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DOES ROI'S INTERNAL CONNECTIVITY STRUCTURE PREDICT ITS TOPOLOGICAL ROLE AS A NODE OF A FUNCTIONAL BRAIN NETWORK?

RESEARCH PLAN

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INTRODUCTION

The human brain consists of clusters of neurons specialized in certain tasks. These clusters are internally strongly connected and spatially separated from other clusters of neurons to which they have weaker connections (Sporns 2013, Tononi et al. 1994). A complex network is a natural model for this structure of integration and segregation in the brain.

In my doctoral thesis, I have investigated methodological questions that relate to construction of functional brain networks. In particular, I have considered different approaches for defining the network nodes, since properties of functional brain networks strongly depend on the selected set of nodes (Zalesky et al. 2010). In fMRI studies, a commonly used approach is to use *a priori* defined Regions of Interest (ROIs) as network nodes. Time series of these ROIs are typically obtained by averaging the time series of voxels that belong to the ROI. In order for the ROI time series to represent the voxel-level dynamics, all voxels of the ROI should behave similarly. This assumed similarity of voxel time series in a ROI is referred to as *functional homogeneity*, and it forms basis for the entire ROI approach.

In my doctoral research, I measured functional homogeneity in terms of spatial consistency that is defined as the mean Pearson correlation coefficient between time series of voxels in the ROI. I found that *the functional homogeneity assumption does not hold in general*: spatial consistency is low for many ROIs in commonly-used parcellations of the brain (Korhonen et al. 2017). Interestingly, there is no visible difference between anatomical atlases and parcellations defined in terms of function or connectivity.

Further, I found that spatial consistency changes in time, which at least partially explains the low spatial consistency values: although voxel time series would synchronize in some time windows, they may be less correlated in other windows, and this time-dependent variation yields a moderate overall consistency value. *The time-dependent changes in spatial consistency reflect the rich internal connectivity structure of ROIs.* During the high-consistency time windows, majority of voxel time series are correlated in all ROIs, but during the low-consistency time windows the voxels may show either uniformly low correlation or a division into subareas anticorrelated with each other.

AIM OF THE RESEARCH

One may well hypothesize that there is a connection between ROI's internal structure and its functional role. Investigating this connection is the next step of my research. In this investigation, I will use the topological role framework introduced by Guimerà & Amaral (2005), concentrating in particular on provincial and connector hubs. In order to reveal the topological roles of network nodes, modules of the network are identified in terms of some community detection method. Next, nodes are classified into topological categories based on the strength of the connections they have to their own module and to other modules.

In this framework, provincial hubs are central in their local network modules. Therefore, one may expect that the internal structure of provincial hubs would be characterized by a uniform correlation distribution and periods of high and low spatial consistency would reflect changes in ROI's activity. On the other hand, connector hubs form bridges between different network modules. An internal structure of non-correlated subareas could help in this.

METHODS

Practically all commonly-used approaches for defining nodes of functional brain networks assume that the nodes are stable, *i.e.* that it is possible to define a set of nodes that would show high functional homogeneity in all subjects and during all cognitive tasks. However, my results about time-dependent changes in spatial consistency seem to question this view. Therefore, *the investigation of the relationship between ROI's internal structure and topological role must start with a well-justified decision on how to define ROIs that will be used as network nodes.* In order to define the nodes, I will compare different approaches in terms of spatial consistency and its temporal variation. Comparing brain networks constructed with different sets of nodes will increase understanding on how node definition affects the network structure.

One promising approach for defining the nodes has been introduced by Kujala et al. (2016). Here, a network is first constructed using voxels as nodes. This voxel-level network is then divided into modules by a community detection method such as the Louvain algorith (Blondel et al. 2008), and a coarse-grained ROI-level network is constructed by calculating the number of connections between the obtained clusters. This approach produces nodes that are optimized for the current set of subjects and data but do not generalize between datasets.

Another interesting approach is to use ROIs from some *a priori* defined parcellation, for example from the connectivity-based Brainnetome atlas (Fan et al. 2016) in the subject space. In this approach, the parcellation defined in the standard space is transformed to the individual space of each subject instead of transforming the functional images of each subject to the standard space. This approach takes into account the between-individual variation in anatomy but enables also comparisons between datasets since the parcellation used acts as a common reference across subjects.

I will explore the connection between ROI's internal structure and topological role by investigating how well measures of internal connectivity can predict ROI's topological role as a provincial or connector hub. *I will validate the predictive power* of the selected measures *using several independent datasets* measured under different cognitive conditions. By comparing networks of rest and task state data *I will investigate how different cognitive tasks change ROIs' functional homogeneity and internal connectivity structure.*

Defining measures for the internal connectivity structure of ROIs will be a key methodological question of my research. Spatial consistency measures the overall level of internal connectivity and can be used as a rough estimate for internal connectivity. Similarly, in a network coarse-grained using the approach of Kujala et al. (2016), weighted self-links are used to quantify the amount of internal connectivity. However, neither of these measures captures the finer-scale structure of internal connectivity: are low-consistency periods caused by uniformly low voxel-level correlations or anticorrelation between subareas? In order to quantify this finer-scale structure I will investigate the distance between correlation distributions inside different ROIs, for example in terms of the Kullback-Leibner divergence and its time-dependency. Further, I will investigate the possibility of modeling the time-dependent internal structure of ROIs as a multilayer network: the data will be divided into time windows, each window will be considered as a layer in a multi-layer intra-ROI connectivity network, and multi-layer clustering methods such the generalized Louvain algorithm for multiplex networks (Mucha et al. 2010) will be used to quantify the changes in the internal connectivity structure.

IMPACT

My research addresses one of the key methodological questions in network neuroscience: what should the nodes of functional brain networks depict? The neuroscientific community still lacks a golden standard for node definition, although the selected set of nodes may significantly affect the obtained network properties. Insufficiently justified choices in node definition and network construction may hinder the community from putting into use the full potential of the network model.

I will search for new methods that will take into account the changing internal connectivity structure of ROIs used as network nodes. *These methods will increase the flexibility of the network model of the human brain* and facilitate investigating the changes in brain network structure on short time scales. Investigating the connection between ROI's internal connectivity and topological role will open new insights on how information transfer and processing is distributed among brain areas.

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