voxels $x$ and $\xi_i$:

$$w(x,\xi_i) = C_L(\xi_i) d(x,\xi_i)^{-n} \quad (3.1)$$

The linear diffusion coefficient $C_L$ is a rotational invariant of a diffusion tensor [99] that measures the amount of linear diffusion in comparison to the overall diffusion. It is defined as

$$C_L = \frac{\lambda_1 - \lambda_2}{\lambda_1 + \lambda_2 + \lambda_3} \quad (3.2)$$

where $\lambda_1, \lambda_2, \lambda_3$ are the three eigenvalues of the tensor, ordered from the largest to the smallest.

For a low-anisotropy voxel $x$ an interpolated tensor $\tilde{T}(x)$ is thus computed according to the following formula:

$$\tilde{T}(x) = \exp_m \left( k \cdot \log_m(T(x)) + (1 - k) \cdot \sum_{i=1}^{N} \frac{w(x,\xi_i)}{W(x)} \log_m(T(\xi_i)) \right) \quad (3.3)$$

where

$$W(x) = \sum_{i=1}^{N} w(x,\xi_i) \quad (3.4)$$

is the total weight at voxel $x$. The parameter $k$ weights the influence of the tensor $T(x)$ and the influence of the neighbouring tensors $T(\xi_i)$. It allows us to divide the local and regional information into two complementary components. As explained above, the tensor logarithm and tensor exponentiation used in this equation are obtained by computing the eigenvalues and eigenvectors of the tensor field.

The weighting provided by $C_L$ ensures that voxels with predominantly linear diffusion will provide more information than voxels with planar or isotropic diffusion. We prefer to use the linear coefficient instead of the more commonly used FA because we eventually aim to eigensolve the interpolated tensor and find proper directions to follow during tracking. For this reason we
want to give the same weight (given equal spatial distance from the voxel to be interpolated) to voxels with planar diffusion and to voxels with isotropic diffusion; using FA would have given more weight to voxels with planar diffusion.

The inverse power law dependence of the weight on the distance extends the area of influence so that even voxels further away will contribute to the interpolation. This approach allows us, by taking the exponent $n > 1$, to consider a wider area of influence than using a weighting that is linearly proportional to the inverse of the distance. As shown in [81], this provides our method with more robustness against noise. In contrast to the approach of [81], we do not extend the radius of influence to the whole dataset, which would not be physically plausible for DTI brain data, but restrict it to a spherical neighbourhood of the voxel under consideration. In the artificial dataset of Fig. 3.3, where the low FA area is very large, a neighbourhood of 10 voxels was used for tracking; a neighbourhood of only 5 voxels was used for the tracking in the synthetic volume and in the brain volume.

### 3.3.2 Extended DTI model

Because low-anisotropy voxels are mainly due to partial volume effects, the tensor model cannot distinguish among cases in which crossing, kissing or branching fibers occur within a single voxel (cf. Fig. 3.1). Thus, interpolation techniques may fail or lead to erroneous results and it is not possible to tell if the tracking is following the correct direction once it encounters a low FA voxel.

![Figure 3.1. Schematics of possible scenarios in a local fiber configuration. Within a voxel the fibers can (a) cross each other, (b) kiss each other or (c) a fiber can split into two branches.](image)

The second ingredient of our approach is meant to tackle this problem as follows. Whenever the tracking enters a low anisotropy voxel $x$, its 3D neighbourhood is divided in 26 sectors $S_i$, one per direct neighbour (on the voxel grid, using 26-connectivity). An interpolated tensor $\tilde{T}_i(x)$ is computed for each sector $S_i$, $i = 1, \ldots, 26$ according to Eq. (3.3), by interpolating the tensors of sector $S_i$ (cf. Fig. 3.2). For each sector $S_i$, centered at a voxel $x$, a likelihood value $l_i(x)$ is
Figure 3.2. Dataset subdivision when a low FA voxel is reached by the tracking (2D case; the 3D case is a straightforward extension). a) The figure shows two fibers meeting in the center of an example dataset. Tensors are displayed as ellipsoids whose major axis corresponds to the main eigenvector and whose eccentricity depicts the amount of anisotropy; the colour indicates the direction of main diffusivity (red: horizontal, blue: vertical). A seed is positioned in the black spot. b) When the tracking (black line) reaches a low FA voxel (square) the dataset is uniformly subdivided into eight sectors; each sector is centered at a direct neighbour of the low-FA voxel. Tensors are computed in each slice according to equation Eq. (3.3).

computed by

\[ l_i(x) = (\tilde{\mathbf{C}}_L^i(x)\tilde{\mathbf{v}}_i(x)) \cdot \tilde{\mathbf{u}}_i \tag{3.5} \]

where \( \tilde{\mathbf{v}}_i(x) \) is the principal eigenvector of the interpolated tensor \( \tilde{\mathbf{T}}_i(x) \) and \( \tilde{\mathbf{u}}_i \) is the unit vector bisecting sector \( S_i \) (here \( \tilde{\mathbf{u}} \cdot \tilde{\mathbf{v}} \) denotes the dot product of two vectors \( \tilde{\mathbf{u}} \) and \( \tilde{\mathbf{v}} \)). \( \tilde{\mathbf{C}}_L^i(x) \) is the average distance-weighted linear diffusion coefficient in sector \( S_i \),

\[ \tilde{\mathbf{C}}_L^i(x) = \sum_{j \in S_i} C_L(\xi_j)d(x,\xi_j)^{-n}. \]

The values \( l_i(x) \) are used as the likelihood for each sector \( S_i \) that the tracking should continue along the direction \( \tilde{\mathbf{u}}_i(x) \) (cf. Fig. 3.2). Because of the impossibility of differentiating between crossing, kissing or branching fibers, we continue tracking along the bisections of the two sectors with the highest likelihood value. Sectors whose unit vector forms an angle bigger than 80 degrees with the incoming tracking direction are discarded (according to the literature, a fiber bundle should not bend more than 80 degrees within a single voxel). Doing so we both spot the singularity and continue tracking along the correct direction.

Although it would in principle be possible to follow more directions, we chose to continue the tracking only along two directions, resolving in this way the crossing of not more than two fibers. It is not possible to determine the number of fibers that may produce the partial volume effect in a voxel, and two is obviously the lower bound.
3.4 Results

In this section we present results of our method for artificial data, phantom data and DTI brain scans; the method is also compared with existing techniques.

3.4.1 Artificial data

High anisotropy area with a low-anisotropy core

The first artificial dataset we used consists of a $20 \times 20 \times 20$ three-dimensional tensor field containing high-anisotropy voxels ($FA = 0.85$) but with a cubic ($7 \times 7 \times 7$ voxels) low-anisotropy core ($FA = 0.1$), cf. Fig. 3.3, left upper picture. Tensors in the high-anisotropy area are aligned to the vertical direction, while tensors in the low-anisotropy area are aligned to the horizontal direction. This dataset is used to compare our method (streamline tracking combined with the new interpolation method) with (i) standard streamline tracking, (ii) the Tensorlines method, (iii) streamline tracking after an interpolation based on bilateral filtering of tensors (see the Appendix) and (iv) streamline tracking using moving least square regularisation. The tests conducted on this dataset explore the ability of the different approaches to reconstruct fibers passing through the low-anisotropy area.

White Gaussian noise was added to each tensor component. Figure 3.3 shows the central slice of the dataset and a comparison among standard streamline tracking, Tensorlines and our new method. Deterministic tractography was achieved using Euler integration. The top right figure shows that standard tracking stops as soon as it reaches the low-FA area. Tensorlines tracking (bottom left) gets distorted already with a low noise level ($\sigma = 0.02$), while our method (bottom right) is able to reconstruct the connection between the upper part and the lower part of the dataset. For illustration purposes, the interpolation was applied to the whole dataset (and not only to the voxels reached by the tracking) to show its effects on directionality and on FA values.

Figure 3.4 shows a comparison among our method, interpolation based on bilateral filtering, and Zhukhov’s moving least square regularisation. Since these methods were all able to track through the low-anisotropy region of Fig. 3.3, we measured the effectiveness of the three interpolation techniques on three different voxels in the dataset: the voxel in the middle of the low-anisotropy area; a voxel with low FA, directly on the border of the inner low-FA core, and a high-FA voxel on the border of the inner core. Three different measures were used to compare the techniques. First, the FA value of the interpolated voxel; this shows the ability of each technique to gather anisotropy from the neighbourhood. Second, the Log-Euclidean distance between the interpolated voxel and a voxel in the high-FA area (before the noise addition); this indicates the ability to reconstruct the tensors. Third, the angular difference, in degrees, between the main eigenvector of the reconstructed tensor and the main eigenvector of a voxel in the high-FA area (before the noise addition); this indicates the ability to perform correct tracking after interpolation.

The experiments were conducted at several noise levels. Gaussian white noise was added individually to each tensor component with standard deviation $\sigma$ varying between 0.001 and 0.025. For each noise level we repeated the experiment 25 times. When adding Gaussian noise,
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Figure 3.3. Top left: the artificial dataset is a $20 \times 20 \times 20$ three-dimensional tensor field consisting of highly anisotropic tensors (FA= 0.85) with a $7 \times 7 \times 7$ low-anisotropy area (FA=0.1) in the middle. The picture shows the central slice of the dataset. Background colour represents FA (black: 0, white: 1); the colour of the ellipsoids represents direction (blue: vertical, red: horizontal). Top right: white Gaussian noise ($\sigma = 0.02$) was added to each tensor component. Streamline tracking (red line) was seeded in a single voxel in the top of the picture. Bottom left: the Tensorlines technique. Bottom right: streamline tracking after our new tensor interpolation.

we maintained the non-negative definiteness of the diffusion tensor. This prevents to generate tensors with non positive eigenvalues which are difficult to interpret physically (since they describe non positive diffusion factors) [8].

As seen in Fig. 3.4, the interpolated tensors present an FA always bigger than 0.3, even at relatively high noise levels (a threshold of FA = 0.2 is usually used as a stopping criterion for streamline tractography). Our method is more effective in restoring high-FA values than the interpolation based on bilateral filtering, and it is also more effective than moving least square regularisation, except for high noise levels. The Log-Euclidean distance between the interpolated tensors and the “expected” tensor is quite small in all three cases. Again, our results show lower Log-Euclidean distances than those achieved by the interpolation based on bilateral filtering,
except for a small region below $\sigma = 0.02$ in Fig. 3.4(f). Compared with moving least square regularisation, our method produces lower Log-Euclidean distances especially for the voxel the center of the low FA region (Fig. 3.4(d)). Regarding the angular error of the three interpolation techniques we see no significant difference, see Fig. 3.4(g, h, i). The average angular error grows roughly linearly with the amount of noise, and it does not exceed 6 degrees (at $\sigma = 0.025$).

**Crossing fibers**

The second artificial dataset consisted of three fibers that meet each other in the center of a $20 \times 20 \times 20$ dataset. Each fiber is represented by a strip of high-FA voxels (FA = 0.85). The dataset was used to evaluate the ability of our method to recognise directional information in different sectors of the dataset. Figure 3.5(left) shows a slice of the dataset where the three fibers cross. Tracking was seeded at the top of the figure and the track did split when it reached the low-FA area. White Gaussian noise was added to each tensor of the dataset and the tracking was repeated 25 times per noise level; the standard deviation of the noise varied from 0.001 to 0.25. Figure 3.5(right) shows statistics on the ability to find the correct fibers as a function of noise level. The blue line represents the probability to find all five segments that meet in the low-FA area (the incoming direction was not considered as a possible solution). The blue shaded area represents its standard deviation. The red line indicates the probability to find the two fibers that the algorithm should detect, i.e., the only two fibers forming an angle smaller than 80 degrees with the incoming direction. The red shaded area is its standard deviation.

### 3.4.2 Phantom data

The next dataset considered was a physical phantom DTI dataset representing two 90 deg crossing fibers. The dataset was made of Dyneema® fibers. The fibres were grouped in parallel bundles of 780 filaments which were crossed, surrounded by a shrinking tube, and immersed in water (Courtesy of E. Fieremans, NYU Medical Center, and J. Sijbers, Univ. of Antwerp). Figure 3.7 shows a comparison among standard deterministic tractography, our method and the results of probabilistic tracking performed with FSL [168]. The white disc indicates the position where the tracking was seeded. No constraints were set on the angles between the incoming and the outgoing directions. Standard deterministic tractography was not able to resolve the crossing: the tracking stopped when it encountered a low FA voxel. Our algorithm (which is deterministic as well) recognised all the fiber segments and it was able to continue tracking in all the directions detected by the much more computationally demanding probabilistic method.

### 3.4.3 Brain data

Results of the tracking for a DTI brain data set are shown in Fig. 3.8. A coronal slice of the brain is shown in the leftmost figure, colour coded according to the FA values (black represents FA=0 and white FA=1). Seeding the tracking in the lower part of the body of the Corpus Callosum, our method was able to detect the blossoming of the upper part of the Corpus Callosum where the fibers reach the cerebral cortex, and to resolve the low-FA area generated by the intersection
Figure 3.4. Comparison between results achieved by our method (red lines), by the interpolation based on bilateral filtering (blue lines), and by the moving least square regularisation method of Zhukov et al. (green lines). Error measures were computed for three different voxels in the dataset shown in Fig. 3.3: a voxel in the middle of the low-anisotropy area (column 1), a voxel with low FA, directly on the border of the inner low-FA core (column 2), and a high-FA voxel on the border of the inner core (column 3). Row 1: FA value of the interpolated voxel. Row 2: Log-Euclidean distance between the interpolated voxel and a voxel in the high-FA area. Row 3: angular error of the interpolated voxel. All error measures are shown as a function of noise level $\sigma$. Each line represents the average of 25 runs and the shaded area indicates the corresponding standard deviation.

of Corpus Callosum and Corona Radiata. Brain dataset courtesy of Gordon Kindlmann, Scientific Computing and Imaging Institute, University of Utah, and Andrew Alexander, W. M. Keck Laboratory for Functional Brain Imaging and Behavior, University of Wisconsin-Madison.
3.4 Results

Figure 3.5. Left: artificial dataset with three fibers crossing in the middle. The figure shows the central slice of the dataset. Tracking was seeded in the black spot. The tracking follows the fiber until the low-anisotropy area in the middle and then detects all other fibers. Right: The blue line shows the probability, as a function of noise level, to detect all five fibers meeting in the center (the incoming direction was not considered as a solution). The red line indicates the probability to find the two fibers that the algorithm should detect (the only two fibers forming an angle smaller than 80 degrees with the incoming direction).

Figure 3.6. Comparison between averaging of tensors in Euclidean versus Log-Euclidean space. First row: three input tensors. Second row: tensor A is obtained by Euclidean averaging, tensor B by log-Euclidean averaging. The tensor in A shows a lower FA compared to the tensor in B.
Figure 3.7. Tracking performed in a physical phantom DTI dataset depicting two crossing fibers. The pictures show a slice of the dataset. The white disc indicates the position where the tracking was seeded. Left: tracking results of standard deterministic tractography; the tracking stopped in the crossing area. Middle: results of our algorithm; crossing fibers were detected and all branches were found. Right: tracking by probabilistic tractography with FSL.

Figure 3.8. Tracking performed for a DTI brain dataset. The red square in the left picture indicates the Corpus Callosum. The right picture shows a magnification of the red area. The white disc indicates the position where tracking was seeded. Our algorithm was able to detect the blossoming of the fibers of the Corpus Callosum below the cerebral cortex (leftmost branch) and the intersection between Corpus Callosum and Corona Radiata (rightmost branch).

3.5 Conclusions

DTI tractography allows the inference of connectivity patterns within white matter of the brain. There are two main limitations of this technique. The first is that the tensor model does not
always reflect the underlying white matter structure, as it is not able to deal with singularities such as crossing, branching, or kissing fibers. The second limitation is the inability of DTI tracking to reconstruct more than one trajectory per seed point.

In this paper we introduced an improved tracking technique that allows DTI streamlining to solve low-anisotropy regions and permits branching of trajectories. Our method performs interpolation for any low-anisotropy voxel met during tracking. Interpolation is computed in Log-Euclidean space [8] and collects directional information in a spherical neighbourhood of the voxel in order to reconstruct a tensor with a higher linear diffusion coefficient than the original. The weight of the contribution of a certain neighbouring voxel is proportional to its linear diffusion coefficient and inversely proportional to a power of the spatial Euclidean distance between the two voxels. This inverse power law provides our method with robustness against noise [81]. In order to resolve multiple fiber orientations, we divide the neighbourhood of the low-anisotropy voxel in 26 sectors, and compute an interpolated tensor in each sector according to the weighted tensor interpolation formula. The tracking then continues along the main eigenvector of the reconstructed tensor.

We tested our method on artificial, phantom and brain data, and compared with existing methods: (i) standard streamline tracking, (ii) the Tensorlines method, (iii) streamline tracking after an interpolation based on bilateral filtering, and (iv) moving least square regularisation. We showed that in contrast to standard streamline tracking, our method is able to continue tracking in low-anisotropy areas, while Tensorlines tracking gets distorted already for low noise levels. Compared to streamline tracking after the interpolation based on bilateral filtering, our method is more effective in restoring high anisotropy values. Compared to the moving least square regularisation, our method generally performed better except for high noise levels. For phantom and real MRI data, we found that our method was able to detect the same tracts as probabilistic tracking.

Due to its ability to resolve cases of multiple fiber orientations in a single voxel our method gives the possibility to obtain, in comparison to standard deterministic tractography, results more similar to those provided by more powerful techniques that are intrinsically able to solve crossing fibers, such as high angular resolution diffusion imaging, which is not always available, or probabilistic tracking with multiple fiber orientations [168], which is computationally much more demanding: while probabilistic tractography requires hours of preprocessing, our method detects and resolves the crossing in a few seconds. Furthermore, in contrast to the probabilistic tractography, in our approach there is no need to perform heuristic thresholding for interpreting the results.

Future work will include a deeper study on the results achievable with this method in comparison with probabilistic tracking and other techniques that allow multiple fiber orientations per voxel. Validation of the results, e.g., by histological analysis, will certainly be a requirement for the practical application of this and other DTI techniques.
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3.6 Appendix

Bilateral filtering of diffusion tensor data is achieved according to the following formula [74]:

\[
T(x) = \exp_m \left( \sum_{i=1}^{N} \frac{w_i(x)}{k(x)} \log_m(T(\xi_i)) \right)
\]  

(3.6)

\[
w_i(x) = \alpha f_1(d_T(T(x), T(\xi_i)) + (1 - \alpha) f_2(d_S(x, \xi_i))
\]

(3.7)

where \(d_T(T(x), T(\xi_i))\) is the tensor dissimilarity between the two tensors \(T(x)\) and \(T(\xi_i)\). \(d_S(x, \xi_i)\) is the spatial Euclidean distance between the voxels \(x\) and \(\xi_i\). Here \(f_1\) and \(f_2\) are monotonically decreasing functions that map \(d_T\) and \(d_S\) in the interval \([0, 1]\). The value \(\alpha\) weights the contribution of the two distances. We used a simplified version of bilateral filtering, by setting \(\alpha\) to zero and thus weighting the contribution of the tensor \(T(\xi_i)\) only according to the Euclidean distance between voxels \(x\) and \(\xi_i\).
Chapter 4

Heuristics for Connectivity-Based Brain Parcellation of SMA/pre-SMA through Force-Directed Graph Layout

Abstract

We propose the use of force directed graph layout as an explorative tool for connectivity-based brain parcellation studies. The method can be used as an heuristic to find the number of clusters intrinsically present in the data (if any) and to investigate their organisation. It provides an intuitive representation of the structure of the data and facilitates interactive exploration of properties of single seed voxels as well as relations among (groups of) voxels.

We validate the method on synthetic datasets and we investigate the changes in connectivity in the supplementary motor cortex, a brain region whose parcellation has been previously investigated via connectivity studies. This region is supposed to present two easily distinguishable connectivity patterns, putatively denoted by SMA (supplementary motor area) and pre-SMA.

Our method provides insights with respect to the connectivity patterns of the premotor cortex. These present a substantial variation among subjects and their subdivision into two well separated clusters is not always straightforward.

4.1 Introduction

Classification of structural and functional regions in human brain cortex is a key aspect of neuroscience [145]. Under the hypothesis of a relation between brain structure and brain function, several techniques for cortex parcellation are available in the literature. The golden standard for cortex structural analysis is based on cyto- or myeloarchitectonical studies of post mortem brains [28, 191, 192], which allow parcellation of brain cortex based on variations of density and size of cell bodies at the microscopic level. Functional identification of several brain areas was achieved by using anatomical landmarks such as sulci [5, 66], or using modern in vivo explorative techniques such as fMRI and PET, which improved and broadened the possibility to locate functional brain areas.
One of the imaging techniques providing insight in anatomical brain connectivity is Diffusion Tensor Imaging (DTI). This is a magnetic resonance modality for measuring white matter connectivity in vivo, bridging the gap between structural studies and post mortem anatomical analysis [101]. DTI is a non-invasive method that allows quantitative assessment of directional information of water self-diffusion in biological tissues. Measuring the anisotropic self-diffusion of water, induced by the fibrous nature of white matter, allows one to infer the directional arrangement of bundles of axons [13, 149]. The principal direction of water diffusion in each white matter voxel is often used for tracking fiber bundles; cf. [16, 134] for a reference on DTI and tracking techniques. Probabilistic tractography [23, 102, 142] estimates fiber tracks using probability density functions that describe the local uncertainty of fiber bundle orientation. This technique provides confidence bounds on the locations of connections from a seed voxel to every other voxel of the brain. Such connections define the connectivity profile of that voxel [88]. Probabilistic tractography has been used to demonstrate different patterns of anatomical connectivity [21]; it has also been used to compute parcellation of brain regions based on connectivity information alone [7, 44, 49, 88, 89, 157].

In this paper we visualise brain connectivity networks by making use of techniques from graph visualisation [76, 122, 189]. In particular, we apply the force-directed graph layout (FDGL) technique, which models a graph as a physical system and tries to find a layout for the nodes and edges of the graph such that the total energy of the system is minimal. We show that FDGL algorithms are well suited for connectivity-based analysis of brain cortical areas. Relations among the connectivity profiles of seed voxels are used to define a graph layout where voxels (graph nodes) are drawn closer to each other when their connectivity profiles are more similar. This technique allows us to investigate the presence and the number of clusters in a dataset by analysing the positions of the graph nodes and by counting the groups of nodes drawn close to each other. Insights on the strength of similarity among voxels and among groups of voxels are also possible, and hypotheses on the reliability of the results can be verified in a follow-up analysis by mapping the density on the original anatomy, i.e., before clustering the data. This approach can be used as an heuristic for determining the number of clusters to be used in a (subsequent) clustering algorithm.

We applied our method to the parcellation of SMA (supplementary motor cortex) and pre-SMA, a brain region that has been previously examined via connectivity-based parcellation (CBP) [7, 21, 101, 138]. On the basis of previous evidence in animal studies [119, 147], a sharp transition in the connectivity properties of SMA and pre-SMA is expected. Nevertheless, neither a quantitative analysis of the difference between SMA and pre-SMA in terms of connectivity patterns, nor the possibility of a smooth transition of connectivity patterns between the two functional areas, has been investigated in the literature.

### 4.2 Related Work

Automatic parcellation of brain cortex, i.e., without a priori knowledge of target regions, was introduced by 88. The authors clustered the connectivity profiles of the voxels of SMA/pre-SMA and recovered the supposed location of the boundary between the two areas. The cross-
correlation matrix (CCM) of the connectivity profiles of SMA/pre-SMA voxels was reordered using a spectral reordering algorithm [11], which minimizes the sum of the reordered matrix entries, multiplied by their squared distance from the diagonal. If the data contain clusters (groups of voxels with similar connectivity), these will be visually distinguishable in the reordered CCM [88] and the investigator can visually separate matrix compartments that identify clusters with distinct connectivity patterns.

Connectivity-based brain parcellation of the premotor cortex was replicated using k-means clustering on CCM by 7, 101 and by 138. In 7, the possibility of the existence of more than two clusters was investigated. In particular, k-means clustering with k=3 was consistently found to divide the most posterior area of the premotor cortex into two clusters which were reported as possibly referring to the primary motor cortex (M1) and SMA. 101 validated the use of k-means clustering for the CBP of SMA and pre-SMA with fMRI techniques. 138 showed how the application of k-means clustering to the same dataset can lead to a variety of rather different parcellations, depending on the initial placement of the starting points of the algorithm.

The output of k-means clustering is strongly dependent on the expected number of clusters, and it may provide misleading results if this number does not correspond to the number of clusters intrinsically present in the data. Compared to k-means clustering, spectral reordering of CCMs has the advantage of not requiring a priori knowledge of the number of clusters. Nevertheless, spectral reordered CCMs often do not show clear separations into two (or more) compartments and visual analysis of such matrices is not always straightforward. Furthermore, any decision taken by the investigator on the partitioning of the spectral reordered CCM is solely based on the layout of the CCM itself and no anatomical reference is taken into account.

### 4.3 Materials and Methods

#### 4.3.1 Data acquisition and preprocessing

Diffusion-weighted (DW) images were acquired from 13 healthy subjects (6 F, 7 M, mean age: 20.94; sd 1.95; max 25, min 18) using a single-shot pulsed gradient spin echo EPI sequence (SENSE factor = 3, TR = 6 s, and TE = 77 ms) on a 3T MR scanner (Intera, Philips Medical Systems, Best, The Netherlands). For each subject 60 DW images were collected using 60 uniformly distributed gradient directions [93], with a maximum gradient strength of 22 mT/m and a b-value of 800 s/mm². In addition, 7 non-DW images (b = 0 s/mm²) were acquired before the DW images and averaged on the scanner. Each image consisted of 51 transverse slices with an in-plane resolution of 1.875 x 1.875 mm² and slice thickness of 2 mm (FOV = 240 x 240 mm² and data matrix size = 128 x 128). The total scan time for one dataset was approximately 7 min.

Diffusion data were corrected for eddy currents and head motion by affine registration to the non-weighted image. Data from the skull was subsequently removed and the non-weighted image was registered to the MNI standard template (voxel size 2 mm³). All these steps were performed using FSL [168, 208].
4.3 Materials and Methods

Figure 4.1. Six synthetic CCMs and the corresponding graph layouts. Graph layouts are coloured by the user according to visually detected clusters (A,B,C). Smooth variabilities in similarity are depicted using colour gradients (D,E,F). Bars below the CCMs show the clusters replotted on the columns of the CCMs.

4.3.2 Tractography

After preprocessing, Bayesian estimation of diffusion parameters was performed as in 23 and implemented in FSL [168]. In order to perform probabilistic tractography of the medial premotor region, we defined a seed region by a binary mask at X(MNI)=-2, spanning from Y=-22 to Y=30 (MNI coordinates), and extending in the Z-direction from above the cingulate sulcus to the dorsal crest of the medial wall; cf. 88. This mask was then transformed into each subject’s DW space by means of an affine transformation with nearest neighbour interpolation. Probabilistic tractography was seeded for each voxel in the mask; five thousand samples were drawn from the orientation distribution of each seed voxel to generate its connectivity profile. Connectivity profiles were then binarised, setting to unity any entry bigger than zero.

In the next step the CCM of the connectivity profiles was calculated. The CCM is a symmetric square matrix where the entry \((i,j)\) is the Pearson’s correlation between the binarised connectivity profiles of seed voxels \(i\) and \(j\), and the \(i^{th}\) row of the CCM contains the correlation of the binarised connectivity profile of the seed voxel \(i\) with the binarised connectivity profiles of all other voxels in the seed region.
4.3.3 Synthetic datasets

Six synthetic datasets were created for testing our approach. Each set consisted of 250 binary vectors simulating binarised connectivity profiles. The vectors had $10^5$ entries, 5% of which were non-zero entries (connectivity profiles of voxels in pre-SMA/SMA cover roughly 5% of the whole brain volume).

The six sets of vectors were created so that the corresponding CCMs corresponded to six qualitatively different cases: (i) two distinct compartments, corresponding to the presence of two completely separated clusters; (ii) two partially overlapping compartments, corresponding to the presence of a non-empty intersection between two clusters; (iii) three pairwise overlapping compartments; (iv) two big compartments connected by a series of smaller overlapping compartments; (v) three compartments pairwise connected by a continuum of smaller overlapping compartments; (vi) a continuum of small overlapping compartments, where each matrix column (row) correlates only with its neighbouring columns (rows).

The synthetic CCMs are shown in Fig. 4.1, where grey values represent the strength of the correlation among connectivity profiles, white representing high correlation. Note that the synthetic CCMs were not spectrally reordered, but they were created this way to facilitate the visual analysis of the compartments.

4.4 Graph Layout

A graph $G = (V, E)$ is defined by a set $V$ of nodes and a set $E$ of edges, where an edge connects a pair of nodes. We use undirected graphs, so if node $i$ is connected to node $j$, then $j$ is connected to $i$. A graphical representation of a graph is called a graph layout. Graphs are usually depicted with their nodes as points in a plane and their edges as arcs connecting the nodes.

There are different styles of representation, suited to different types of graphs or different purposes of presentation. The arrangement of nodes and edges emphasises different characteristics of the graph, assists in the understanding of graph properties, and reveals patterns in the data. Such graph drawing styles are known under the heading of graph aesthetics [50]. FDGL is a consolidated visualisation method whose purpose is to position the nodes and the edges in an aesthetically pleasing way. Our main consideration here is that proximity in the layout corresponds to a certain similarity measure defined in the data space.

The purpose of FDGL is to find a position $\vec{p}_i$ for each node $i$ of the graph such that nodes corresponding to highly correlated connectivity profiles are drawn near each other. This is achieved by using a physical analogy. Nodes are modelled as particles on which forces are acting. The optimal layout corresponds to the situation when the physical system is in equilibrium, i.e., the energy of the system is minimal. Two forces act on each node: a Hooke’s spring force $F_A$, attracting nodes, and a Coulomb-like repulsion force $F_R$, repelling nodes. The total force $F_T(i)$ acting on a node $i$ is thus:

$$F_T(i) = \sum_j F_A(i, j) \frac{(\vec{p}_i - \vec{p}_j)}{|\vec{p}_i - \vec{p}_j|} - \sum_j F_R(i, j) \frac{(\vec{p}_i - \vec{p}_j)}{|\vec{p}_i - \vec{p}_j|}$$

(4.1)
where $F_A(i, j) = CC(i, j) |\vec{p}_i - \vec{p}_j|$, $F_R(i, j) = \frac{CC(i, j)}{|\vec{p}_i - \vec{p}_j|^2}$, and $CC(i, j)$ is the cross-correlation between the connectivity profiles of seed voxels $i$ and $j$.

Force directed algorithms are known to be sensitive to local minima. However, finding the global minimum is not critical in our application. It suffices to reach a good approximation of the global minimum such that the initial position of the nodes does not drastically influence the outcome, thus providing a graph representation that is roughly reproducible in all the experiments. To approximate the equilibrium we proceed via steepest descent: starting from random positions, nodes are moved along the directions of the resulting force until the total potential energy is below a certain threshold value.

For evaluating the influence of the initial position of the nodes on the final outcome of the layout, we ran our algorithm multiple times on the same dataset. In each run, the initial position of the nodes was randomly generated and the size of the smallest rectangle containing the graph layout (whose longest side is parallel to a line connecting the two most distant nodes) was computed. This allowed us to compare the size of the graph. In addition, we compared the position of the barycentre of the graph across runs (cf. Fig. 4.5).

The force-directed algorithm yields a layout such that visual exploration of relations among nodes is intuitive. Several techniques are at our disposal for exploring such relations: simple graphical primitives drawn by the user and data-driven approaches such as local density of nodes. Graphical primitives can be used to label nodes, or groups of nodes, and to relate them with both the corresponding entries of the CCM and their locations in the brain (cf. Fig. 4.1). A local density of nodes is computed using the adaptive Gaussian kernel density estimation method proposed by 150. By interpolating the positions of the graph nodes, a continuous density function is obtained and iso-density lines can be created (cf. Fig. 4.3).

We use the density of graph nodes as an indicator of groups of voxels with highly correlated connectivity profiles. By counting the number of density peaks (local maxima) of the density function, the number of clusters in the data can be inferred. Similarity of the connectivity profiles of voxels within a cluster, similarity of profiles in different clusters, and relationships among clusters can also be assessed by exploring the density map and the position of the graph nodes.

4.5 Results

4.5.1 Synthetic data

Synthetic CCMs and their corresponding graph layouts are shown in Fig. 4.1. Nodes are labelled with gray values chosen by the user. Below each layout, the labelling of the nodes (seed voxels) is mapped along the columns of the CCMs, showing that the clusters perceived by the user reflect the actual compartments in the CCMs.

Fig. 4.1A shows that well-defined compartments of a CCM are represented by graph nodes that have been tightly grouped in circular regions: since the connectivity profiles within a compartment are similar, the attractive forces among the corresponding nodes have overcome the repulsive forces during the force-directed layout. A graph representation of overlapping compartments is shown in Fig. 4.1B, C. When two or more compartments of the CCM partially
Figure 4.2. The effects of noise addition to the data presented in Fig. 4.1A. Noise ranges from 0% (A) to 80% (I). The size of the nodes differs in every picture because the spreading of the layout increases with the amount of noise.

Figure 4.3. Comparison of spectral reordering and FDGL. A) Spectral reordered CCM of the area SMA/pre-SMA of subject 1. B) Results of k-means clustering on the CCM, for 2 and 3 clusters. C) Results of k-means clustering on the graph layout, for 2 and 3 clusters. D) The FDGL. E) Iso-density lines. F) The colour map used for mapping the density. G) The continuous density function.
Figure 4.4. Reproducibility of our method. Top: statistics on the size of the smallest rectangle containing the graph layout and on the position of its barycenter. Bottom: result of a single run (left), average density over 50 runs (center) and standard deviation of the density in each voxel (right). Colour maps are shown in the bottom of the figure.
Table 4.1. Degree of overlap of k-means clustering results performed on the entries of the CCM and on the positions of the nodes in the graph layout, for subjects 1-5.

|        | subj.1 | subj.2 | subj.3 | subj.4 | subj.5 |
|--------|--------|--------|--------|--------|--------|
| 2 clusters | 98.8%  | 95.9%  | 89.8%  | 84.6%  | 77.5%  |
| 3 clusters | 76.2%  | 95.7%  | 84.8%  | 94.3%  | 98.7%  |

Figure 4.5. Top: plot of the graph densities of subject 1 on the MNI standard template. The regions with highest density overlap with the putative positions of SMA and pre-SMA. Centre: k-means clustering of SMA and pre-SMA into 2 clusters. Bottom: k-means clustering of SMA and pre-SMA into 3 clusters.

4.5.2 Subject data

Next we apply our method to data acquired from 13 healthy subjects, as described in section 4.3. The results of five subjects are shown in Fig. 4.3 and Fig. 4.7, while results of the remaining 8 subjects, as well as clustering and tractography results, are shown in the supplementary materials.

Figure 4.3 shows the results for SMA/pre-SMA data from subject 1. Figure 4.3A shows the spectral reordered CCM, as described in 88. Figure 4.3B shows results of k-means clustering of the CCM, for k=2 and for k=3 clusters. Gray values identify which rows in the CCM belong to the same cluster. Figure 4.3C shows results of k-means clustering of the graph layout. The clusters are mapped to the rows of the CCM. Figure 4.3D shows the graph layout, where nodes are coloured according to their density using the colour map shown in Fig. 4.3F. Figure 4.3E shows iso-density lines of the continuous 2D density function in Fig. 4.3G. The colour map in
Figure 4.6. Frequency maps of the number of times each voxel is connected to the somatomotor area (top) and to prefrontal areas (bottom). Somatomotor area was defined by using a mask of the primary motor cortex, corticospinal tract, and lateral premotor cortex (BA6). The prefrontal area was defined by a mask of BA44, BA45, superior parietal lobe, and medial frontal gyrus (MFG). All masks except MFG were taken from Eickhoff’s Anatomy Toolbox [55]. The mask of MFG was taken from the Harvard-Oxford Cortical Structural Atlas. Colour maps are shown on the right. The green line represents Y(MNI)=0.

Fig. 4.3F was chosen to enhance the details of the 2D density function and to ease its readability.

Figure 4.4 shows statistics on the reproducibility of our method. The smallest rectangle containing the graph layout of Fig. 4.3 is shown in the top image of Fig. 4.4. This rectangle has its longest side parallel to the imaginary line connecting the two most distant nodes in the layout. Since orientation of the rectangle depends on the initial random position of the nodes and usually differs from one run to the other, the coordinates of its barycentre are computed according to the node of the rectangle most close to the barycentre itself. Average and standard deviations were computed running our algorithm fifty times on the data from subject 1. Figure 4.4 (bottom) shows statistics on the mapping of the densities to the anatomy. The result of a single run is shown bottom left. The average of the density maps over fifty runs is shown in the center. The corresponding standard deviations are shown on the right. We see that the position of the density peaks is similar across runs, and the standard deviation is small, although there is a little higher variability in the anterior region, dorsal with respect to the cingulate sulcus. These results indicate that our method is consistent across runs and highly reproducible.

Quantitative comparisons between k-means clustering of graph layout and k-means clustering of the CCM for subjects 1-5 are shown in Table 4.1. Both quantitative and qualitative comparisons of clustering results for the remaining 8 subjects are shown in the supplementary materials. We observe high consistency of the clustering results. This confirms the soundness of our ap-
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Figure 4.7. Spectral reordering, graph layout and MNI mapping of subjects 2-5.
proach and validates the hypothesis that high similarity of connectivity profiles corresponds to proximity in the graph layout.

Figure 4.5 shows the results of our method (top figure) and the result of k-means clustering on the graph (center and bottom figures) for the SMA/pre-SMA of subject 1. The density peaks shown by our method correspond to two groups of voxels, one in the posterior and one in the frontal premotor cortex, situated in the putative location of SMA and pre-SMA (the colour map is the same as Fig. 4.3). In agreement with column “subj. 1” of Table 4.1, the position of the density peaks best matches the results of k-means clustering with k equal to 2 rather than k equal to 3.

Figure 4.6 shows a group-wise comparison of tractography results on each voxel of the region of interest (ROI). Two ROIs were used as targets for probabilistic tractography. These ROIs are the somatomotor area (M1 and cortico-spinal tract) and the prefrontal areas BA44, BA45, superior parietal lobe, and medial frontal gyrus. The figure shows the frequency of connections from each voxel to the somatomotor area (top) and to the prefrontal brain regions (bottom) in the group of subjects. The voxels in the posterior regions of the ROI (putatively SMA) are connected to the somatomotor area in all subjects. The frequency of this connectivity pattern decreases as we move toward the front of the ROI (putatively pre-SMA). Accordingly, the region showing most frequent connectivity with prefrontal brain regions lays in the frontal part of our ROI. An important result is that these two connectivity patterns do not separate SMA/pre-SMA in two clear regions, but overlap in the central region of the ROI.

4.6 Discussion

The medial frontal cortex of the hemispheres, above the cingulate sulcus, is composed of different cortical regions featuring different architecture, functionality and anatomical connections with the rest of the brain. The most posterior sector is part of the primary motor cortex M1 (BA4, [28]). SMA, adjacent to M1, is involved in practical issues such as response selection or production. Pre-SMA is involved in the establishment or retrieval of sensory-motor associations [148, 177].

Tracer injection studies in macaque showed that SMA and pre-SMA are also distinct in terms of their anatomical connections with other parts of the brain: SMA has direct connections to the spinal cord and to M1; pre-SMA is not directly connected with final motor pathways but mainly with other regions of the prefrontal cortex. The two regions also differ in their projections to the cingulate, parietal and temporal cortex [119].

Using results from animal studies on the macaque, 147 showed the presence of a relatively sharp subdivision between SMA and pre-SMA, localised around the plane through the anterior commissure (Y(MNI)=0). However, this boundary is idealised and based on evidence from animal studies; in a single subject examination no anatomical landmark can be used to effectively discriminate SMA from pre-SMA.

Connectivity based parcellation of SMA/pre-SMA was performed by 88, 7, 101, and 138. In 88, 101 and 138 the location of the boundary between SMA and pre-SMA was investigated. In 7 results of k-means clustering with k=2 were investigated and the possibility that k-means with k=3 could distinguish M1, SMA and pre-SMA was discussed.
Given the recovered similarity in the tractography results between the two posterior clusters, the lack of a macroscopic landmark to distinguish SMA from M1, and the inter-subject variability on the location of the border M1/SMA (cf. probabilistic maps for M1 in the cytoarchitectonic atlas of Juelich [55]), it is possible that at least part of M1 is included in the ROI. Nevertheless, the posterior boundary of the mask used for these parcellation studies (MNI Y=-22), introduced by 88 and used in several SMA/pre-SMA parcellation studies, localises the boundary between medial M1 and medial SMA as described in the probabilistic cytoarchitectonic atlas of Juelich [55].

With our method we were not able to find well defined clusters covering the areas of SMA and pre-SMA, but rather a continuum of similarity among connectivity profiles when moving from the posterior to the anterior premotor area. Like in 138 a substantial variability among the connectivity patterns of the subjects was found (cf. Fig. 4.6).

Subjects 1, 3, 6, 8, 11, 12 and 13 showed the presence of two density peaks. These divide the premotor cortex into two sagittal regions that could correspond to SMA and pre-SMA. The other datasets (subjects 2, 4, 5, 7, 9, and 10) showed the presence of three density peaks. Our speculative explanation is that these peaks, mapped sagitally along the premotor cortex, could refer to the presence of two groups of voxels with similar connectivity profiles (possibly SMA/pre-SMA) and a third region (a transitional area) where connectivity profiles are equally similar to those in SMA and to those in pre-SMA (cf. Fig. 4.1B, Fig. 4.6). This solution would be consistent with the results proposed in 138, which indicate both a substantial inter-subject variability in the location of the border between SMA and pre-SMA, and the existence of a gradual change in connectivity between the posterior and the anterior regions of the ROI.

Another possible explanation is that either SMA or pre-SMA can be divided into two smaller regions with different connectivity patterns. Also, as proposed in 7, this could be due to the inclusion of M1 in the ROI.

A comparative study of structural and functional data (i.e., functional localization of M1, SMA, and pre-SMA) in each subject would be an asset for the understanding of the relation between functional regions and similarity in connectivity patterns.

### 4.7 Acknowledgements

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### 4.8 Supplementary Material
Figure 4.8. Data of subjects 6, 7, 8, 9. Spectral reordering of the CCM(A). Comparison between k-means clustering with 2 and 3 clusters on CCM (B) and on graph layout (C); clusters are indicated by colours and mapped along the rows of the CCM. Graph layout (D). Iso-density lines (E) of the continuous density function (G). Images D, E, G are colour-coded according to the colour map F. MNI mapping of densities and k-means results (k=2 and k=3) on graph layout (H).
Figure 4.9. Data of subjects 10, 11, 12, 13. Spectral reordering of the CCM(A). Comparison between k-means clustering with 2 and 3 clusters on CCM (B) and on graph layout (C); clusters are indicated by colours and mapped along the rows of the CCM. Graph layout (D). Iso-density lines (E) of the continuous density function (G). Images D, E, G are colour-coded according to the colour map F. MNI mapping of densities and k-means results (k=2 and k=3) on graph layout (H).
Figure 4.10. Visual comparison between clustering of graph nodes and clustering of CCM for both 2 and 3 clusters for subjects 1-13. For each subject the four subfigures show: clustering of graph nodes for 2 clusters (top left); clustering of CCM for 2 clusters (top right); clustering of graph nodes for 3 clusters (bottom left); clustering of CCM for 3 clusters (bottom right). The green line represents $Y(MNI)=0$. See also Table 1 of the paper and Table 4.2 below for quantitative results.
Figure 4.11. Probabilistic tracking results seeded in k-means clusters found with k=2.
Figure 4.12. Probabilistic tracking results seeded in k-means clusters found with k=3.
Table 4.2. Overlap of k-means clustering results performed on the entries of the CCM and on the positions of the nodes in the graph layout, for subjects 6-13.

|         | subj.6 | subj.7 | subj.8 | subj.9 | subj.10 | subj.11 | subj.12 | subj.13 |
|---------|--------|--------|--------|--------|---------|---------|---------|---------|
| 2 clusters | 96.1%  | 91.4%  | 98.3%  | 93.9%  | 87.4%   | 95.7%   | 96.1%   | 96.3%   |
| 3 clusters | 77.5%  | 87.1%  | 74.7%  | 71.9%  | 85.3%   | 71.9%   | 83.7%   | 69.3%   |
Chapter 5

Graph averaging as a means to compare multichannel EEG coherence networks and its application to the study of mental fatigue and neurodegenerative disease

Abstract

A method is proposed for quantifying differences between multichannel EEG coherence networks represented by functional unit (FU) maps. The approach is based on inexact graph matching for attributed relational graphs and graph averaging, adapted to FU-maps. The mean of a set of input FU-maps is defined in such a way that it not only represents the mean group coherence during a certain task or condition but also to some extent displays individual variations in brain activity. The definition of a mean FU-map relies on a graph dissimilarity measure which takes into account both node positions and node or edge attributes. A visualization of the mean FU-map is used with a visual representation of the frequency of occurrence of nodes and edges in the input FUs. This makes it possible to investigate which brain regions are more commonly involved in a certain task, by analysing the occurrence of a FU of the mean graph in the input FUs. Furthermore, our method gives the possibility to quantitatively compare individual FU-maps by computing their distance to the mean FU map. The method is applied to the analysis of EEG coherence networks in two case studies, one on mental fatigue and one on patients with corticobasal ganglionic degeneration (CBGD). The method is proposed as a preliminary step towards a complete quantitative comparison, and the real benefit of its application is still to be proven.

5.1 Introduction

Nowadays, many neuroimaging methods are available to assess the functioning brain, such as functional Magnetic Resonance Imaging (fMRI), Positron Emission Tomography (PET), Electroencephalography (EEG) and Magneto-Encephalography (MEG). A recording with one of these imaging modalities provides a measurement of brain activity as a function of time and
position. A more recent innovation is connectivity analysis, in which the anatomical or functional relation between different (underlying) brain areas is calculated [62]. Of particular interest is the comparison of functional brain networks under different experimental conditions, or comparison of such networks between groups of subjects. In the last decade a multitude of topological network measures has been developed [135, 156, 174] in an attempt to characterize and compare brain networks. However, such topological measures are calculated by thresholding, binarizing and symmetrizing the connectivity matrix of the weighted and directed brain network. Thus, spatial information is lost and only global network information is retained. For interpretation and diagnosis it is essential that local differences can be visualized in the original network representation [56, 163]. This asks for the development of mathematical methods, algorithms and visualization tools for the local comparison of complex networks – not necessarily of the same size – obtained under different conditions (time, frequency, scale) or pertaining to different (groups of) subjects.

In this paper, we propose a basis for a local network comparison method for the case of EEG coherence networks. EEG is the oldest noninvasive functional neuroimaging technique. Electrodes, positioned on the scalp, record electrical activity of the brain. Synchronous electrical activity recorded in different brain regions is assumed to imply functional relations between those regions. A measure for this synchrony is EEG coherence, which is computed between pairs of electrode signals as a function of frequency [73, 124]. Visualization aids the interpretation of the experimental results by transforming large quantities of data into visual representations. A typical visualization of an EEG coherence dataset is a two dimensional graph layout (the EEG coherence graph) where vertices represent electrodes and edges represent significant coherences between electrode signals. For multichannel EEG (at least 64 electrodes) [95, 175] this layout suffers from a large number of overlapping edges and results in a cluttered layout. Reorganizing the edges or varying the attributes of the edges without reducing their number can lead to less cluttered visualizations [75, 207]. Also, the positions of the vertices in the layout can be reorganized [65], but in the case of EEG this is not appropriate, because the electrodes have meaningful positions as they relate to brain activity in specific areas.

Another approach to simplify the EEG graph is based on the selection of a small number of electrodes as representative for all other electrodes in a certain region of interest (ROI), which are assumed to record similar signals because of volume conduction effects [67,95,159]. Several researchers have employed a hypothesis-driven selection of markers; this, however, neglects individual variations and does not make optimal use of the available information. An alternative is a data-driven approach where electrodes are grouped into functional units (FUs), which are defined as spatially connected cliques in the EEG graph, i.e., sets of electrodes that are spatially close and record pairwise significantly coherent signals [179]. A representation of the FUs in an EEG recording is called a FU-map; see Figure 5.3 for a simple example. FU-maps can be used as a preprocessing step for conventional analysis.

In EEG research, several datasets are usually compared in a group analysis, for which several methods exist. Obviously, multiple FU-maps can be compared visually when displayed next to each other, but this method is limited as humans are notoriously weak in spotting visual differences in images. In this paper we propose a method for comparing several FU-maps which is more quantitative, although it still involves visual assessment to a certain degree. Our method is
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based on inexact graph matching for attributed relational graphs [30] and graph averaging [32]. In our work we introduce a modification of the algorithm proposed in [32] to obtain a mean FU-map, given a set of FU-maps corresponding to different subjects or different experimental conditions. The basic assumption underlying our work is that the position of the electrodes on the scalp is fixed for all the subjects and that the same projection is used to create the two-dimensional FU representations. Our approach gives the possibility to quantitatively compare individual FU maps by computing their distance to the mean FU-map. Although our method was specifically designed for EEG coherence network comparison, we believe it to be of sufficient generality to be extended to other types of networks as well.

A preliminary version of this paper appeared in [43]. Here we expand on this by studying the robustness of the method for changes in parameters and by applying the method in two case studies, one on mental fatigue and one on patients with corticobasal ganglionic degeneration (CBGD). These case studies show the potential of our method for large data sets, and also reveal a number of limitations of the current method, which we discuss in Section 5.5.

The main contributions of this paper are:

- The definition of a graph dissimilarity measure for EEG functional unit maps, which takes into account both node positions and node or edge attributes;
- A definition of the mean of two attributed graphs representing FUs, following [32], and its extension to an arbitrary number of such graphs;
- An algorithm for computing the mean of a set of FU-maps, with a quantitative measure of dissimilarity between this mean FU-map and each of the input FU-maps;
- Visualization of the mean FU-map employing a visual representation of the frequency of occurrence of nodes and the average coherence between nodes in the input FUs.
- The applicability of the method is demonstrated in two case studies.

5.2 Related Work

The principal concept in our approach is that of graph matching, that is, the problem to find a one-to-one mapping among the vertices of two graphs (graph isomorphism). This is a very challenging problem and several solutions are available in the literature. Graph matching is an NP-complete problem and thus exponential time is required to find an optimal solution. Approximate methods, with polynomial time requirements, are often used to find suboptimal solutions.

In many cases, exact graph matching is not possible, and one has to resort to inexact graph matching. Bunke and Allerman [30] proposed such a method for structural pattern recognition, where one has to find which of a set of prototype graphs most closely resembles an input graph. This requires some notion of graph similarity. They considered attributed relational graphs [181], where nodes and edges carry labels of the form \((s, x)\) where \(s\) is the syntactic component and \(x = (x_1, \ldots, x_n)\) is a semantic vector consisting of attribute values associated with \(s\). Their similarity notion was defined in terms of graph edit operations (deletion, insertion, and substitution of nodes and edges) by which one graph can be (approximately) transformed to another one. The costs apply both to the syntactic and semantic part. The optimal inexact match was then defined
as the inexact match with minimal graph edit distance. These notions were used by Bunke & Kandel [32] and Bunke & Günter [31] to define the **weighted mean** of a pair of graphs \( G, G' \) as a graph \( G'' \) such that \( d(G, G'') = (1 - \gamma)d(G, G') \) and \( d(G'', G') = \gamma d(G, G') \), where \( d(\cdot, \cdot) \) is the graph edit distance and \( 0 \leq \gamma \leq 1 \). It was shown how to compute the weighted mean graph based on the algorithms for graph edit distance computation. Bunke & Günter [31] also introduced **median graphs**, which were further studied in [87]. Building upon this, Jain and Obermayer [80] proposed the sample mean of graphs.

Another area in which graph comparison plays a role is that of graph animation. For example, Diehl et al. [51] consider drawing of dynamic graphs where nodes can be added or removed in the course of time. This problem is simpler than ours since in graph animation a significant fraction of nodes and edges in different time frames do not change and can be identified a priori. So the graph matching problem does not arise here.

A different approach for comparing multiple FU-maps for EEG coherence was proposed in [179]. First a mean EEG coherence graph was computed, i.e., the graph containing the mean coherence for every electrode pair computed across a group. Then a FU-map was created for this mean EEG coherence graph just as for a single EEG graph. Such a mean-coherence FU-map is meant to preserve dominant features from a collection of individual EEG graphs. Nevertheless, this approach has some drawbacks. Most importantly, individual variations are lost in such a map. Hence one still would have to visually compare individual FU-maps to the mean-coherence FU-map, and so the need for a quantitative method for comparing FU-maps remains.

### 5.3 Methods

Given an EEG coherence graph, a functional unit (FU) represents a spatially connected set of electrodes recording pairwise significantly coherent signals (for the definition of significance, see [73]). The **intra-node coherence** of a FU is defined as the average of the coherences between the electrodes in the FU. Given two FUs, the **inter-node coherence** is the average of the coherences between all electrodes of the first FU and all electrodes of the second FU. FUs are displayed in a so-called **FU-map**. This is a derived graph, in which the nodes, representing FUs, are located at the barycenter of the electrodes in the FU, while edges connect FUs if the corresponding inter-FU coherence exceeds a threshold based on the significance of the coherence. To determine spatial relationships between electrodes, a Voronoi diagram is employed with one electrode in each Voronoi cell. Note that the FU-map preserves electrode locations. The choice of the threshold on the coherence is the only source of variability in the computation of the FU-map. We refer to [179] for a detailed description of the computation of coherence and its significance. An example of a FU-map is given in Figure 5.3, where two FUs are connected by a link if the average coherence between them exceeds a threshold, which was set to 0.22, corresponding to a confidence level of 0.99 [179].
5.3.1 Matching of two attributed graphs

A FU-map $A$ can be represented as an attributed graph $G_A$, that is, a graph where nodes and edges are equipped with attributes. The nodes in this graph $G_A$ correspond to FUs of $A$, and two nodes of $G_A$ are connected by a link if the average coherence between the corresponding FUs exceeds the significance threshold. Each node $m$ of $G_A$ is equipped with the following information: (i) the set of electrodes of the FU corresponding to $m$; (ii) the position of the barycentre of these electrodes; (iii) the intra-node coherence of the FU corresponding to $m$. The weights of the edges between two nodes $m$ and $n$ of $G_A$ represent the inter-node coherence between the two FUs of $A$ corresponding to $m$ and $n$. When $m$ is a node in the graph $G_A$, the FU corresponding to $m$ is denoted by $FU_{m,A}$, and an electrode $i$ in this FU is referred to as $FU_{m,A}(i)$. Also, by the “position” of a node $m$ we mean the position of the barycentre of the electrodes in $FU_{m,A}$.

The problem of comparison among FU-maps is thus reduced to the comparison of attributed graphs. From now on, we will tacitly identify FUs of a FU-map $A$ and nodes of the attributed graph $G_A$ representing these FUs. Therefore, instead of “graph $G_A$” we will simply write “graph $A$”, and when $m$ is a node of $G_A$, instead of “electrodes of the FU corresponding to $m$” we will say “electrodes of $m$”. Also, by “graph” we will always mean “attributed graph”.

Let $A$ and $B$ be two FU-maps we intend to match. In general, the number of FUs in $A$ will be different from that in $B$ and also their positions could differ. Furthermore, the number of edges in $A$ and in $B$, and their weights, are generally expected to be different. To be able to quantify the difference between $A$ and $B$, our first goal is to find the best possible match between the nodes of $A$ and those of $B$, i.e., to determine which nodes of $A$ correspond to which nodes of $B$. Secondly, given this match we quantify the difference between the two graphs by a dissimilarity measure, which is based on the matching of the two attributed graphs.

Definition 1 (Matching of two graphs). Given a graph $A$ with $M$ nodes and a graph $B$ with $N$ nodes, where $M \leq N$, we call $\tilde{A}$ the extension of $A$ obtained by adding $N - M$ nodes to $A$. A matching between $A$ and $B$ is a bijective function $\text{match} : V_{\tilde{A}} \rightarrow V_B$ which assigns any node of $\tilde{A}$ to a node of $B$ and vice-versa.

With a finite sequence of addition and shifting of nodes we can transform any attributed graph $A$ to any other graph $\tilde{B}$ via its extension $\tilde{A}$. Assigning a cost to each of these operations allows us to quantify the total cost of the transition from $A$ to $B$. Intuitively, in the case of a FU-map comparison both the spatial position of nodes and the number of common electrodes between nodes in two different FU-maps determine the costs. Therefore we use the following criteria for assigning costs.

Given a node $m$ in graph $A$ and a node $n$ in graph $B$, we define their spatial distance $D(m, n)$ as the 2D Euclidean distance between their positions. Next, this distance is normalized to the interval $[0, 1]$ by scaling it to the maximum possible distance in a FU-map. Note that the position of the electrodes in an EEG is fixed between successive recordings, so measuring Euclidean distances of two points in two different FU-maps is justified. We also define an overlapping distance, the Jaccard distance [79], that describes dissimilarity of two FUs $m$ and $n$ according to the number of common electrodes. We recall here that for any two sets, their Jaccard distance is
defined as one minus the cardinality of their intersection over the cardinality of their union. So,
\[
J(m, n) = 1 - \frac{|FU_{m,A} \cap FU_{n,B}|}{|FU_{m,A} \cup FU_{n,B}|}
\]
Note that \(J(m, n) \in [0, 1]\). Now we can define several costs related to node operations.

**Definition 2 (Cost of node operations.)** The cost of shifting a node \(m\) in \(A\) to match a node \(n\) in \(B\) is defined as the weighted mean between their spatial distance \(D(m, n)\) and their Jaccard distance \(J(m, n)\).

\[
C_{m,n}^S = \lambda J(m, n) + (1 - \lambda) D(m, n), \quad (5.1)
\]
where the weight factor \(\lambda\) satisfies \(\lambda \in [0, 1]\). The cost of adding a node \(\tilde{m}\) to \(A\) is set to the maximum cost of 1. The total cost of the matching of \(A\) to \(B\) is defined as the sum of the costs of the single operations applied to \(A\).

Note that \(0 \leq C_{m,n}^S \leq 1\). Unless stated otherwise, \(\lambda\) was set to 0.5 in our experiments.

It is easy to see that there is more than one sequence of operations that maps \(A\) to \(B\). Since the solution is not unique, we define the optimal matching between \(A\) and \(B\) as the cheapest matching (lowest total cost) from the nodes of \(A\) to the nodes of \(B\). If there exists more than one optimal matching one of the cheapest solutions is chosen arbitrarily. We verified that the multiplicity of the solutions is generally caused by the multiplicity of the matchings of FUs that are in \(\tilde{A}\) (and not in \(A\)) to FUs in \(B\). Thus, all the cheapest solutions yield the same matching of the FUs in \(A\) and the FUs in \(B\).

**Definition 3 (Dissimilarity measure between two graphs.)** Given two graphs \(A\) and \(B\), let \(A\) be the graph with the smallest number of nodes. The dissimilarity \(\delta(A, B)\) between \(A\) and \(B\) is defined as the total cost of their optimal matching.

Given an optimal matching between \(A\) and \(B\) we can now define their mean graph \(C\).

### 5.3.2 Mean of two attributed graphs

We start from two FU-maps represented by attributed graphs \(A\) and \(B\) with \(M\) and \(N\) nodes respectively, where we assume without loss of generality that \(M \leq N\), and an optimal matching between the two. To make the definition general we allow that either \(A\) or \(B\) is already the result of an earlier graph averaging operation (we need this in Section 5.3.3 below). Each electrode \(e\) in a graph \(A\) has an attribute multiplicity, denoted by \(mult_A(e)\), which indicates how often the electrode occurs in the graph \(A\). If \(A\) represents a single FU-map then \(mult_A(e) = 1\). If \(mult_A(e) > 1\) this means that the same electrode \(e\) occurs in more than one of the graphs of which \(A\) is the average. Similarly, an additional node attribute occurrence is introduced, indicating how many times a node \(m\) occurs in a (possibly averaged) graph \(A\); we write \(occ_A(m)\) for this occurrence. If \(m\) is a node in a graph \(A\) corresponding to an individual FU-map, we set \(occ_A(m) = 1\).

Now we define the mean graph \(C\), denoted by \(C = [A, B]\), as follows.
Algorithm 5.1 MEAN OF TWO ATTRIBUTED GRAPHS

1: INPUT: graph $A$ with $M$ nodes and extension $\tilde{A}$, graph $B$ with $N$ nodes, $M \leq N$, and the optimal matching $\mathcal{M}^*$.
2: OUTPUT: mean FU-map $C'$
3: initialize an empty graph $C$
4: for all $n \in B$ do
5:   create a node $k$ in $C$ at the position of $n$
6:   $occ_C(k) \leftarrow occ_B(n)$
7:   $m \leftarrow \text{match}^{-1}(n)$ \{ $m$ is the node matching to $n$ \}
8:   if $m \in A$ then
9:      $occ_C(k) \leftarrow occ_C(k) + occ_A(m)$
10:     move the position of $k$ halfway between the position of $m$ and $n$
11:    intra_coh_k \leftarrow \text{average coherence between the electrodes in } m \text{ and the electrodes in } n$
12:    for all electrodes $e$ of $m$ do
13:       for all electrodes $e'$ of $n$ do
14:          $mult_C(e) \leftarrow mult_C(e) + mult_A(e)$
15:          $mult_C(e') \leftarrow mult_C(e') + mult_B(e')$
16:          if $e$ is not yet assigned to a node of $C$ then
17:              assign $e$ to node $k$
18:          else \{ let $h$ be the node of $C$ to which $e$ is already assigned \}
19:              if $h \neq k$ and $intra_coh_k > intra_coh_h$ then
20:                 reassign $e$ to node $k$
21:          if $e'$ is not yet assigned to a node of $C$ then
22:              assign $e'$ to node $k$
23:          else \{ let $h$ be the node of $C$ to which $e'$ is already assigned \}
24:              if $h \neq k$ and $intra_coh_k > intra_coh_h$ then
25:                 reassign $e'$ to node $k$
26:    for each pair of nodes $k, h$ in $C$, $k \neq h$ do
27:       weight of edge $(k, h) \leftarrow \frac{1}{2} \text{ (coherence between the electrodes of } k \text{ and } h \text{ which correspond to } A \text{ + coherence between the electrodes of } k \text{ and } h \text{ which correspond to } B)$
28: return $C$

1. If a node $m$ in $A$ matches a node $n$ in $B$, the occurrence of the corresponding node $k$ in $C$ is computed by $occ_C(k) = occ_A(m) + occ_B(n)$, and the position of $k$ is the average of the positions of $m$ and $n$.
2. If a node $\tilde{m}$ was added to $A$ to match a node $n$ in $B$, we set $occ_A(\tilde{m}) = 0$, so that the occurrence of the corresponding node $k$ in $C$ equals $occ_B(n)$, and we let the position of $k$ be the position of $n$.
3. The intra-node coherence of a node $k$ in $C$, corresponding to a node $m$ in $A$ matched to a node $n$ in $B$, is defined as the average coherence between the electrodes in $m$ and the electrodes in $n$ (excluding electrodes which are common to $m$ and $n$, i.e., self-coherences are not taken.
into account).

4. A node $k$ in the graph $C$, corresponding to a node $m$ in $A$ matched to a node $n$ in $B$, has as attribute the electrodes of $m$ and the electrodes of $n$. The multiplicity of an electrode $e$ is the sum of the multiplicities of $e$ in $A$ and in $B$: $\text{mult}_C(e) = \text{mult}_A(e) + \text{mult}_B(e)$. However, if an electrode $e$ of $m$ or $n$ was already assigned to another node $h$ of $C$ in a previous step of the algorithm, then this conflict is resolved by (re)assigning electrode $e$ to the node with the highest intra-node coherence (i.e., $k$ or $h$).

5. The weight of an edge between nodes $k$ and $h$ of $C$ is the average of the coherence between the electrodes of $k$ and $h$ which correspond to $A$, and the coherence between the electrodes of $k$ and $h$ which correspond to $B$.

The pseudo-code for the creation of the mean graph $C$ is given in Algorithm 5.1. Note that the graph average is a commutative operation, i.e., $[B, A] = [A, B]$.

The graph $C$ is visualized in the same way as for the input FU-maps $A$ and $B$. That is, the nodes and edges are superimposed on the Voronoi diagram associated to electrode positions (which are common to $A$ and $B$). Electrodes which do not belong to one of the input graphs $A$ and $B$ will be drawn as empty Voronoi cells. The result, when drawn in the plane in this way, will be referred to as the “mean FU-map”.

To illustrate how the average of two FU-maps is computed, we show two synthetic FU-maps $A$ and $B$ and their average $C$ in Figure 5.1. In this example each synthetic FU-map contains only 9 electrodes (note that the cells in which the electrodes are located are only drawn schematically, i.e., they are no real Voronoi cells). Only three FUs are present in each FU-map: $A_1$, $A_2$ and $A_3$ in $A$, and $B_1$, $B_2$ and $B_3$ in $B$. Each FU has a different colour. Its barycenter is represented by a coloured circle, and its cells are coloured with a less saturated version of the same colour. Note that the circles representing the barycenters can be located outside the FU in case this has a concave shape. In $C$, we assume that the optimal matching matched $A_1$ with $B_1$, $A_2$ with $B_2$, and $A_3$ with $B_3$. We also see that because $A_1$ and $B_1$ have two electrodes in common, those are coloured with a more saturated red. The same holds for $A_3$ and $B_3$. The central electrode, belonging to $A_3$ and to $B_1$, was eventually assigned to $C_1$ instead of to $C_3$ because the intra-node coherence of $C_1$ was higher than the intra-node coherence of $C_3$.

### 5.3.3 Generalized mean graph

When more than two subjects are involved in an EEG experiment the need of defining an average among several FU-maps arises. Such an average can be defined as a direct extension of the average of two graphs previously defined.

First we extend the definition of the average of two attributed graphs $A$ and $B$ by including a weighting factor $\mu$: we write $C = [A, B]_\mu$ for the weighted average graph. Item 1 and 5 in Section 5.3.2 are adapted as follows. The position of a node $k$ in $C$, resulting from the matching of a node $m$ in $A$ with a node $n$ in $B$, is obtained by weighting the position of $m$ by $1 - \mu$ and the position of $n$ by $\mu$ (line 10 of Algorithm 5.1). Accordingly, when computing the edge weights in line 27 of Algorithm 5.1, the FUs in $A$ are weighted by $1 - \mu$ and the FUs in $B$ by $\mu$. 
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Definition 4 (Average of multiple attributed graphs.) Let $A_1, A_2, ..., A_n$ be $n$ attributed graphs. The average $\hat{A}_n$ of these $n$ graphs is recursively defined by:

$$\hat{A}_2 = [A_1, A_2]_\frac{1}{2}$$

$$\vdots$$

$$\hat{A}_n = [\hat{A}_{n-1}, A_n]_\frac{1}{n}$$

This definition entails that for two graphs the weighting factor is $\frac{1}{2}$, i.e., equal weighting. But when the average graph is computed between $\hat{A}_{n-1}$, which itself is an average of $n - 1$ graphs, and the last graph $A_n$, the former is weighted by $1 - 1/n$ and the latter by $1/n$.

Defining $\hat{c}_1, ..., \hat{c}_n$ as the costs of the matching corresponding to the computations of $\hat{A}_1, ..., \hat{A}_n$, the dissimilarity $\delta(A_1, A_2, ..., A_n)$ among the $n$ graphs is defined as the mean of the costs $\hat{c}_i$.

Note that the result of the graph averaging operation defined in equation (5.2) depends on the order of the input graphs, i.e., it is not associative. This is due to the following. When the FUs corresponding to two nodes in different FU-maps overlap, their common electrodes are assigned to the node with the highest intra-node coherence. Thus, when computing the graph average, nodes with low intra-node coherence could be reduced in size, or even disappear, depending on the order of processing.

Therefore, we consider all possible permutations of the $n$ input graphs. Actually, we need only to consider half of all $n!$ permutations, since averaging two graphs is a commutative operation. A permutation $P$ for which the dissimilarity $\delta(A_{P(1)}, A_{P(2)}, ..., A_{P(n)})$ is minimal is an optimal permutation and is used to compute the average graph.

5.3.4 Robustness

Robustness of the algorithm was assessed by studying the effect of the variation of the parameter $\lambda$ (see Eq. 5.1) in the computation of the mean FU-map, as shown in Figure 5.5. Values of $\lambda$ in
the range from $0.35 - 0.65$ were considered, with steps of 0.05, and results for the dissimilarities between the FU-maps in Figure 5.4 are shown in Figure 5.2. We observe that values of $\lambda$ in the range $(0.45, 0.6]$ do not influence the relative dissimilarity between the input FU-maps and the mean FU-map. E.g., the FU-map with smallest dissimilarity to the mean FU-map for $\lambda = 0.5$ also has the smallest dissimilarity for $\lambda \in (0.45, 0.6]$. We conclude that the results are not very sensitive to the exact choice of $\lambda$ when restricted to the indicated interval.

**Figure 5.2.** Dissimilarity between the FU-maps shown in Figure 5.4 and their mean graph, for values of $\lambda$ in the range $0.35 - 0.65$. Colours represent dissimilarities of different graphs. Graphs A-E in Figure 5.4 are represented by red, green, blue, cyan, and magenta, respectively.

### 5.4 Results

Five EEG data sets, recorded using 128 electrodes, were selected from a P300 experiment in which the participants had to count target tones of 2000 Hz, that were alternated with tones of 1000 Hz. The alpha frequency band (8-12 Hz) was considered for the computation of the FU-maps; please refer to [179] for details.

Figure 5.3 shows the FU-maps of two subjects $A$ and $B$ (out of the five), their mean FU-map $C$, and the dissimilarities between $A$ and $C$ and between $B$ and $C$. Figure 5.4 shows the FU-maps of all five subjects. FU-maps $A$ and $B$ of Figure 5.4 are the same as in Figure 5.3. Figure 5.5 shows the average of the FU-maps shown in Figure 5.4, and Table 5.1 shows the dissimilarities between the FU-maps in Figure 5.4 and their mean FU-map.

The visualization of the average graphs contains two types of information: the graph nodes and edges, and the Voronoi cells corresponding to the electrodes. Nodes are represented as circles and edges as line segments. The colours of the circles are based on a four-colouration of the graph. Cells are drawn in the same colour as the node they belong to, but in a less saturated version. The saturation is proportional to the multiplicity of a cell. White cells do
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Figure 5.3. Two FU-maps, A and B, and their average FU-map C. Spatial clusters of coloured cells correspond to FUs, white cells do not belong to any FU. Circles represent the barycentres of the FUs and are connected by edges whose colour indicates their inter-node coherence. In C, colour saturation is proportional to the multiplicity of a cell (electrode) in a graph node, and the size of the nodes reflects their occurrence in the input graphs. Only statistically significant edges are included. Dissimilarities between A/B and C are shown.

Table 5.1. Dissimilarities between the graphs shown in Figure 5.4 and their mean graph, shown in Figure 5.5.

| graph | A       | B       | C       | D       | E       |
|-------|---------|---------|---------|---------|---------|
| δ     | 4.312   | 4.076   | 5.283   | 4.465   | 5.177   |

not belong to any node. The size of a circle is proportional to the occurrence of that node in the input graphs. That is, when computing the mean among several graphs this size will indicate how many of the input graphs the node belongs to. The edges of the graph represent the statistically significant [73] coherences between pairs of nodes; the coherence value is mapped to the colour of the edges. Note that the mean FU-map differs from an ordinary FU-map by the visual enrichments related to node occurrence and cell multiplicity, which represent variations of the input FUs.
Given the usually small number of nodes in the input graphs, computing the optimal matching can be achieved using brute force. The computational time requirements of the exploration of all the possible matchings are $O(N!)$ with $N$ the maximum number of nodes in $A$ and $B$, and for $N = 10$ it can be performed in roughly 10 s on a modern PC. The determination of the generalized average graph is achieved by evaluating all possible permutations of the graphs. The total time complexity is thus $O(n!N!)$ with $n$ the number of graphs. Computing the average of the 5 graphs in Figure 5.4 took roughly 3 min.

### 5.5 Case studies

As mentioned in the introduction, the method presented here is expected to be of particular relevance for comparison of functional brain networks under different experimental conditions or for comparison of such networks between groups of subjects. To test this expectation we have submitted the data of two previously recorded EEG datasets to the analysis proposed in this paper.

Electrical brain activity measured by EEG is rhythmical. Several frequency bands are recog-
nized (delta, theta, alpha, beta, gamma), although there is no clear consensus on the boundaries between them. For our experiments, we used the following definition of frequency bands: 1-3Hz (delta), 4-7Hz (theta), 8-12Hz (alpha), 13-23Hz (beta), 24-35Hz (gamma) [139, 176].

5.5.1 Study on Mental Fatigue

Brain activity was recorded from a group of five healthy participants between 19 and 24 years old, using an EEG cap with 59 scalp electrodes. The subjects participated in an experiment in which a task switching paradigm was used to study the effects of mental fatigue on cognitive control processes [117, 118, 178].

The aim of the current analysis is to indicate ROIs and coherences of interest between these ROIs when no strong hypothesis can be formulated based on existing evidence.

During the experiment, coloured letters (vowels and consonants) were displayed at different positions of a screen, and the participants were requested to make a left or right button press depending on the position, colour and identity of the displayed letters, as quickly and accurately as possible. The task switched from colour to letter identity every second trial. The task was performed continuously for 120 minutes. Six blocks of 20 minutes each were used for the analysis. Because effects of mental fatigue are supposed to be more pronounced in conditions where relatively high demands are placed on cognitive control processes [118], analysis was further restricted to switch trials. To examine the effects of mental fatigue, brain responses during the first block and brain responses during the last block of 20 minutes were compared. For a detailed description of the experiment, please refer to [117, 178].

\[1\]These subjects are different from those in [178].
5.5.2 SEP study in CBGD

In the second dataset we used somatosensory evoked potential (SEP) data to investigate the cortical response to electrical stimulation of the median nerve at the wrist, obtained in patients with corticobasal ganglionic degeneration (CBGD) and healthy age-matched controls. CBGD is a progressive neurodegenerative disease involving the cerebral cortex and the basal ganglia, and patients are characterized by marked disorders in movement and cognitive dysfunction.

Five subjects (two males, mean age: 66, std. dev. 6.5 years) were chosen from a population of patients suspected to have CBGD. The subjects were recruited from the Movement Disorder Clinic of the University of Groningen and diagnosis of possible CBGD was based on the criteria proposed by Mahapatra et al. [121] and on a FDG PET scan [52]. Subjects were sitting in a comfortable chair and were instructed to relax and to keep their eyes open. Stimulation of the median nerve at the left wrist was applied 500 times per session for a total of 2 sessions. The stimulus intensity was slightly above motor threshold and produced a small thumb twitch and multichannel EEG was recorded using a 128-electrode cap. Five elderly subjects (three males, mean age: 63, std. dev. 3.2 years) [186] without history of head injury or other neurological conditions were used as controls. For a detailed description of the experiment, please refer to [186].

5.5.3 Experimental Results

Figures 5.6 and 5.7 show FU-maps for each of the participants in the study on mental fatigue, and the average FU map for each frequency band, for the non-fatigued and fatigued condition, respectively. For the SEP study, the results are shown in Figures 5.8 and 5.9, for the control group and the CBGD patients, respectively. In each of the figures, data of the single participants are displayed in rows 1 to 5; each column represents a different frequency band. The bottom row shows the average FU-map for each frequency band. The numbers above each FU-map indicate the dissimilarity between the FU-map and the average FU-map. Visually it can be confirmed that the individual FU-maps with the smallest dissimilarities are indeed most similar to the average FU-map, for both the fatigue and the SEP study. The maximal dissimilarity equals the difference in the number of nodes between the two networks, plus the number of nodes that needed to be shifted. This explains why the dissimilarities in the fatigue study are generally lower than in the SEP study, as there are fewer nodes in the fatigue study networks. In row 6, colours identify different FUs and colour saturation identifies the multiplicity of a cell (electrode) in a FU. Colours are again assigned by applying four-colouration. Note that colouration is random: there is no relation between FUs with the same colours or between the colourings of FUs in different FU-maps. The size of a node reflects its occurrence in the input FU-maps. As in rows 1 to 5, lines identify statistically significant inter-FU coherences. As described in Section 5.3.2, edges in the mean FU-map are computed by averaging the edges of the input FU-maps. If the averaging produces edges that are not statistically significant, these are not drawn.

Table 5.2 shows the dissimilarity (mean and standard deviation) between individual FU-maps and the average FU-map for both the fatigue and the SEP study.

For the fatigue study, in the lower frequency bands where the five participants have similar
FU-maps, the average dissimilarity is smaller than in the higher frequency bands where inter-subject variability is more outspoken. Notice that in Table 5.2, for all frequency bands except theta, the mean dissimilarity with the average FU map is smaller in the fatigued condition than in the non-fatigued condition. In addition, the standard deviation is smaller for the fatigued than for the non-fatigued condition, indicating that the dissimilarities between individual FU-maps and the mean FU-map are more comparable in the fatigued condition. A smaller standard deviation does not mean that the individual maps are more alike, a smaller mean dissimilarity does. These results are in agreement with previous findings indicating that people rely more on automatic task performance when they are fatigued, so that less variability is expected under those circumstances.

In the SEP study, the mean FU-maps show more significant coherences for the CBGD patients than for the healthy controls. The individual FU-maps show coherences for subjects in each of the groups, but the coherence networks seem to be more extended in the CBGD group. The smaller standard deviations in the CBGD group indicate that the dissimilarities between individual FU maps and the mean FU-map are more comparable in the CBGD group. A possible explanation is that the disease process in CBGD, which particularly affects the part of the cortex processing sensory stimulation, is causing the coherence networks to be more extended and more homogeneous in CBGD. In addition, visual inspection shows that the FU-maps are more similar between frequency bands for the CBGD patients than for the controls. These observations suggest that a more focused analysis of the original data concentrating on specific frequency bands could be useful.

### Table 5.2. Mean and standard deviation (std.) of dissimilarities between individual FU-maps and the average FU-map, for each frequency band (Freq.), in the mental fatigue and SEP study.

| Freq. | δ   | θ   | α   | β   | γ   |
|-------|-----|-----|-----|-----|-----|
| non-fatigued mean | 1.42 | 1.62 | 3.47 | 3.57 | 3.56 |
| std.  | 0.43 | 1.28 | 2.03 | 3.75 | 0.94 |
| fatigued mean     | 0.92 | 2.05 | 2.94 | 2.78 | 3.49 |
| std.  | 0.19 | 1.06 | 0.27 | 0.05 | 0.41 |

| Freq. | δ   | θ   | α   | β   | γ   |
|-------|-----|-----|-----|-----|-----|
| controls mean | 3.20 | 4.78 | 6.22 | 6.12 | 3.81 |
| std.  | 2.21 | 0.56 | 5.21 | 2.51 | 1.01 |
| patients mean  | 3.51 | 5.34 | 5.99 | 5.75 | 5.36 |
| std.  | 1.12 | 0.81 | 0.45 | 0.53 | 0.57 |
5.6 Conclusions

We proposed a method based on inexact graph matching for quantifying differences between multichannel EEG coherence networks represented by functional unit maps. We defined a class of cost functions to compute the mean of two attributed graphs representing FU-maps of two subjects and extended the notion of mean graph to the case with multiple subjects. A visualization of the mean FU-map was used with a visual representation of the frequency of occurrence of nodes and edges in the input FUs. A feature of our method is the possibility to locate FUs which are common among all subjects. This may reflect which brain areas are mostly involved in certain tasks. The applications showed that the method can help identify dissimilarities between EEG networks that are obtained under varying conditions or in different groups of subjects.

Currently, our method has a number of limitations. First, the method is proposed as a preliminary step towards a complete quantitative comparison, and its real benefits, including the statistical significance of the network comparisons, still have to be assessed. Second, some of the algorithms in our method perform exhaustive search and have time requirements which are exponential in the number of FUs in the input graphs. This becomes problematic when the number of FU-maps increases. In such cases, a heuristic search approach with polynomial time requirements would be in order. Another issue concerns the four-colouration scheme we use: there is no relation between different FUs with the same colours or between the colours of FUs in different FU-maps. This makes visual comparison in visualizations with many FU-maps less intuitive, but there does not seem to be an easy way to amend this. Some further limitations were revealed by the two case studies we performed. First, when the number of images becomes large, colour saturation is difficult to distinguish between different FU-maps. Also, FU-maps with identical dissimilarity values are not necessarily the same, so visual inspection is still required. Furthermore, the magnitude of the dissimilarity value depends on network size, but this could be addressed by introducing a normalization operation. Finally, and most importantly, it is currently not obvious which parts of the individual maps are responsible for the differences with the average FU-map. It would be very useful if this information could be added to the visualization of the individual maps.
Figure 5.6. FU-maps for the non-fatigued condition. FU-maps from each participant (numbered 1 to 5) were computed for five frequency bands (columns). Average FU-maps for all frequency bands are shown in the bottom row. For explanation of the picture, see caption of Figure 5.3.
5.6 Conclusions

| Freq (Hz) | 1-3  | 4-7  | 8-12 | 13-23 | 24-35 |
|-----------|------|------|------|-------|-------|
| 1         | ![Image](image1) | ![Image](image2) | ![Image](image3) | ![Image](image4) | ![Image](image5) |
| 2         | ![Image](image6) | ![Image](image7) | ![Image](image8) | ![Image](image9) | ![Image](image10) |
| 3         | ![Image](image11) | ![Image](image12) | ![Image](image13) | ![Image](image14) | ![Image](image15) |
| 4         | ![Image](image16) | ![Image](image17) | ![Image](image18) | ![Image](image19) | ![Image](image20) |
| 5         | ![Image](image21) | ![Image](image22) | ![Image](image23) | ![Image](image24) | ![Image](image25) |
| av.       | ![Image](image26) | ![Image](image27) | ![Image](image28) | ![Image](image29) | ![Image](image30) |

Figure 5.7. **FU-maps for the fatigued condition.** FU-maps from each participant (numbered 1 to 5) were computed for five frequency bands (columns). Average FU-maps for all frequency bands are shown in the bottom row. For explanation of the picture, see caption of Figure 5.3.
Graph averaging as a means to compare multichannel EEG coherence networks and its application to the study of mental fatigue and neurodegenerative disease

|     | Freq (Hz) |       |       |       |       |
|-----|-----------|-------|-------|-------|-------|
|     | 1-3       | 4-7   | 8-12  | 13-23 | 24-35 |
| 1   | 2.812     | 4.023 | 5.144 | 3.796 | 3.721 |
| 2   | 4.01      | 5.313 | 6.636 | 6.147 | 4.254 |
| 3   | 3.795     | 5.739 | 9.014 | 8.13  | 5.2   |
| 4   | 4.567     | 4.785 | 3.051 | 5.719 | 2.544 |
| 5   | 1.721     | 4.055 | 7.562 | 6.791 | 3.8   |
| av. |           |       |       |       |       |

**Figure 5.8. FU-maps for the control subjects in the SEP study.** FU-maps from each participant (numbered 1 to 5) were computed for five frequency bands (columns). Average FU-maps for all frequency bands are shown in the bottom row. For explanation of the picture, see caption of Figure 5.3.
|          | Freq (Hz) |          |          |          |          |
|----------|-----------|----------|----------|----------|----------|
|          | 1-3       | 4-7      | 8-12     | 13-23    | 24-35    |
| 1        |           |          |          |          |          |
| 2        |           |          |          |          |          |
| 3        |           |          |          |          |          |
| 4        |           |          |          |          |          |
| 5        |           |          |          |          |          |
| av.      |           |          |          |          |          |

Figure 5.9. **FU-maps for the CBGD patients in the SEP study.** FU-maps from each patient (numbered 1 to 5) were computed for five frequency bands (columns). Average FU-maps for all frequency bands are shown in the bottom row. For explanation of the picture, see caption of Figure 5.3.
Chapter 6

Data-Driven Visualization of Functional Brain Regions from Resting State fMRI Data

Abstract

Functional parcellation of the human cortex plays an important role in the exploration and understanding of brain functions. Traditionally, functional areas are defined according to anatomical landmarks. Recently, new techniques were proposed in the literature that do not require a priori segmentation of the cortex. Such methods allow functional parcellation to be achieved by solely using functional information. We propose here a data-driven approach for the exploration of functional connectivity of the cortex. The method extends a known parcellation method, used in multichannel EEG analysis, to define and extract functional units (FUs), i.e., spatially connected brain regions that record highly correlated fMRI signals. We apply the method to the study of fMRI data and provide a visualization, inspired by the EEG case, that uses linked views to facilitate the understanding of both the location and the functional similarity of brain regions. Initial feedback on our approach was received from four domain experts, researchers in the field of neuroscience.

6.1 Introduction

Parcellation of the gray matter of the human cortex into functionally distinct areas is a key aspect of neuroscience. In the standard approach [60, 68], anatomical landmarks such as sulci and gyri are used to delineate boundaries between areas of interest for the interpretation of functional neuroanatomy, with the default assumption that brain structure reflects functional specialization. Nevertheless, several studies showed that there is a limited correspondence between anatomical boundaries and functional specialization, and often cytoarchitectonic analysis is used as a means to access functional parcellation (e.g., [5]). Another criterion for the identification of functionally different brain areas is the connectivity with other brain regions [94]. A recently developed branch of research uses diffusion imaging to perform parcellation of functional brain regions under the assumption that differences in connectivity patterns should play an important role in identifying functionally different cortical areas [22, 42, 88].
Several approaches have been proposed in the literature for performing gray matter parcellation solely based on functional similarity, i.e., comparing functional activation of different brain regions and studying their interconnections. The most insightful method for such studies consists of analyzing the signals from single brain cells, as often performed in animal studies [137]. This method has a very high spatial resolution, but its application to the simultaneous analysis of several brain regions is difficult. To analyze the whole brain, functional magnetic resonance imaging (fMRI) is the method of choice. This technique has a much lower spatial resolution but allows us to explore the whole brain at once. fMRI analysis detects variations in the BOLD signal, which is an indirect indicator of neurological activity, and is usually based on the study of brain responses to certain stimuli [116]. Obviously, functional comparison between two brain regions is possible only when these respond differentially to the stimuli.

Resting state fMRI, introduced by Biswal et al. [26], is the study of brain activity during cognitive rest [166]. Connectivity studies in resting state conditions revealed that the functional network of the human brain shows a complex structure even when no brain exercise is performed, and shows stable patterns of activity [153, 154]. Variations in BOLD signals that reflect spontaneous physiological activity have been observed, usually below the frequency of 0.1 Hz, in resting state functional networks. Resting state fMRI has recently provided prospects for the understanding of the functional brain.

In this paper, we present a functional parcellation technique that is based on a visualization approach previously developed for EEG data. The original method, introduced by ten Caat et al. [179], aims for the clustering of multichannel EEG networks and has its main strength in the fact that it is totally data driven. Data-driven approaches have the advantage that they do not require any a priori hypotheses about the effects to be expected. Therefore, they are particularly suitable in exploratory phases of research. Also, they can better deal with individual variations, since no assumptions on the location of functional brain areas are made. We extend the method of [179] to the fMRI domain. The method provides the possibility to locate FUs and investigate inter-FU similarities. Compared to the EEG case, major computational and visualization challenges arise due to the fact that much larger graphs have to be processed. Finally, we report on an informal evaluation of the results with medical domain experts.

### 6.2 Related work

Seed-based methods have been the first approach to functional connectivity analysis. Such methods investigate the network of brain regions whose activation correlates with that of a given region of interest (ROI). Although successful, seed-based methods have been shown to provide significant variability with respect to the choice of the ROIs, due to the lack of standard ROI selection procedures [37–39].

To avoid this experimenter bias, several clustering methods have been applied to automatically identify ROIs; examples include hierarchical clustering [37, 59], unsupervised segmentation [69], multivariate analysis [180], and others. A possible solution has been proposed by Salvador et al. [158] and consists of using a priori knowledge, when available, on functional activation and anatomical segmentation to identify ROIs.
So far, independent component analysis (ICA) [100] of resting state data seems to be the most successful technique for localizing functional regions. ICA has the advantage to be data driven, so neither ROI selection nor \textit{a priori} knowledge of functional activation is required. ICA is a method for separating a signal into its independent components, and it has been successfully applied to resting-state as well as task-related fMRI analysis. ICA gained consensus in the neuroscience community and is nowadays the most common technique for the analysis of resting state fMRI. An interesting result achieved by ICA is the ability to extract the so called “default-mode network”, a functional set of brain regions that are active when a subject is not focused on performing tasks. Note, however, that in ICA there is no concept of links between regions, hence the method is not directly comparable to the graph-based technique proposed in this paper.

6.3 Methods

As our method is based on previous work on extracting FU maps for EEG data, we first give an outline of that approach.

6.3.1 Functional Unit Maps for EEG recordings

Functional unit (FU) maps have been introduced by ten Caat \textit{et al.} [179] as a multiscale approach to visualize both local and global similarities in the electrode signals recorded during an EEG experiment.

The method is based on the analysis of a graph, called “coherence graph”, where nodes represent EEG electrodes and edges connecting nodes are weighted by the coherence (correlation at a given frequency band) of the signals recorded at their nodes. The coherence graph is pruned and only statistically significant edges are kept. FUs are computed as maximal cliques in the pruned coherence graph, i.e., as spatially connected sets of nodes that correspond to electrodes registering similar signals. The reason to define FUs as sets of spatially connected nodes is based on the assumption that EEG electrodes which are spatially close usually record signals from a single source as the result of volume conduction [103].

For the computation of the FUs and for the visualization of the results, a notion of neighborhood among electrodes is necessary along with the coherence of the registered signals. Electrode positions are thus projected from the scalp to a horizontal 2D plane, and neighborhoods between electrodes are computed on this plane using a Voronoi tessellation. FUs are computed by an algorithm based on the watershed method [25], whose time complexity is $O(n^2 \log(n))$, where $n$ is the number of electrodes.

The visualization of the FUs and their clustering in an EEG recording is called a \textit{FU map}. An example of such a FU map is shown in Figure 6.1. A FU map is the 2D representation of the scalp, where cells, representing electrodes, are colored according to the FU they belong to. Four-coloration of the FUs is used, so that two contiguous FUs always have different colors.

A FU map shows two kinds of information, both at local and global scale. At a local scale, it shows which neighboring electrodes register similar signals and form the FUs. At a global scale, it shows the similarity between the FUs, defined as the coherence between the average
6.3 Methods

Figure 6.1. FU map for a multichannel EEG recording [179]. Voronoi cells represent EEG electrodes, colored according to the FU they belong to (four-coloration of the FUs is used). White Voronoi cells do not belong to any FU. Circles represent the barycenters of the FUs, and two circles are connected by a link if the average coherence between the corresponding FUs is significant.

signals recorded in two FUs. Similarity between FUs is visualized by using links connecting the barycenters of the FUs, color-coded according to the strength of their similarity. Links are only shown if the average coherence between the corresponding FUs is significant.

Notice that because of the graph pruning, cells exist that do not belong to any FU. These are colored in white. Please refer to [179] for a complete description of the clustering method and its application to multichannel EEG.

6.3.2 FU in fMRI

We provide here first a summary of the steps needed to compute a FU map using functional MRI data. We will describe the details of each step in the next subsections.

The algorithm creates a graph where each node represents a fMRI time series, recorded at a certain position on the brain cortex, and edges are weighted according to the correlations between the time series. We call this a “correlation graph”. The correlation graph corresponds to the coherence graph in the EEG case. FUs are computed on the correlation graph by using the same method as in the EEG case. Results are displayed in two ways. First, the FUs are mapped on a 3D cortical mesh, as this is the representation most familiar to neuroscientists, which are the potential end users of the method. However, drawing edges between FUs on the brain surface would lead to a very cluttered display, due to the very large number of FUs present (note that the spatial resolution of fMRI data is much higher than the spatial resolution of EEG data). Therefore, to ease the exploration of the locations of the FUs, we draw the edges between FUs in a 2D visualization, similar to that of the EEG case, where FUs registering highly similar signals are connected by edges. The 2D and 3D visualizations are presented in a linked view.

The steps of our algorithm for computing FU maps of fMRI recordings are as follows.
1. Downsample an available high-resolution (HR) mesh of the brain cortex to obtain a low-resolution (LR) mesh. Then map the fMRI time series on the LR surface mesh.

2. On the LR mesh:
   (a) Create the correlation graph;
   (b) Compute the fMRI FU map;
   (c) Label the FUs by using four-coloration;
   (d) Map the colored FUs on the cortical mesh.

3. Map the labels of the LR mesh back to the HR mesh.

4. Map the colored FUs to a flattened 2D version of the HR cortical mesh. Draw links between FUs in which, on average, highly correlated (or anti-correlated) fMRI signals were recorded.

5. Display the 3D cortex mesh and the flattened 2D mesh in a linked visualization.

We now discuss these steps in more detail.

### 6.3.3 Mapping of the fMRI data on the cortex mesh

The first step of the algorithm consists of mapping the fMRI signal to the nodes of two cortical meshes, one per hemisphere. We use the cortical meshes provided by CARET, an application for functional and structural analysis of the brain cortex [188]. There are two reasons to use hemicortical meshes instead of one single mesh for the whole brain. First, CARET provides both 3D and 2D versions of the hemicortical meshes.

The 2D version is helpful to visualize all the cortical surface, as the brain cortex is highly folded. CARET is a well known application and its cortical meshes are extensively used in the neuroscience community. Second, using two meshes can speed up computations in case the investigator is only interested in the analysis of a single hemisphere.

The meshes available in CARET represent population-averaged [187] hemicortical surface reconstructions in standard MNI space (see section 6.4.1 for an explanation of MNI space). The meshes consist of $15 \cdot 10^4$ nodes in total, the average distance between two nodes being 1 mm (the value of the mean distance between nodes is computed by CARET, no information of the standard deviation is available).

Voxels in fMRI data have a resolution of 5 cubic mm. The cortical meshes provided by CARET are therefore downsampled to obtain low resolution meshes with $5 \cdot 10^3$ nodes and an average distance between nodes of 4.8 mm. The downsampling allows a better match between the resolution of the mesh and the resolution of the fMRI data, and eases the computation of the FUs since the time requirements of our algorithm increase as $O(n^2 \log(n))$, with $n$ the number of mesh nodes (see section 6.3.1). The downsampling is performed using a tool available in CARET. It is important to note that this downsampling does not affect the topology of the mesh.
Functional MRI data are mapped on the downsampled hemicortical surfaces by using the Gaussian mapping implemented in CARET. This algorithm uses a spatial Gaussian kernel to assign an fMRI time series to each node of the mesh, which is the average time series of the voxels in a neighborhood of the mesh node. We used a Gaussian kernel of 10mm.

Coregistration of single subject’s data to the MNI standard template and spatial Gaussian smoothing of the data are both fundamental steps in the standard fMRI analysis, to be performed before any analysis on the data. The registration steps allow the comparison of multiple datasets and the analysis of results in a standard space. Gaussian smoothing reduces the signal-to-noise ratio in single voxel time series, and it is a critical step for the comparison of results among subjects. Nevertheless, since both functions and structures are unique in each subject’s data, these operations are approximative and could reduce the accuracy of the subsequent analysis steps. There is no standard way for performing coregistration and smoothing, and different analysis programs use different techniques and/or parameters. A Gaussian kernel of ca. 10mm is, on average, the standard operator for spatial smoothing in fMRI. An alternative to Gaussian smoothing is wavelet denoising [206].

6.3.4 Creation of the correlation graph

In this step we create two graphs, one per hemisphere, in which the vertices represent the nodes in the downsampled cortical meshes and the weight of an edge equals the correlation between the fMRI signals of the nodes of the edge. Edges whose correlation is not statistically significant ($p > 0.05$) are pruned. Cross correlations of fMRI time series, and $p$-values associated with the correlations, are computed in Matlab©. Furthermore, edges whose correlation is lower, in absolute value, than 0.975 (95% of the range in which the correlation is defined) are also pruned. The pruning is necessary to be able to create results consistent with anatomical and functional evidence. Other threshold values were tested and their results are discussed in section 6.5.

The main difference in the creation of the correlation graph, with respect to the creation of the coherence graph in the EEG scenario, is that correlation can assume negative values. The choice of using correlation was driven by the fact that it is possible to register negative correlated (anti-correlated) fMRI signals at two different brain regions. The computation of the FUs in the fMRI domain is performed solely using positive correlations, since the aim of the method is to locate brain regions that work in synchrony. But similarities between FUs are computed by using either positive or negative correlation, with the aim to locate which FUs registered highly correlated, or highly anti-correlated, average signals.

6.3.5 Computation of the fMRI FU map

In this step we compute the FUs, still on the LR meshes. To do this we need both the correlation graphs and a notion of neighborhood for the graph nodes. Neighborhood is implicitly defined in the cortical meshes: two graph nodes are neighbors if the corresponding mesh nodes are vertices of the same polygon (note that CARET provides triangular meshes). The computation of the FUs is performed in Matlab, and takes approximately 15 minutes in total for both hemispheres.
6.3.6 Four-coloration of the FU map

FUs are labelled using a four-coloration of the FU map of each hemisphere, so that neighboring FUs are labelled differently. Four different gray values are used as labels, and are assigned to the nodes belonging to the FUs so that all mesh nodes in a FU are colored with the same gray value.

Like in the EEG scenario, there could be nodes that do not belong to any FU. Although cells unassigned to FUs are colored in white in the EEG case, in the fMRI case we use black to color such unassigned mesh nodes. The reason for this choice is that we will eventually use Phong lighting in the visualization of the 3D cortical meshes, and the detection of anatomical landmarks such as sulci and gyri (both used to provide context and ease the detection of the FUs) could be difficult in black regions.

To improve the visualization of the results, the next step is to map the FU labels to the original high resolution cortical meshes.

6.3.7 High-resolution FU map

In this step we map the labels of the mesh nodes from the low resolution meshes back to the original high resolution hemicortical meshes provided by CARET. This operation is performed in two steps. The first step is a “one to one” mapping from each node in the low-resolution mesh to its closest node in the high-resolution mesh. Step two is a labeling of the remaining nodes in the high resolution mesh. This step is performed by using a watershed method: the flooding algorithm uses each node which was labeled in the first step as a basin marker and propagates the labels along the mesh surface [179]. The mapping of the FUs to the high-resolution map is not strictly necessary, but it produces a visualization that the final users are more comfortable with and in which the locations of cortical regions are more easily accessible.

6.3.8 Creation of the 2D map with FU edges

As for the EEG scenario, an important feature of our visualization is the possibility to investigate inter-FUs similarities. This goal is achieved by drawing edges that connect those FUs that registered highly correlated average signals. We draw the edges only in a 2D view, because drawing them in the 3D view would lead to a cluttered display. The 2D representation of the cortical meshes is a flattened version of the 3D meshes produced by CARET. An edge between two FUs is drawn when the correlation of the average signal in the nodes of the first FU and the average signal in the nodes of the second FU is bigger than the threshold used for pruning the correlation graph.

Edges are colored according to the value of the correlation using two colormaps: one for the positive correlations and one for the negative ones. The vertices of the edges between FUs are the barycenters of the FUs, which are visualized by small red circles that serve as identifiers for the FUs (cf. Figure 6.5). If a FU has a concave shape, i.e., its barycenter falls outside the FU, the FU is represented by a cell of the FU that is nearest to the position of the barycenter. In this case, edges connecting that FU to other FUs leave from that cell.
The visualization of the flattened version of the meshes is paired with a linked visualization of the 3D cortical meshes, and interaction between the two visualizations is possible. The user can interactively check which areas in the flattened cortical meshes correspond to which areas in the 3D meshes by means of a pointer that shows the correspondence.

### 6.4 Experimental results

#### 6.4.1 Data acquisition and preprocessing

A resting-state fMRI dataset (single subject, healthy, male, 30 years old) was selected from an experiment in which the participants were requested to rest with their eyes open in the MRI scanner and fixate a crosshair projected on the monitor. The data were registered to the MNI brain [27] (the standard average brain used as a reference for comparing brain scans of different subjects). A low-pass filter was subsequently applied to remove fMRI signals with frequency higher than 0.1 Hz. Both registration and filtering are standard preprocessing steps in fMRI resting state analysis, and were performed using FSL [168], a library of analysis tools for brain imaging data.

#### 6.4.2 Results

The first step of the algorithm is illustrated in Figure 6.2, which shows the differences between the original cortex mesh (on the left) and the downsampled mesh (on the right).

![Figure 6.2](image)

*Figure 6.2. The original CARET mesh (left) for the left hemisphere, and the corresponding downsampled version used to map the fMRI signal (right). The mesh on the left has $7.5 \cdot 10^4$ nodes, the mesh on the right has $2.5 \cdot 10^3$ nodes. Edges between mesh nodes are represented by segments whose greyscale values vary according to the sulcal depth.*

Figure 6.3 shows an example of the FU maps represented on the low-resolution mesh. Notice how the low number of polygons in the cortical mesh in the figure prevents the user to clearly
**Figure 6.3.** Four-coloration of the FU map for the low-resolution mesh. Black nodes do not belong to any FU. The mesh is rendered using Gouraud shading.

**Figure 6.4.** High-resolution FU maps, seen from different viewpoints. Top row, from left to right: top view, front view, back view; bottom row, from left to right: right view, left view, color labels (black is used for nodes that do not belong to any FU). Mapping the FU labels from the low-resolution meshes to the original high resolution meshes allows the user to better localize the FUs in the anatomy. The high resolution cortical meshes are colored with the FU labels and shaded using Phong lighting on the GPU.

identify most of the anatomical landmarks in the mesh. Figure 6.4 shows an example of a high-resolution FU map seen from different viewpoints.

Figure 6.5 shows the linked view of the 2D and 3D representations of the FU maps. On top,
the meshes are visualized in 3D and shaded using Phong lighting for optimal quality. FUs, sulci and gyri are clearly visible, as the user is able to change the point of view. It is also possible to visualize one single hemisphere at a time and examine the FUs in the interhemispheric fissure (the gap between two hemispheres). The bottom part of the figure shows the two (individually) flattened brain hemispheres and the edges between the FUs. Colormaps for positive and negative correlations are displayed on the right. Note that for this dataset all the edges carry positive correlation values, since after thresholding no negative correlations between signals registered in the FUs remained.

6.5 Feedback from domain experts

To evaluate the potential of our method we conducted interviews with four medical domain experts, researchers in the field of neuroscience. One of the participants was familiar with the visualization of FU maps in the EEG domain. The aim of the study was the validation of the results via comparison of the location of the FUs to the location of known functional or cytoarchitectonic brain regions, and the validation of the found similarities between FUs. Evaluation of the visualization and its comparison with the visualization of FU maps in the EEG case was also part of the interview.

As a general comment, the domain experts found the results interesting, and they reported that the results were “reasonably symmetrical in the two hemispheres” and that “several FUs follow anatomical landmarks”. They also reported that “several FUs reflect actual functional regions”, but “there are also brain regions where the results diverge from the current functional evidence”.

The experts commented on the consistency of the results with functional and cytoarchitectonic evidence mainly for the following regions. The subdivision in small FUs in the posterior parietal lobe, especially in the left hemisphere, appeared to be consistent both with the functional and cytoarchitectonic differentiation of this region. In the inferior frontal gyrus, the FU map detects a tripartition of Broca’s area (Brodmann’s areas 44, 45, 47) and, consistent with functional evidence, the tripartition is more evident in the left hemisphere (these areas are located around the green dot in figure 6.5, top). A tripartition appears also in the Insula (the grey region in figure 6.5, bottom right, from which five FU edges leave), consistent with functional, cytoarchitectonic, and connectivity evidence. In the occipital lobe, the FUs locate the secondary visual areas consistently with its cytoarchitectonic properties, but the location of the FUs in the medial aspects of the occipital lobe is not fully consistent with functional evidence, especially in the right hemisphere. The subdivision in anterior and posterior regions of the cingulum is also interesting, although this only occurs in the right hemisphere and the FUs in the interhemispheric fissure generally disagree with functional evidence. The middle temporal area is identified in both hemispheres, especially in the left hemisphere. The subdivision in dorsal and ventral parts of the premotor area was also found to be consistent with functional results, although a more defined differentiation along the central sulcus was expected.

The experts stressed the fact that a task-related fMRI analysis would be necessary to completely assess the benefits of the method, since only with such an analysis it is possible to reliably
Figure 6.5. Linked visualizations of the FU map. Top: a 3D rendering of the cortical mesh, shaded using Phong lighting to enhance both the FUs and the anatomical landmarks consisting of sulci and gyri, which are recognizable by neuroscientists. Bottom: the flattened meshes and the edges between FUs that recorded highly correlated fMRI signals. FUs are represented by gray values using the same colormap as in figure 6.4, edges between FUs are colored according to the shown colormaps for positive and negative correlations. In this dataset, no significant negative correlations between FUs were found. The green spheres represent the same spot in the two meshes.

locate functional regions in a single subject analysis. One of the experts suggested that the lack of FUs in the motor areas could be caused by the fact that no motor task was performed. There is apparently no explanation for the lack of FUs in the ventral part of the occipital and temporal
lobes. Another expert proposed that once the real benefits of the method are assessed, a possible application could be a pre-surgery assessment of functional areas when task-related fMRI is not possible, e.g., in the case of coma.

The domain experts were more cautious when commenting on the links between the FUs. They agreed that the information provided by these links could be used as an explorative tool, since it is known that the brain is dynamically active even during resting state conditions, but the extent to which brain regions interact during resting state is still not clear. One of the experts positively commented on the edge connecting the two FUs located on the left and right part of the cingulum, which reflects the structural connectivity of this region. Another one commented on the relatively high number of edges leaving from the Insula in the right hemisphere, suggesting that it could reflect the high structural connectivity this region is known to have with several brain areas. The experts were also expecting to find links between the medial prefrontal cortex, the posterior cingulum and precuneus, the inferior parietal cortex and the medial temporal lobe. This network represents the “default mode network”, as detected by ICA in resting state analysis. Our algorithm does not find this “network”, which actually is not a network but a set of regions determined by ICA. As ICA is not directly comparable with our method, further analysis and consideration of more subjects would be necessary to understand the differences between the outcomes of the two methods.

The experts were satisfied with the possibility, provided by the linked visualization, to compare the 2D and the 3D maps, and all of them agreed that the linked view is essential to provide an intuitive anatomical context. The participant familiar with the visualization of FU maps in the EEG domain found the 2D visualization very intuitive.

A current limitation of the method is the need of setting a threshold for the pruning of the correlation graph. We set this threshold to 95% of the range of correlation, but noticed that changes in the threshold can produce different results. We asked the medical experts to explore FU maps computed using different thresholds. Bigger and fewer FUs are found if the threshold is set to lower values (e.g., lower than 0.95), smaller and more numerous ones are found if the threshold is set higher (e.g., bigger than 0.98). In both cases, the domain experts thought that the FU map did not reflect the functional or cytoarchitectonic evidence. They reported that only small variations occurred when varying threshold values in the range [0.95-0.98].

6.6 Discussion

In this paper we proposed a method, building upon a method previously used in multichannel EEG analysis, that allows the visualization of brain functional connectivity from resting state fMRI data. Since only one subject was used in the experimental part, our method should be considered a “proof of principle” at this stage.

We evaluated the potential of our method by performing interviews with four medical domain experts, whose main interest was the possibility to localize functional and cytoarchitectonic regions by means of resting state analysis alone, i.e., without any focused task and without a priori hypothesis. They were less interested in the possibility to investigate functional similarities between functional units, since they could not compare the results to a ground truth, which currently
is not available. A relation to the “default mode network” obtained by the ICA method could not be established.

As a general conclusion, the domain experts agreed that this method could provide insights in the localization of functional and cytoarchitectonic brain areas via resting state fMRI. Because the precise location of functional areas changes among subjects, a task-related fMRI study could provide further validation of the technique by allowing a better comparison between the location of the FUs and the exact locations of functional brain areas.

Several opportunities for future work exist. First, a continuation of this line of research could be the quantitative comparison of FU maps, using the method proposed in [43]. This method allows the comparison of FU maps among several subjects by detecting both the average functional behavior in the group of subjects and the individual differences. Second, a reimplementation of the algorithm for computing the FUs, e.g., in C/C++, would result in a substantial speedup. Another possibility for future work is to study visualization of functional brain regions by FU maps computed for joint EEG/fMRI data. Such simultaneous measurements have become feasible recently. Another possible improvement could consist of implementing interaction facilities in the linked visualization. These could give emphasis to certain aspects of the visualization, such as brain regions, graph edges, connected graph components, or symmetry across the hemispheres. A user study involving neuroscientists and medical domain experts would be necessary to identify which key features would improve our visualization tool.
Chapter 7

Summary and conclusion

7.1 Discussion

In this thesis we investigated structural and functional brain connectivity by means of DTI, fMRI and EEG analysis. By focusing both on the analysis and on the visualization of the results, we tried to provide techniques that could be useful to improve the understanding of the complex system that is our brain.

In Chapter 2 we extended the application of DTI to the study of auditory pathways in tinnitus patients and controls. We considered DTI tracks that connect the inferior colliculus, the auditory cortex and the amygdala, and vice versa. Such an approach does not identify new connections, but it allows the quantification of properties of known connections in the brain. The first interesting result is the ability to track the classical auditory pathway, as the connections follow the expected pathway of the classical auditory system. In order to summarize the track properties, we computed three quantities for each connection in each subject: the fractional anisotropy, the weighted fractional anisotropy, and the connection strength. Although these three measures are the result of considerable data reduction, they allow for straightforward comparisons between subjects and subject groups. We found a number of differences and similarities between tinnitus patients and healthy controls, and results that indicate that the limbic system may play a major role in tinnitus. For the first time, an anatomical pathway that might function differently between tinnitus patients and normal hearing controls was shown.

In Chapter 3 we introduced an improved tracking technique that allows DTI streamlining to solve low-anisotropy regions and permits branching of trajectories. Our method performs interpolation for any low-anisotropy voxel met during tracking. Interpolation is computed in Log-Euclidean space and collects directional information in a neighbourhood of the voxel in order to reconstruct a tensor with a higher linear diffusion coefficient than the original. Also, in order to resolve multiple fiber orientations, we divide the neighbourhood of the low-anisotropy voxel in 26 sectors, and compute an interpolated tensor in each sector according to our weighted tensor interpolation formula. We tested our method on artificial, phantom and brain data, and compared with existing methods. Because our method can resolve cases of multiple fiber orientations in a single voxel, it can produce results that are similar to those provided by more powerful techniques such as probabilistic tracking with multiple fiber orientations.

In Chapter 4 we proposed the usage of force-directed graph layout as an explorative tool
for connectivity-based parcellation studies, and showed how our method tackles some problems of the techniques proposed in the literature. With a representation of the data that intuitively shows relations among (groups of) seed voxels, our method can be used as an exploratory tool to analyse the dataset and eventually decide to apply a clustering method. The principal application of our method is the definition of the number of clusters in the dataset, which can be localised and enumerated by the inspection of the peaks in the density map and of the iso-density lines. The exploration of the density maps is performed using both the graph layout and the mapping of the densities on the brain, so that hypotheses on the presence of clusters can be verified before running any clustering algorithm. We applied our technique to the study of the premotor cortex and showed that substantial variability among subjects occurs, and that a subdivision into two well separated clusters (as reported in the literature) is not always straightforward.

In Chapter 5 we proposed a method based on inexact graph matching for quantifying differences between multichannel EEG coherence networks represented by functional unit maps. We defined a class of cost functions to compute the mean of two attributed graphs representing FU-maps of two subjects and extended the notion of mean graph to the case with multiple subjects. A visualization of the mean FU-map was used with a visual representation of the frequency of occurrence of nodes and edges in the input FUs. A feature of our method is the possibility to locate FUs which are common among all subjects. This may reflect which brain areas are mostly involved in certain tasks. The applications showed that the method can help identify dissimilarities between EEG networks that are obtained under varying conditions or in different groups of subjects. Our method still has a number of limitations and is proposed as a preliminary step towards a complete quantitative comparison of multichannel EEG networks.

In Chapter 6 we proposed a method, built upon a method previously used in multichannel EEG analysis, that allows the visualization of brain functional connectivity from resting state fMRI data. This method should be considered a “proof of principle” at this stage. We evaluated the potential of our method by performing interviews with four medical domain experts, who agreed that this method could provide insights in the localization of functional and cyto-architectonic brain areas via resting state fMRI.

7.2 Perspectives

The study of the structural and functional behavior of the brain through the application of computer science methods is a fascinating and challenging topic in neuroscience, and will flourish in the next years as technology improves and new and more powerful techniques will allow us to investigate the marvels of our nervous system with more and more accuracy.

I think there are two major factors that could improve the quality of the research in the field of brain visualization. First comes a stronger collaboration between research scientists and medical experts. Neuroscience, intended here as the analysis and visualization of brain connectivity, is a highly interdisciplinary science in which both neurology and computer science play an important role: the expertise from both fields is needed for the generation and verification of high-quality hypotheses. Nowadays we see several scientific works in which clinical relevance is put aside in favour of beautiful visualizations: brain visualization is not an art, but a tool that should serve
the clinical needs. I believe that a strong collaboration between researchers in brain visualization and physicians experienced in the clinical environment would be beneficial for the generation and verification of interesting hypotheses, that could effectively help physicians both to propose a diagnosis and to find solutions. As an example, in Chapter 5 we proposed a visualization method for the comparison of multichannel EEG networks. The proposed visualization is very rich in information, quantitatively and qualitatively, both on the group results and on the individual differences. The method is very interesting per se, but I think that the most interesting results still have to be achieved. Further analysis of the results, detailed comparisons between subjects, and discussions about the medical relevance would yield both new medical hypotheses and improvements of the visualization method.

Second comes the synergy of different techniques: I believe that extensive per subject analysis is necessary to gain knowledge of the human brain. Trying to get the complete picture of the brain’s behavior by using all the available technologies will allow a better understanding of the complex functional and structural networks. Several studies have been proposed on the combination of fMRI and DTI results. Lately, a new branch of research is trying to acquire fMRI and EEG data simultaneously. A combined analysis using DTI, fMRI, EEG, as well as other imaging techniques such as, for instance, PET, SPECT, and CT would allow a better understanding of the brain networks. Also, when a collaboration between research and clinical environments is available, the results of invasive analysis could provide detailed information that would be beneficial to a better understanding of the results. As an example, in Chapter 4 we proposed a parcellation method of the premotor cortex based on DWI analysis. The results showed that a separation between SMA and preSMA is not always straightforward in single subject analysis, and that there is great variability among subjects. It is well known that both preSMA and SMA are easily distinguishable in task-related fMRI and in cyto-architectonic analysis: to understand the parcellation results, and to understand why the variability among subjects occurs, DWI analysis alone is not enough: only a combination of these three acquisition methods would allow a full understanding of the functional and structural differences in the region.
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Samenvatting

Een belangrijk deelgebied binnen de neurowetenschappen wordt bestreken door het onderzoek naar hersenconnectiviteit. In dit proefschrift gebruiken we hersenafbeeldingstechnieken om inzicht te krijgen in twee aspecten van hersenconnectiviteit: anatomische en functionele connectiviteit.

Er is sprake van anatomische connectiviteit tussen twee hersengebieden als er een fysieke verbinding tussen de twee gebieden bestaat. Met fysieke verbindingen in het brein bedoelen we de aanwezigheid van zenuwvezels. Deze kunnen worden gevisualiseerd door middel van DWI (diffusion weighted imaging), een MRI (magnetic resonance imaging) methodologie die gebaseerd is op de meting van de diffusie van water in biologische weefsels. Omdat de diffusie van water in de witte stof van het brein voornamelijk optreedt langs de richting waarin de zenuwvezels lopen, maakt DWI het mogelijk om in vivo onderzoek te doen naar de anatomische connectiviteit van het brein.

We spreken van functionele connectiviteit tussen twee hersengebieden als de functionele reacties van deze gebieden op een zekere stimulus (bijvoorbeeld een visuele, auditieve of tactiele stimulus) statistisch gecorreleerd zijn. Hierbij is de aanname dat een onderlinge afhankelijkheid van functionele reacties in twee hersengebieden inhoudt dat beide gebieden betrokken zijn bij de verwerking van de aangeboden stimulus. Functionele connectiviteit van het brein kan bijvoorbeeld worden onderzocht door middel van technieken zoals fMRI (functionele MRI) of EEG (elektro-encefalografie). Overigens zijn voor dit doel nog vele andere technieken beschikbaar die niet zijn onderzocht in dit proefschrift.

De studie naar hersenconnectiviteit stelt de onderzoeker voor twee belangrijke uitdagingen. De eerste betreft de analyse van beschikbare gegevens met het doel om connectiviteits eigenschappen van het brein te ontdekken, zoals de vraag welke gebieden betrokken zijn bij het verwerken van een bepaalde stimulus, of wat de anatomische overeenkomsten en verschillen zijn tussen een groep patiënten en een controlegroep. De tweede uitdaging betreft de ontwikkeling van algoritmen waarvan de toepassing op bestaande gegevens in het medische domein inzichten oplevert die voorheen niet aanwezig waren.

Hoofdstuk 2 en 4 zijn voorbeelden van onderzoek uit de eerste categorie van uitdagingen. In hoofdstuk 2 bekijken we tinnitus, een auditieve aandoening met als symptoom de perceptie van geluid in de afwezigheid van een geluidsbron. De centrale vraag is of tinnitus samengaat met veranderingen in anatomische connectiviteit. We laten zien dat de aanwezigheid van tinnitus verband zou kunnen houden met verschillen in connectiviteits eigenschappen van de auditieve hersenbanen en van de verbindingen tussen het lymfatische en het auditieve systeem. In hoofdstuk 4 onderzoeken we de overeenkomsten tussen de anatomische en functionele connectiviteit van de premotor cortex, onder de aannames dat het ene type connectiviteit zijn weerslag heeft op het
andere. We laten zien dat anatomische connectiviteit niet altijd de functionele segregatie van dit hersengebied weerspiegelt en dat er aanzienlijke individuele verschillen bestaan in anatomische connectiviteitseigenschappen.

De tweede uitdaging komt aan de orde in de hoofdstukken 3, 5 en 6. In hoofdstuk 3 stellen we een interpolatiemethode voor die een verbetering geeft van DTI (diffusion tensor imaging) tractografie door middel van de detectie van zenuwbundels die zich vertakken in een voxel (volume element). In hoofdstuk 5 beschrijven we een methode voor de kwalitatieve vergelijking van meerdere multikanaals-EEG coherentienetwerken. Deze aanpak maakt het mogelijk om de hersengebieden te vinden die betrokken zijn bij de verwerking van bepaalde stimuli, en stelt ons niet alleen in staat om individuele functionele verschillen te detecteren, maar ook om functionele hersennetwerken te construeren die gemiddeld over een groep van personen weergeven. In hoofdstuk 6 stellen we een methode voor om te detecteren welke hersengebieden vergelijkbare activiteit vertonen in zogenaamde rusttoestand (resting state)-fMRI.

Het onderzoek naar de anatomische en functionele eigenschappen van het brein door middel van methoden uit de informatica vormt een fascinerend en uitdagend onderwerp binnen de neurowetenschappen. Ik vermoed dat hersenafbeeldingstechnieken, een krachtig gereedschap voor het verbeteren van de mogelijkheden voor de diagnose van hersenaandoeningen, een verdere bloei zullen vertonen in de komende jaren. Technologische verbeteringen en nieuwe en krachtiger technieken zullen ons in staat stellen de wonderen van ons zenuwstelsel met toenemende nauwkeurigheid te onderzoeken.
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