Pursuing the Flow of Information: Connectivity between Bilateral Premotor Cortices Predicts Better Accuracy in the Phonological Working Memory Task

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Abstract—Using Magnetoencephalography (MEG) we studied functional connectivity of cortical areas during phonological working memory task. Six subjects participated in the experiment and their neuronal activity was measured by a 306-channel MEG system. We used a modified version of the visual Sternberg paradigm, which required subjects to memorize 8 alphabet letters in 2s for a late recall period. We estimated functional connectivity of oscillatory regional brain activities during the encoding session for each trial of each subject using beamformer source reconstruction and Granger causality analysis. Regional brain activities were mostly found in the bilateral premotor cortex (Brodmann area (BA) 6: PMC), the right dorsolateral prefrontal cortex (BA 9: DLPFC), and the right frontal eye field (BA 8). Considering that the left and right PMCs participate in the functions of phonological loop (PL) and the visuospatial sketchpad (VS) in the Baddeley's model of working memory, respectively, our result suggests that subjects utilized either single function or both functions of working memory circuitry to execute the task. Interestingly, the accuracy of the task was significantly higher in the trials where the alpha band oscillatory activities in the bilateral PMCs established functional connectivity compared to those where the PMC was not working in conjunction with its counterpart. Similar relationship was found in the theta band oscillatory activities between the right PMC and the right DLPFC, however in this case the establishment of functional connectivity significantly decreased the accuracy of the task. These results suggest that sharing the memory load with both PL- and VS- type memory storage circuitries contributed to better performance in the highly-demanding cognitive task.

I. INTRODUCTION

Our working memory function is not like that of a computer memory. Sometimes we happen to forget the once memorized item such as a phone number of friend which was given just a short while ago, even though we can retrieve it perfectly in another day. Although we intuitively understand that the ability of human working memory has some fluctuation that may depend on the internal or external environment of ourselves, the neuronal basis of this cognitive fluctuation has not been well understood. Recent advances in neuroimaging techniques allow us to investigate the brain regions involved in the cognitive processing with good spatial

and time resolution. Baddeley [1] proposed the conceptual model of working memory, comprising a main control circuitry of the central executive (CE), and two storage circuitries of the phonological loop (PL) and the visuospatial sketchpad (VS). Each circuitry consists of distributed cortical areas. Two subsystems are separately distributed in the brain; PL comprises the left premotor cortex (PMC), the left Wernicke's area, and the left Broca's area to encode and maintain phonological items. On the other hand, VS comprises the bilateral associative visual cortex, the right PMC, the right supramarginal gyrus, and the right inferior prefontal gyrus to form and maintain visually encoded items such as sceneries or pictures. These two storage circuitries have reciprocal connections to the bilateral dorsolateral prefrontal cortex (DLPFC), the main control circuit of CE. Studies in animals and humans support that this network among these circuitries is essential component to maintain working memory. Recent evidence further demonstrated that the oscillatory brain activations in a specific frequency band play a role in declarative memory encoding and retrieval [2]. These results suggest the relationship between the fluctuation of behavioral performance and the change in dynamics of brain oscillatory activities during the cognitive task of working memory. We therefore studied the regional brain activity and their functional connectivity during phonological working memory task to determine the relationship between the existence of functional connectivity and the behavioral outcome in the short-term working memory task using Magnetoencephalography (MEG).

II. MATERIALS AND METHODS

A. Subjects

Six young-adult (21-24 years old, four women) subjects without perceived vision problem participated in the experiment. This study was approved by the Institutional Review Board and all subjects gave informed consent for participation.

B. Working memory task and MEG data acquisition

We used a modified visual Sternberg task [3] as shown in Fig. 1. Visual stimulation was presented on a screen located 1.5 m in front of the subjects. Each trial comprised the following steps: first, the word "Blink" appeared on the screen, and the subjects were encouraged to blink. As a prompt to start, the letter "Start" appeared 1 s later; it was followed by presentation of a random list of 8 letters flashed on the screen for 2s (encoding period). After a 3s retention interval (blank screen, maintenance period), the probe was presented.

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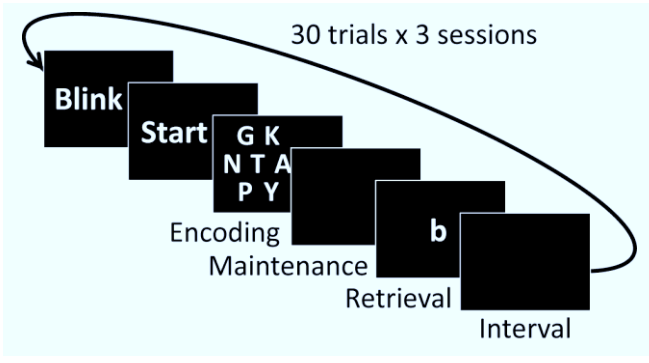
Figure 1. Schematic illustration of the visual Sternberg task.

The subjects indicated whether the probe was on the list or not by pushing a button (retrieval period). All the visual representations were programmed and controlled using Presentation software (Neurobehavioral Systems, Albany). Three sessions of thirty trials were presented to every subject, between which subjects took approximately 10min of rest outside of the MEG scanner.

We used a 306-channel system (Vectorview; Elekta Neuromag, Helsinki) to collect MEG data. The signals were band-passed at 0.1–130 Hz and digitized at 400 Hz. Electro-oculogram (EOG) and the button press responses were measured simultaneously with the MEG. We used MEG data only from the 204-channel gradiometer to take full advantage of the low-noise nature of the gradiometer for further analysis. We also focused our analyses on the data during encoding period to avoid contamination of motor-related neuronal activity due to the preparation and the execution of button press. Also, a morphological T1 scan of each subject's brain was performed using a 1.5T EXCITE HD MRI scanner (General Electric, Milwaukee, WI). The volume covered the entire brain with a 64 x 64 matrix and 33 slices (voxel size = 3.75mm x 3.75 mm x 4 mm, slice thickness = 3.8 mm, gap = 0.2 mm).
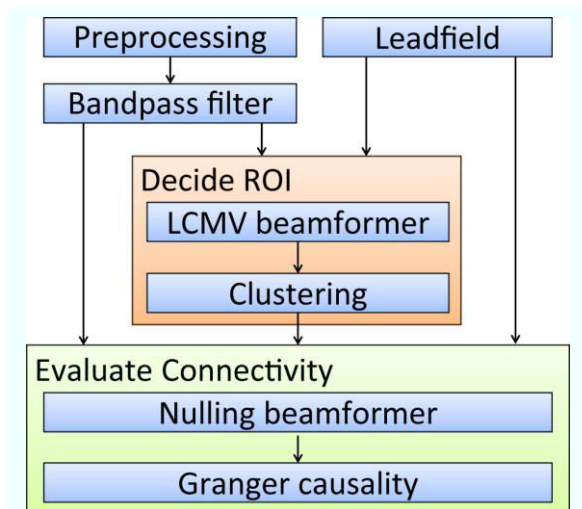

Figure 2. Flowchart of the analysis.

C. Data analysis

We determined the regional brain activity and their functional connectivity following several steps which are shown in Fig. 2. First, blink artifacts were removed using independent component analysis ("Preprocessing" in Fig. 2). The noise-removed data were subjected to band-pass filters to extract oscillatory activity in the frequency bands of delta (1-3 Hz), theta (4-7Hz), alpha (8-13 Hz), beta (14-24 Hz), low-gamma (30-79 Hz), and high-gamma (80-130 Hz; "Bandpass filter"). We then determined the distribution of the equivalent current sources using Linearly Constrained Minimum Variance (LCMV) beamformer [4] for each frequency band of each trial in each subject. Mesh points were given at 1cm intervals within the cortical area ("LCMV beamformer"). We further applied a hierarchical grouping method with Mojena's stopping rule [5] to the positions and the mean moments through the trial period of the estimated sources in order to divide the current sources into several groups ("Clustering"). We hypothesized each group as a region of interest (ROI) demonstrating regional brain activity and defined the center of the ROI to be the mesh point with the largest moment amplitude. At the centers of the selected ROIs, we calculated the time-course change of the moment of the current sources using Nulling Beamformer, which is a modified beamforming approach to accurately measure cortical interactions compared to conventional beamformer approaches such as LCMV beamformer [6] ("Nulling beamformer"). Since Nulling beamformer requires the exact positions of source currents among the mesh points [6], we first needed to apply LCMV beamformer and cluster analysis to the preprocessed and filtered MEG data to determine them. Finally, we evaluated the connectivity between sources at the centers of ROIs by means of Granger causality [7] ("Granger causality"). The anatomical positions of the centers of ROIs were determined in the MNI coordinates with reference to the MRI T1 image of the subject using SPM5 software (Welcome Department of Cognitive Neurology, London, UK).

The paired *t*-test was used to compare behavioral performances depending on the connectivity of the selected pairs of ROIs. The total 90 trials were divided into two groups depending on the establishment of connectivity between the pair of ROIs and on the frequency band of interest for each subject. The accuracy rate and the reaction time were averaged within groups, which were further subjected to the statistical comparison between groups.

III. RESULTS

LCMV beamformer combined with cluster analysis determined approximately 7 ROIs for every single trial data. As shown in Fig. 3ab, ROIs were mostly localized in the bilateral PMC (Brodmann area (BA) 6), the right DLPFC (BA 9), and the right frontal eye field (BA 8). Table I indicates the mean occurrence rate of the current sources in the above cortical areas through all trials. Oscillatory activities in theta, alpha, and beta bands appeared in more than 60% of trials of memory encoding in the bilateral PMC. Although the occurrence rate was not so high, ROIs were also localized at the left DLPFC, the bilateral supramarginal gyrus / Wernicke's area (BA 40), the bilateral frontal pole, the left frontal eye field, the bilateral somatosensory association cortex (BA 7),
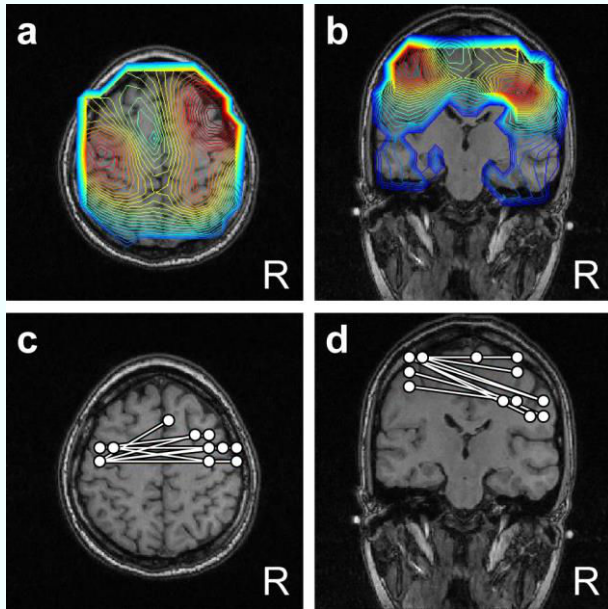
Figure 3. Results of the LCMV beamformer analysis averaged over all trials (a, b) and the connectivity analysis among the extracted ROIs (c, d) from a representative subject (Subject 5). Results were projected on her MR image. a and c are the transverse view and b and d are the coronal view. a, b: contours in red color in a and b indicate larger current sources. c and d: white dots indicate the centers of ROIs detected from the LCMV beamformer and clustering analysis. Line between pairs of dots indicate the functional connectivity found between the ROIs. R indicates the right side.

and the left insular cortex, the first two regions of which are also part of the Baddeley's model of working memory [1].

We next investigated the functional connectivity among the above ROIs (Figure 3cd). As shown in Table II, the simultaneous and functionally connected activation of pairs of ROIs rarely happened, about zero to 18% of total trials. Although Granger causality analysis gives not only the presence but also the direction (cause-and-effect relationship) of causality among the ROIs, we focused only on the presence of causality in this study and summed the occurrence rates of functional connectivity of bilateral direction (for example, sum the occurrence rates from R6 to L6 and from L6 to R6 for ROI pairs R6 – L6) due to the small number of occurrence rate of functionally connected activations. We found functional connectivity mostly from oscillatory activities of theta, alpha, and beta bands between the bilateral PMCs, the right PMC-DLPFC, and the right PMC-frontal eye field.

Tables III and IV show the comparison of the behavioral parameters of accuracy rate and reaction times between trials in which the functional connectivity between the selected pair of ROIs was established and not. We found that establishment of functional connectivity in alpha band activity between the bilateral PMCs significantly increases the accuracy rate (P<0.01). Reaction time also tended to be reduced (P<0.1) when there was functional connectivity between them. Interestingly, establishment of functional connectivity in theta

TABLE I. LOCALIZED NEURONAL ACTIVITIES AND THEIR OCCURRENCE RATE THROUGH ALL TRIALS

ROU [a]	Occurrence rate [% of all trials]					
	Delta	Theta	Alpha	Beta	Low-gamma	High-gamma
R6	56.0	94.2	91.7	84.0	69.7	57.1
L6	43.4	68.1	77.1	73.3	33.5	51.9
R9	29.3	45.5	42.1	42.9	22.7	25.2
R8	29.3	44.7	45.7	35.2	36.1	24.3

a. R and L indicate right and left hemispheres, respectively. The number indicates the corresponding Brodmann area.

TABLE II. OCCURRENCE RATE OF FUNCTIONAL CONNECTIVITY BETWEEN PAIRS OF ROIS THROUGH ALL TRIALS

ROU[a] pairs	Occurrence rate [% of all trials]					
	Delta	Theta	Alpha	Beta	Low-gamma	High-gamma
R6 – L6	6.1	16.0	17.9	16.7	1.5	4.7
R6 – R9	4.9	12.8	11.3	12.2	0.8	3.2
R6 – R8	4.5	11.8	12.4	0	0.8	1.7
R8 – L6	0	5.1	4.7	4.0	0	0

a. R and L indicate right and left hemispheres, respectively. The number indicates the corresponding Brodmann area.

TABLE III. CHANGE IN BEHAVIORAL PARAMETERS DEPENDING ON THE ESTABLISHMENT OF FUNCTIONAL CONNECTIVITY BETWEEN BILATERAL PMC (R6-L6)

Frequency band	Accuracy rate [%]		Reaction time [ms]	
	C [a]	NC [b]	C	NC
Delta	90.3	71.5	523.2	564.6
Theta	81.9	83.2	568.8	553.3
Alpha	91.2 [†]	81.3	532.1 [*]	594.3
Beta	86.4	86.5	550.3	551.2
Low-gamma	93.8	83.8	720.1	500.2
High-gamma	90.2	79.6	562.7	547.8

a. Functional connectivity was established. b. Functional connectivity was not established.
†. Larger than *NC* (P<0.01). *. Shorter than NC (P<0.1).

TABLE IV. CHANGE IN BEHAVIORAL PARAMETERS DEPENDING ON THE ESTABLISHMENT OF FUNCTIONAL CONNECTIVITY BETWEEN RIGHT PMC AND RIGHT DLPFC (R6-R9)

Frequency band	Accuracy rate [%]		Reaction time [ms]	
	C [a]	NC [b]	C	NC
Delta	86.1	85.2	538.7	585.0
Theta	78.0 [‡]	97.9	573.5	546.3
Alpha	90.3	76.7	550.2	589.2
Beta	90.5	89.4	614.5	552.9
Low-gamma	100.0	91.1	649.4	530.8
High-gamma	86.1	97.4	510.6	538.9

a. Functional connectivity was established. b. Functional connectivity was not established.
‡. Smaller than *NC* (P<0.05).

band activity between the right PMC and the right DLPFC decreased the accuracy rate (P<0.05). We did not find statistical difference in any frequency bands between any combinations of ROIs.

IV. Discussion

We used a modified Sternberg task to investigate the relationship between establishment of functional connectivity during memory encoding and the behavioral outcome in the late retrieval. Our study demonstrated that the dynamics of cortical connectivity is fluctuating and that the establishment of some of these connectivity pathways during encoding plays a critical role determining success or failure of the short-term working memory function.

Our combined LCMV beamformer and clustering analysis localized current sources in cortical regions proposed as part of the working memory circuitry [1]. The DLPFC is a core structure of CE circuitry which is a control system of limited attentional capacity. The current study used 8 letters to memorize simultaneously, which is slightly higher than the average number of items to be hold in working memory [8], therefore allocating attention was necessary even in the young-adult subjects. The left and right PMC is considered as a cortical area for phonological and visuospatial output buffer for retrieval and rehearsal process, respectively [1]. Since we used letters as stimuli, subjects memorized them utilizing their sounds, their shapes, or both characteristics. Conrad and Hull [9, 10] reported the difference in recall score between sequences of similar sounding letters such as V, B, G, T, P, C and dissimilar set such as W, X, K, R, Y, Q. The fluctuation of current source distribution over trials may originate from the trial-to-trial difference of the strategy which subjects took to memorize the letters.

Another interesting finding was that the functional connectivity between the bilateral PFC during encoding contributed to the accurate and fast retrieval but those between the right PFC and the right DLPFC interfered with the working memory process. The former connectivity indicates the interaction between two types of memory storage systems of PL and VS and the latter connectivity does the facilitated communication between cortical areas within the single memory storage system of VS. These results suggest that the collaborative operation of both PL and VS circuitries improve the outcome performance, possibly sharing the high memory load. Further study would confirm this hypothesis of cognitive load sharing, for example by investigating whether or not the interaction between PL and VS circuitry decreases with lower memory load (decreasing the number of letters to remember).

To summarize, we leveraged the high temporal resolution of MEG to gain an understanding of the temporal relationships of cortical functional connectivity involved in the short-term working memory task. Although with 6 subjects the results are preliminary, beamformer analysis combined with causality analysis would be a powerful tool to investigate the trial-to-trial dynamics of regional brain activity and connectivity, namely "the flow of information" in our brain, from which we may predict the behavioral outcome.

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