The graph theoretical analysis of the SSVEP harmonic response networks

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Abstract Steady-state visually evoked potentials (SSVEP) have been widely used in the neural engineering and cognitive neuroscience researches. Previous studies have indicated that the SSVEP fundamental frequency responses are correlated with the topological properties of the functional networks entrained by the periodic stimuli. Given the different spatial and functional roles of the fundamental frequency and harmonic responses, in this study we further investigated the relation between the harmonic responses and the corresponding functional networks, using the graph theoretical analysis. We found that the second harmonic responses were positively correlated to the mean functional connectivity, clustering coefficient, and global and local efficiencies, while negatively correlated with the characteristic path lengths of the corresponding networks. In addition, similar pattern occurred

with the lowest stimulus frequency (6.25 Hz) at the third harmonic responses. These findings demonstrate that more efficient brain networks are related to larger SSVEP responses. Furthermore, we showed that the main connection pattern of the SSVEP harmonic response networks originates from the interactions between the frontal and parietal–occipital regions. Overall, this study may bring new insights into the understanding of the brain mechanisms underlying SSVEP.

Keywords Steady-state visual evoked potentials (SSVEP) · Harmonic response · Graph theoretical analysis · Brain network · Functional connectivity

Introduction

Steady-state visual evoked potential (SSVEP) is a periodic response to a repetitive visual stimulus with a frequency above 4 Hz (Regan 1989). It consists of the fundamental frequency of the stimulus as well as its harmonics, and has high signal-to-noise ratio (SNR). Thus, it is often taken as a useful tool to study the neural processes underlying brain rhythmic activities, and has been successfully applied in cognitive neuroscience, clinical researches and neural engineering (Jensen et al. 2011; Vialatte et al. 2010).

When SSVEP serves as control signals in brain–computer interface (BCI) systems, different subjects show different performances with the same system (Friman et al. 2007; Zhang et al. 2012). When we analyzed the responses of each subject to the same stimuli, we found that the SSVEP responses of the fundamental frequency varied among the subjects. In our previous studies, the experimental results from both scalp electroencephalograph (EEG) of humans and intracranial EEG of rats consistently

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indicated that this phenomenon was related to the differences of the SSVEP brain network topological structures of the fundamental frequency (Xu et al. 2013; Zhang et al. 2013b). Using the flickering stimuli, we found that the fundamental SSVEP responses were positively correlated with the clustering coefficient, global and local efficiencies, while negatively correlated with the shortest path length of the functional networks at the fundamental frequency (Zhang et al. 2013b). The results of another study showed that the SSVEP responses were correlated with the topological measures of the resting-state functional connectivity networks at the corresponding stimulus frequencies (Zhang et al. 2013a). These results indicate that functional brain network topological parameters may play significant roles in the SSVEP generation. Besides, Vialatte et al. have analyzed the synchrony of SSVEP in single-trial level, and concluded that local oscillatory bursts display significant patterns of large scale synchrony during flickering light stimulation (Vialatte et al. 2009). Other research work has demonstrated that the fundamental and harmonic SSVEP responses have different spatial and functional roles (Kim et al. 2011; Pastor et al. 2007). Pastor et al. hold that the first and harmonic components of the SSVEP emerge from different regions of the parieto-occipital cortex using PET and low resolution brain electromagnetic tomography (LORETA). Kim et al. postulated that the first and second harmonic responses display divergent posterior scalp topographies, and voluntary visual-spatial attention greatly modulates the second harmonic responses but has negligible effects on the first harmonic responses. However, almost all the studies above mainly focus on the local activities of SSVEP harmonic responses, few have explored the functional networks underlying SSVEP harmonic responses. Accordingly, it is worthwhile to study the corresponding functional network topology of the harmonic responses as we have already done with the fundamental responses under the flickering stimulus.

Increasing evidence demonstrates the value of brain network topology for understanding cognitive processes and diseases (Han et al. 2014; Li et al. 2009; Dubbelink 2014; Pei et al. 2014; Yener and Basar 2010). The graph theory serves as a powerful tool to investigate the brain network topology (Bullmore and Sporns 2009; Rubinov and Sporns 2010). Meanwhile, EEG is often adopted to construct brain network because it is noninvasive and has high temporal resolution (Bonita et al. 2014; De Vico Fallani et al. 2008; Han et al. 2013; Zhang et al. 2014). In the current study, we still focused on the EEG-based network to probe the association between SSVEP harmonic responses and the corresponding network topology of the harmonic response entrained by the flickering stimulus using the graph theoretical analysis.

Based on our previous findings for the fundamental frequency responses, we hypothesize that the larger SSVEP

harmonic responses are to be measured, the more efficient harmonic functional brain networks will exist. Owing to the small amplitude of higher order harmonics and no more than the second harmonics involved in most of the literature (Di Russo et al. 2007; Kim et al. 2011; Pastor et al. 2007), we focus on the second and third harmonics in the current study.

Materials and methods

Eleven healthy right-handed adults (males, mean age was 25 years old) with normal or corrected to normal vision participated in this study. Before the experiment, all participants signed an informed consent form. The study was approved by the Human Research and Ethics Committee of the University of Electronic Science and Technology of China.

EEG acquisition and preprocessing

Four frequencies, 6.25, 8.33, 12.5 and 16.67 Hz were used, generated by two light-emitting diodes (LED). The experiment settings and data acquiring procedure were described in our previous study (Zhang et al. 2013b). The EEG Data were recorded at 250 Hz, and with a bandpass filter between 0.3–70 Hz and a 50 Hz notch filter (50 Hz in China). All data were stored on a disk for off-line analysis. For each frequency, 2-min data were recorded using a 129-channel EEG system referenced to Cz. To reject electrodes with a preponderance of noise resulting from insufficient contact with the scalp, 29 electrodes which were primarily on the outer ring of the electrode array were eliminated from the study due to excessive artifact (Murias et al. 2007). In addition, the EEG amplitudes of one electrode contaminated by the obvious artifacts (e.g. amplitude exceeded 100 μ V) were replaced by the mean value of its three nearest neighboring electrodes (Silberstein et al. 2001; Wu and Yao 2007). Then, we chose 9–12 artifact-free data segments (6 s long) at each frequency for each subject. After the above preprocessing procedure, the data were re-referenced to zero reference by the reference electrode standardization technique (REST) (Yao 2001).

Brain network construction

Eighteen standard electrodes, i.e., Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, C4, T4, T5, P3, Pz, P4, T6, O1, O2 were chosen to construct the networks in order to alleviate volume conduction influence. The coherence was adopted to measure the functional connectivity between two electrodes. Coherence between two signals $x(t)$ and $y(t)$ at a

specific frequency was calculated as following formula (Murias et al. 2007; Srinivasan et al. 1998):

$$C(f) = \frac{|C_{xy}(f)|^2}{C_{xx}(f)C_{yy}(f)} \quad (1)$$

where $C_{xy}(f)$ was the cross-spectrum between $x(t)$ and $y(t)$, and $C_{xx}(f)$, $C_{yy}(f)$ were the auto-spectra.

When calculating the coherence matrix, we adopted the same procedure as in the previous work for the fundamental frequencies network analysis (Zhang et al. 2013b). For each subject, a 2.4 s time window with an overlap of 1.2 s was used to extract data epochs for all the data segments at each frequency. Then, for the fundamental and the two harmonic frequencies of the stimulus, 27–36 coherence matrices (of size 18 by 18) were obtained respectively in each epoch. Furthermore, the coherence matrices were averaged for the fundamental frequency and each harmonic frequency respectively. Each averaged matrix was used as the original connectivity matrix for the corresponding response.

The estimated functional connectivity graph is a full-weighted matrix. Therefore, in order to reduce some spurious edges, we removed some edges based on the sparsity threshold. Sparsity was defined as the ratio of the total number of edges divided by the maximum possible number of edges in a network (Yao et al. 2010; Zhang et al. 2011). The threshold was the sparsity value which was chosen based on the assumption that all brain networks were fully connected and the number of false-positive paths should be minimal with it. With this method, the resulting networks had the same numbers of nodes and edges (Yao et al. 2010; Zhang et al. 2011). The procedure regarding the selection of the threshold was similar to the previous research (Zhang et al. 2013b). In current work, the determination of the sparsity value was based on all the original connectivity matrixes of the fundamental frequencies and their harmonics. By varying the sparsity value from 0 to 1 with a step of 0.01, we selected the edges with the ranked top connection strengths and deleted the remaining edges according to the number of the remaining edges in each network determined by the sparsity value. Then the final sparsity value utilized was defined as the minimum that could keep the concerned network fully connected.

The weighted graph analysis was used to calculate mean functional connectivity (mean coherence), and the corresponding network properties such as clustering coefficient, characteristic path length, global efficiency, and local efficiency (Rubinov and Sporns 2010; Zhang et al. 2011).

The clustering coefficient of the weighted network G with N nodes quantifies the likelihood that the direct neighbors of any node are also connected with each other. Supposing that w_{ij} is the weight between nodes i and j in

the network, and k_i is the degree of node i , then the clustering coefficient can be calculated as:

$$C_i = \frac{\sum_{j,h \in G} (w_{ij}w_{ih}w_{jh})^{1/3}}{k_i(k_i - 1)/2} \quad (2)$$

Let d_{ij} represent the shortest path length between node i and node j , the characteristic path length is

$$L = \frac{1}{N(N-1)} \cdot \sum_{i \in G} \sum_{j \in G, j \neq i} d_{ij} \quad (3)$$

The characteristic path length is the average of the shortest absolute path lengths between the nodes of the network, and it quantifies the level of global communication efficiency of a network.

The global efficiency characterizes the efficiency of a system transporting information in parallel, is defined as

$$E_{global} = \frac{1}{N(N-1)} \cdot \sum_{i \in G} \sum_{j \in G, j \neq i} d_{ij}^{-1} \quad (4)$$

The local efficiency represents the fault tolerance level of the network in response to the removal of a node, is defined as

$$E_{Local} = \frac{1}{2} \sum_{i \in G} \frac{\sum_{j,h \in G, j \neq i} (w_{ij}w_{ih}[d_{jh}(G_i)]^{-1})^{1/3}}{k_i(k_i - 1)} \quad (5)$$

where $d_{jh}(G_i)$ is the shortest path length between node j and node h that only contains neighbors of i .

These network properties were computed with the brain connectivity toolbox (Rubinov and Sporns 2010).

The SSVEP responses calculation and expression

To reduce the possible effect of background activities, we expressed SSVEP responses as SNR (Srinivasan et al. 2006). Based on the fast Fourier transform (FFT) on the EEG data, SSVEP SNR was defined as the ratio of the power of the interested frequency divided by the mean power value of the 1 Hz band which was centered on the interested frequency but excluded the interested frequency itself. For each subject, the SNRs of the fundamental and the two harmonic responses on 18 electrodes at each stimulus frequency were firstly calculated for each epoch, and then each kind of SNRs were further averaged across the epochs and the 18 electrodes. After above procedures, we investigated the relationship between the fundamental and two harmonic responses and their corresponding topological properties using the Pearson's correlation analysis.

Fig. 1 The topographies of a representative subject and the averaged topographies related to basic frequencies and its harmonics of the four stimulus frequencies. The first, third and fifth columns are the topographies of the fundamental, second harmonic and third harmonic

responses of the representative subject respectively. The second, fourth and sixth columns are the averaged topographies of the fundamental, second harmonic and third harmonic responses across subjects respectively

Results

The SSVEP harmonic responses

To display the SSVEP responses, we firstly illustrated topographies of one subject and also the averaged topographies related to fundamental frequencies and their harmonics. For each frequency, the amplitudes of fundamental and harmonic responses were obtained by FFT at each data epoch.

Then, the amplitude of each component was averaged across epochs respectively, and we obtained the topographies of each subject related to fundamental frequencies and their harmonics. For each component, in order to get the averaged topographies across subjects, we firstly averaged the amplitudes across all the electrodes and took the obtained value as the normalization factor (NF) for each subject. The average SSVEP amplitude on each electrode was divided by the NF value to obtain the normalized SSVEP amplitude of each component of each subject, and then these normalized SSVEP amplitudes were averaged across all subjects. The topographies of one

subject and the averaged topographies related to fundamental frequencies and their harmonics are given in Fig. 1.

The SSVEP SNRs of the second and third harmonic of different subjects at the four frequencies were shown in Fig. 2. For most of the subjects at the frequencies (6.25, 8.3 and 12.5 Hz) the responses to the third harmonic have lower amplitudes than to those to the second one. Because the third harmonic of 16.6 Hz coincided with the 50 Hz notch frequency, it was not further analyzed. For each component at each frequency, the inter-individual variability existed among subjects.

The relationship between SNRs and mean functional connectivity

Based on the procedure given in “[EEG acquisition and preprocessing](#)” section, we finally chose the sparsity value 0.67 to reduce the spurious edges of all averaged networks before computing the topological properties. For all the four frequencies, we replicated the results reported in our previous studies that SSVEP fundamental frequency responses were closely correlated with network properties

Fig. 2 The SNRs of the second and third harmonics at the four frequencies across different subjects. **a** 6.25 Hz, **b** 8.3 Hz, **c** 12.5 Hz, and **d** 16.6 Hz. The result was not presented for the third harmonic of 16.6 Hz (50 Hz notch frequency)

(Zhang et al. 2013b). Here we omitted the results on the fundamental frequency responses, and mainly focused on the possible relationship between harmonic responses (the second and third harmonics) and the corresponding network properties.

Figure 3 demonstrates the relationships between the second harmonic SNRs and the mean functional connectivity of corresponding networks across 11 subjects at four frequencies. At each frequency, the mean functional connectivity showed a significantly positive correlation with the SNRs. For the third harmonic responses, only the 6.25 Hz showed significant correlation as shown in Fig. 4. At the 8.3 and 12.5 Hz, the results were: $r = 0.34$, $p = 0.3$ and $r = -0.5$, $p = 0.1$, respectively.

The main contribution to the SSVEP fundamental frequency responses could be made by the connections from the occipital to frontal regions (Zhang et al. 2013b). In order to explore the merit of each connection to the SNRs of the second harmonic responses, we computed the correlation coefficients between the strengths of each connection and the averaged SNRs across subjects. The topology maps are shown in Fig. 5. All the links in Fig. 5

denote the connections which are positively correlated with the SNRs. In order to reveal the connection patterns, we presented four lines with different widths related to four subintervals of the correlation's magnitude as indicated in the Fig. 5. It seems that the connections between the parietal–occipital and frontal regions remain to be the major contribution to the second harmonic. For the completeness, Fig. 6 shows the connections which were negatively correlated with the SNRs. These links were sparse, and widely distributed without any specific patterns. As shown both in Figs. 5 and 6, obviously the connections of positive correlation with SNR outnumbered those of negative correlation (Fig. 7).

The relationship between the SNRs and the topological properties

We found the significant correlation between the SNRs and the topological properties for the second harmonic as shown in Table 1 and Fig. 8. The SNRs were significantly positively correlated with the clustering coefficient, global efficiency and local efficiency, but negatively correlated

Fig. 3 The correlation between the mean functional connectivity of network and SNRs second harmonic responses across subjects. **a** 6.25 Hz; **b** 8.3 Hz; **c** 12.5 Hz; **d** 16.6 Hz. The red lines indicate the fitted linear trends. The r denotes correlation coefficients, p denotes significant level of correlation coefficients. (Color figure online)

Fig. 4 The correlation between the mean functional connectivity of network and SNRs of the third harmonic responses across subjects at 6.25 Hz

with the characteristic path length. These mean that larger SNRs correspond to larger clustering coefficient, global efficiency and local efficiency, but shorter characteristic path length. The shorter characteristic path length and higher global efficiency of the networks indicate more efficient parallel information transfer in the brain (Li et al. 2009). Our results presented here may suggest that larger harmonic responses are related to more efficient functional

networks composed of locally and non-locally distributed brain regions.

In addition, we found the third harmonic SNR was correlated with its corresponding brain network properties only for 6.25 Hz stimulus as shown in Fig. 9. No significant correlations were found for the other three higher frequencies as listed in Table 2. As explained above, the results of the third harmonic of 16.6 Hz was not calculated.

Discussion

The literature has reported that the SSVEP responses correlated with the functional brain network topological structure (Zhang et al. 2013a, b). These findings may open new ways for cognitive and clinical researches using the SSVEP. For the spectrum of SSVEP data, it usually consists of the fundamental frequency of the stimulus as well as its harmonics of the flickering frequency. One study has demonstrated that the fundamental and harmonic SSVEP responses have different spatial and functional roles (Kim et al. 2011). It is meaningful to explore the mechanism for the harmonic responses from network perspective.

Figure 3 and Table 1 revealed that the second harmonic responses were correlated with the mean functional connectivity and the network topological properties. They were consistent with our previous study on the fundamental frequency responses and could be replicated for all the four

Fig. 5 The topology of the positive correlation between the connection strength of each connection and the SNRs across subjects at the second harmonic frequency. **a** 6.25 Hz; **b** 8.3 Hz; **c** 12.5 Hz;

d 16.6 Hz. The *lines* with different widths indicate the magnitudes of the correlation coefficients related to four subintervals as shown in the figure

Fig. 6 The topology of the negative correlation between the connection strength of each connection and the SNRs across subjects at the second harmonic frequency. **a** 6.25 Hz; **b** 8.3 Hz; **c** 12.5 Hz; **d** 16.6 Hz. The *line* widths indicate the magnitude of the absolute

values of the correlation coefficients. The *lines* with different widths indicate the magnitudes of the correlation coefficients related to four subintervals as shown in the figure

Fig. 7 The fronto-parietal connections that showed significant correlation with SNRs of the second harmonic of the four stimulus frequencies. The *blue* and *red* lines indicate the links significantly positively or negatively correlated with the SNRs, respectively

($p < 0.05$). The *lines* with different widths indicate the magnitudes of the correlation coefficients related to four subintervals which are the same to the Figs. 5 and 6. (Color figure online)

frequencies that we adopted here (Zhang et al. 2013b). However, except for the lowest frequency 6.25 Hz, no significant correlations were found between the third harmonic response and network properties. Therefore, the higher harmonics and more subjects' data deserved to be probed to investigate the consistency of our results in the future.

Based on the results of the second harmonics, we further infer that the constructions of the functional network play

an important role for SSVE responses. Sensory functional brain networks can be investigated using steady-state paradigms with a periodic stimulus. The different topological brain networks may modulate the same flickering inputs to shape different outputs. More efficient network organizations may generate larger responses, in which a shorter characteristic path length and a higher global efficiency mean more efficient parallel information transfer and

Table 1 Summary of the relationship between the second harmonic network topological properties and the second harmonic SNRs across subjects at the four flickering frequencies

Frequencies (Hz)	Clustering coefficient		Path length		Global efficiency		Local efficiency	
	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>
6.25	0.88	***	−0.85	***	0.87	***	0.87	***
8.33	0.93	***	−0.95	***	0.93	***	0.94	***
12.5	0.75	**	−0.70	*	0.74	**	0.78	**
16.67	0.76	**	−0.77	**	0.82	**	0.70	*

r denotes correlation coefficients, *p* denotes significant level of correlation coefficients

*** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$

Fig. 8 The correlations between the SNRs and the four network properties of the second harmonic responses at the 6.25 Hz. Clustering coefficient (a), global efficiency (c) and local efficiency (d) are significantly positively correlated with SNRs, but the opposite goes for characteristic path length (b). The red lines indicate the fitted linear trends. *r* denotes correlation coefficient, *p* denotes significant level of the correlation coefficient. (Color figure online)

integration in the brain, and a larger clustering coefficient and local efficiency mean fast local information processing. Taken together, more efficient functional networks are related to larger fundamental or harmonic responses. In fact, some studies have shown similar relationships between the brain network topology and the measurements of brain function (Li et al. 2009; Vakhtin et al. 2014; Zhou et al. 2012). For instance, Li et al. have found that more efficient network organization is associated with better intellectual performance (Li et al. 2009).

Although previous literature demonstrates different spatial and functional roles of the fundamental and harmonic SSVEP responses (Kim et al. 2011; Pastor et al.

2007), source localization is the main concern. The current study focused on the brain topology which involved widely distributed but interconnected brain regions during the generation of the harmonic responses. In fact, Fig. 4a in the study by Kim et al. demonstrated that the first and second harmonic topographic patterns were similar, except that the first harmonic had a medial posterior focus while the second harmonic had a contralateral posterior focus. In light of network, our results reveal that the second harmonic responses also involve locally and non-locally distributed brain regions besides the parieto-occipital cortex. The main connection pattern originates from the interactions between the frontal and parietal–occipital regions which are similar

Fig. 9 The correlation between the third harmonic SNRs and the four network properties at 6.25 Hz. Clustering coefficient (a), global efficiency (c) and local efficiency (d) are significantly positively correlated with SNRs, but the opposite goes for characteristic path length (b). The red lines indicate the fitted linear trends. r denotes correlation coefficient, p denotes significant level of the correlation coefficient. (Color figure online)

Table 2 Summary of the relationship between the third harmonic network topological properties and the third harmonic SNRs across subjects at the four flickering frequencies

Frequencies (Hz)	Clustering coefficient		Path length		Global efficiency		Local efficiency	
	r	p	r	p	r	p	r	p
6.25	0.84	0.001	−0.74	0.009	0.75	0.008	0.84	0.001
8.33	0.38	0.25	−0.35	0.28	0.34	0.31	0.36	0.28
12.5	−0.51	0.11	0.57	0.07	−0.54	0.09	−0.51	0.11
16.67	–	–	–	–	–	–	–	–

r denotes correlation coefficients, p denotes significant level of correlation coefficients

to the fundamental frequency response (Zhang et al. 2013a, b). This result may be complementary to the previous studies about the SSVEP second harmonic responses (Di Russo et al. 2007; Kim et al. 2011; Pastor et al. 2007).

SSVEPs involve both local and distant widely distributed brain regions (Vialatte et al. 2010). Furthermore, it has been reported that the occipital and frontal cortices were the two main sources of SSVEP (Srinivasan et al. 2007). In our previous studies, we have found that the long connections from the parietal–occipital to frontal region were significantly correlated with the SNRs with both SSVEP data and resting-state data (Zhang et al. 2013a, b). Here, we verified that the connections from the parietal–occipital to frontal region were significantly correlated with the

harmonic responses. Taken together, it turns out to be that the above results strengthen the case for parietal–occipital and frontal regions being the two main sources for both fundamental frequency and second harmonic responses.

Methodologically, the graph theory is a useful tool to explore the underlying neural mechanisms of some neurological or cognitive phenomena (Li et al. 2009; Stam et al. 2009; Yao et al. 2010; Zhang et al. 2011). This tool can generate more valuable findings than some traditional analysis methods, providing the potential biomarkers for observation of the diseases and cognitive function (Stam et al. 2009). It is plausible that the network analysis based on graph theory may bring new insights to both the SSVEP mechanisms and the relevant research using the SSVEPs as

the task tags. We systematically investigated the relationship between SSVEP and possibly existing brain networks, based on scalp recorded EEG data processed using graph theoretical approaches. However, we haven't involved cognitive tasks in any of our existing work. The future work is to combine the flickering stimulus with the various cognitive activities, such as visual attention and working memory (Ding et al. 2006; Wu et al. 2010).

In addition, we only explored the correlations between SNRs and network metrics in the current study. This is because previous studies have demonstrated that SSVEPs involve both local and distant widely distributed brain regions (Vialatte et al. 2010; Srinivasan et al. 2007; Zhang et al. 2013b). However, the nodal network metrics (nodal strength) may reveal the local node roles to the SSVEPs, which is also worthwhile to be explored. Thus, one possible extension in the future study is to investigate the correlation between nodal metrics and nodal SNR for both the fundamental and harmonic responses.

A final note of caution concerns volume conduction and the reference when performing the analysis for the scalp EEG network. In the current and our previous studies, we tried to alleviate the influence of volume conduction by choosing 18 widely spaced electrodes that cover the main SSVEP recording regions, and the influence of the reference by adopting the novel zero-reference (Qin et al. 2010).

Conclusion

In this paper, we firstly explored the relationship between the SSVEP harmonic responses and the corresponding brain network using the graph analysis. We found that the second harmonic responses demonstrated strong correlation with the organization of the networks, and the same held for the third harmonic at the lowest frequency (6.25 Hz). It is concluded that more efficient topological organizations of the harmonic networks entrained by the stimulus are related to larger SSVEP harmonic responses. These results may enhance the understanding of the SSVEP mechanism, and open new windows for the cognitive and clinical researches by integrating the SSVEP with the graph theoretical analysis.

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