Published in final edited form as:
Connectomics Neuroimaging (2017). 2017 ; 10511: 17–24. doi:10.1007/978-3-319-67159-8_3.

Consciousness Level and Recovery Outcome Prediction Using High-Order Brain Functional Connectivity Network

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Abstract

Based on the neuroimaging data from a large set of acquired brain injury patients, we investigate the feasibility of using machine learning for automatic prediction of individual consciousness level. Rather than using the traditional Pearson's correlation-based brain functional network, which measures only the simple temporal synchronization of the BOLD signals from each pair of brain regions, we construct a high-order brain functional network that is capable of characterizing topographical information-based high-level functional associations among brain regions. In such a high-order brain network, each node represents the community of a brain region, described by a set of this region's low-order functional associations with other brain regions, and each edge characterizes topographical similarity between a pair of such communities. Experimental results show that the high-order brain functional network enables a significant better classification for consciousness level and recovery outcome prediction.

1 Introduction

Studying the relationship between consciousness and brain activity has drawn a lot of attention in the recent years, especially using resting-state functional MRI (rs-fMRI) to investigate how brain functional network supports consciousness [1, 2]. The resting-state brain functional architecture can be characterized by different brain networks defined by correlated spontaneous brain activity between the regions of interest (ROIs). However, it is still unclear which key brain regions and their corresponding networks are essential to consciousness emergence and maintenance [3]. Perri *et al.* [4] reported that negative default mode network (DMN) connectivity seemed to be of metabolic neuronal origin, characterized by patients who have emerged from disorders of consciousness. Qin *et al.* [5] investigated three different functional networks to distinguish between conscious and unconscious states, and found that the salience network connectivity correlated with consciousness, while the DMN connectivity can be used to predict the recovery of consciousness. Wu *et al.* [3] summarized that the functional connectivity strength mainly in the DMN was disrupted with varying degrees of consciousness loss, and hence this disruption could be a potential biomarker for consciousness level prediction.

In these previous works, brain networks were usually constructed first based on the simple Pearson's correlation (PC), and then a particular group-level statistical analysis, such as oneway ANalysis Of VAriance (ANOVA), were applied to investigate if there exists any significant group differences in the population-averaged brain networks between different consciousness-level groups. Note that the PC-based network construction only captures the pairwise relationships through simple correlation operations. It is incapable of capturing any higher-order, complex relations between the brain regions, thus causing difficulty for the subsequent statistical analyses to exploit the consciousness level. Moreover, the hypothesis-driven analysis, such as in [5], limits our understanding of the biological substrate of consciousness with respect to the whole-brain complex network due to simply including a few predefined brain regions while ignoring other brain regions' contribution. To address these limitations, we investigate the relevant machine learning methods for automatic prediction of individual consciousness level according to the whole-brain complex networks.

For the construction of complex brain networks, some previous research have utilized certain prior knowledge and network information for building the respective models. Typical models include sparse representation (SR) [6], joint low-rank and sparse (SLR) method [7], and weighted sparse group representation method [8]. However, again in all these models, the networks are constructed by considering only pairwise interactions between ROIs. The higher order relations between the ROIs (i.e., nodes in the brain network) were overlooked in most of the previous works. To extract the underlying complex relationships from the network, in this paper, we propose a simple but effective high-order brain functional connectivity network (BFCN) construction method. In particular, the high-order BFCN is constructed based on the conventional low-order BFCN. Each node in the high-order BFCN represents the community of each ROI described by a set of low-order network values, and the edge between each pair of the nodes represents the correlation between the two communities. This high-order BFCN can model complex interactions and relationships among brain regions at a higher level, without introducing any extra parameters.

We use our proposed high-order BFCN for prediction of individual consciousness level. Experimental results on using rs-fMRI data for acquired brain injury (ABI) classification show that the high-order network enables a successful classification between the consciousness preserved and unresponsive patients. We also apply our high-order BFCN to predict whether the unresponsive patients would regain consciousness, from which we obtain a promising accuracy of 87.18%.

2 Materials

Our dataset comprises 53 patients with ABI but with the fully preserved consciousness state, and 39 ABI patients with unresponsive wakefulness state (including 26 in vegetative state and 13 in coma). These different groups of patients are categorized as follows [9]. (1) The *preserved* consciousness patients were able to communicate and had experienced brain injury. (2) The *vegetative state* patients were characterized by no evidence of awareness of self or environment and also an inability to interact with others; no evidence of sustained, reproducible, purposeful, or voluntary behavioral responses to visual, auditory, tactile, or noxious stimuli; no evidence of language comprehension or expression; intermittent wakefulness manifested by the presence of sleep-wake cycles; sufficiently preserved hypothalamic and brainstem autonomic functions to permit survival with medical and nursing care; bowel and bladder incontinence; and variably preserved cranial nerve reflexes and spinal reflexes. (3) The *coma* patients were characterized by no arousal/eye-opening, no behavioral signs of awareness, impaired spontaneous breathing, impaired brainstem reflexes, and no vocalizations of more than 1 h. Both *vegetative state* and *coma* patients are categorized as "unresponsive" subjects, while all other patients belong to another group of "consciousness preserved" subjects. The rs-fMRI data of these patients were collected from 2010 to 2014 via a Siemens 3.0 T scanner with the following parameters: TR = 2 s, slice number = 33, slice thickness = 4 mm, matrix size = 64 × 64. The data was preprocessed by using SPM8 (http://www.fil.ion.ucl.ac.uk/spm/) similar to [3]. It is important to note that the T1-weighted images of these subjects were also acquired and used to guide the registration using group-wise registration algorithm in SPM8 (DARTEL) for avoiding registration error due to lesions. The subjects with excessive head motion or large lesions that induced severe brain distortions were excluded during data screening.

The consciousness levels of the patients were assessed using the Glasgow Coma Scale (GCS) [10] and the Coma Recovery Scale-Revised (CRS-R) [11] on the day of the scanning. The recovery outcome was assessed using the Glasgow Outcome Scale (GOS) [12] at 3 months after scanning. The GOS provides a measurement of outcome, ranging from 1 to 5. The GOS score of less than 3 was defined as nonawakened, and the GOS score of larger or equal 3 as awakened [3]. In our 39 subjects (26 in vegetative state and 13 in coma), 17 of them regained consciousness after 3 months while the remained 22 of them were still nonawakened. We will learn a model with our high-order networks to predict both consciousness level (53 consciousness preserved *vs.* 39 unresponsive) and recovery outcome (17 awakened *vs.* 22 nonawakened).

3 High-Order BFCN Construction

Low-Order BFCN

In this subsection, we will introduce the basics of low-order BFCN construction method for brain disorder diagnosis, and then extend the definitions to capture high-order network characteristics in the next subsection.

Assume each brain is parcellated into N ROIs. Here, each ROI has a mean time series $x_i \in R^K$, $i = 1,2, \ldots, N$, where K is the number of time points. x_i can be represented as $x_i = [x_{1i}; x_{2i}; \ldots; x_{Ki}]$. Thus, each subject is represented by a matrix, $X = [x_1, x_2, \ldots, x_N] \in R^{K \times N}$. The BFCN construction is simply defined as finding a connectivity matrix $W \in R^{N \times N}$, which can be formulated as a matrix-regularized network learning method [7]:

$$\min_W f(X, W) + \lambda R(W) \quad (1)$$

where $f(X, W)$ is a data-fitting term, and $R(W)$ is a matrix-regularized term. Using different $f(X, W)$ or $R(W)$, we can obtain different BFCN construction methods. For instance, in the Pearson's correlation (PC) coefficient based BFCN, the connectivity matrix is calculated by [13]:

$$\min_W \sum_{i, j = 1}^{N} \left\| x_i - W_{ij} x_j \right\|^2, \quad (2)$$

Sparse representation (SR) is another popular method to construct BFCN:

$$\min_W \left(\sum_{i = 1}^{N} \left\| x_i - \sum_{j \neq i} W_{ij} x_j \right\|^2 + \lambda \sum_{i = 1}^{N} \sum_{j \neq i} \left| W_{ij} \right| \right), \quad (3)$$

where the regularization term enforces sparsity in the network, since it is known that BFCN is intrinsically sparse [14]. By importing the modularity prior as the matrix-regularized term, Qiao *et al.* [7] also proposed joint sparsity and low rank (SLR) regularizations in BFCN construction, by using both L_1-norm and trace norm of W:

$$\min_W \left(\sum_{i = 1}^{N} \left\| x_i - \sum_{j \neq i} W_{ij} x_j \right\|^2 + \lambda_1 \left\| W \right\|_1 + \lambda_2 \left\| W \right\|_* \right). \quad (4)$$

Note that if we set $\lambda_1 = 0$, we would have only a low-rank regularization. As can be seen, all these BFCN construction methods use pairwise relationships between ROIs, and hence they are low-order network construction techniques.

High-Order BFCN

We propose a high-order BFCN construction method, which can implicitly capture high-order relationships among ROIs, rather than just the pairwise relations. Specifically, we propose to capture a second-level relationship built on the previous lower-order BFCN. As a result, we can additionally capture inter-regional resemblances in the BFCN. In order to achieve this goal, we can first use any method for constructing the low-order BFCNs as introduced in the previous subsection. In this low-order network, for each node (i.e., brain ROI), we have a vector (i.e., rows in the low-order network matrix) measuring the relations between this node and all other nodes. Let's call this vector a node's *community*. Then, based on this low-order BFCN, a second layer of correlations can be computed between any pairs of brain ROIs. Figure 1 illustrates the computation procedure to build a high-order network, given a low-order BFCN.

Specifically, assume $W_j = [W_{1j}, \ldots, W_{mj}, \ldots, W_{Nj}]$ represent the community of the node j (corresponding to the ROI x_j) described by a set of W_{mj}, $\forall m \in \{1..N\}$. Here, W_{mj} represents the interaction relationship of the node m and the node j. Thus, we can calculate the Pearson's correlation coefficients between the node j's community and any arbitrary node q's community as follows:

$$H_{jq} = \frac{\left(W_j - \overline{W_j}\right)^T \left(W_q - \overline{W_q}\right)}{\sqrt{\left(W_j - \overline{W_j}\right)^T \left(W_j - \overline{W_j}\right)} \sqrt{\left(W_q - \overline{W_q}\right)^T \left(W_q - \overline{W_q}\right)}}. \quad (5)$$

This way, H_{jq} would be a correlation between the communities of the two nodes j and q. Hence, it describes a more complex relationship between ROI x_j and ROI x_q at a higher level. With the assumption that W_j has been centralized by $W_j - \overline{W_j}$ and further normalized by $\sqrt{(W_j - \overline{W_j})^T (W_j - \overline{W_j})}$, the PC coefficient can be simply represented as $H_{jq} = W_j^T W_q$. In the high-order network, the new edge between nodes j and q would have the weight of H_{jq}. Dropping the indices and writing in a matrix form, we would have $H = W^T W$ to represent the high-order BFCN. Under such settings, it is easy to construct high-order networks from the corresponding various low-order networks, such as $H_{(PC)} = W_{(PC)}^T W_{(PC)}$ and $H_{(SLR)} = W_{(SLR)}^T W_{(SLR)}$, with $W_{(PC)}$ and $W_{(SLR)}$ as the low-order BFCNs estimated based on *Pearson's correlation* and *sparse and low-rank regularization*, respectively.

It is worth pointing out that some machine learning methods also tried to use the linear transformation $W^T W$ to select features [15, 16]. The main difference is that these machine learning methods aim at solving the over-determined problem (with more subjects than features in matrix) or under-determined problem (with more features than subjects in W) by using the linear transformation. In our work, we do not have these problems as our network W is a $N \times N$ matrix, and we want to use the high-order network $W^T W$ to extract more complex correlation on community level.

4 Experiments

Network Construction and Experimental Setting

In our experiments, for each subject, 200 ROIs are defined based on Craddock's 200 atlas, and the mean rs-fMRI signals are extracted from each ROI to construct the BFCN. We construct two types of low-order BFCNs as described in Sect. 2, including PC and SLR. Based on these two low-order BFCNs, we can construct two respective high-order BFCNs, namely H_PC and H_SLR. For the regularization tuning parameters (i.e., λ_1 and λ_2 in Eq. 4) involved in the SLR low-order BFCN model, we use the same setting as in [7], and search their optimal values in the set $\{2^{-5}, 2^{-4}, \ldots, 2^0, \ldots, 2^4, 2^5\}$. Note that there are no parameters to tune for the construction of high-order BFCN.

As we have 200 ROIs as nodes in a network, and since the connectivity matrix is symmetric, we will vectorize the lower-triangle of the matrix and use it as the feature vector for each network. As a result, we will have $\frac{200 \times (200 - 1)}{2} = 19900$ edges to describe each connectivity network. For each of the BFCNs, we use these edge strength values in the networks as features. We then select the most informative features among all these features, and then learn a classifier model. For feature selection, we use a simple information theoretic feature selection techniques, which evaluates the information gain for every single feature, and selects the features with the most information gain. Specifically, we measure the information gain ratio with respect to the class label for each feature, similar to [17]. Then, we choose all the features with information gain ratio values larger than 0.01 in our experiments. After the selected features are identified, we employ a polynomial kernel SVM with $c = 1$ as the classifier.

Classification Results on Consciousness Level Prediction

In the following, we report four evaluation measures: accuracy, sensitivity, specificity, and F-Score for both low-order and high-order networks using the above feature selection and classification methods. The reported values are the mean of 10 different runs of 10-fold cross validation, and hence introduce reliable results with no over-fitting effects to the particular population of the data. For selection of tuning parameters in SLR, we further conduct an inner leave-one-out cross validation on the training set to obtain their best parameter values.

The results are shown in Fig. 2. From these results, we can conclude that the high-order BCNF obtains a better performance in all experiments. Furthermore, we can see that H_SLR obtains the best classification results, with 78.04% accuracy, 86.39% sensitivity, 66.82% specificity, and 81.72% F-Score.

Results on Recovery Outcome Prediction

From the previous subsection, we can see that the H_SLR can generate the best classification accuracy results. Therefore, we use H_SLR to predict the recovery outcome of unresponsive patients. In order to be able to compare with previous methods [3, 5] on the same application, we implement two different cross-validation settings: (1) leave-one-out cross validation (LOOCV), and (2) 5 runs of leave-two-out cross validation (LTOCV). Note that, for the 2^{nd} case, we average results from 5 different runs and reported the average.

As shown in Table 1, our proposed method can obtain the best accuracy of 87.18%, compared to other methods, under LOOCV.

5 Conclusion

In this paper, we proposed a simple *but* effective high-order brain functional connectivity network construction method for predicting both consciousness level and recovery outcome in acquired brain injury. Our proposed high-order network treats the community of each ROI as its features and the correlation between any pair of communities as the edge between the two ROIs. Compared to the low-order network, the high-order network can extract more information at the high level. The experiments on both consciousness level prediction and recovery outcome prediction in ABI show that our proposed high-order network can obtain a better classification performance. In future work, other relationships between communities will also be investigated to build the high-level network.

Acknowledgments

This work is partially supported by National Natural Science Foundation of China (Grant Nos. 61403200), Natural Science Foundation of Jiangsu Province (Grant No. BK20140800), and NIH grants (EB006733, EB008374, EB009634, MH107815, AG041721, and AG042599).

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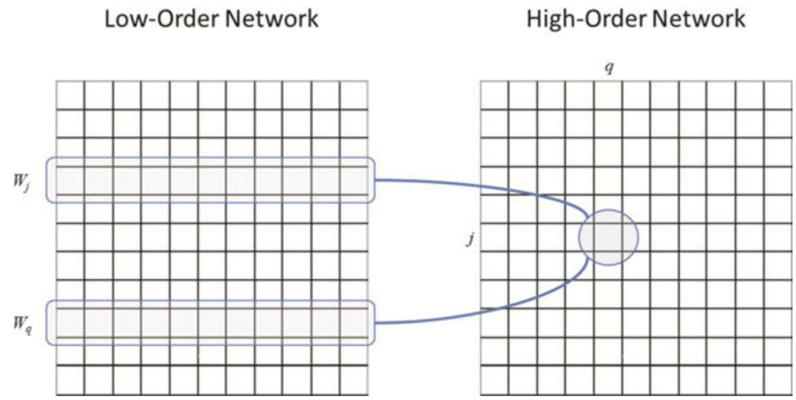

Fig. 1.
Construction of high-order BFCN based on low-order BFCN. Each element in the high-order BFCN is calculated based on a pair of ROI communities from the low-order BFCN.

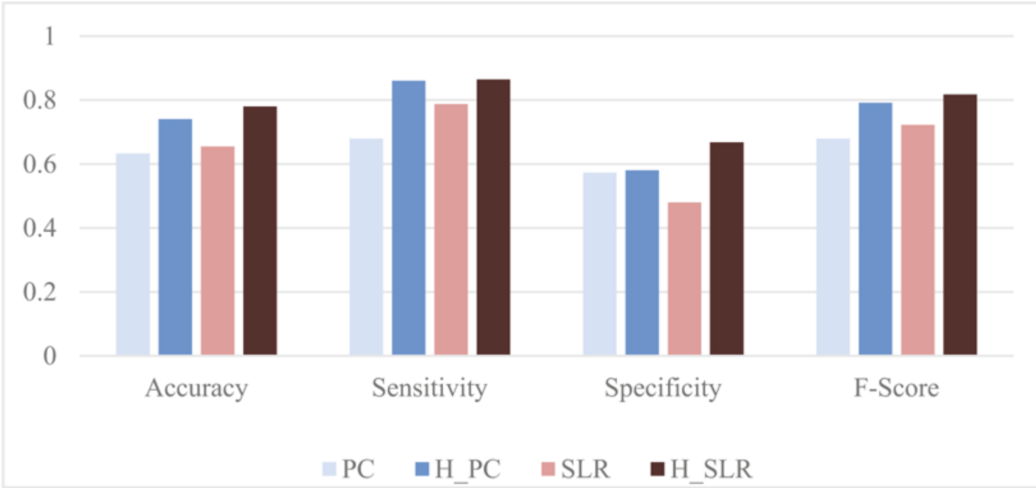

Fig. 2.

Comparison of classification results between low-order BFCNs (including PC and SLR) and high-order BFCNs (including H_PC and H_SLR).

Table 1

Comparison of accuracy on different methods.

Method	LOOCV (%)	LTOCV (%)
H_SLR +SVM	87.18	81.54
PC + SVM [3]	81.25	75.61
PC + ANOVA [5]	74.00 *	N/A

Note that the comparisons are conducted under different cross-validation mechanism. N/A means the result is not available from the corresponding reference.

*This accuracy was obtained based on a classification model trained using all subjects (i.e., not via stringent machine learning).