On the Topological Changes of Brain Functional Networks under Priming and Ambiguity

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SUMMARY The relationship between different brain areas is characterized by functional networks through correlations of time series obtained from neuroimaging experiments. Due to its high spatial resolution, functional MRI data is commonly used for generating functional networks of the entire brain. These networks are comprised of the measurement points/channels as nodes and links are established if there is a correlation in the measured time series of these nodes. However, since the evaluation of correlation becomes more accurate with the length of the underlying time series, we construct in this paper functional networks from MEG data, which has a much higher time resolution than fMRI. We study in particular how the network topologies change in an experiment on ambiguity of words, where the subject first receives a priming word before being presented with an ambiguous or unambiguous target word.

key words: brain functional networks, MEG, complex networks, network topology

1. Introduction

The investigation of real world networks by means of complex network measures has recently seen an enormous increase in interest in a wide variety of research areas. Not only topologies of information and communication networks, but also those of gene regulatory networks, transportation networks, social networks, or brain networks are being quantified and evaluated using complex network measures, e.g., clustering coefficient, characteristic path length, or modularity. Such measures help to evaluate the topological complexity of the network as opposed to pure random or regular connectivity and provide a general means of comparing network topologies from entirely different fields [1]. The two most well-studied types of networks are scale-free networks [2], where the node degree, i.e., the number of neighbors of each node, follows a heavy-tailed distribution and small world networks [3], which exhibit a high clustering coefficient and small shortest path lengths, allowing any node to be reached from any other node in only a few hops.

Most work to date on complex networks considers stationary situations where connectivity does not change over time. In many real-world cases, however, there are inevitably some changes in the connectivity pattern although they may occur at varying time scales. Particularly, the functional connectivity in the brain [4, 5], represented by the networks formed by temporal correlations of neural activities between different brain areas, shows a large amount of such reconfigurations depending on the situation and context [6]. The common method of acquisition of brain data is by functional magnetic resonance imaging (fMRI) through 3D scans of the entire brain, but this method has a rather small temporal resolution of about 1–3 seconds/scan. The spatial resolution for common 3T fMRI is given in voxels, which are 3-dimensional units with sides of approximately 3 mm length. However, fMRI does not measure the neural activity directly, but rather the hemodynamic response of blood oxygen levels. Less common than fMRI to determine functional networks is magnetoencephalography (MEG) [7] due to its smaller number of channels, which are located at sensors on the surface of the head, each channel constituting a node of the brain functional network [8]. Samples can be measured here at a much smaller time scale (in the range of milliseconds), permitting a more detailed investigation of time series similarity for instance by coherence [6], joint recurrence rate [9], synchronization likelihood [7], or wavelet correlation [10], differentiated by their frequency bands. However, the main problem in neuroscientific studies with MEG is to determine the exact location of neural activity from the sensors located on the surface of the head. This is referred to as the inverse problem for source localization. In this study, we focus on brain networks from the viewpoint of network science and therefore only consider the data directly obtained by the MEG measurements without source localization.

In this paper we make use of the large number of MEG measurement samples to identify and compare the brain functional networks extracted from the data in [11], where the influence of context on brain activity is studied for ambiguities of Japanese words. The experiments are conducted with priming, i.e., first a prime word is presented that establishes a related (or unrelated) context, and then a target ambiguous (or unambiguous) word is shown. We extract networks for priming and target phases and investigate their connection structure as well as the changes from one network to the other. We do not focus on neuroscientific conclusions in this paper, but our goal is rather to characterize which complex network measures are particularly suitable

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for observing significant changes in connectivity of brain functional networks for this experiment. By studying reorganization of networks in the brain under changing circumstances, we aim to find hints on how information network topologies can be configured appropriately even if there is ambiguity in the interpretation of the situation.

The remainder of this paper is organized as follows. In Sect. 2, we briefly describe the underlying experiment in [11] from which MEG measurement data is used and describe how the functional networks for prime and target periods are extracted from this data. We then summarize the considered complex network measures in Sect. 3. Evaluation results are shown in Sect. 4 for two ways of generating the functional networks, and the paper is concluded in Sect. 5.

2. Description of Experiment and Extraction of Functional Networks

In this section we first describe the MEG experiment as well as the method to extract the measured time series data. Then, we discuss how to construct the functional networks from this data.

2.1 Summary of MEG Experiment

Functional networks are usually constructed from the whole experimental time series to uncover the interactions of the involved brain regions, so only a single network results for each subject. Some neuroscientific experiments investigate certain dynamic behavior of the brain, for instance the recognition of ambiguous words [11] or images [12], as well as how the brain resolves those situations by changing its activity patterns in different regions during recognition. Typically, a prime is first presented to the subject to help identify the context of the target for recognition. In [11], pairs of Japanese words are presented to native-speaking subjects that consist of either a related or unrelated prime word, after which an ambiguous or unambiguous target word follows. For example, in one epoch first the prime with the ideographic characters (kanji) of “funsui” (fountain) are presented, followed by the ambiguous word “kōen” as phonetic characters (hiragana) that can have several meanings such as lecture, park, public performance, etc. By providing a related prime word, the context is prepared, which facilitates understanding of the ambiguous target. In this experiment, not only the combination of related prime and ambiguous target are shown to the subjects, but also other combinations including unrelated primes and unambiguous targets, i.e., words that do not require the presence of the prime for a correct understanding. Thus, an epoch of the stimulus presentation sequence contains one word pair of the type RA, UA, RU, and UU as combinations of related/unrelated prime with ambiguous/unambiguous targets (Table 1). Further details of the experiment can be found in [11].

We have as input for the construction of functional networks in the next sections the MEG time series data from $N = 148$ channels, each having a length of $M = 1764$ samples (sampling rate of 678 Hz). A single epoch corresponds to the presentation of a prime/target pair from one of the four categories RA, UA, RU, and UU, each for 300 ms, followed by unstimulated periods of 700 ms (Fig. 1). For one subject 400 epochs are measured with randomly selected prime/target pairs from one of the four categories in Table 1 and we use the data from three male subjects. As initial preprocessing step, each time series is detrended and normalized to have a mean of 0 and variance of 1.

2.2 Generating the Similarity and Adjacency Matrices

Figure 2 illustrates the process of generating the similarity and adjacency matrices from the measured MEG time series data. Examples of the time series from four channels are shown in Fig. 2(a). The periods during which the prime and target are presented to the subject are shown in red and green, respectively. These parts of the time series are used for constructing the functional networks by first obtaining two similarity matrices $W_p^{(k)}$ and $W_T^{(k)}$ for prime and target periods of epoch $k$, respectively (Fig. 2(b)).

Functional networks depend on the choice of a similarity measure between the time series of each channel. A link is established between the two nodes representing channels according to the similarity in the dynamics of their time series. As most common type of similarity measure a correlation matrix is constructed among the time series $x_i^{(k)}(t)$ and $x_j^{(k)}(t)$ of each pair of channels $(i, j)$ for epoch $k$ (Fig. 2(b)).

Similarity $w_{i,j}^{(k)}$ is measured using Pearson’s correlation coefficient

$$w_{i,j}^{(k)} = \frac{\langle x_i^{(k)}(t)x_j^{(k)}(t) \rangle - \langle x_i^{(k)}(t) \rangle \langle x_j^{(k)}(t) \rangle}{\sigma(x_i^{(k)})\sigma(x_j^{(k)})} \quad (1)$$

where $\sigma(x_i^{(k)})^2 = \langle x_i^{(k)}(t)^2 \rangle - \langle x_i^{(k)}(t) \rangle^2$.

After determining the similarity matrices, we use a threshold $\theta$ to discretize them and obtain two binary adjacency matrices $A_F$ and $A_T$ representing the functional net-

| Table 1 Categories of prime/target word pairs. |
|----------|---------------------------------|-----------------|
| abbreviation | prime          | target          |
| RA | related | ambiguous          |
| UA | unrelated | ambiguous          |
| RU | related | unambiguous          |
| UU | unrelated | unambiguous          |
works of the prime and target periods (Fig. 2(c)). If the similarity \( w_{ij}^{(k)} \geq \theta \), a link is established between nodes \( i \) and \( j \), otherwise no connection is made. We can classify each prime and target network of each epoch to either one of the stimulus types of RA, UA, RU, and UU. However, due to variations in the responses to the same stimulus type, there are also differences in the functional networks. In order to take this stochastic nature into account, we average over all correlation matrices from different epochs and different subjects having the same prime/target category and obtain by this way four adjacency matrices for graphs corresponding to the prime phase and the target phase, respectively.

3. Complex Network Measures

Complex networks describe random networks in the real world based on specific topological features, such as heavy-tailed degree distribution, high clustering coefficient, or hierarchical modularity. We briefly review the measures for characterizing a network consisting of the set of nodes \( N \) and the set of links \( L \), but refer to more detailed explanations and formal definitions in other publications, e.g., [13], [14]. For the numerical evaluations, we use the Brain Connectivity Toolbox and the definitions of the following metrics of interest from [14]. In order to analyze the network, we consider its graph, where \( n = |N| \) is the number of nodes corresponding to the MEG channels and \( \ell = |L| \) is the number of links. The network graph is represented by its adjacency matrix \( A = (a_{ij})_{n \times n} \) where \( a_{ij} = 1 \) if there is a link between nodes \( i \) and \( j \), and \( a_{ij} = 0 \) otherwise.

3.1 Link Density

The link density \( D \) is the ratio between the number of links \( \ell \) compared to the case if all nodes would be fully interconnected.

\[
D = \frac{2\ell}{n(n-1)}
\]  

(2)

3.2 Node Degree

The degree \( k_i \) of node \( i \) describes the number of neighbors to which node \( i \) is connected. In this paper we only consider the average degree \( K \) over all nodes to have a single network-wide measure.

\[
K = \frac{1}{n} \sum_{i \in N} k_i \quad \text{with} \quad k_i = \sum_{j \in N} a_{ij}
\]  

(3)

3.3 Assortativity Coefficient

In order to study if the degrees of nodes that are interconnected are correlated with each other, we use the assortativity coefficient [15]. A high assortativity means that high degree nodes tend to connect among each other while a negative assortativity indicates that high degree nodes prefer to connect to low degree nodes.

\[
r = \frac{\ell^{-1} \sum_{(i,j) \in L} k_i k_j - \left( \ell^{-1} \sum_{(i,j) \in L} \frac{1}{k_i + k_j} \right) \ell^{-1} \sum_{(i,j) \in L} \left( k_i + k_j \right)^2}{\ell^{-1} \sum_{(i,j) \in L} \frac{1}{k_i^2 + k_j^2} - \left( \ell^{-1} \sum_{(i,j) \in L} \frac{1}{k_i + k_j} \right) \ell^{-1} \sum_{(i,j) \in L} \left( k_i + k_j \right)^2}
\]  

(4)

The notation \( (i,j) \in L \) means that a link between nodes \( i \) and \( j \) exists in the set of all links \( L \).

3.4 Global Efficiency

The global efficiency \( E \) is a measure that characterizes the
In this section we evaluate the measures that we introduced for functional networks generated with the correlation coefficient as similarity measure. We consider first the correlation among channels over the entire time series and then separate time series for only the prime and target periods. In both cases, nodes of the networks are the channels of the MEG experiment and links are established between nodes if the correlation of their time series is above a threshold $\theta$.

4.1 Functional Networks over Entire Time Series

As the simplest way of extracting functional networks, we first compare the correlations over the entire time series for every pair of channels in order to decide if a link is established or not. This includes not only the prime and target phases, but also the unstimulated time periods. Figure 3(a) shows a radar chart of the considered network measures, which all lie very close to each other with no significant differences visible.

We project the nodes from their original normalized 3-dimensional coordinates onto the 2-dimensional x/y plane, where nodes with larger z-coordinate are found closer to (0,0), while the nodes with the smallest z-coordinates are located on the outside (Fig. 3(b)). The upper part of the plot is the frontal area that is responsible for conscious thought, the
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Fig. 4 Differences between prime and target networks and their complex network measures ($\theta = 0.8$).

The rear part is called occipital lobe where the processing of visual input signals takes place. The parietal lobe lies between the frontal and occipital lobes and its function is to integrate the sensory information from various senses, while the left and right temporal lobes deal with auditory input and visual object recognition. The rough locations of these major lobes are shown in Fig. 3(b).

Figure 3(c) illustrates a superposition of the network topologies of all four categories with a threshold of $\theta = 0.8$. The majority of links are common in all four categories (marked in red), indicating here as well only subtle differences between each category. Links only existing in one or two categories are annotated by their type, whereas links in three categories are shown in strikethrough of the fourth category that is absent.

In summary, the use of the entire time series is not suitable for differentiating between word categories, since the durations of the relevant prime and target periods are rather short compared to the idle periods. We will therefore focus in the following only on the prime and target stimulation periods.

4.2 Results from Prime and Target Networks

We now compare between the networks of the two time periods corresponding to the presentation of the prime and target word, respectively. Since it is difficult to visually compare the network graphs, we illustrate the changes by what we define as a difference graph $\Delta A = A_T - A_P$. As the adjacency matrices consist of binary values 0 or 1, the entries of this matrix are $\Delta a_{i,j} \in \{-1, 0, 1\}$, which indicates whether a link from the prime network is absent, unchanged, or present in the target network, respectively.

4.2.1 Individual Threshold Values

When looking at the complex network measures in Fig. 4(a) with threshold $\theta = 0.8$, we notice that a related prime tends to be associated with decreased efficiency, average degree, and density, but increased assortativity. The results also show that the threshold of $\theta = 0.8$ is too high in this evaluation, since some nodes become disconnected and removed from the network, resulting in a number of nodes that varies from prime to target.

Figure 4(b) shows the resulting difference graphs for all four categories. The thin purple lines are those existing in the prime network, but not in the target network, whereas thick blue lines are links present only in the target network. Unchanged links are not shown.

Some overall tendencies can be recognized. First, there are many link removals in the frontal and occipital areas, as well as added links in both temporal lobes, but particularly densely in the right hemisphere. Such changes in connectivity appear plausible, as the occipital area is only involved in the primary processing of the visual input, whereas the higher level processing takes place in the temporal regions. It can also be noticed that the left and right hemispheres appear to be more interconnected via the parietal area when an ambiguous word is shown than in the case of unambiguous targets.

In Figs. 5(a) and 5(b) we show the same results for a lower threshold of $\theta = 0.7$, thus including more links in the resulting networks and maintaining a constant number of nodes. It can be seen that the locations of the added and
removed links correspond to those of the higher threshold $\theta = 0.8$. While the numerical results in Fig.5(a) have in general larger values, the higher degree of interconnection among nodes (larger average degree and clustering coefficient) leads to a lower modularity and higher efficiency compared to Fig. 4(a).

4.2.2 Varying Threshold Range

As is common for brain functional networks, the choice of the threshold value has a big influence on the complex network measures. A too small threshold causes too many low correlation links to be included, while a too high threshold leads to low connectivity. In order to find some general tendencies in the transition from prime to target network, we use various absolute thresholds $\theta$ from 0 to 1 for which we compute the corresponding complex network measures. We determine for each category a critical threshold $\theta^*$ at which the first node becomes disconnected from the rest of the network and calculate the differences of the same metric from target network minus that of the prime network.

Figure 6(a) shows the differences of measures for varying thresholds for category RA. The y-axis shows that most differences are only minimal, but some metrics drastically change as the threshold increases, especially after crossing the critical threshold $\theta^*$. In order to judge if a metric for the target has the tendency to be above or below that of the prime, we show the normalized histograms over numerically evaluated threshold values in the interval $[0, \theta^*)$. The histograms for RA in Fig. 6(b) reveal that indeed some of the differences have a tendency to be positive or negative, while most of the metrics remain rather unaffected. The other word categories UA, RU, and UU have also been evaluated in the same manner, but are omitted in this paper due to space restrictions.

Table 2 summarizes the mean and standard deviation (SD) of the differences between metrics over thresholds in the interval $[0, \theta^*)$. From this table we can make the following conclusions. Changes between the two networks in terms of number of nodes, density, efficiency, clustering coefficient, and modularity are insignificant, all having a mean and standard deviation close to 0. On the other hand, average degree, assortativity, and average betweenness do reflect some differences among the prime and target networks. In particular, the sign of betweenness appears to change according to whether the priming is related or unrelated.

5. Conclusion

This paper shows how an MEG experiment with priming and ambiguity influences the changes in topology of brain functional networks. Simply considering the entire time series of the experiment is insufficient to recognize any significant changes between the networks. By using only the two stimulation phases, we obtain visible, albeit small, differences in the constructed networks for the priming and the target phases. During the transition from prime to target network, links are primarily added in the temporal regions, while they are removed in the occipital and frontal regions. Use of a decreased threshold results in the same effects, but some absolute complex network measures change due to the larger number of considered links. Most complex network measures are unable to discriminate between each category of presented word pairs over a wide range of thresholds, ex-
Table 2
Differences between prime and target network measures (mean and SD) over range of thresholds.

<table>
<thead>
<tr>
<th>type</th>
<th>$\theta^*$</th>
<th>density</th>
<th>degree</th>
<th>efficiency</th>
<th>assortativity</th>
<th>clust. coeff.</th>
<th>modularity</th>
<th>betweenness</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mean</td>
<td>SD</td>
<td>mean</td>
<td>SD</td>
<td>mean</td>
<td>SD</td>
<td>mean</td>
<td>SD</td>
</tr>
<tr>
<td>RA</td>
<td>0.73</td>
<td>0.01</td>
<td>0.31</td>
<td>0.01</td>
<td>1.16</td>
<td>0.93</td>
<td>0.01</td>
<td>0.00</td>
</tr>
<tr>
<td>UA</td>
<td>0.71</td>
<td>0.01</td>
<td>0.08</td>
<td>0.00</td>
<td>-0.08</td>
<td>0.16</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>RU</td>
<td>0.70</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.64</td>
<td>0.77</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>UU</td>
<td>0.70</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.06</td>
<td>0.17</td>
<td>0.00</td>
<td>0.00</td>
</tr>
</tbody>
</table>

Fig. 6 Differences of metrics (target minus prime) for category RA varied by threshold.

(a) Differences of network metrics for varying thresholds. The dashed line indicates the critical threshold $\theta^*$ at which the first node becomes disconnected from the network after which the metrics show large fluctuations.

(b) Histograms of metric differences for networks determined by thresholds in the interval [0, $\theta^*$] illustrate that some metrics reveal a tendency to increase or decrease.

except for degree, assortativity, and betweenness.

The study of dynamics in brain functional networks by complex network science does not only benefit neuroscience, but also helps in designing robust and adaptive information networks of the future. Priming can be regarded as assisting the network to reconfigure itself by providing early indications of an upcoming event, e.g., overload or attacks. The prime pattern itself may be relevant to the condition or not, i.e., it may be compromised by transmission errors or misclassification. Furthermore, ambiguous target situations may be easier resolved by providing suitable priming. The functional networks identified in our study can be characterized by the differences of average degree, assortativity, and average betweenness centrality regardless of the applied threshold.

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References


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