Connectomics: Parcellation & Network Analysis Methods

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Target audience. Clinicians interested in performing functional-connectivity analysis

Highlights

- Interactions between distant brain functional modules underpin cognition and can be impacted by pathologies
- Fluctuations in the observed functional signal reveal these interactions via *functional connectivity*
- Data analysis of *functional connectivity* requires the definition of modules via brain parcellations
- Networks analysis of the inter-region connections can reveal clinical markers

Extracting functional parcellations

Regions for connectome analysis. Regions of interests used in functional-connectivity analysis must capture specific brain functions. To study connectivity in task-related networks, regions can be defined from activation maps. In resting-state studies, a small number of well-known networks capture most of the structure of intrinsic activity. Regions in these networks can either be defined from the literature, or via data-driven methods. Conversely, relying on anatomical atlases or segmenting cerebral structures can be useful to work from well-identified neurological objects or enable multi-modal studies.

Clustering approaches. Starting from functional-imaging data, *clustering* methods can be used to group together voxels that have similar functional response, forming functionally homogeneous parcels. A wide variety of approaches exist with different strengths and weaknesses. To consider this trade-off space a first question is: how many parcels are desired? For a large number of parcels simpler methods with less computational requirement may be preferable. Another factor to consider is whether to enforce spatial constraints. From a statistical standpoint, finding a large number of clusters from noisy observations is a very challenging task and it is useful to add constraints or prior information. However, there often is little guaranty to recover the underlying structure: parcels extracted present a certain amount of arbitrary choice due the method used and the noise in the signal. This problem is partly overcome by looking for stable structures across datasets and methods. We will illustrate these trade offs with parcellations extracted from resting-state fMRI using the most popular clustering methods.

Linear decomposition models. Another class of data-driven approaches useful to define regions relies on *unmixing* the signals arising from different brain networks. These approaches output continuous maps of networks from which regions can be segmented. Independent component analysis (ICA) is a fast and powerful method for that extracts both brain networks and noise components. Functional networks representative of a population can be extracted by a joint analysis of resting-state time-series from all subjects. In practice, defining regions from the spatial maps resulting from ICA often requires manual operations as the maps present structured background noise. For this reason, recent advances have introduced methods imposing sparsity of the maps via a *dictionary learning* procedure.

Networks analysis

Extracting signals. Given regions of interest or network maps that define the nodes of a functional connectome, extracting signals that represent well the brain activity and reject noise is crucial. This step requires a careful choice of confounds to regress out movement artifacts, scanner-induced signal fluctuations, physiological noise such as cardiac and respiratory signals. Using the global signal captures these effects, but is controversial as it systematically introduces negative correlations.

Estimating functional connectomes. Correlations in the signals capture interactions between the nodes. The correlation matrix gives a general view of the connectome. It displays blocks of heavily-correlated regions that correspond to brain networks. However, the limitation of correlations to measure inter-node

interactions is that they capture indirect effects. Partial correlations are useful to extract conditional connectivity between a pair of nodes, removing effects of other nodes. In addition, zeros in the partial correlation matrix give the independence structure of the signal. However, this partial correlation matrix is challenging to estimate. Sparse inverse covariance estimators provide powerful tools to compute jointly the correlation matrix, the partial correlation matrix and the corresponding independence structure, resulting in a detailed and interpretable picture of the structure of the functional connectome.

Inter-subject comparison. Functional connectomes, represented by correlation or partial correlation matrices, capture cognitive processes as well as disease mechanisms. Revealing such markers requires inter-condition or inter-subject network analysis, relying on comparison of connectomes. Testing each connections for differences can identify those that vary, but is subject to several methodological challenges arising from multiple comparisons as well as the distributed nature of inter-subject variability in connectomes. An alternative strategy relies on network-level tests. Networks appear in the correlation matrix as overlapping blocks that often co-vary across subjects or conditions. As functional network are natural units of brain function, network-level integration and between-network cross-talk provide a concise description of the connectome that can capture markers of pathologies or cognition. We will illustrate this approach on a specific example of how the behavioral impact of strokes is reflected in resting-state networks.