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Binding of verbal and spatial information in human working memory involves large-scale neural synchronization at theta frequency

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Whether neural synchronization is engaged in binding of verbal and spatial information in working memory remains unclear. The present study analyzed oscillatory power and phase synchronization of electroencephalography (EEG) recorded from subjects performing a working memory task. Subjects were required to maintain both verbal (letters) and spatial (locations) information of visual stimuli while the verbal and spatial information were either bound or separate. We found that frontal theta power, and large-scale theta phase synchronization between bilateral frontal regions and between the left frontal and right temporal–parietal regions were greater for maintaining bound relative to separate information. However, the same effects were not observed in the gamma band. These results suggest that working memory binding involves large-scale neural synchronization at the theta band.

Keywords: Binding; EEG; Synchronization; Theta; Working memory

Introduction

Working memory allows the current task-related information to be temporarily stored and manipulated. The model of working memory proposed by Baddeley and Hitch (1974) includes an attention controller, the central executive and two subsidiary systems (i.e., the phonological loop and the visuospatial sketchpad) for holding verbal and visual information respectively. Recently, much attention has been paid to the brain mechanisms involved in the integration of different information in working memory, and the episodic buffer, a new component of working memory which emphasizes the integration of information from a number of sources is proposed (for review, see Baddeley, 2000).

There were neuroimaging studies examining feature conjunction in working memory with the match-to-sample task (Shafritz et al., 2002; Simon-Thomas et al., 2003). Using functional magnetic resonance imaging (fMRI), Shafritz et al. (2002) showed that the parietal cortices were more involved in feature conjunction task than in single feature tasks (color or shape). The event-related potential (ERP) study of Simon-Thomas et al. (2003) found that the P300 at the retrieval period was stronger in the processing of combined features than in the processing of single features (form or location). This observation suggested that feature conjunction "upregulates frontal–parietal association networks" (Simon-Thomas et al., 2003). The EEG study of Busch and Herrmann (2003) varied the numbers of objects and features independently and found that object load and feature load influenced short-term memory task at different stages. Specifically, during the maintenance period, the induced 10 Hz oscillation was modulated by object load rather than feature load supporting the view that information storage in short-term memory is object-based rather than feature-based.

Moreover, two experiments (Prabhakaran et al., 2000; Campo et al., 2005) investigated the neural basis of binding verbal and spatial information in working memory. In a paradigm designed to compare the bound and separate condition, letters (letters in Prabhakaran et al. (2000) and words in Campo et al. (2005)) and locations were remembered either conjointly as they were presented together, or separately as the verbal information appeared in other locations. Using fMRI, Prabhakaran et al. (2000) showed that the frontal areas were involved in binding of verbal and spatial information in working memory during the maintenance period. Campo et al. (2005) analyzed sources of the evoked event-related field (ERF) in a magnetoencephalography (MEG) study. They found that in addition to the frontal areas, the temporal–parietal areas were involved in the binding process during the maintenance period as well. Importantly, the results of Campo et al. (2005) also showed that the binding-related activity took place in early latencies of the maintenance period, which provided unique temporal information to the understanding of the brain processes involved in working memory binding.

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Taken together, previous neuroimaging studies have investigated the neural substrates of working memory binding, particularly where and when the binding process takes place. These findings suggest that working memory binding involves both frontal and temporal–parietal areas, and the bound and unbound information are processed at different stages.

Another important mechanism for binding is neural synchronization. The classical binding theory suggests that binding is achieved by convergence of axonal projections, that, axons of neurons whose responses should be bound are converged onto a common neuron at the higher processing level (Barlow, 1972; Riesenhuber and Poggio, 1999). However, the classical binding mechanism encounters the challenges of the flexibility and complexity of binding (Gray, 1999; von der Malsburg, 1999). Instead, the temporal binding hypothesis proposes that binding is implemented by the synchronization of neuronal discharges corresponding to the features that are to be bound together (Singer, 1999; von der Malsburg, 1999), which provides a flexible and dynamic mechanism for binding. The temporal binding hypothesis has been supported by the evidence from studies of perceptual processing, which showed that neural synchronization at the gamma (about 40 Hz) band is associated with binding of perceptual information (for reviews, see Singer, 1999; Engel and Singer, 2001). However, it still remains unclear whether neural synchronization is also engaged in binding of information in working memory. The current EEG study was designed to investigate this issue by adopting the task paradigm of Prabhakaran et al. (2000) and analyzing both the oscillatory power (TallonBaudry et al., 1996) and phase synchronization (Lachaux et al., 1999). Specifically, if working memory binding involves neural synchronization, we would like to see whether the neural synchronization occurs at the gamma band as in perceptual binding, or instead, at other frequency bands.

EEG activity includes both the induced (not phase-locked to stimulus onset) and evoked (phase-locked to stimulus onset) activities. Given that the largely oscillatory induced activity is considered to reflect dynamic brain processes and is thought to play an important role in binding (for reviews, see Pfurtscheller and da Silva, 1999; Tallon-Baudry and Bertrand, 1999; Bastiaansen and Hagoort, 2003), we investigated mainly the induced oscillatory activity. When investigating the phase coupling of two oscillations of different brain regions, coherence is the traditional method (Ruchkin, 2005). But it has been suggested that coherence measures both power and phase correlations thus cannot purely reflect the phase synchronization (Lachaux et al., 1999). Lachaux et al. (1999) developed a method (phase-locking value, PLV), which separates the phase and amplitude components and directly measures the phase synchronization. The PLV method has been applied in many cognitive functions such as perception (Rodriguez et al., 1999), attention (Gross et al., 2004) and memory (Tallon-Baudry et al., 2001). We thus adopted the PLV method to measure phase synchronization (Lachaux et al., 1999).

The synchronized activity[1] at the theta (about 6 Hz) band is involved in either verbal or spatial working memory tasks (Gevins et al., 1997; Sarnthein et al., 1998; Klimesch et al., 1999; Tesche and Karhu, 2000; Raghavachari et al., 2001; Jensen and Tesche, 2002; Schack et al., 2002, 2005). However, whether the synchronized theta activity is associated with verbal–spatial binding remains unclear. The theta band thus was of our particular interest. In addition, given the association between the synchronized gamma (about 40 Hz) activity and perceptual binding (Singer, 1999; Engel and Singer, 2001) as mentioned above, an interesting question would be whether working memory binding also involves the synchronized gamma activity. Therefore, another frequency band we paid attention to was the gamma band.

The performance of a match-to-sample working memory task can be divided into three periods: encoding, maintenance and retrieval. The encoding and retrieval periods include perceptual analyses, whereas the maintenance period is relatively a pure internal mental process as the contamination of perception is minimized due to the absence of external stimuli. As suggested by Chafee and Goldman-Rakic (1998), the maintenance period is “one of the best candidates for a critical neural correlate of working memory”. Therefore, same as Prabhakaran et al. (2000) and Campo et al. (2005) did, the present study only analyzed the maintenance period.

The verbal and spatial information are respectively stored in the phonological loop and the visuospatial sketchpad of working memory (Baddeley and Hitch, 1974; Baddeley, 2000) thus investigating the verbal–spatial binding would provide a critical neural correlate of working memory binding. In addition, by analyzing both local oscillatory power and lager scale phase synchronization, the present study would give an overall character of neuronal synchronization.

Materials and methods

Subjects

Ten graduate and undergraduate students from the University of Science and Technology of China (9 males, 1 female, mean age 22 years) participated in this experiment with informed consent. They all had normal or corrected-to-normal vision.

Procedure

The experiment paradigm (see Fig. 1) was almost the same as that used by Prabhakaran et al. (2000) except that a baseline was added and the inter-trial interval was randomized in the present EEG experiment. The experiment consisted of a bound and a separate condition with each including 200 trials. Each trial started with a fixation cross displayed for 1.2 s. Then the sample stimulus comprising four upper case consonants and four parentheses was presented for 2 s. The parentheses were located randomly on the circumference of a vertical imaginary ellipse. In the bound condition, each letter was displayed in a parenthesis, so that the letters and the parenthesis locations were bound. In the separate condition, the letters were presented centrally in the display thus were separated from the parenthesis locations. In both conditions, subjects were required to remember both the letters and the parenthesis locations (only the verbal information of the letters and only the spatial information of the parentheses; the locations of the letters were not required to be remembered), and maintain them for a fixation period of 5 s. After that, a probe stimulus comprising a lower case letter in a parenthesis was displayed for 2.5 s. During this period, subjects had to judge whether both the letter and the parenthesis location had been presented in the sample stimulus.

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[1] Previous studies analyzed either the oscillatory power or phase synchronization or both of them. For the sake of comparison with the previous studies, we used the term “synchronized activity” to include both oscillatory power and phase synchronization.

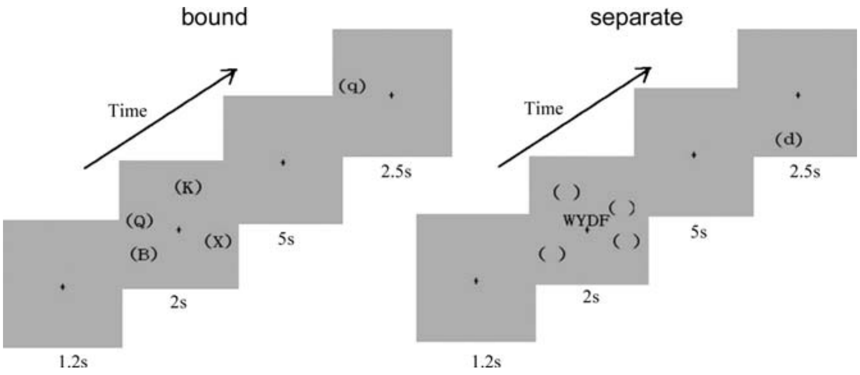

Fig. 1. Illustration of the experiment procedure. In the example of the bound condition, the probe letter and location have appeared in the sample display; in the example of the separate condition, the probe location was not shown in the sample display.

Whether that particular letter had been in that particular parenthesis was not regarded. For both the bound and separate conditions, in half of the trials the probes were correct (match) and in the other half the probes were wrong (non-match). Because the letters appeared in upper and lower cases respectively during the encoding and retrieval periods, subjects were not likely to remember the visual characteristics rather than the verbal identities of these letters. The inter-trial interval (with a fixation in the center of the screen) was randomized between 2 and 3 s. The order of the bound and separate conditions was counterbalanced across subjects.

The stimuli were displayed in black on a gray background at a viewing distance of 1.1 m. A letter or a parenthesis subtended a visual angle of 0.45° and the major axis of the vertical imaginary ellipse subtended a visual angle of 2.34°.

EEG data recording

The EEG was recorded using a Neuroscan system with 32 Ag/AgCl electrodes referenced to linked/shorted bilateral mastoids. Electrodes were placed according to the international 10–20 system and the impedance of each was kept below 5 kΩ. To monitor eye movements, both horizontal and vertical electro-oculograms (HEOG and VEOG) were also recorded. Data were sampled at 250 Hz and filtered with a 0.05–100 Hz band-pass filter.

EEG data analyses

The 5s maintenance period were cut out as epochs for the data analyses. For each of the subjects, epochs with incorrect performance or over ±75 μv HEOG/VEOG fluctuation were excluded from further analyses. The data from two subjects were rejected for severe eye movement contaminations. On average, the other eight subjects had 158 epochs for the bound condition and 150 epochs for the separate condition after removing incorrectly performed and artifact contaminated epochs.

Time–frequency power (TFP)

The TFP was obtained by convoluting the epochs with complex Morlet's wavelets (TallonBaudry et al., 1996). This wavelet transform was firstly performed on each single trial and the transform results were then squared, converted to dB and averaged across all trials. This procedure results mainly in an induced activity (Rodriguez et al., 1999)[2]. The frequency ranged from 3 to 45 Hz in 1 Hz steps. The number of cycles of wavelets (NCW) was increased slowly with frequency (at 6 Hz, the NCW was 3; at 40 Hz, the NCW was 10), which could provide better temporal resolution at low frequencies and better frequency resolution at high frequencies (Delorme and Makeig, 2004). According to Kaiser et al. (2004), "effects may be detected only when conditions are compared directly, without baseline correction," both power and phase synchronization (see below) in the bound and separated conditions were compared directly, without baseline subtraction. As a wide time range (5 s) and a wide frequency range (43 Hz) were analyzed, the time and frequency that showed significant differences in power between the bound and separate conditions in the TFP significance maps (see below) were selected as the time and frequency of interest (TFOI) for the subsequent phase synchronization analyses (Rodriguez et al., 1999; Gross et al., 2004).

Phase synchronization

Phase synchronization analyses based on the Morlet's wavelet transform (Lachaux et al., 1999) were performed on the TFOI (Rodriguez et al., 1999; Gross et al., 2004). The NCWs were the same as that used in the TFP analyses. The phase synchronization was defined as the absolute value of the sum of the phase differences of two electrodes divided by the number of epochs. The value of the phase synchronization lies between 0 and 1. 0 Means phases are randomly dispersed among all trials. 1 Means phases are totally phase locking in all trials. The phase synchronization was calculated for 12 electrodes located in four brain regions (left frontal region — F7, F3, FT7; right frontal region F8, F4, FT8; left temporal–parietal region—P7, P3, TP7 and right temporal–parietal region—P8, P4, TP8), which yielded 66 (11*12/2) electrode pairs. These electrodes covered bilateral frontal and temporal–parietal regions and the four brain regions were largely separated (Summerfield and Mangels, 2005). Our interests were focused on the phase synchronization between different brain regions rather than within each brain region. Analyzing phase synchronization between the electrodes in such largely distant brain regions may reduce the possibility of the

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[2] Researchers still do not reach agreement on whether the evoked activity (time–frequency analysis is performed on the averaged evoked potentials) should be subtracted first (Herrmann et al., 1999; Rodriguez et al., 1999). In fact, we have also analyzed the data by subtracting the evoked activity first and the results were consistent with the present ones. According to most papers, we used the method without subtracting the evoked activity.

spurious synchronization resulting from the volume conduction in some extent (Rodriguez et al., 1999).

Statistic method

Generation of TFP significance maps

Power values in the bound and separate conditions were directly compared by paired *t*-test. The resulting *t* values were than subjected to the random permutation test (Kaiser et al., 2004; Summerfield and Mangels, 2005) to correct for the type-I error during multiple comparisons (there were 32 electrodes for power comparisons). Corrections for TFP were based on TFP pixels. Subject–condition power values were swapped 1000 times. In each permutation the *t*-test repeated for each electrode and the maximum *t* value from all the electrodes was logged for each permutation. The TFP pixels whose *t* values fell within the 95th percentile (*P* value≤0.05) of the

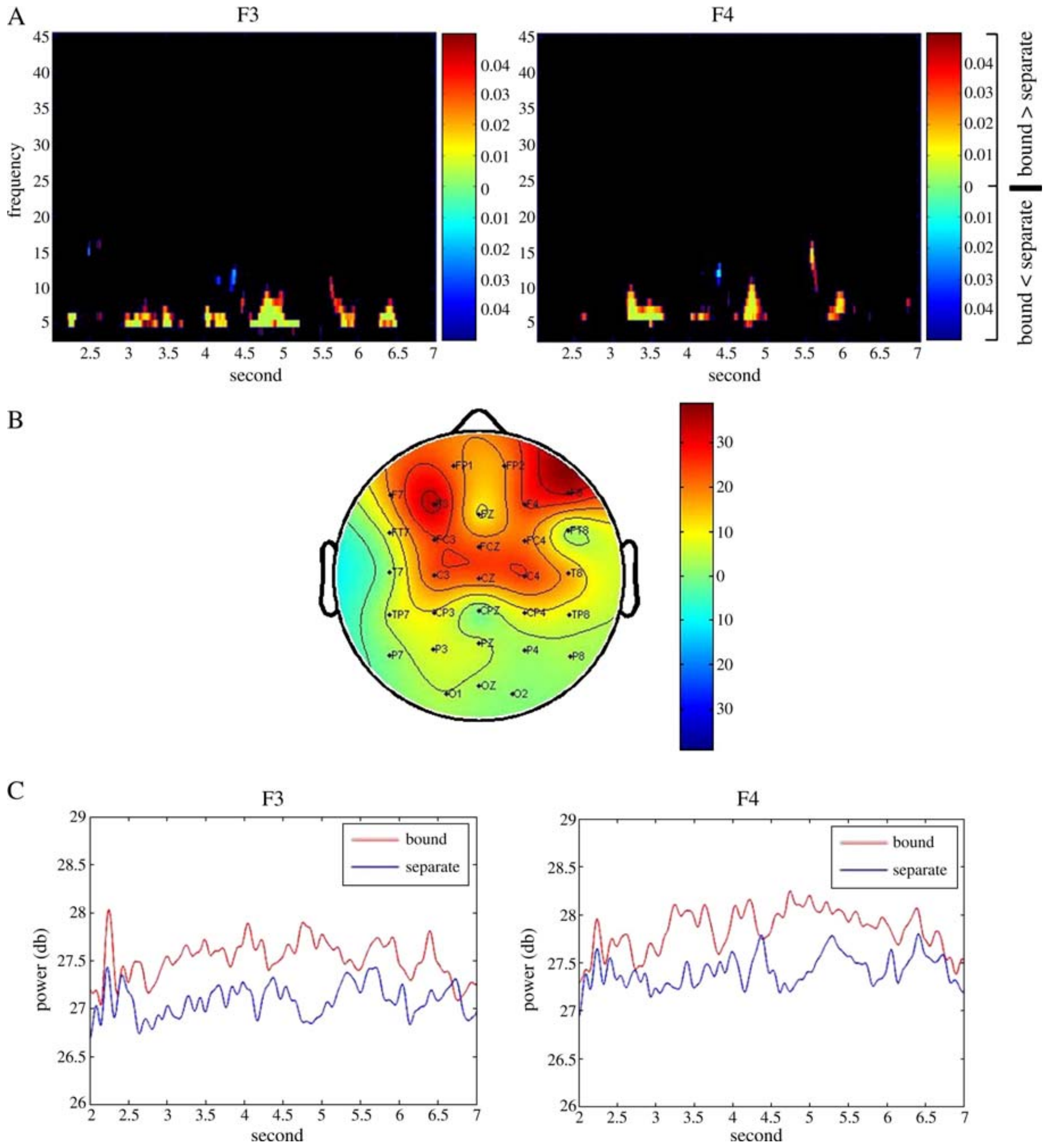

Fig. 2. Greater frontal theta power (about 6 Hz) in the bound than in the separate condition. (A) Time–frequency power (TFP) significance maps of two frontal electrodes (F3 and F4). Increased power in the bound than in the separate condition was observed at about 6 Hz during the time window of about 2.2–6.5 s. The color indicates the scale of *P* values (≤0.05). The top part of the color bars indicates greater whereas the bottom part indicates lesser power in the bound relative to separate condition. TFP pixels with the power differences not reaching significance are displayed in black. (B) TFP significance topography map. Increased 6 Hz power in the bond than in the separate condition was observed over the frontal sites. The color indicates the scale of the percentage of 6 Hz pixels reaching significance level (*P*≤0.05). A percentage of 30% means that for a given electrode, in all of the 1075 pixels at 6 Hz, there were 323 pixels reached significance. The top part of the color bar indicates greater whereas the bottom part indicates lesser power in the bound relative to separate condition. (C) The mean time courses of the 6 Hz power of electrodes F3 and F4.

Table 1
The 6 Hz power comparison between the bound and separate conditions in the four brain regions

Brain regions	Conditions	Mean (db)	MSE (db)	Paired *t*-test
LF	Bound	26.683	0.652	
	Separate	26.342	0.628	
	Difference	0.341	0.081	$t = 4.18$, $P = 0.004$
RF	Bound	27.048	0.612	
	Separate	26.669	0.591	
	Difference	0.379	0.096	$t = 3.946$, $P = 0.006$
LP	Bound	23.141	0.637	
	Separate	23.101	0.65	
	Difference	0.04	0.067	$t = 0.575$, $P = 0.583$
RP	Bound	23.218	0.455	
	Separate	23.221	0.469	
	Difference	−0.003	0.089	$t = -0.033$, $P = 0.975$

The paired *t*-tests were performed on the power differences with the P values less than 0.05 marked in red. LF: left frontal region; RF: right frontal region; LP: left temporal–parietal region; RP: right temporal–parietal region.

distribution of maximum shuffled *t* values were deemed to be significant. In addition, because *P* values are always positive, we could thus not indicate whether the power was greater or less in the bound than in the separate condition, which is respectively indicated by the top and bottom parts of color bars in the significance map (see Fig. 2A). The identified TFOI was then used for phase synchronization analyses.

Generation of phase synchronization significance maps

Phase synchronization values in TFOI were firstly averaged (Rodriguez et al., 1999; Gross et al., 2004) and then directly compared by paired *t*-test between the bound and separate conditions. The random permutation test (Kaiser et al., 2004; Summerfield and Mangels, 2005) was also performed to correct for the type-I error during multiple comparisons (there were 66 electrode pairs for phase synchronization comparisons). Corrected *P* value ≤0.05 was set as the significance threshold.

Result

Behavior data

Subjects performed significantly (t=2.82, P=0.017) better in the bound (Mean accuracy=89.2%, MSE=1.5%) than in the separate (Mean accuracy=86%, MSE=1.4%) condition. For the reaction times (RT), though the condition difference did not reach significance (t=−1.549, P=0.165), subjects did respond faster in the bound (Mean RT=1232 ms, MSE=42 ms) compared to the separate (Mean RT=1299 ms, MSE=74 ms) condition. These results were consistent with previous studies (Prabhakaran et al., 2000; Simon-Thomas et al., 2003; Campo et al., 2005), indicating that binding decreases the task difficulty.

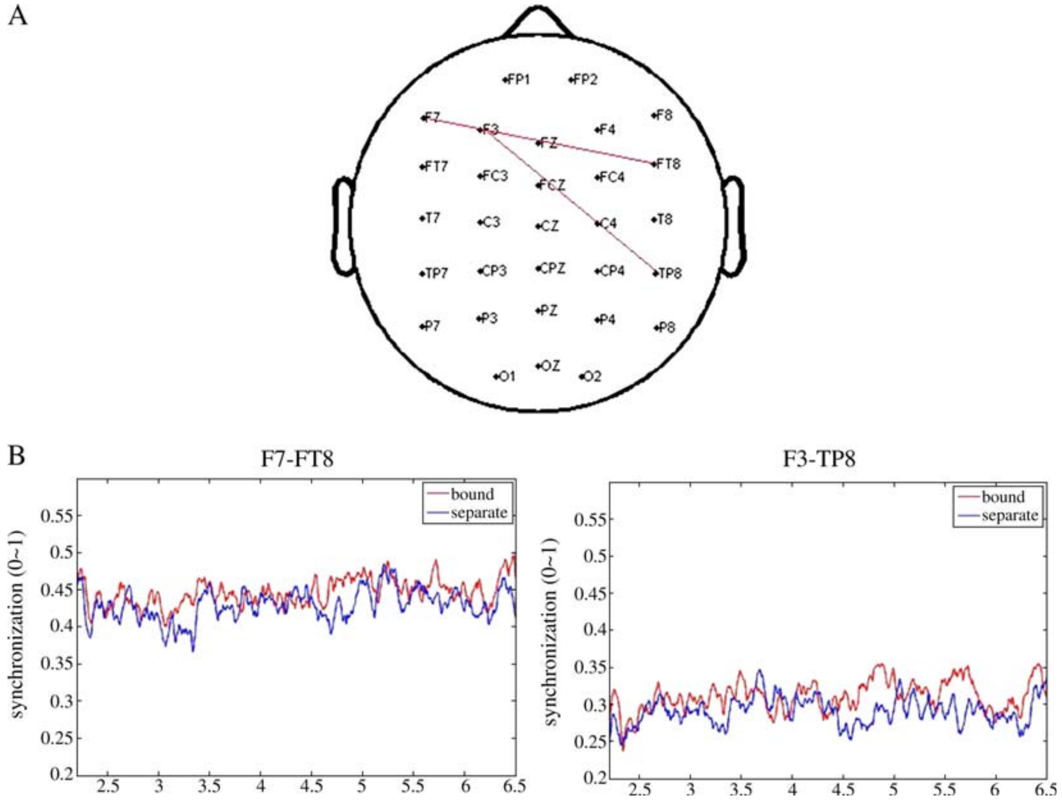

Fig. 3. Greater 6 Hz phase synchronization in the bound than in the separate condition. (A) Phase synchronization significance map for the 6 Hz frequency. Electrode pairs in which the 6 Hz phase synchronization was significantly ($P \leq 0.05$) different between the bound and separate conditions are plotted on the scalp. Red and blue lines respectively indicate phase synchronization being greater and lesser in the bound than in the separate condition. Here no blue line was obtained. (B) The mean time courses of the 6 Hz phase synchronization of electrode pairs F7-FT8 and F3-TP8.

EEG data

Time–frequency power significance maps

In the bilateral frontal regions, the power was significantly greater in the bound than in the separate condition at about 6 Hz and during the time interval of about 2.2–6.5 s (Fig. 2). This effect was not found in the gamma or other frequency bands. The time interval of 2.2–6.5 s and the frequency of 6 Hz were then taken as the TFOI and used for phase synchronization analyses.

Fig. 2 provided the power information about single electrode, and the power values of the averaged electrodes were also calculated. They may complement each other. For the 12 electrodes located in the four brain regions (as mentioned above), the power values in the TFOI were averaged for each brain region. The Mean, MSE of power in the bound and separate conditions and the power differences between the two conditions are listed in Table 1. The paired *t*-tests were performed on the power differences (Table 1), showing that over the bilateral frontal regions, the 6 Hz power was significantly greater in the bound than in the separate condition, which was consistent with Fig. 2.

Phase synchronization significance maps

Between bilateral frontal regions and between the left frontal and right temporal–parietal regions, the 6 Hz phase synchronization was significantly greater in the bound than in the separate condition (Fig. 3)[3].

Same to the power analyses, the phase synchronization values of the averaged electrode pairs were also calculated. For the electrode pairs between the four brain regions, the phase synchronization values in the TFOI were averaged for each permutation of electrode pairs (there were six permutations of electrode pairs between the four brain regions (see Table 2)). The Mean, MSE of phase synchronization in the bound and separate conditions and the phase synchronization differences between the two conditions are listed in Table 2. The paired *t*-tests were performed on the phase synchronization differences (Table 2), showing that between bilateral frontal regions and between the left frontal and right temporal–parietal regions, the 6 Hz phase synchronization was significantly greater in the bound than in the separate condition, which was consistent with Fig. 3.

In addition, although the frequency in the TFOI was 6 Hz (see Fig. 2), as a particular interest to compare working memory binding with perceptual binding, the phase synchronization significance map of 40 Hz (the time interval was the same as that in TFOI) was also generated. However, the phase synchronization map was a “blank map”, that, no significant ($P>0.05$) electrode pair was observed, indicating that there was no significant difference in the 40 Hz phase synchronization between the bound and separate conditions.

Table 2
The 6 Hz phase synchronization comparison between the bound and separate conditions for the six permutations of electrode pairs

Permutations	Conditions	Mean (0–1)	MSE (0–1)	Paired *t*-test
F-F	Bound	0.442	0.024	
	Separate	0.426	0.022	
	Difference	0.016	0.004	$t=4.16$, $P=0.004$
P-P	Bound	0.237	0.024	
	Separate	0.229	0.023	
	Difference	0.008	0.004	$t=2.054$, $P=0.079$
L-L	Bound	0.364	0.028	
	Separate	0.368	0.025	
	Difference	−0.004	0.005	$t=-0.694$, $P=0.51$
R-R	Bound	0.473	0.018	
	Separate	0.464	0.016	
	Difference	0.01	0.012	$t=0.783$, $P=0.459$
LF-RP	Bound	0.21	0.022	
	Separate	0.192	0.016	
	Difference	0.018	0.007	$t=2.523$, $P=0.04$
RF-LP	Bound	0.144	0.021	
	Separate	0.138	0.019	
	Difference	0.006	0.003	$t=1.785$, $P=0.117$

The paired *t*-tests were performed on the phase synchronization differences with the *P* values less than 0.05 marked in red. F–F: left frontal region–right frontal region; P–P: left temporal–parietal region–right temporal–parietal region; L–L: left frontal region–left temporal–parietal region; R–R: right frontal region–right temporal–parietal region; LF–RP: left frontal region–right temporal–parietal region; RF–LP: right frontal region–left temporal–parietal region.

Discussion

For the bound condition compared to the separate condition, greater frontal theta (about 6 Hz) power and large-scale theta phase synchronization between bilateral frontal regions and between the left frontal and right temporal–parietal regions were observed. The same effects, however, were not found in the gamma band. These results suggest that large-scale theta neural synchronization is involved in working memory binding of verbal and spatial information.

The synchronized theta activity has been reported increasing with the task difficulty in many previous working memory studies (Gevins et al., 1997; Sarnthein et al., 1998; Klimesch et al., 1999; Tesche and Karhu, 2000; Raghavachari et al., 2001; Jensen and Tesche, 2002; Schack et al., 2002, 2005; Silberstein et al., 2003; Sauseng et al., 2005). However, in the present study, the task difficulty in the bound condition was lower than that in the separated condition. This may be explained by the decreased number of objects (four objects in the bound condition while eight objects in the separate condition) through binding though equal amount of information (four letters and four locations) was required to be maintained in both the bound and separate conditions (Luck and Vogel, 1997). Recently, Alvarez and Cavanagh (2004) suggest that both the visual information load and the number of objects influence capacity limits on visual working memory, which are determined by the total amount of visual information load (“the product of the number of objects and the visual information of each object”). Moreover, Campo et al. (2005) propose that the bound condition results in less interfering between the processing of verbal and spatial information, thus facilitating the processing of both information. Therefore, the lower task difficulty in the bound condition may be the result of multiple factors. The higher synchronized theta activity in the lower task difficulty condition we observed here suggests that the increased synchronized theta activity is related to binding rather than the task difficulty.

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[3] As suggested by Kaiser et al. (2004), to avoid the possibility that the random permutation correction is too strict, the uncorrected results may be helpful to evaluate the effect. We thus also provided the uncorrected 6 Hz phase synchronization significance map (see Fig. 5 in the Supplementary materials) to help evaluate the greater 6 Hz phase synchronization in the bound condition.

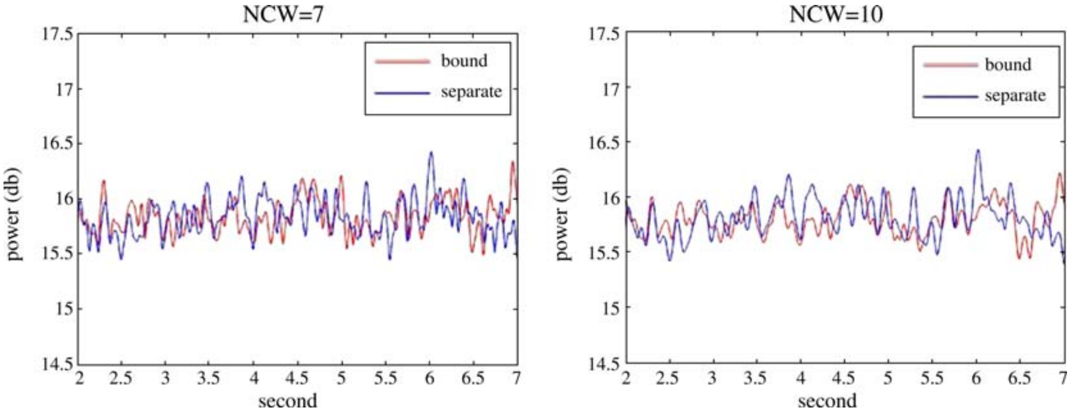

Fig. 4. The mean time courses of the 40 Hz power of electrode F3 in the bound and separate conditions. The number of cycles of wavelets (NCW) = 7 and 10.

The greater frontal theta power and the greater theta phase synchronization between bilateral frontal regions in the bound condition suggest the engagement of the frontal areas in the binding process. The theta phase synchronization between the frontal and temporal–parietal areas may indicate that the temporal–parietal areas are involved in the binding process as well. These observations are consistent with the previous studies using the similar paradigm (Prabhakaran et al., 2000; Campo et al., 2005), but moreover, the present results provide new EEG evidence supporting that both the frontal and temporal–parietal areas are engaged in binding of verbal and spatial information in working memory. In the study of Prabhakaran et al. (2000), the binding-related activity was observe only in the frontal area. However, we and Campo et al. (2005) both found that the binding-related activity also exists in the temporal–temporal parietal areas. In addition, the involvement of temporal–parietal areas was revealed by interactions (phase synchronization) in the present study, while in Campo et al. (2005), its involvement was revealed by activation (ERF). These differences could be explained by two possible reasons. One is that EEG, MEG and fMRI measure different aspects of the brain activity so that differences in measurements may result in discrepancies in results. The other reason could be that, cortical activation and interactions can provide different information about cognitive operations (Gerloff et al., 1998; Buchel et al., 1999). For instance, similar to the present study, frontal power and frontoposterior interactions were also found in a mental calculation task (Mizuhara et al., 2004). This may be why the involvement of temporal–parietal areas was identified by interactions (phase synchronization) in the present study.

The involvement of large-scale neural synchronization in working memory binding was presently observed at the theta rather than gamma band, which is associated with perceptual binding (Singer, 1999; Engel and Singer, 2001). In the binding process, information encoded in different brain regions needs to be integrated by cortical interactions between those brain regions. Given that the perception process mainly involves restricted sensory cortices while the working memory process involves a widespread network (D'Esposito et al., 1998; Jonides et al., 1998; Haxby et al., 2000), perceptual binding may involve much smaller scale cortical interactions than working memory binding. As shown in the study of von Stein and Sarnthein (2000), while small-scale cortical interactions are correlated with high-frequency (e.g., gamma) synchronization, large-scale cortical interactions are related to low-frequency (e.g., theta) synchronization. Our results are consistent with the findings of von Stein and Sarnthein (2000). The absence of the difference in the 40 Hz synchronized activity between the bound and separate conditions may also be due to the possible opposite binding and task difficulty modulation on the 40 Hz synchronized activity. As there is evidence showing that the gamma activity increases with the memory task difficulty (Tallon-Baudry et al., 1998; Schack et al., 2002; Howard et al., 2003), it is possible that in the present experiment, even though binding could make the gamma activity stronger in the bound condition, the higher task difficulty would make it stronger in the separate condition, hence, generating non-significant difference between the two conditions. Another possibility of absence of 40 activity difference could be due to the large number of cycles of wavelets (NCW) = 10 we used in analyzing the 40 Hz activity. Changes of gamma phase can be very transient thus might be lost when calculating the phase over a long filter window with the NCW = 10. To examine this possibility, we have performed additional analyses on the 40 Hz frequency with a smaller NCW = 7. However, the results were still the same without any significant difference in the 40 Hz activity between the bound and separate conditions (see the Appendix below).

In rodents, theta oscillations are considered occurring in the hippocampus in learning and memory tasks (Kahana et al., 2001). However in human, besides the hippocampus, intracranial EEG (iEEG) studies have also found theta oscillations in many cortical regions including the frontal, temporal, parietal and occipital cortices (for reviews, see O'Keefe and Burgess, 1999; Kahana et al., 2001). Of particular interest is the findings of a recent iEEG study (Raghavachari et al., 2006) that during a Sternberg task, theta oscillations in different brain regions were not well correlated, and distant brain regions were almost never coherent. These results indicate the local mechanisms for theta generation, which are not well consistent with the observations of large-scale theta interactions during working memory tasks in scalp EEG studies (Sarnthein et al., 1998; Sauseng et al., 2005). Future work will be needed to investigate this gap between the iEEG and scalp EEG. Specifically, the large-scale neural synchronization found in the present working memory binding task could be further examined with iEEG as the iEEG can also overcome the inherent problem of scalp EEG, the volume conduction (Raghavachari et al., 2006).

Conclusion

The presented EEG study investigated oscillatory power and phase synchronization in a working memory task in which the verbal and spatial information were either bound or separate. We found that the frontal theta power and large-scale theta phase synchronization between bilateral frontal regions and between the left frontal and right temporal–parietal regions were greater for maintaining bound relative to separate information. Our results suggest that large-scale neural synchronization at the theta band is involved in working memory binding thus provides the neurophysiological evidence supporting the temporal binding hypothesis in working memory (Singer, 1999; von der Malsburg, 1999; Baddeley, 2000). However, the present results do not oppose to the classical binding theory (Barlow, 1972; Riesenhuber and Poggio, 1999). As Singer (1999) suggested, the temporal binding mechanism and the classical binding mechanism may complement rather than contradict each other in the binding processes.

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Appendix A

One reviewer suggested that the number of cycles of wavelets (NCW) = 10 used in the main text may be too large for the 40 Hz activity and this may be a possible account for the absence of significant difference in the 40 Hz synchronized activity between the bound and the separate conditions.

To examine this possibility, we reanalyzed the 40 Hz activity with a smaller NCW = 7, which was adopted by Rodriguez et al. (1999) to investigate the gamma activity in a perceptual task.

A.1. Methods

A.1.1. EEG data analyses

Both the time frequency power (TFP) and phase synchronization were analyzed. All were the same as those in the main text, except that only the 40 Hz frequency was analyzed and a smaller NCW = 7 instead of 10 was used.

A.1.2. Statistic method

Both the TFP and phase synchronization significance maps were generated. All were the same as those in the main text, except that only the 40 Hz frequency was analyzed.

A.2. Results

No significant difference in power or phase synchronization was found. The TFP significant map was a “black horizontal line” (same as that at the 40 Hz frequency in Fig. 2A, TFP pixels with the power differences not reaching significance are displayed in black. As only the 40 Hz frequency was analyzed here, it was a horizontal line). The phase synchronization map was a “blank map”, that, no significant electrode pair was observed.

To better depict the effect of using a smaller NCW, we compared the time courses of the 40 Hz power with the NCW = 7 to those with the NCW = 10 (Fig. 4). A smaller NCW indeed improved the temporal resolution. Compared to the NCW of 7, the time courses with the NCW of 10 were a little smoothed. However, the shapes of the time courses did not largely change, and as a result, the differences between the bound and separate conditions also did not largely change.

A.3. Discussion

At 40 Hz, the NCW = 10 resulted in the wavelet duration of 79.6 ms and the NCW = 7 resulted in the wavelet duration of 55.7 ms. A smaller NCW of 7 did improve the temporal resolution. However, this discrepancy is not very large and the difference in the 40 Hz activity between the bound and separate conditions was still not significant. Therefore, adopting the NCW = 10 may not be the most important factor for the absence of the 40 Hz activity difference.

Appendix B. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.neuroimage.2007.02.011.

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