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Research article

Resting state dynamic functional connectivity: Network topology analysis

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ABSTRACT

Biologically inspired cognitive architectures are based on the data obtained by studying the mechanisms of the brain's functional networks operations, the causality of their integration and differentiation into the neuro-physiological structures of the cognitive processes of consciousness. One of the critical network involved in maintaining the core level of consciousness at the resting state is the default mode network (DMN). The DMN reduces its activity with an external stimulation and behavioral task and increases with perceived mental states as imagination, internal dialogue, and others. A complete loss of consciousness is characterized by the synchronization of DMN with the anticorrelated with DMN network. When the level of consciousness changes in the processes of cognitive activity, there is a complex picture of the combination of positive and negative connections between different networks and regions of the brain. At the same time, the changes in the intrinsic brain organization during the cognitive process and the resting state still an open question. The primary purpose of this work is studying the dynamics of the different brain networks interactions at the resting state, such as executive and attention networks, cerebellum, DMN, visual and auditory network, brainstem, the somatosensory and motor networks and subcortical network. We used three algorithms for clustering states in neural network connectivity dynamics: direct clustering of the functional network with the k-means algorithm, modularity-based and topological based clustering. We obtained that in the dynamics of functional connectomes there are three expressed states, determined by different types of interactions between DMN networks, attention and other neural networks.

1. Introduction

Quantitative analysis has become widespread in the neurocognitive sciences. Representing interactions in human brain as a complex set of interacting functional networks Bullmore and Sporns (2009) led to the emergence of a new scientific trend in neurobiology (Fornito, Zalesky, & Bullmore, 2016; Mišić et al., 2016) – brain connectivity analysis (BC – Brain Connectomics). So far, in the area of brain connectivity analysis based on MRI studies, two directions are developed – structural and functional connectivity. In case of structural connectivity (SC) the nodes (graph theory notation) are small regions (less than 1/1000 of the cortex) of gray matter, separated using brain atlases. The node weight is estimated by the number of structural (DTI) connections. For functional connectivity (FC) each node corresponds to group of voxels with the same activation patterns. For extraction of functional networks

from BOLD signal time series independent components analysis (ICA) approach Calhoun, Liu, and Adali (2009) or correlation analysis (Van Den Heuvel, 2010) can be used. The fundamental discovery in this area was the detection of spontaneous oscillations of the BOLD signal at the resting state, which is, as it turned out, allow us to study the network organization without any stimulation (Fox & Raichle, 2007; Fox et al., 2005; Friston, Frith, Liddle, & Frackowiak, 1993).

Studying FC in the human brain allows us to understand how the integration and differentiation of functional networks are related to behavior and how this organization changes in case of pathology (Boly et al., 2012; Greicius, 2008). FC studies in patients with DOC (DOC-disorders of consciousness) showed preferential changes in DMN (Heine et al., 2012; Soddu et al., 2012; Vanhaudenhuyse et al., 2010). The default network mode (DMN) is the most studied large-scale neural network of the human brain (Ushakov et al., 2016). The activity of DMN

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decreases with external stimulation or behavioral activity and increases in conscious mental states: imagination, inner dialogue, etc. There is an assumption that DMN is the central hub collecting all information about internal subjective perceptions. Recent studies with the controlled change in consciousness with the propofol injection showed that a decrease in the level of consciousness is accompanied by a smaller value of negative correlation between DMN and the anticorrelated network with DMN (Di Perri, Stender, Laureys, & Gosseries, 2014). It was discovered the phenomenon of anticorrelation between frontal pole (FP) and DMN. Also a decrease in anticorrelation was demonstrated in case of anesthesia (Amico et al., 2014; Boveroux et al., 2010), for patients with UWS-unresponsive wakefulness syndrome (Boly et al., 2012) and during sleep (Sämman et al., 2011). Reversal of the correlation dependence from negative to positive was found in the study of patients with consciousness disorders (Di Perri et al., 2016). For normally functioning brain structures anticorrelation is not unique for FP-DMN networks. For example, anticorrelation between the hemispheres became smaller with a decrease in the level of consciousness (Amico et al., 2017). Previously, authors (Jack et al., 2013) shows reciprocal relationships between social networks and physical interaction networks. More about different changes in FC could be read in (Demertzi et al., 2014).

Connectivity analysis could be useful in the task of disease classification. With the data on the level of connectivity of the auditory network patients with different levels of consciousness disorders were correctly classified (Demertzi et al. (2015)). Also, the analysis of brain networks for patients in coma has shown a radical reorganization of the central priority hubs (Crone et al., 2014; Koch, Massimini, Boly, & Tononi, 2016), which suggests a potential opportunity to diagnose disorders with the general estimation of the connectivity of a large set of networks. For analysis healthy subjects in different states, including sedation and sleep, along with the patients with consciousness disorders, such as coma, UWS, MCS (MCS-minimally conscious state), EMCS (EMCS-emerging from MCS), LIS (LIS-locked-in syndrome) the connICA method was proposed. In this approach, stable features were extracted using individual connectivity matrices of the main RSN (visual, somatomotor, attention, limbic, frontotemporal, default, subcortical, cerebellum) and used as input parameters for ICA (Amico et al., 2017).

Weakening in RSN connectivity, both between networks and within modules, with further lowering of consciousness level is more typical for DOC (Boly et al., 2012; Di Perri et al., 2014; Fernández-Espejo et al., 2012; Koch et al., 2016; Owen, Schiff, & Laureys, 2009), and probably related to structural lesions (Kraus et al., 2007; Perlberg et al., 2009; Sidoros et al., 2008). The VIS-SM symptom, in addition to pathology, is clearly expressed in anesthesia with sevoflurane (Deshpande, Keressens, Sebel, & Hu, 2010; Hudetz, 2012; Peltier et al., 2005). Sevoflurane also affects the attention network (Palanca et al., 2015), frontal and thalamo-cortical networks (Ranft et al., 2016). A similar effect is caused by propofol (Crone, Lutkenhoff, Bio, Laureys, & Monti, 2017). In the normal state, the visual and default networks are anticorrelated. It is believed that normal interactions between these networks are violated by loss of consciousness, leading to a loss of the global mental space necessary for conscious perception (Dehaene & Changeux, 2011; Demertzi et al., 2015). The key feature of the consciousness level remains a negative relationship between FP and DMN and as we approach the deepest unconscious, the strength of anticorrelation in FP-DMN decreases until it reverses to the positive values. This is supported by data on the positive correlation in FP-DMN for patients with UWS and MCS and partial recovery of anticorrelation for EMCS (Di Perri et al., 2014; Liu et al., 2017). In general, when the level of consciousness changes, there is a complex picture of the combination of positive and negative links between different networks and regions.

2. Review of connectivity analysis methods

Functional networks analysis consists of the two main stages and at each stage there are open questions for investigations. The first one is

connectivity definition. From the raw time series of resting state fMRI data or ICA components, some connectivity metrics should be constructed. There have been many functional connectivity metrics employed to measure the functional connection. Possible metrics are Pearson correlation, mutual information and spectral coherence (Smith (2012), Chen, Kang, and Wang (2015)), also there are different exotic metrics, for example Meszlényi, Hermann, Buza, Gál, and Vidnyánszky (2017). Each of them has advantages and disadvantages, but none of them is perfect. Up to date, the most commonly used approach for connectivity estimation is sliding window correlation computing (Hutchison et al. (2013)).

The second stage is time-dependent complex networks analysis. It is supposed that during the resting state there are reproducible, stable patterns, so-called connectivity states (Hutchison et al. (2013)). Formally it implies that network dynamics should have a cluster structure, and each cluster should belong to one of these states. Cluster analysis can be directly performed with the values of the network matrix. This approach was used for resting state clustering in the paper (Allen et al. (2014)). From the other side, metrics from network analysis could be used for clustering. Each network could be seen as a weighted graph, so we can use metrics from graph theory for describing it (Rubinov and Sporns (2010) and Stam and Van Straaten (2012)). One of the important network characteristics is modularity. It measures the strength of division of a network into modules or clusters, so it also could be used for cluster analysis. It was successfully used for detecting community structure in networks (Newman and Girvan (2004)). Modularity-based clustering was suggested for time-varying brain networks analysis in (Yu et al. (2016)). The main idea proposed in this paper was to construct correlation networks of time-varying networks and apply to this network of networks community detection algorithm. Average value of each community could be considered as the connectomic state.

Another tool for describing complex network is topological data analysis. It was already applied for brain network analysis, see (Giusti, Ghrist, and Bassett (2016), Stolz, Harrington, and Porter (2017), Sizemore, Giusti, and Bassett (2016)). Topological data analysis (TDA) is based on algebraic topology methods and provides additional metrics for network analysis (Carlsson (2009)). It provides tools for description structure not only for binary connection but also for higher order interactions. In TDA we can work directly with the weighted graph, and do not need to perform any thresholding. Now there is the variety of well-documented software to perform topological data analysis (TDA) with binding to Matlab, R and Python (JapaPlex, PHAT, Perseus, Dionysis, CAPD RedHom, etc.). So it could be used for data analysis along with other methods.

In this work for exploring dynamics in resting state, we partly repeat approach suggested by (Allen et al. (2014)). The number of patients in our experiment was less, namely 25 volunteers, but the scan length is 33 min opposite to 5–10 min in typical resting state scan length. We repeated the basic steps suggested in the (Allen et al. (2014)) experiment for obtaining dynamic connectom networks for each volunteer, after that we performed direct k-means clustering. Also we made modularity-based and topological clustering for the same networks. In (Allen et al. (2014)) 7 stable state were revealed, but we could not reproduce this result.

With TDA approach we additionally describe the structure of interrelations in connectivity matrices. There are different approaches how to process weighted matrices (Giusti et al. (2016)). We used so-called clique complexes. At this case, we start from the highest correlation level and see connection equal or above this level, after that decrease this level with some step and see how the relationship changes. The result of TDA is a set of characteristics which describes changes in connectivity structure with the correlation level. We add to this characteristics statistics of functional networks participated in connections by types. Positive and negative correlations were considered separately. As a result of this approach, we could reveal three stable connectivity states at the group level. Detailed description can be found in part Section 4.3.

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