Topological changes of the effective connectivity during the working memory training

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Abstract—**Working memory (WM) refers to the retention of information over a short period of time. Accumulated evidence showed that training WM would lead to beneficial effects in untrained tasks, which could be attributed to the strengthening of the functional connections between brain regions through repeated training task. In this proof of concept investigation, we applied a graph theoretical approach to analyze the early changes of functional connectivity from two subjects undergoing a spatial *n*-back WM training task for three continuous days. A significant decreased clustering coefficient and normalized shortest path length was revealed, suggesting a reduced local efficiency with an increased global efficiency after WM training. Our findings thereby provide insightful implications for understanding the mechanisms of brain dynamics in cognitive training.**

I. Introduction

Working memory (WM) refers to the retention of information over a brief period of time, a function that is of central importance for a wide range of cognitive tasks and for academic achievement [1]. Deficits of WM are typically considered the primary source of cognitive impairment in numerous special-needs populations (e.g., ageing) and have been observed in many neuropsychiatric conditions (for a review, see [2]). Considering the importance of WM, it is not surprising that attempts to improve WM have a long history.

In recent years, an increasing number of cognitive training studies have demonstrated not only improvements in the trained task but also untrained tasks [3], suggesting training-induced plasticity in a common neural network for WM. Moreover, altered patterns of brain activity in the fronto-parietal cortices during untrained cognitive tasks after WM training have been demonstrated [4, 5]. These studies have been useful in identifying neural markers of WM training effect. Nonetheless, they have not addressed the issue of what are the effects of WM training on whole neural networks. This is due mainly to the fact that analyses are usually carried out in a univariate fashion.

Rather than investigating the individual regions in isolation, the human brain can be considered as a large-scale network of interconnected brain regions – the human connectome. This connectome has the capability to provide fundamental insights into the organization and integration of brain networks [6]. Through utilizing functional connectivity approach, Cole and colleagues demonstrated a central role for fronto-parietal cortices flexible hubs in cognitive control and adaptive implementation of task demands [7]. It has also been suggested that repeated co-activation of regions in cognitive training task could lead to the strengthening of the functional connections between them [8].

Graph theory is a natural framework for the mathematical representation of complex networks. Recently, graph theory has attracted considerable attention in brain network research because it provides a powerful way to quantitatively describe the segregation and integration of brain network form perspective of the topological organization [6]. Based upon the prior research on the WM training effect of functional connectivity, we are specifically interested in the topological changes of the functional connectivity brain networks during the WM training task. Moreover, several recent studies have revealed beneficial effects in both young [9] and old adults [10], with greater training gains for young participants [11]. Therefore, our secondary goal of the present study was to examine whether there would be differences of the functional connectivity network between young and old participants during WM training.

II. Methods and Materials

A. Subjects

Two healthy, right-handed individuals (young: 32 years, old: 60 years) recruited from the National University of Singapore, participated in the study. Written inform consent was obtained from each participant, and the study was approved by the Institutional Review Boards of the National University of Singapore.

B. Training task

For the training task, the spatial *n*-back task was adopted where squares at eight different locations were presented sequentially on a computer screen at a rate of 3 s (stimulus duration = 500 ms; inter-stimulus interval = 2500 ms) [12]. Participants were required to memorize a series of stimuli and their temporal order, update the list of recent items, and select the responses that corresponded to the previously observed stimuli, depending upon the *n*-back rule [3]. The level of the task would change according to the participants' performance. The whole training task was conducted in three continuous days with two training sessions which comprised 20 blocks consisting of 20+*n* trails. The duration of each block was about 1 min. A schematic figure with 3-back task was illustrated in Fig.1.

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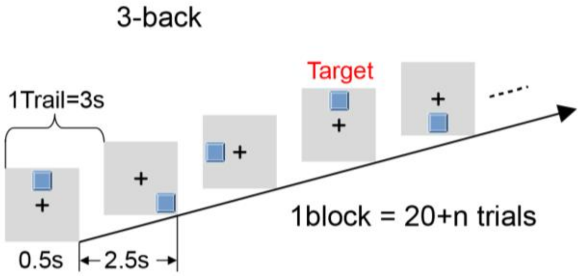

Fig.1. The spatial *n*-back task was used as the training task, a 3-back condition was illustrated as an example.

C. EEG recording and preprocessing

EEG signals from 64 channels were recorded during the task, and digitized at a sample rate of 256 Hz using an ASA-Lab system (ANT B.V., Netherlands). EEG activity was referenced to the average of both mastoids. Vertical EOG were recorded using two electrodes placed above and below the left eye. The recorded EEG signals were re-referenced to the average reference. Artifacts due to eye movements or significant muscle activity were removed offline via an independent component analysis approach [13]. The resulted signals were digitally band pass filtered with cut-off frequencies at 0.5 and 40 Hz. EEG data preprocessing were carried out with EEGLAB [14].

D. Effective connectivity analysis

Cortical effective connectivity is achieved through the computation of the partial directed coherence (PDC) [15]. PDC was selected in this work for its low computational complexity. Besides, PDC has been proved superior in analyzing the phase coupling among multichannel EEG signals for its ability of distinguishing direct and indirect causality flows [16]. The formulation and explanation of this method could be found in our previous papers [17, 18]. Briefly, PDC values can be derived from a multivariate autoregressive model of the multichannel EEG signals as:

$$\sum_{r=0}^{p} A_r X(t-r) = W(t), \quad [1]$$

where $X(t)$ is an 64-dimensional time series, $W(t)$ is a multivariate uncorrelated white noise vector, $A_r = \{a_{ij}(r)\}$ is an 64×64 coefficient matrix which could be estimated via Yule-Walker algorithm. p is the model order which is determined using the AIC criterion (p=10 in this study). Then the PDC from j^{th} channel to i^{th} channel could be calculated as:

$$PDC_{ij}(f) = \left|A_{ij}(f)\right| \Big/ \sqrt{\sum_m A_{mj}^*(f) A_{mj}(f)} \quad [2]$$

where $A_{ij}(f)$ are the elements of the matrix $A(f)$ ($A(f) = \sum_{r=0}^{p} A_r e^{-j2\pi fr}$). To minimize the contribution of noise in the causality interaction estimation, a surrogate approach was employed to assess the significance of PDC for a given pair of EEG channels [19]. Briefly, time series from each ROI and each trial were transformed to the frequency domain by means of a Fourier transform. We multiplied the discrete Fourier transform of the data by random phases and performed the inverse transform to obtain the surrogate data. We then repeated the estimation of PDC values on these surrogate data. An empirical distribution of PDC spectra was obtained via performing the surrogate approach 100 times. The significance threshold was set at 0.05 ($p<0.05$) for each EEG channel-pair [19]. To further investigate the association between the training effect and different EEG frequency bands, PDC values within different frequency bands were further estimated for each block.

E. Graph theory analysis

Graph theory is a natural framework for the mathematical representation of complex networks. Recently, it has attracted considerable attention in brain network research because it provides a powerful way to quantitatively describe the segregation and integration of brain network from the topological perspective [20]. In this study, network metrics, i.e., weighted clustering coefficient, C_p, weighted shortest path length, L_p, normalized clustering coefficient, γ, normalized shortest path length, λ, and small-worldness, σ, were adopted to reveal the involvement of network efficiency. In this study, graph theory analysis was performed with Brain Connectivity Toolbox [21].

The clustering coefficient C_i of a node i is defined as:

$$C_i = \frac{\sum_{j,m}\left(a_{ij}+a_{ji}\right)\left(a_{jm}+a_{mj}\right)\left(a_{mi}+a_{im}\right)}{2\left[\left(H^T+H\right)_i\left(\left(H^T+H\right)_i-1\right)-2H_{ii}^2\right]}, \quad [3]$$

where a_{ij} is the element from the asymmetry weighted PDC matrix and H is the adjacency matrix ($H_{ij(i\neq j)}=1$ for $a_{ij(i\neq j)}\neq 0$). The weighted clustering coefficient, C_p, of a direct network is the average of the clustering coefficient over all nodes. The clustering coefficient is an index of local structure of a graph. In network, a path between node i and node j refers to an edge that directly connects them or a sequence of edges that link them through other nodes. Then the shortest path length between node i and j is defined as the minimum one of the sum of the edge lengths along all possible paths. Further, the shortest path length L_p of a weighed graph was defined as the mean of the shortest path length of all pairs of nodes. In this work, the reciprocal of the PDC weight ($1/a_{ij}$) was denoted as the length of an edge. A network with high C_p value has tightly connected local clusters and hence the loss of an individual node has an impact on the structure of the network. While L_p indicates how well integrated a graph is, and how easy it is to transport information or other entities in the network [6]. To examine the small-world properties, the normalized clustering coefficient, $\gamma=C_p/C_{rand}$, and the normalized shortest path length, $\lambda=L_p/L_{rand}$, were computed, where C_{rand} and L_{rand} denote the average weighted clustering coefficient and the average shortest path length of an ensemble of 100 surrogate random networks. These random networks were derived from the original brain network by randomly rewiring the edges between nodes while preserving the degree distribution and connectedness [22]. The small-worldness could be summarized from the normalized metrics as: $\sigma=\gamma/\lambda$. A real network is considered small-world if it meets the following criteria: $\gamma \gg 1$ and $\lambda\approx 1$, or $\sigma>1$. In this work, the comparison of the topological architecture for the effective connectivity network were estimated at a specific sparsity scale S=15%, which captured the connectivity backbone and maintained a fully-connected brain networks.

F. Statistical analysis

To investigate the influence of training effect on the topology of the cortical connectivity network and to determine the between-group differences, we conducted a repeated-measure ANOVA, with training-day as within group factor (T) and group as between group factor (G). A value of $p<0.05$ was considered significant. All analyses were performed using the statistical software program SPSS for Windows, version 17.0 (IBM, Armonk, New York).

III. Results

A. Behavioral results

Analysis of the training behavioral results revealed that both groups improved in their performance on the *n*-back WM task (Fig.2). Although the training effect in the old subject was also significant, young participant overperformed in the mean *n*-back levels throughout the whole training sessions. It is noteworthy mentioning that the mean *n*-back level could be well explained by a linear fitted function for both groups (young: p1=3.6, p2=1.4, R^2=0.95; old: p1=1.7, p2=0.4, R^2=0.99).

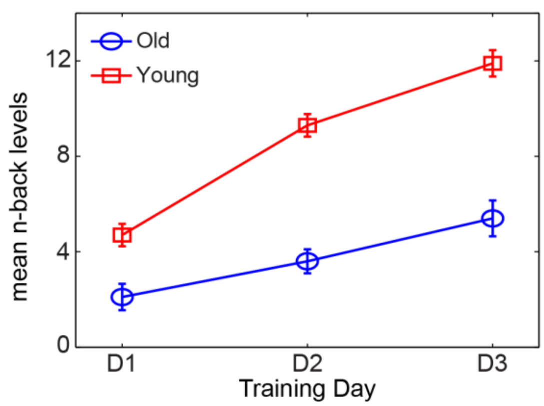

Fig.2. Subject behavioral performance increase in the trained task. For three continuous training days, the mean level and the standard deviations of *n* achieved by the participants were presented.

B. Network results

We found that both participants demonstrated small-word organization of the effective connectivity network, as exemplified by γ values were larger than 1, the λ indexes were nearly 1. Training effect on the network metrics were statistically estimated through a repeated ANOVA; and the results were summarized in Table I. For all four frequency bands, C_p, γ, and σ showed significantly training-day effect ($p<0.05$). In all frequency bands except delta, λ was also found to be significantly reduced after three days' training. Significant group effect ($p<0.05$) was only observed in Alpha band, where old participant exhibit significantly smaller λ as well as higher C_p and γ compared to young subject.

Interestingly, significant training day by group interactions were revealed in λ in delta band and γ in alpha band. Further investigation indicated that this interaction resulted from a significantly decreased of λ and γ in old participant but an insignificant decrease in young participant.

IV. Discussion and Conclusion

The human brain forms a large-scale interconnected structural network that functionally links adjacent and distant brain areas [23]. Such functional coupling is present during the processing of cognitive task and it is even present during rest. Recent advances in neuroimaging techniques and graph theory methods allow for the investigation of human brain networks from topological perspective and accumulated studies have shown that human brain networks have special topological organization, such as small-worldness – an optimal brain network architecture characterized by high efficiency of information transfer with low wiring cost [6]. In this study, we employed graph theoretical analysis to investigate the changes in effective connectivity networks due to a short-term WM training task.

Recently, Takeuchi and colleagues reported an altered structural connectivity patterns after two-month WM training, providing anatomical evidence that WM training could augment the human brain connectome [3]. Similar positive training effects were also observed in functional connectivity between regions with age-related disruption in cognitively relevant brain networks [24]. In the current work, significantly decreased clustering coefficients were revealed in all frequency bands, suggesting a reduced local efficiency after short-term WM training. Moreover, the normalized shortest path length showed statistical decreases, indicating a more global efficient configuration. According to the 'neural efficiency theory' proposed by Haier [25], when participants are doing well on a task, they recruit fewer neurons than when they are not doing well. We speculate the decreased local clustering coefficients might attribute to the less local activation after WM training. However, the significant reduced shortest path length indicates a more efficient global information transformation in both groups after WM training. Group differences between young and old participant were mainly observed in alpha band. Compared to young subject, old participant exhibited more optimal small-world architecture with higher weighted clustering coefficient and less weighted shortest path length, indicating a higher gain for old people in the WM training task.

There are several issues that should be addressed. First, it could be argued that the outcome of the current study is not convincing for small subject size. While our study has revealed some consistent changes of the effective connectivity networks for both subjects after WM training, we did not intend to make any generalization and focused on the feasibility assessment of the connectivity approach in this proof of concept study. Further study involving a higher number of subjects is essential to replicate the observations. Second, the training period in the current work is three continuous days; an extension of the current work with long-term training tasks is under consideration to evaluate the influence of training length. Finally, accumulating studies reported a key role of fronto-parietal cortex in the WM training. To reveal the training effect on a localized fashion,

TABLE I. COMPARISONS OF THE GLOBAL NETWORK MEASURES AT DIFFERENT FREQUENCY BANDS (SPARSITY=15%).

Metrics	Delta (0.5-4Hz)			Theta (4-8Hz)			Alpha (8-12Hz)			Beta (12-30Hz)		
	Training	Group	T×G	Training	Group	T×G	Training	Group	T×G	Training	Group	T×G
C_p	**0.046**$^{\downarrow}$	ns	ns	**0.012**$^{\downarrow}$	ns	ns	**0.042**$^{\downarrow}$	**<0.01**$^{\blacktriangle}$	ns	**<0.01**$^{\downarrow}$	ns	ns
L_p	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
γ	**<0.01**$^{\downarrow}$	ns	ns	**<0.01**$^{\downarrow}$	ns	ns	**<0.01**$^{\downarrow}$	**0.048**$^{\blacktriangle}$	**0.045**	**<0.01**$^{\downarrow}$	ns	ns
λ	ns	ns	**<0.01**	**0.035**$^{\downarrow}$	ns	ns	**0.012**$^{\downarrow}$	**<0.01**$^{\blacktriangledown}$	ns	**<0.01**$^{\downarrow}$	ns	ns
σ	**<0.01**$^{\downarrow}$	ns	ns	**<0.01**$^{\downarrow}$	ns	ns	**<0.01**$^{\downarrow}$	ns	ns	**<0.01**$^{\downarrow}$	ns	ns

Note: C_p = weighted clustering coefficient, L_p = weighted shortest path length, γ = normalized clustering coefficient, λ = normalized shortest path length, and σ = small-worldness. T×G: training by group interactions. **Bold** indicates variables are statistically significant ($p<0.05$), ns, non-significant. $^{\downarrow}$, decreased with training; $^{\uparrow}$, increased with training; $^{\blacktriangledown}$, Old < Young, $^{\blacktriangle}$, Old > Young.

graph theory measures such as betweenness centrality and nodal strength, should be employed in the future.

In sum, we quantitatively analyzed the changes in small-world properties of functional brain networks during WM training. Our results of global network metrics demonstrated more efficient network architectures after WM training. We interpret our finding as a proof of principle, providing insights on how the WM training benefits the brain connectome.

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