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A prediction framework of functional from structural connectomes reveals relationships between NODDI and tensor-based microstructural indices

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Introduction
Predictive modelling of functional connectomes from structural connectomes explores commonalities across multi-modal imaging data [1]. Brain structure not only constrains but also shapes functional connectomes. We exploit this property to devise a statistically sound way, based on a connectivity identification framework. This applies the Randomised Lasso (RL) principle to sparse Canonical Correlation Analysis (sCCA) [2], and transports functional connectomes on a common Riemannian manifold to retain their symmetric positive definite (SPD) geometry [3]. This framework highlights the structural connections that are consistently selected in predicting functional connectomes, across microstructural indices. Fractional anisotropy (FA) and mean diffusivity (MD) are derived from the conventional tensor model, whereas intra-cellular volume fraction (ICVF), orientation dispersion index (ODI), the concentration parameter (Kappa) and the volume fraction of the isotropic compartment (ISO) are derived from a more biophysically plausible model based on Neurite Orientation Dispersion and Density Imaging (NODDI) [4].

Methods
NODDI data were obtained from 19 healthy volunteers on a 1.5T Siemens scanner based on three shells of Diffusion Weighted (DW)-MRI with b=2400smm⁻², b=800smm⁻² and b=300smm⁻² were acquired with 240x240x150mm FOV, voxel size of 2.5x2.5x2.5mm and TR/TE=8300/98ms. Resting-state (rs)-fMRI were acquired: TR/TE=2160/30msec, effective voxel size 4.03.33.3mm, FOV 210x210x120mm. We run probabilistic tractography on the data acquired with b=2400smm⁻², and we obtain the streamlines that connect each pair of cortical FreeSurfer regions. For each pair of regions we average the microstructural indices to obtain brain connectomes based on number of streamlines (NSTREAMS) and weighted averages of FA, MD, ICVF, ODI, Kappa and ISO, fig.1. Functional connectivity matrices are estimated as the normalised inverse of the covariance of the averaged fMRI time-series within each region, fig.2. We learn the relationship between microstructural indices (X) and rs-fMRI (Y) across subjects based on sCCA. sCCA extracts sparse vectors that are multiplied by X and Y.
to maximize their linear relationship. sCCA is applied on vectorised versions of functional and structural connectivity across subjects. However, there is no guarantee that the results from linear operations on the elements of a SPD matrix will also lie on an SPD manifold. A solution is to project each functional connectome into a common tangent space (SPD-sCCA), which is constructed based on the average precision matrix. To alleviate the dependence of the extracted connections on the regularisation parameter we use RL [5].

Results

Based on leave-one-out cross-validation, we demonstrate that SPD-sCCA outperforms trivial sCCA, fig.3. Fig.4 shows the results of RL. Fig.5 shows the pair-wise relationships of micro-structural indices.

Conclusions

Our results demonstrate a strong relationship between FA and ODI, as well as between ICVF and MD. This relationship is also reflected in the pattern of identifiable structural connections that mostly contribute to the prediction of functional from structural connectomes.

Keywords: prediction, sparse sCCA, functional connectomes, structural connectomes, microstructural indices

References

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Fig. 1: Averaged structural connectomes are displayed as three-dimensional graphs mapped in MNI brain space. Their centres and radii represent the location of each region and its volume, respectively. The colour-coding of the spheres corresponds to different parts/lobes of the brain. Structural connections are represented as cylinders with diameter proportional to their weight, scaled independently in each graph.

Fig. 2: Average functional connectomes across all subjects.

Fig. 3: Summary of the prediction performances of trivial sCCA (green violin plots) and SPD sCCA (blue violin plots) for each of the microstructural indices, NSTREAMS, WFA, WMD, WICVF, WODL, WISO and Whappa. Prediction performance is estimated based on the geodesic distance between measured and estimated functional connectomes. Violin plots are a combination of box-plots and kernel density plots, showing the probability density function of the measures. $d_{A1}$ is a distance metric thus the smaller the distance, the better the prediction. SPD sCCA outperforms trivial sCCA across all indices apart from WMD. However, results for WMD are not statistically significant because trivial sCCA only predicts three SPD functional connectomes out of 19 cross-validation loops.
Fig. 4: Identification results for: a-d) NSTREAMS, e-h) WFA, i-l) WMD. First column shows the corrected coefficients for all connections with non-zero values across all subjects. Second column shows the connections that are rejected with a significant p-value<0.05 based on a binomial distribution. The probability of a connection to be selected randomly is defined based on the sparsity of the connectomes and it is equal to 0.04. Third column shows the remaining connections. Fourth column shows the connections that are selected significantly above chance (p-value<0.05) according to a binomial distribution.

Fig. 5: Identification results for: a-d) WICVE, e-h) WODL, i-l) Wkappa and m-p) WISO. First column shows the corrected coefficients for all connections with non-zero values across all subjects. Second column shows the connections that are rejected with a significant p-value<0.05 based on a binomial distribution. The probability of a connection to be selected randomly is defined based on the sparsity of the connectomes and it is equal to 0.04. Third column shows the remaining connections. Fourth column shows the connections that are selected significantly above chance (p-value<0.05) according to a binomial distribution.
Comparing connectivity-based groupwise parcellations generated from resting-state fMRI and DTI data: Preliminary results

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Identification of functional and structural connections within the connectome has gained a lot of attention due to its potential to reveal the brain’s neural organisation in health and disease. A critical stage in connectome analysis is the parcellation of the cerebral cortex into a set of distinctive subregions that can be used as the network nodes. Many studies have used anatomical atlases for this purpose, but recently a number of parcellation techniques have been introduced that are driven by BOLD correlations captured via rs-fMRI and/or tractography connectivity profiles obtained by diffusion tensor imaging (DTI). In this study, we compute groupwise parcellations using two different graphical models, one of which is generated with rs-fMRI and the other is derived from diffusion tractography. We compare parcellations of different modalities to each other in order to understand the effects of the functional and structural connectivity on the generation of cortical parcellations.

We conducted our experiments on a set of 40 healthy subjects from the latest release of the Human Connectome Project (www.humanconnectome.org). Structural, functional, and diffusion datasets for each subject have been preprocessed and denoised by the HCP minimal preprocessing pipelines [1]. Parcellations are computed using a novel technique based on joint spectral decomposition [2]. A multi-layer graph is constructed across a group of subjects in which subject-specific connectivity is decoded in spatially constrained correlation networks and cortical surfaces are mapped to each other based on the similarity of their connectivity profiles. This graphical model can effectively handle the between-subject variability within the group, yet is tolerant to changes in the connectivity at the single-subject level. 20 different parcellations have been computed for each modality by randomly selecting 20 subjects each time.

Our preliminary results indicate that parcellations computed from different datasets do not entirely match with each other in terms of Dice similarity. We obtained average Dice scores of 0.57 (0.04), 0.56 (0.02), and 0.58 (0.02) for 100, 200, and 300, parcels respectively. We observed that the right hemisphere has slightly higher scores than its left conjugate. We also computed stability graphs of the parcellations [3] in order to locate cortical areas that have been consistently assigned to the same parcels across different groups (Fig. 1). Although, stability graphs demonstrate a high consistency in some cortical areas (especially in the visual and cingulate cortex, and partly in the temporal lobe), a more sophisticated analysis is necessary before drawing any conclusion regarding the
nature of this finding. It may be due to a link between structural and functional connectivity or some kind of bias related to the graphical model used to derive the parcellations.

**Keywords:** Groupwise parcellation, Functional connectivity, Resting-state fMRI, Diffusion tractography, Spectral clustering

**References**

Fig. 1: Stability graphs transformed into degree matrices and imposed onto the cortical surfaces to show the consistency of parcellations across different groups of subjects and for different parcellations (K = 100, 200, and 300). All values have been scaled into the range [0, 1] for better visualization.
A pipeline for automatic semantic annotation of human connectomics revealed by diffusion tractography

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Introduction

Different non-invasive neuroimaging modalities and multi-level analysis of human connectomics datasets yield a great amount of heterogeneous data which are hard to integrate into an unified representation. Biomedical ontologies can provide a suitable integrative framework for domain knowledge as well as a tool to facilitate information retrieval, data sharing and data comparisons across scales, modalities and species [1]. Especially, it is urgently needed to fill the gap between neurobiology and in vivo human connectomics in order to better take into account the reality highlighted in Magnetic Resonance Imaging (MRI) and relate it to existing brain knowledge. However, none of the current ontologies addressing cerebral connectivity relationships can be used to represent connectivity assessed by diffusion tractography (the only neuroimaging modality that can reconstruct white matter fiber bundles in a non invasive way in the living brain). The main contribution reported in this paper is a pipeline dedicated to automatic semantic annotation of human connectomics revealed by tractography [2].

Methods

The pipeline for semantic annotations takes as inputs: (1) atlas-based segmentation results delineating different gray matter regions [3] and major white matter fiber bundles [4], (2) binary connectivity matrices assessed by tractography. Finally, the pipeline generates a set of RDF annotations referring to the terms of the Human Connectomics Ontology (HCO) [2] represented in OWL.

Results

Each gray matter region is represented as an instance of the “hco:Gray_matter_par” class. If the gray matter region is a cortical parcel, then the cortical parcel is related to the instance of the overlapping gyrus using a part-whole relationship. Binary connectivity matrices provide the information about connections revealed by tractography. First, the two gray matter regions corresponding to the row and column of a connectivity matrix are represented as instances of the
“hco:MR_Node” class and are related together using the “hco:mr_connection” relationship. Second, an instance of the “hco:MR_Route” class is created and related to the two corresponding instances of the “hco:MR_Node” using the “hco:tracto_connects” relationship. If the route of the connexion is part of a white matter fiber bundle, then this is encoded using a part-whole relationship.

Conclusions

This pipeline for automatic annotations is not entirely generic, since it depends on a specific data structure representing segmentation results and connectivity matrices. However, it can be easily adapted to other situations. This approach can facilitate both data sharing and comparison of data across individuals and neuroimaging modalities.

Keywords: ontology, connectome, tractography, data sharing, neuroanatomy

References

Gender classification and manifold learning on functional brain networks

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Changes in blood oxygenation and blood flow that occur in response to neural activity can be detected with fMRI, which constitutes the primary neuroimaging technique used in functional connectivity analysis. Resting state fMRI is considered to reflect brain activation during rest and is recognised as a valuable technique for the investigation of complex patterns of brain functional organisation. These complex patterns have been extensively explored in conjunction with certain demographic measures, as well as disconnection syndromes [1]. The network nodes can either coincide with anatomical ROIs or represent functionally coherent regions identified by methods like ICA and clustering techniques [2]. An association matrix can, subsequently, be generated by compiling all pairwise associations between nodes.

Brain networks can be modelled based on correlation analysis of rs-fMRI timeseries data among brain regions and, thus, be characterised by symmetric positive semi-definite matrices. Additionally, if the network nodes are functionally distinct, then the functional network can be represented by a symmetric positive definite (SPD) matrix. Using a finite-dimensional Euclidean setting to represent the different networks as vectors is inaccurate, since certain desirable properties are not satisfied in this space. Alternatively, a manifold has the desired properties for the representation and mean calculation of SPD matrices. In this study we adopt a Log-Euclidean Riemannian framework of SPD matrices that utilises full information of brain functional networks for computing their mean and mapping them to lower-dimensional spaces where classification and regression analyses can easily be employed [3].

This framework was tested on simulated classes based on the preprocessed fMRI data of 100 healthy subjects (46 male-54 female) from the HCP [4] and led to 7% higher classification accuracy compared to the Euclidean setting. Several studies have indicated a significant role of brain connectivity in sexual dimorphism [5]. Hence, we further examined the suitability of different parcellations (including structural, functional and random) for defining the network nodes on gender classification using Linear Discriminant Analysis. Interestingly, for the same number of parcels (68) the Desikan-Killiany anatomical parcellation outperformed the functional parcellations (664.5% accuracy), while among those the parcellation by [6] allowed the best distinction between the genders with accuracy 594.5%.

Keywords: Functional MRI, Manifold learning, Network modelling, SPD matrices
References


Figure 1: Mean SPD covariance matrices for male and female subjects calculated on the Riemannian manifold. Apparently, it is not easy to distinguish between the two genders visually.
Capturing Simulated Network Topology using Heat Kernels

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Introduction

Graph analysis is a popular technique for characterising the brain; abstracting brain connectivity into nodes (anatomical regions) connected by edges representing structural or functional relationships. Network topology of brain connectivity has proven useful for characterising differences in patient/control experiments. Typical analyses statistically compare global graph metrics such as network efficiency. Such analyses yield graph features that are a static representation of the network. A heat kernel, \(H\), encodes information on the distribution of path-lengths in a network [1], where \(H_t(i,j)\) describes the probability of information flowing between nodes \(i\) and \(j\) through the network after time \(t\). \(H_t\) is based on a graph’s normalised Laplacian, a fundamental geometric characterisation of a network. Assessing the efficacy of \(H\) to differentiate between simulated networks with distinctive topologies will support its use in real neuroimaging data. For example, determining the network type of an observed network and subsequent deviations of it may be indicative of disease [2].

Aim

Investigate the validity of applying heat kernels to neuroimaging data by determining the differences in equilibrium time of heat transference for three distinct, simulated network topologies: lattice-like, small-world, and ErdsRnyi random graphs.

Method

We generate surrogate networks, where each hemisphere is represented by an empty half sphere each divided into 100 regions using Poisson disk sampling. The synthetic network is first represented by its spatial adjacency matrix. The density of the network is increased by connecting each node to nodes reachable within \(n\) steps, where \(n=[2,3,4]\). Subsequently, \(p=[1\%,10\%,100\%]\) (i.e. lattice, small-world, random graphs) of the edges are randomised to allow for inter-hemispheric connections. 100 samples of each \((n,p)\)-network are generated. Adjacency matrices are weighted randomly via normal distribution (mean=1, std=0.25) and the normalised Laplacian derived. \(H_t\) is calculated for all networks at \(t=[0.05,0.1,\ldots,20]\). \(H_t\) entries are labelled as ‘left’, ‘right’ or ‘inter-hemispheric’, and further subdivided as to whether an edge between the nodes exist (E) or not (E). Equilibrium
time is determined by first calculating the absolute relative percentage change, PC, in heat kernel value across time. For each label we estimated equilibrium as the median time interval where PC was less than 2%. 2-sample t-tests comparing E labelled equilibrium times were performed between pairs of graph topology (9 tests/n), correcting for multiple comparisons.

Results

For labels E, the majority of (n,p)-networks reached equilibrium after one time-step. For labels E, equilibrium was achieved at an earlier time for small-world networks than for both the lattice and random networks for all densities with significant differences between each of the three network topologies (p<0.001). The results demonstrate the ability of heat kernels to capture heat transfer across a network that is associated with the underlying topology. In addition, heat kernels are able to discriminate between three topologies, where small-world networks seem to be the most efficient.

Conclusion

We have demonstrated the potential for heat kernels to be a useful technique for investigating heat diffusion on networks with the ability to differentiate between topologies.

Keywords: Graph topology, Heat kernel, Surrogate networks

References

Figure: A heat transition map for n=3 and p=10% surrogate network, representing small world topology. Each column depicts heat transfer between a pair of nodes in time. Columns were grouped to represent within hemisphere (Hemisphere 1, 2) and between hemisphere (Interhemispheric) node pairs. Within each group, columns were ordered (from left to right) by decreasing weight of the corresponding edge in the original connectivity matrix.
Enhanced inference of network structure from functional connectivity - 2015 International conference on Brain Informatics and Health

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Introduction

A diverse set of approaches are used to characterise brain network connectivity from BOLD FMRI imaging data driven by the complexity and size of these data. Large-scale multivariate approaches applied to the entire voxel time series data can map patterns of correlated brain activity (functional connectivity, FC). FC approaches identify functional networks and their modulations, and artefacts that may contaminate analyses. Effective connectivity approaches (EC) move from correlations to more neurophysiologically meaningful variables, such as direct and indirect connectivity and causal relations. These approaches are computationally demanding, and must be applied to a smaller set of network nodes derived from the data. Problematically, it is difficult to make inferences regarding EC structure from FC analyses. FC can fail to distinguish between distinct changes in signal and noise properties that imply very different changes in EC. Here, we demonstrate an enhanced FC analysis that solves this problem. This analysis can be used to: 1) Produce more robust and interpretable seed-based, psycho-physiological interaction and other FC analyses. 2) Make stronger inferences regarding the network in which the brain signals are embedded. 3) Appraise network modelling by identifying the distinct types of changes in data that underlie the network model fits.

Methods

Regional brain activity is modelled as consisting of a sum of random variable signal components. These may correspond to both neural or non-neural sources. Correlation (e.g. FC) between a pair of regions is determined by the relative contributions of signal components in both regions. The enhanced FC analyses determines whether observed changes in FC can be explained by increases or decreases in signal component variances (which may be shared or not shared across the pair of regions) (Fig 1). Changes which cannot be explained by simple signal variance changes must be due to more wholesale changes in dynamics, for example, a switch of a regions connectivity between two functional systems. The FC categorisation is achieved using quadratic optimisation, with constraints limiting putative change of variance components. This remains a pairwise analysis, permitting spatial mapping to link results to scenarios such as a change in...
noise levels, or increases in the strength of a shared neural activity component. We tested the approach on fMRI data from 16 subjects in which signal dynamics were modulated by different constant (steady-state) motor and visual conditions.

Results

Steady state visual and motor conditions reliably modulated brain functional and effective connectivity. Our expanded FC analysis identified a variety of distinct changes in network dynamics. Fig. 1 shows results for a comparison between a visuo-motor condition and rest. A significant proportion of changes in FC could be explained by increases in the variance of activity in visual networks, which produced stronger internal FC, and decoupling from non-visual regions. Motor activity reduced the variance of common BOLD signal activity across motor networks and elsewhere. However, correlations between the motor system and putamen and cerebellum increased in a manner suggestive of increased integration. These results predicted the results of network modelling approaches such as SEM and DCM.

Keywords: Network structure
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