

INTERINDIVIDUAL REACTION TIME VARIABILITY IS RELATED TO RESTING-STATE NETWORK TOPOLOGY: AN ELECTROENCEPHALOGRAM STUDY

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Abstract—Both anatomical and functional brain network studies have drawn great attention recently. Previous studies have suggested the significant impacts of brain network topology on cognitive function. However, the relationship between non-task-related resting-state functional brain network topology and overall efficiency of sensorimotor processing has not been well identified. In the present study, we investigated the relationship between non-task-related resting-state functional brain network topology and reaction time (RT) in a Go/Nogo task using an electroencephalogram (EEG). After estimating the functional connectivity between each pair of electrodes, graph analysis was applied to characterize the network topology. Two fundamental measures, clustering coefficient (functional segregation) and characteristic path length (functional integration), as well as “small-world-ness” (the ratio between the clustering coefficient and characteristic path length) were calculated in five frequency bands. Then, the correlations between the network measures and RT were evaluated in each band separately. The present results showed that increased overall functional connectivity in alpha and gamma frequency bands was correlated with a longer RT. Furthermore, shorter RT was correlated with a shorter characteristic path length in the gamma band. This result suggested that human RTs were likely to be related to the efficiency of the brain integrating information across distributed brain regions. The results also showed that a longer RT was related to an increased gamma clustering coefficient and decreased small-world-ness. These results provided further evidence of the association between the resting-state functional brain network and cognitive function. © 2011 IBRO. Published by Elsevier Ltd. All rights reserved.

Key words: cognitive function, EEG, functional connectivity, phase lag index, graph analysis.

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Abbreviations: EEG, electroencephalogram; fMRI, functional magnetic resonance imaging; PLI, Phase lag index; RT, reaction time.

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Most studies investigating cognitive functions and their neural correlation were aimed at localizing brain regions that are responsible for the tasks (Dolan, 2008). Recently, the viewpoint of cognitive function has been inclined to the dynamic interconnections between distributed brain regions (Bressler and Menon, 2010). It has been suggested that the pattern of the network topology might be of great importance for human brain function (Reijneveld et al., 2007; Bassett and Bullmore, 2009; Bullmore and Sporns, 2009; Li et al., 2009; van den Heuvel et al., 2009).

Our brain is not inactive even during the non-task-related resting-state (Raichle et al., 2001; Greicius et al., 2003; Raichle and Snyder, 2007). The brain activity during the resting-state may reflect the brain's potential processing abilities (Ramos-Loyo et al., 2004) and is correlated with individual differences in the cognitive process (Kounios et al., 2008). A resting functional magnetic resonance imaging (fMRI) study has shown that human intellectual performance was dependent on the efficiency of our brain integrating information across distributed brain regions (van den Heuvel et al., 2009). However, the association between non-task-related resting-state functional brain network topology and the efficiency of information processing has not been well identified.

Network topology could be studied using the graph theory. By estimating the functional connectivity between pairs of brain regions or electrodes, we can obtain the graph representation of the functional brain network (Stam and Van Dijk, 2002; Bullmore and Sporns, 2009; Stam et al., 2009). Various measures such as the clustering coefficient and characteristic path length can be used to characterize the network (Bullmore and Sporns, 2009; Rubinov and Sporns, 2010). The clustering coefficient is a measure of functional segregation, whereas the characteristic path length is the functional integration (Rubinov and Sporns, 2010). A type of network, named small-world (Watts and Strogatz, 1998), which could be quantitatively measured by small-world-ness (Humphries and Gurney, 2008), has been suggested to be optimal for information processing (Lago-Fernández et al., 2000; Latora and Marchiori, 2001). Moreover, the existence of small-world topology in functional brain networks has been recently confirmed by a few studies (Watts and Strogatz, 1998; Stam, 2004; He et al., 2007; Bullmore and Sporns, 2009).

In the present study, we investigated the relationship between the electroencephalogram (EEG) non-task-related resting-state brain network topology and reaction time (RT) in a Go/Nogo task. The RT has been suggested to reflect the overall efficacy of sensorimotor processing

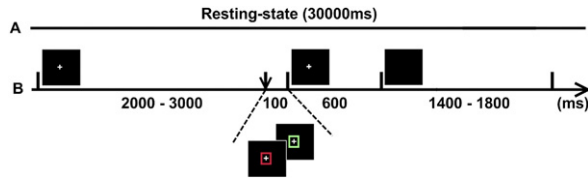


Fig. 1. Experimental paradigm. (A) A resting-state of 5 min (B) Go/Nogo task design. Subjects were instructed to observe the cross fixation for 2000–3000 ms before a red or green square appeared for 100 ms after the cross. The subject was instructed to respond as quickly as possible, only upon seeing the green square. The square appeared for 100 ms followed by another cross fixation of 600 ms. Before the next trial began, the screen was blank for 1400–1800 ms. For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.

(Reinhart et al., 2011). We hypothesized that a shorter RT was related to higher efficiency of the brain integrating information (i.e. shorter characteristic path length).

EXPERIMENTAL PROCEDURES

Participants

Twelve healthy, right-handed college students (four females and eight males, age range: 19–21 years) with normal or corrected-to-normal vision were recruited. None of the subjects used any medication nor did they or their relatives suffer from psychiatric or neurological disease. All subjects gave their informed and written consent before participation.

Procedure

Before recording the EEG, the subject was seated in a semi-sitting position in a quiet room and was asked to stay relaxed and refrain from extensive head motion. Continuous EEG was recorded during the following conditions. First, the subject was asked to keep his/her eyes closed for 5 min (Fig. 1A). Then, after a break of 1 min, the subject performed a Go/Nogo task (Fig. 1B). The Go/Nogo task was adopted to maintain a high level of attention in the subjects throughout the experiment (Nikulin et al., 2008). In the present study, we were going to explore the relationship between non-task-related resting-state EEG and RT, which was provided by the task. Hence, any further EEG analysis mentioned in the present article was focused on the resting-state data.

At the beginning of each trial the subjects were asked to fixate on a warning cue, which is a central cross. After a random delay of 2000–3000 ms, the imperative cue appeared for 100 ms, being a Go cue (green square) or Nogo cue (red square). The subject

was asked to press a button on the SRbox (Psychology Software Tools Inc., Pittsburgh, PA, USA) as quickly as possible when only seeing the Go cue. Following the Go/Nogo cue, the cross was further presented for 600 ms. The screen was blank for 1400–1800 ms before the beginning of the next trial. The Go and Nogo cues were presented in random order with equal probability. Each subject completed four blocks, each of which consisted of 60 trials.

EEG recording

EEG data were recorded using EGI's 64-channel HydroCel Geodesic Sensor Net (Electrical Geodesics, Inc., Eugene, OR, USA) with a reference to the vertex (Cz) electrode. All impedances were kept less than 50 k Ω . The data were sampled at a frequency of 1 kHz. The following processing steps were completed by using EEGLAB (<http://sccn.ucsd.edu/eeqlab/index.html>) (Delorme and Makeig, 2004). The raw data were first subjected to a band-pass filter between 0.5 and 100 Hz. To filter out the line noise, a 50-Hz notch filter was then applied. The data were then down-sampled to 500 Hz. For each subject, the first five artifact-free (with all samples' amplitudes not exceeding $\pm 80 \mu\text{V}$) epochs of 4096 samples (8.192 s) were selected (Stam et al., 2009). One subject was excluded from further analysis due to extensive artifacts. All epochs were then converted to a current source density (CSD) yielding reference-free data using the methods proposed by Kayser and his coworkers (Kayser and Tenke, 2006). Epochs were band-pass filtered into the following frequency bands: delta (0.5–4 Hz), theta (4–8 Hz), alpha (8–13 Hz), beta (13–30 Hz), and gamma (30–45 Hz). Further analyses were performed on those bands separately.

Behavior data analysis

For each subject, the Go-cue-related mean RT was calculated. Any RT lower than 100 ms and greater than 500 ms was not included in the calculation (Gonzalez Andino et al., 2005). After the removal of those samples, the RT distributions of each subject were plotted as boxplots as shown in Fig. 2. The mean RT of each subject was calculated by averaging the RTs while excluding the outliers.

Phase lag index

Phase lag index (PLI), which measures consistency of the phase differences (phase synchronization) between the two signals, is reflective of the functional connectivity between pairs of electrodes (Stam et al., 2007, 2009). It was shown to be less affected by volume conduction than traditional measures such as coherence and was sensitive to non-linear data (Stam et al., 2007, 2009). A higher PLI value would indicate stronger functional connectivity, which is usually interpreted as shorter distance between two electrodes (Stam et al., 2009). The PLI is defined as follows (Stam et al., 2007)

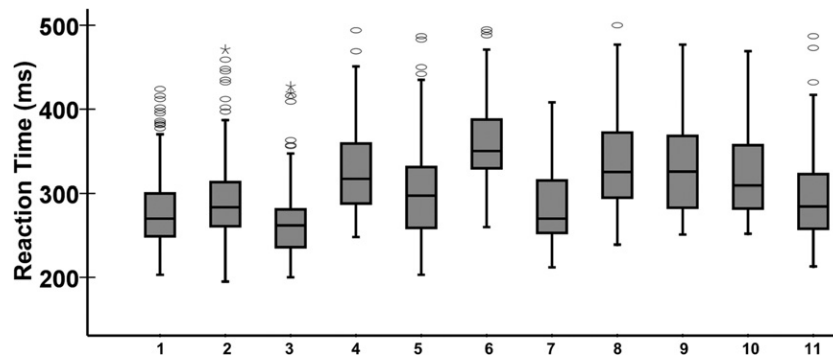


Fig. 2. The RT distribution for each subject. Box plots show the median, interquartile range and extremes. Ellipses and asterisks indicate outliers and extreme outliers separately.

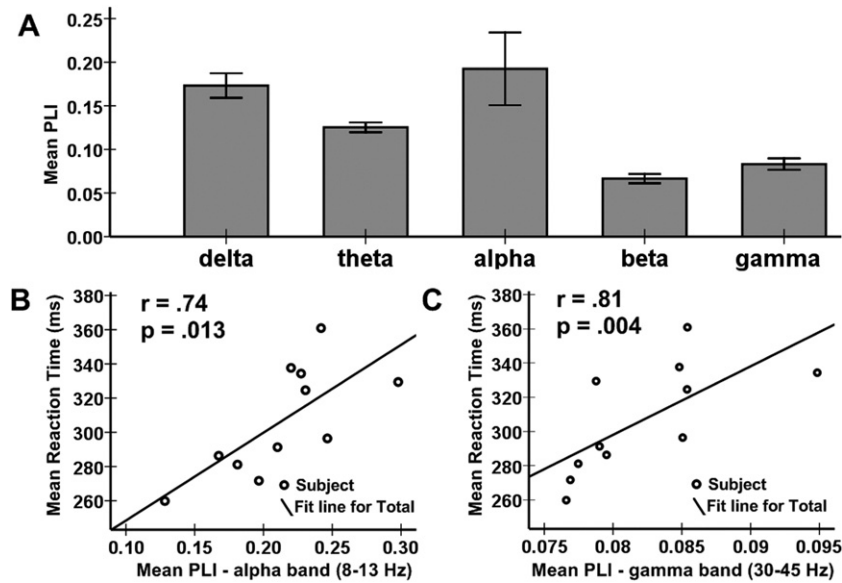


Fig. 3. Mean PLI and its correlation with the RT. (A) Mean PLI of each frequency band. Error bars are $\pm$ SDs. (B) The correlation of the mean PLI in the alpha band and RT. (C) The correlation of the mean PLI in the gamma band and RT.

$$PLI = |\langle \text{sign}[\Delta\varphi(t_i)] \rangle|$$

where $\Delta\varphi(t_i)$ is the instantaneous phase difference between two electrodes at time point i , $\text{sign}[\Delta\varphi(t_i)]$ is 1 when $\Delta\varphi(t_i)$ is positive and $\text{sign}[\Delta\varphi(t_i)]$ is -1 when $\Delta\varphi(t_i)$ is negative; $\langle \bullet \rangle$ denotes average over time (see Stam et al., 2007 for more information).

The PLI between all possible pairs of EEG channels (except the two on the cheek) were calculated, resulting in a 62x62 matrix of PLI values for each epoch, frequency band, and subject. Then, for each frequency band, the average PLI matrix was calculated by averaging across epochs per subject.

Graph analysis

In the present study, treating the electrodes as vertices and PLI between them as edges, the EEG data can be topologically represented by an undirected weighted graph. Two fundamental measures are the clustering coefficient, which is calculated as the fraction of the vertex's neighbors that are also the neighbors of each other, and the characteristic path length, which is the average shortest path length between all pairs of vertices (Watts and Strogatz, 1998).

The clustering coefficient was defined as follows (Onnela et al., 2005; Rubinov and Sporns, 2010):

$$C^w = \frac{1}{N} \sum_{i \in N} \frac{\sum_{j, h \in N} (w_{ij} w_{ih} w_{jh})^{1/3}}{\sum_{j \in N} w_{ij} (\sum_{h \in N} w_{ih} - 1)}$$

where N is the number of electrodes (here, $N=62$) and w is the PLI value between vertices i and j .

The characteristic path length was defined as follows (Rubinov and Sporns, 2010):

$$L^w = \frac{1}{N} \sum_{i \in N} \frac{\sum_{j \in N, j \neq i} d_{ij}^w}{n - 1}$$

where N is the number of electrodes (here, $N=62$), w is the PLI value between vertices i and j , and d_{ij}^w is the shortest path length between vertices i and j .

Both the clustering coefficient and characteristic path length are dependent on weights and network size (Stam et al., 2009). 50 surrogate networks were generated by randomly reshuffling

the edge weights while keeping the symmetry of the matrix. Then, the normalized clustering coefficient and characteristic path length were calculated as $C_{\text{normalized}}^w = C^w / \langle C_{\text{surrogate}}^w \rangle$ and $L_{\text{normalized}}^w = L^w / \langle L_{\text{surrogate}}^w \rangle$, where $\langle \bullet \rangle$ denotes the average over ensembles of the measures of the 50 surrogate networks (Stam et al., 2009). The "small-world-ness" was then calculated as in Humphries and Gurney (2008). The calculation of the graph measures mentioned previously was performed using the MATLAB toolbox developed by Rubinov and Sporns (Rubinov and Sporns, 2010).

Correlation analysis

The correlation between all network measures and RT were evaluated using the non-parametric Spearman rank correlation coefficient to avoid the normality assumptions.

RESULTS

Behavioral performance

The subjects performed the task with an accuracy range from 94.2% to 100% (mean: 98%). The box plots in Fig. 2 showed the distribution of each subject's RTs between 100 and 500 ms. The mean RT across the subjects was 306.69 ms (SD: 32.15 ms).

Functional connectivity and RT

Mean PLI of each frequency band is shown in Fig. 3A. Correlation analysis revealed significant positive correlations between mean PLI in alpha and gamma bands and RT (Fig. 3B, C). To identify which links were more correlated with RT in the alpha and gamma bands, the correlation coefficient between RT and the PLI of each possible electrode pair was calculated. The topological locations of the links showed a significant correlation ($P < 0.01$, uncorrected) with the RT, which are shown in Fig. 4. The network measures, normalized clustering coefficient, normalized characteristic path length as well as small-world-ness were found to be related to the RT in the gamma band (Fig.

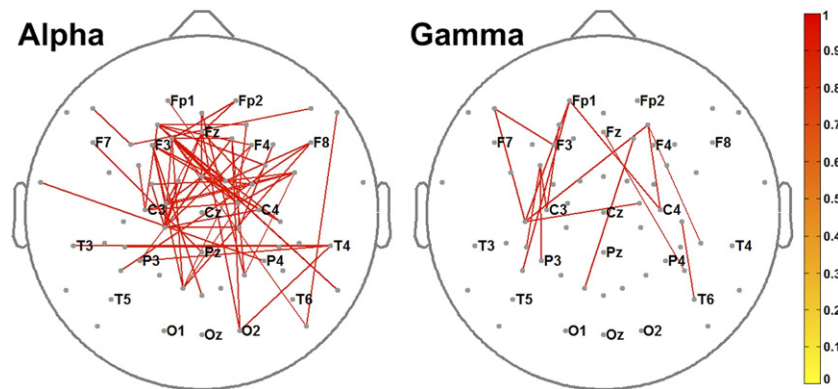


Fig. 4. Spatial topography of links that showed a significant correlation with the RT in the alpha and gamma bands. Lines are color-based on the correlation coefficient between each link and RT. For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.

5). An increased normalized clustering coefficient was correlated with a longer RT in the gamma band (Fig. 5A). A significant positive correlation between the normalized characteristic path length and RT was observed (Fig. 5B). Furthermore, the gamma band small-world-ness was found to be negatively correlated with RT (Fig. 5C). However, the results showed no significant correlation between RT and the alpha normalized clustering coefficient, characteristic path length, or small-world-ness.

DISCUSSION

The current study found that various eye-closed non-task-related resting-state functional connectivity network measures were correlated with the RT in a Go/Nogo task. Specifically, the correlation between the mean PLI and RT was observed in alpha and gamma bands. Moreover, the network topology measures were also found to be correlated with RT in gamma but not in any other band. These results might suggest that the non-task-related resting-state EEG measures might be reflective of the efficiency of sensorimotor processing in healthy subjects in the Go/Nogo task.

On one hand, in the current study, the overall alpha synchronization was found to be positively correlated with

RT (Fig. 3). Alpha has been suggested to be an important timing mechanism for the cognitive process and is related to the speed of information processing (Klimesch et al., 1996). The local and long-range alpha synchronizations have been associated with various cognitive functions (Gonzalez Andino et al., 2005; Hanslmayr et al., 2007a, b; Doesburg et al., 2009). In detail, it was found that increased pre-stimulus alpha power was related to a slower response in healthy subjects (Gonzalez Andino et al., 2005). This pre-stimulus local alpha synchronization was interpreted to be a reflection of inhibitory processing (Gonzalez Andino et al., 2005). The event-related alpha synchronization was suggested to be a functional correlate of inhibition in a motor task (Klimesch et al., 2007). The inhibitory mechanism of alpha synchronization might explain the positive correlation between the mean PLI and RT in our study. Of note, Doesburg and colleagues found that successful visuo-spatial attention was related to long-range alpha synchronization between the low-level visual and high-level visual cortices (Doesburg et al., 2009). On the other hand, Hanslmayr et al. showed that visual perception was negatively correlated with alpha synchronization (Hanslmayr et al., 2007b). Another study conducted by Hanslmayr and coworkers also showed that lower alpha

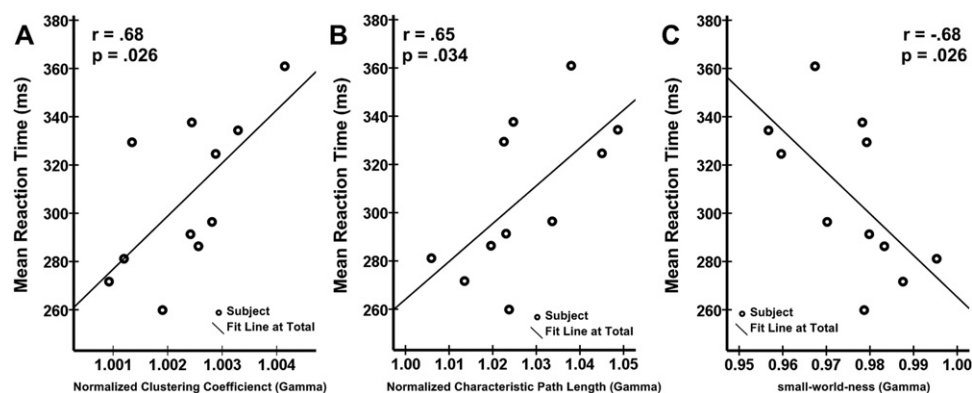


Fig. 5. Correlations between gamma network topology measures and RT. Mean RTs were significantly correlated with the gamma band (A) normalized clustering coefficient, (B) normalized characteristic path length, and (C) small-world-ness.

synchronization was related to better perception performance (Hanslmayr et al., 2007a). These studies might have further indicated that the role of alpha synchronization may depend on the type of tasks (Doesburg et al., 2009). Most of those studies mentioned previously focused on research of the relationship between pre-stimulus oscillations and cognitive performance. Thus, it was difficult to make straightforward comparisons with previous studies discussed previously because of the different tasks and analytical procedures. While the oscillations during the pre-stimulus period are a reflection of the subject's level of performance and attention effects on neural activities (Hanslmayr et al., 2007a), the resting-state alpha synchronization was more likely to reflect the potential processing abilities of the brain and can be predictive of cognitive performance (Ramos-Loyo et al., 2004; van den Heuvel et al., 2009). Recent studies have shown that the resting-state alpha frequency and power were related to the RT (Jin et al., 2006). According to our results, we speculated that the overall decreased alpha synchronization was likely to facilitate the sensorimotor processing and thus resulted in a shorter RT. In parallel, we also have to note that the electrodes showing significant correlation with RT were mainly in the prefrontal, frontal, sensorimotor, parietal-occipital, and occipital regions (Fig. 4A). These regions were mainly involved in the default mode network (DMN), dorsal attention network, and visual processing network (Mantini et al., 2007). In a simultaneous EEG and fMRI study, Mantini and coworkers found strong correlation between the alpha fluctuation and those networks (Mantini et al., 2007). The frontal regions have been suggested to play an important role in top-down modulation procedures such as visuo-spatial attention, working memory, and visual feature processing (Sauseng et al., 2005; Buschman and Miller, 2007; Siegel et al., 2008; Zanto et al., 2010, 2011). The alpha synchronization in fronto-parietal networks was related to the neural correlates of consciousness (Palva and Palva, 2007). Thus, we could further speculate that the state of the subject's consciousness during the resting-state might be directly related to the RT. Alpha oscillation had also been linked to motor function. Pfurtscheller and colleagues found that the central area alpha would desynchronize before the onset of imagining hand movement (Pfurtscheller et al., 1997). In our study, stronger alpha synchronization between electrode pairs, including the ones over the sensorimotor area (Fig. 4), was related to a longer RT. Taken together, these results might indicate that alpha desynchronization would facilitate motor execution.

On the other hand, the current study revealed the correlation between non-task-related resting-state gamma measures and task-related RT. A significant positive correlation between the gamma mean PLI and RT was observed (Fig. 3C). The connections that showed significant correlation with RT were mainly frontal-central and frontal-parietal pairs (Fig. 4B). The pre-frontal was one of the regions composing the resting-state network related to self-referential mental activity (Mantini et al., 2007). Strong correlation between the network and the gamma power was also observed by Mantini and coworkers (Mantini et

al., 2007). Furthermore, gamma activity has been widely associated with higher cognitive functions, such as top-down attention processing, memory, and learning (Singer, 1993; Tiitinen et al., 1993; Sarnthein et al., 1998; Debener et al., 2003; Kaiser and Lutzenberger, 2003; Tallon-Baudry, 2004; Gonzalez Andino et al., 2005). By adopting a visual perception task, Hanslmayr and colleagues demonstrated that pre-stimulus gamma synchronization was related to better visual perception (Hanslmayr et al., 2007a). Gonzalez and coworkers also found that increased gamma power was related to a shorter human RT (Gonzalez Andino et al., 2005). The results of those studies seemed to lead to the conclusion that increased gamma synchronization should lead to a shorter RT, whereas the opposite was reported here. One possible reason for the discrepancy would be that the task adopted in this paper was different from that in those studies. Another important interpretation would be that we analyzed the non-task-related resting-state EEG instead of the pre-stimulus period recordings. The pre-stimulus gamma activity has been suggested to reflect the current attention and expectation of the upcoming relevant behavioral stimulus that would affect behavioral performance (Hanslmayr et al., 2007a). However, the resting-state gamma would be more reflective of the potential processing ability. The result suggested that the resting-state gamma synchronization would also facilitate sensorimotor processing during the Go/Nogo task.

In the present paper, the network measures were found to be correlated with RT in the gamma band, whereas no such relationship was found in other bands. In more detail, both the normalized clustering coefficient and characteristic path length were found to be positively correlated with the RT (Fig. 5A, B). Recent studies have shown that the human functional brain network is organized in a highly efficient small-world manner, and its network topology might be of great importance to human brain function (Sporns et al., 2004; Reijneveld et al., 2007; Bassett and Bullmore, 2009; Bullmore and Sporns, 2009; Li et al., 2009; van den Heuvel et al., 2009). The normalized clustering coefficient measures the efficiency of local information transformation, whereas the normalized characteristic path length measures the global efficiency of information transformation (Bullmore and Sporns, 2009). The greater clustering coefficient implies greater local information processing, whereas a smaller characteristic path length implies greater global efficiency information processing. Our results indicated that increased efficiency of the brain integrating information locally would result in slower sensorimotor processing. On the contrary, increased global brain information integration efficiency would facilitate the sensorimotor processing in the task and thus result in a faster response. It was interesting to note that a recent fMRI resting-state study found that the decreased normalized path length would lead to a higher intelligence quotient (van den Heuvel et al., 2009). Our results revealed that for the resting-state brain network, higher small-world-ness was likely to facilitate sensorimotor processing. However, it was worth noting that the gamma small-world-ness ranged between 0.956 and 0.995, which implied that the network

might not be a small-world one (Humphries and Gurney, 2008). This was mainly because a great number of weak connections were taken into consideration when the weighted network analysis was adopted in the current study.

Recently, a few studies have demonstrated that EEG activity shows great difference between eye-closed and eye-open resting-states (Barry et al., 2007, 2009; Chen et al., 2008; McAvoy et al., 2008). Thus, our current findings could not be generalized to the eye-open condition. To this point, a direct examination of the relationship between eye-open EEG activity and the behavioral outcomes would be of great interest in a future study. Last but not least, it was worth noting that neurological and psychiatric disorders, such as Parkinson's disease, show excessive synchronization of neuronal activity and longer reaction time (Williams et al., 2005; Hammond et al., 2007). Patients with Alzheimer's disease showed decreased overall synchronization (Stam et al., 2009), but had a longer choice reaction time (Gordon and Carson, 1990). Thus, reconciling the current results with neurological or psychiatric disorder studies should be done with caution.

CONCLUSION

In conclusion, the present study indicates that non-task-related resting-state functional connectivity and network topology are related to RT in Go/Nogo task. Increased mean PLI in alpha and gamma bands is related to a longer RT. It was also found that a shorter normalized gamma characteristic path length was related to a shorter RT. Furthermore, a shorter RT was related to a decreased normalized gamma clustering coefficient and increased small-world-ness.

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