Synchronization between prefrontal and posterior association cortex during human working memory

J. Sarnthein*, H. Petsche, P. Rappelsberger, G. L. Shaw†, and A. von Stein*‡

Institut für Neurophysiologie, Universität Wien, Währingerstrasse 17, A-1090 Wien, Austria; and †Center for Neurobiology of Learning and Memory, University of California, Irvine, CA 92717

ABSTRACT We measured coherence between the electroencephalogram at different scalp sites while human subjects performed delayed response tasks. The tasks required the retention of either verbalizable strings of characters or abstract line drawings. In both types of tasks, a significant enhancement in coherence in the θ range (4–7 Hz) was found between prefrontal and posterior electrodes during 4-s retention intervals. During 6-s perception intervals, far fewer increases in θ coherence were found. Also in other frequency bands, coherence increased; however, the patterns of enhancement made a relevance for working memory processes seem unlikely. Our results suggest that working memory involves synchronization between prefrontal and posterior association cortex by phase-locked, low frequency (4–7 Hz) brain activity.

Working memory is typically defined as our ability to keep events actively "in mind" for short periods of time. Information in working memory is continuously updated as it is used to guide behavior. Extensive research in humans and nonhuman primates supports the idea that working memory is based on a neuronal circuit involving prefrontal cortex and posterior association areas (1–16). However, the nature of the interactions between brain regions participating in working memory has not yet been identified.

Inspired by recent physiological studies in cats and monkeys, which report synchronized activity of cortical neurons during processing of visual stimuli (17, 18), we propose that phase-locking of neuronal activity may be involved in working memory to support interactions between distant brain areas. Scalp electroencephalogram (EEG) recordings can measure activity of distant areas of the cortex with high temporal resolution. Because coherence describes the phase-locked component shared by two signals, large-scale cortical interactions can be detected over the whole cortex (19). These reasons led us to perform coherence analysis on human scalp EEG recorded while subjects performed working memory tasks. We present evidence that synchronized neuronal activity occurs in the 4- to 7-Hz frequency range between prefrontal and posterior regions during working memory retention in humans.

METHODS

Experimental Design. The experiment (Fig. 1) consisted of two tasks, both requiring the active retention of a stimulus in short-term memory. In task I, the stimulus was a string of 6–8 standard keyboard characters. First, the stimulus was presented for 6 s (perception interval) at 10° of visual angle on a computer screen (Macintosh VGA passive matrix liquid crystal display). After stimulus offset, subjects actively retained the

stimulus in memory for 4 s (retention interval) while fixating the dark screen. Finally, subjects were cued by a white screen onset to reproduce the stimulus with paper and pencil. Although there was no auditory stimulation in task I, subjects reported transforming the visually presented characters into phonological equivalents and rehearsing them subvocally during the retention interval and thus accessing the verbal memory system (20). Mean performance was consistent with normal digit span (6 symbols, 88%; 7 symbols, 62%; 8 symbols, 47%). In task II, stimuli were abstract line drawings activating visuo–spatial working memory. Accurate reproduction of drawings during the reproduction interval was not quantified but reported to be demanding. Although in both tasks the stimuli were perceived visually, the nature of the stimuli addressed different aspects of the working memory system (20).

As a control condition, in the beginning of the session, a 2-min period was chosen during which subjects fixated the dark computer screen. This period equals the retention interval except for the active rehearsal of stimuli in memory. Furthermore, to exclude unspecific arousal of the brain during the retention interval, we considered only those results to be relevant for working memory retention which (*i*) distinguished retention from perception and (*ii*) were reproducible between the two types of tasks.

EEG Coherence. The EEG of six normal female volunteers (ages 28 ± 5 years) was recorded. Electrode sites of the International 10–20 system (24) were used for 19 scalp electrodes referred to digitally averaged signals at both ear lobes. Recordings were made with a sampling rate of 128 Hz, a time constant of 0.3 s, and low pass filtering at 35 Hz. Nonoverlapping, artifact-free, 2-s epochs were Fourier transformed, and averaged power spectra, C_{xx}, and cross-power spectra, C_{xy}, for all 171 electrode pairs were computed for perception, retention, and control condition. Spectral bins were averaged to obtain mean values for the six frequency ranges δ (2–4 Hz), θ (4–7 Hz), $\alpha1$ (7–10 Hz), $\alpha2$ (10–13 Hz), β (13–19 Hz), and γ (19–32 Hz). Coherence K_{xy} for two signals, x and y, is equal to the average cross power spectrum normalized by the averaged powers of the compared signals: $K_{xy} = |C_{xy}|^2/(C_{xx}C_{yy})$. Coherence is the frequency domain equivalent to the cross-covariance function and is a measure of the similarity of two signals. Its value lies between zero and one, and it estimates the degree to which phases at the frequency of interest are dispersed (23). $K_{xy} = 0$ means the phases are evenly dispersed among all epochs. $K_{xy} = 1$ means the phases of signals x and y are identical in all epochs, i.e., the two signals are totally phase-locked at this frequency. Following EEG convention, the term synchronization is used here for any
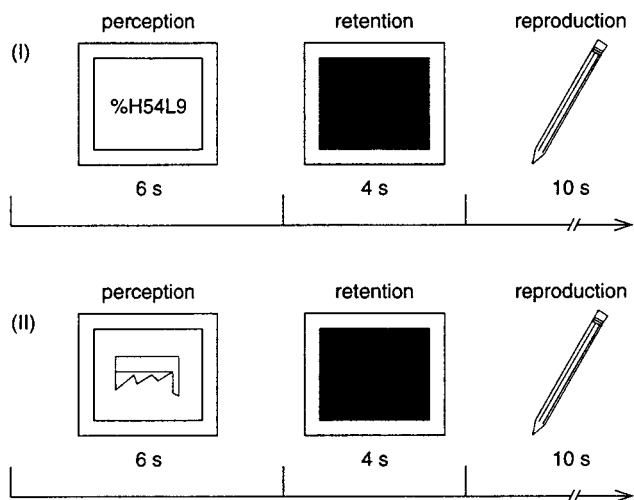
FIG. 1. Schematic drawing of the events on each trial of the verbal (I, *Top*) and visuo-spatial (II, *Bottom*) working memory tasks. First a stimulus was presented for 6 s (perception). During the ensuing dark-screen interval of 4 s, subjects actively retained the stimulus in memory (retention). Finally, subjects reproduced the stimuli with paper and pencil (reproduction).

phase-locked correlated signals, not only those with zero phase lag. In this sense, an enhancement of coherence signifies increased synchronization between two cortical sites.

Statistical Procedure. With each subject performing 20 trials in each session, coherence estimates are based on 2×20 degrees of freedom for each of the conditions: perception, retention, and control. Four of the six subjects participated in two sessions on different days, leading to a total of 10 recording sessions in our study. A typical example of coherence values are the coherence levels measured at electrode pair Fz-T5 for all 10 sessions (Fig. 2). In 7 of 10 sessions, coherence was higher for task than for the control condition. The significance level of coherence-increase between task and control was evaluated by applying paired Wilcoxon tests to group results and yields $P < 0.02$ in this example (21, 22). For all of the electrode pairs, the enhancement of coherence was plotted as a line connecting electrode sites in probability maps (Figs. 3–5) (21), if the significance level was $P < 0.05$ or better. We did not highlight pairs where $P < 0.02$ or $P < 0.01$ because we wanted to discuss the patterns as a whole. Because in this procedure significance
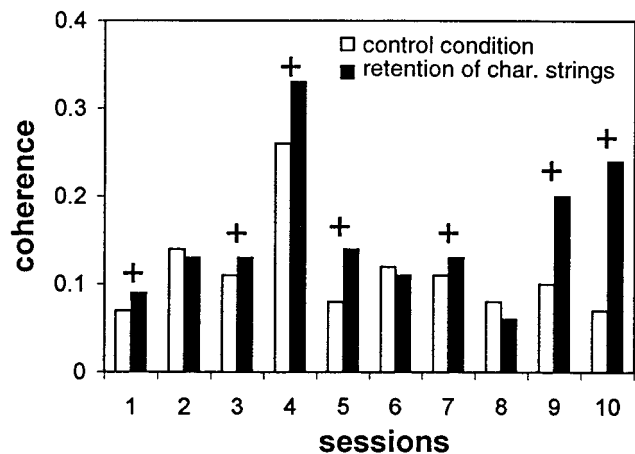

FIG. 2. Sample of raw θ-coherence values obtained for recordings from one electrode pair (Fz-T5) during retention of character strings (black bars) and control (white bars). In seven of the 10 recording sessions, coherence is higher during retention. The Wilcoxon test indicates a significant increase in coherence ($P < 0.02$).

levels were not corrected for multiple comparisons, we also performed an ANOVA, which will be described in *Results*.

RESULTS

The most striking result was the different patterns of coherence-increase during the perception and retention intervals in the 4- to 7-Hz θ range. While subjects retained strings of characters (task I), coherence increased between electrodes over prefrontal cortex and posterior association cortex. This result is illustrated in Fig. 3*a*, in which a significant increase of coherence ($P < 0.05$ or better) is marked by a connection between the two electrodes of a pair. More connections appear in the left hemisphere. At this stage, however, we are only interested in the functional enhancement of coherence between anterior and posterior electrode sites and neglect any effects of hemispheric lateralization. During retention of abstract line drawings (task II, Fig. 3*b*), the pattern of θ coherence-increase again showed prominent connections between prefrontal cortex and posterior association cortex, similar as during the retention of character strings. This reproducibility supports our central hypothesis that these interactions relate to working memory processes.

The patterns of enhanced θ coherence were specific to the retention interval; during perception intervals, little synchronization of θ EEG was observed (Fig. 4). Furthermore, the θ coherence patterns during retention and perception intervals showed no similarity. To quantify this comparison between patterns, we introduced a measure for similarity S as the ratio of equal connections with respect to the total number of connections in both maps (Table 1). The θ patterns corresponding to the retention intervals of the two types of tasks (verbal and visual; Fig. 3 *a* and *b*) show a high similarity (S = 0.35), whereas no similarity is found between retention and perception (S = 0). Among all frequency ranges, only the 4- to 7-Hz θ patterns (*i*) distinguished perception from retention and (*ii*) were similar between both memory tasks.

As a different approach to test the significance of our main hypothesis, we performed a 3×36 repeated measures ANOVA with cognitive state (control, perception, and retention) and topography (36-anterior–posterior electrode pairs) as within subject factors. For the cognitive state, coherences of tasks I and II were averaged to facilitate post-hoc testing. To select anterior–posterior electrode pairs, we defined four quadrants Fp1, F3, F7 (left anterior); Fp2, F4, F8 (right anterior); P4, T6, O2 (right posterior), and P3, T5, O1 (left posterior). The size of these quadrants also should be a safe estimate of the localization that can be achieved by ongoing EEG. A packet of nine electrode pairs thus describes the interaction of EEG activity between two quadrants. We considered those four packets whose main direction is anterior–posterior. The corresponding 36 coherence values for each cognitive state entered the ANOVA after coherence values were Fisher-z-transformed. In the θ band, both main effects were highly significant (cognitive state: F(2, 20) = 6.35, P = 0.007, Greenhouse–Geisser corrected P = 0.009; topography: F(35, 350) = 0.000). The effect of topography simply states that cortex is inhomogeneous, but the significant cognitive-state main effect warrants the use of post-hoc *t* tests. The difference between perception and control was not significant, whereas retention differed significantly from both control (P = 0.034) and perception (P = 0.011), df = 10 in all cases. This result supports the hypothesis that anterior–posterior θ coherence is enhanced during the retention intervals with respect to both perception and control.

In all other frequency bands, the ANOVA yielded nonsignificant results. Also, the similarities of coherence patterns quantified in Table 1 do not point to a relevance for working memory in other bands. It is interesting to note, however, that coherence patterns in the γ range (19–32 Hz, Fig. 5) were

(a) retention of
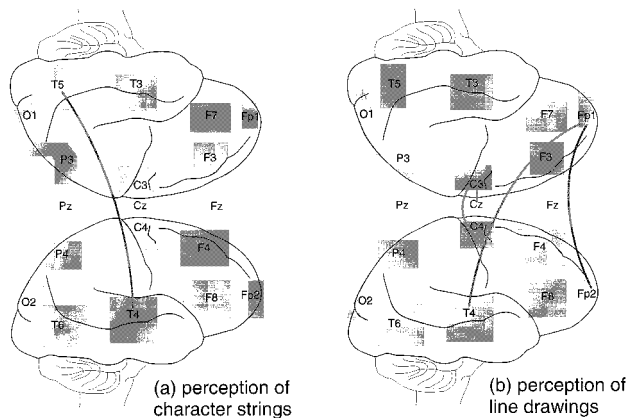character strings

(b) retention of
line drawings
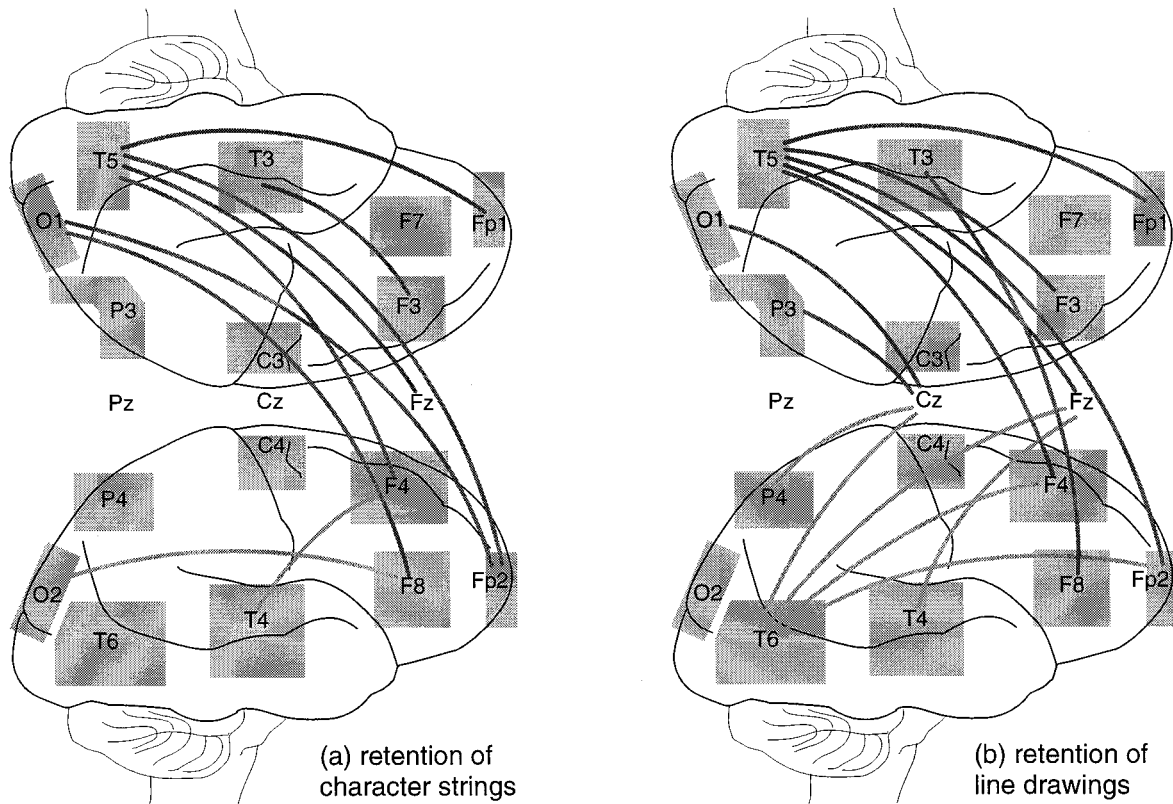
theta band (4-7 Hz)
retention intervals

FIG. 3.   Enhanced coherence in the θ range (4–7 Hz) during preception and retention intervals. Connections between electrode sites represent significant increases of coherence above control (*P* < 0.05 or better). The significance level was evaluated by applying paired Wilcoxon tests to group results. The shaded areas indicate the range of positions of individual electrodes as determined in an MRI study (24). Note that the occipital electrodes (O1, O2) are placed not over primary visual areas, but closer to the parieto-temporo-occipital association region. (*a*) During retention of character strings in memory (task I), enhanced coherence appeared between prefrontal and posterior cortex. In posterior cortex, the left hemisphere was predominantly involved. (*b*) Coherence-increases during retention of abstract line drawings in memory (task II). Patterns of enhanced coherence were similar to those in the verbal memory task *a*, although more connections appeared in the right hemisphere.

rather similar within tasks between perception and retention intervals (verbal: S = 0.54, visual: S = 0.52). Additionally, a

(a) perception of
character strings

(b) perception of
line drawings

theta band (4-7 Hz)
perception intervals

FIG. 4.   Enhanced θ coherence (4–7 Hz) during perception of character strings (*a*) and line drawings (*b*) (*P* < 0.05 or better). The number of significant coherence-increases was small compared with the retention intervals. Furthermore, the two patterns showed no topographic similarity.

high degree of similarity across tasks (verbal and visual; S = 0.60) was found between the γ range patterns for the two perception intervals.

DISCUSSION

We observed enhanced EEG coherence in the 4- to 7-Hz θ range between electrodes over prefrontal and posterior association cortex while subjects retained stimuli in working memory. The importance of these areas for working memory is well established by extensive experiments on humans and nonhuman primates by using a variety of techniques. Single-cell recordings have found prefontal and parietal neurons most active during delay periods in delayed response tasks (1–5). Several imaging studies on working memory in humans have reported increased activity in both prefrontal cortex and posterior regions (1, 5–16). How do these regions interact during working memory activity? Anatomical studies indicate high connectivity between frontal and posterior association cortices (2); a functional interaction is implied by the fact that cooling parietal cortex reduces the activity of prefrontal neurons in macaque brain (4, 5). However, the dynamics of the interaction itself have remained unclear. Oscillatory activity observed at 2–5 Hz in single cells during short-term memory tasks (25, 26) has been proposed as evidence for an interaction mediated by reverberations (5, 27, 28). Our findings suggest that synchronized neuronal activity occurs in the 4- to 7-Hz
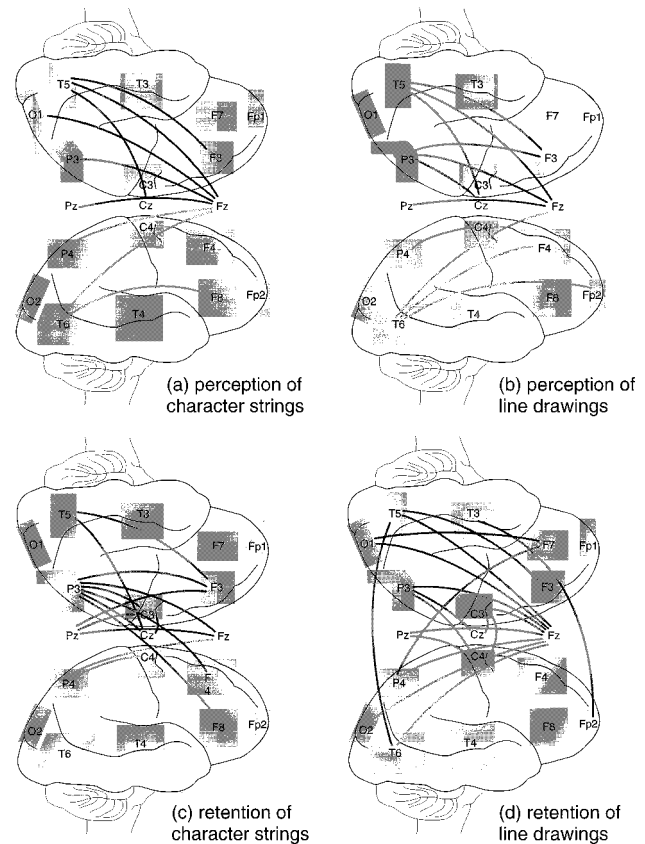
Neurobiology: Sarnthein *et al.*

Proc. Natl. Acad. Sci. USA 95 (1998)   7095

Table 1.   Similarity between patterns of enhanced coherence

			Verbal		Visual	
			p	r	p	r
δ	Verbal	p	1			
		r	0	1		
	Visual	p	0	0	1	
		r	0	0	0	1
θ	Verbal	p	1			
		r	0	1		
	Visual	p	0	0	1	
		r	0	0.35	0	1
α2	Verbal	p	1			
		r	0	1		
	Visual	p	0.31	0	1	
		r	0	0.22	0.27	1
α1	Verbal	p	1			
		r	0	1		
	Visual	p	0	0.11	1	
		r	0	0.21	0.60	1
β	Verbal	p	1			
		r	0	1		
	Visual	p	0.27	0.12	1	
		r	0.40	0	0.14	1
γ	Verbal	p	1			
		r	0.54	1		
	Visual	p	0.60	0.42	1	
		r	0.41	0.42	0.52	1

The table compares the EEG coherence patterns of the two task conditions (visual and verbal) in each frequency band for both perception (p) and retention (r). The similarity S between two patterns is quantified as the ratio of equal connections with respect to the total number of connections in both maps. For example, Fig. 3 *A* and *B* share eight connections (Fr-T5; Fp2-T5; Fz-T5; Fp1-T5). Dividing by 23, the total number of connections, gives S = 0.35. In θ, the patterns during retention were highly similar but different from all other conditions; in γ, all patterns showed a high degree of similarity. (In the diagonals, patterns are compared to themselves, leading to a similarity of S = 1.)

(a) perception of character strings

(b) perception of line drawings

(c) retention of character strings

(d) retention of line drawings

gamma band (19-32 Hz)

FIG. 5.   Enhanced coherence in the γ range (19–32 Hz) during retention and perception intervals ($P < 0.05$ or better). In both the visual and the verbal task, the topographic pattern during perception intervals (*a* and *b*) were similar to that during retention intervals (*c* and *d*). γ range coherence patterns were also similar between tasks. Compared with the θ patterns (Fig. 3), γ band coherence-increases involved a higher percentage of ipsilateral electrode pairs.

range between prefrontal and posterior regions during short-term memory retention in humans. This result suggests that synchronization plays a role in the interaction of posterior association cortex, where sensory information is thought to be stored, and prefrontal cortex, where relevant current information is held and continuously updated (1–5).

Our choice of stimuli was guided by the common dissociation of working memory into verbal and visuo–spatial components (20). And, indeed, although the patterns of enhanced coherence were very similar among the two types of tasks, also some differences appear. However, the discussion of hemispheric lateralization of the coherence patterns has to happen with due caution as our results in this respect are merely descriptive. Our finding of a left hemisphere predominance during the subvocal rehearsal of character string agrees with other studies using blood flow measurements (6–9) and various EEG measures (13–15) in verbal memory tasks. The lateralization is not strict because we found prefrontal involvement bilaterally, compatible with many of the above studies. During the retention of abstract line drawings, both left and right hemisphere were involved, in agreement with other investigations of the neural substrate of visuo–spatial memory tasks in humans (6, 7, 10, 11). During the retention of both character strings and drawings, we found more connections involving right prefrontal cortex than left. This finding might reflect the reported importance of right prefrontal cortex for episodic memory retrieval (12). In general terms, not only our

gross discrimination of activity in posterior and anterior cortex is in agreement with other studies, but also the lateralization to left and right brain hemisphere seems plausible.

Although individual frequency ranges are not physiological entities, different EEG frequencies appear to have different functional correlates. In the θ range (4–7 Hz), significant increases in long-distance coherence between the regions of interest stood out in the retention interval. Coherence patterns in all other frequency ranges did not seem to be relevant for working memory. Nevertheless, as an aside, it is interesting that γ synchronization (19–32 Hz) increased during both perception and retention intervals and patterns showed a high similarity (Table 1). Synchronization in the γ band has been correlated with sensory processing (17, 18) and with increased attentiveness (29). Together with these findings, our results support the idea that locally driven synchronization, as in sensory processing, might take place in the γ range, whereas interareal interactions, as in working memory, might appear in lower frequencies. This interpretation is consistent with the possibility that γ oscillations occurring simultaneously with longer-range θ waves might allow for a nesting of fast into slow oscillations, a mechanism recently proposed to provide a temporal structure for ensembling neurons involved in working memory retention (30).

We observed a coherence-increase in the θ (4–7 Hz) range, we are led to speculate about the involvement of hippocampus in the brain circuit relevant for working memory processes.

The hippocampus contains θ-pacemakers, and, although the working memory of the hippocampal patient H.M. is not impaired, the hippocampal formation is activated in studies of delayed recall in normal humans (16). Furthermore, hippocampus has widespread connections to all parts of cortex (both anatomically and functionally) (27, 28), and phase-locked hippocampo-cortical loops have been proposed to be correlated with both encoding and retrieval of memories (27, 28). Given the importance of rhythmic θ activity in this loop (27, 28, 31), it seems likely that cortical activity engaged in memory retention may involve activity in the same frequency range (15).

Our EEG coherence findings suggest that low-frequency (4–7 Hz) interactions between prefrontal cortex and posterior association areas mediate working memory processes. We propose that a reentrant network organization consisting of prefrontal cortex, the sensory-related regions of the posterior lobe, and perhaps the hippocampal formation may operate as an integrated unit by means of synchronization in the θ range.

1. Goldman-Rakic, P. S. (1997) *Nature (London)* **386,** 559–560.
2. Goldman-Rakic, P. S. (1988) *Annu. Rev. Neurosci.* **11,** 137–156.
3. Wilson, F. A. W., Scalaidhe, S. P. & Goldman-Rakic, P. S. (1993) *Science* **260,** 1955–1958.
4. Quintana, J., Fuster, J. M. & Yajeya, J. (1989) *Brain Res.* **503,** 100–110.
5. Fuster, J. M. (1995) *Ann. N.Y. Acad. Sci.* **769,** 173–181.
6. Cabeza, R. & Nyberg, L. (1997) *J. Cognit. Neurosci.* **9,** 1–26.
7. Smith, E. E., Jonides, J. & Koeppe, R. A. (1996) *Cereb. Cortex* **6,** 11–20.
8. Paulesu, E., Frith, C. D. & Frackowiak, R. S. (1993) *Nature (London)* **362,** 342–345.
9. Shallice, T., Fletcher P., Frith, C. D., Grasby, P., Frackowiak, R. S. & Dolan, R. J. (1994) *Nature (London)* **368,** 633–635.
10. Petrides, M., Alivisatos, B., Meyer, E. & Evans, A. C. (1993) *Proc. Natl. Acad. Sci. USA* **90,** 873–877.
11. Swartz, B. E., Halgren, E., Fuster, J. M., Simpkins, E., Gee, M. & Mandelkern, M. (1995) *Cereb. Cortex* **3,** 205–214.
12. Tulving, E., Kapur, S., Craik, F. I., Moscovitch, M. & Houle, S. (1994) *Proc. Natl. Acad. Sci. USA* **91,** 2016–2020.
13. Gevins, A., Smith, M. E., McEvoy, L. & Yu, D. (1997) *Cereb. Cortex* **7,** 374–385.
14. Lang, W., Starr. A., Lang, V., Lindinger, G. & Deecke, L. (1992) *Electroencephalograph. Clin. Neurophysiol.* **82,** 285–295.
15. Klimesch, W., Schimke, H. & Schwaiger, J. (1994) *Electroencephalograph. Clin. Neurophysiol.* **91,** 428–441.
16. Squire, L. R., Ojemann, J. G., Meizin, F. M., Petersen, S. E., Videen, T. O. & Raichle, M. E. (1992) *Proc. Natl. Acad. Sci. USA* **89,** 1837–1841.
17. König, P. & Engel, A. K. (1995) *Curr. Opin. Neurobiol.* **5,** 511–519.
18. Singer, W. (1993) *Annu. Rev. Physiol.* **55,** 349–374.
19. Petsche, H., von Stein, A. & Filz, O. (1996) *Cognit. Brain Res.* **1,** 115–123.
20. Baddeley, A. (1992) *Science* **255,** 556–559.
21. Rappelsberger, P. & Petsche, H. (1988) *Brain Topogr.* **1,** 46–54.
22. Weiss, S. & Rappelsberger, P. (1996) *Neurosci. Lett.* **209,** 17–20.
23. Challis, R. E. & Kitney, R. I. (1991) *Med. Biol. Eng. Comput.* **29,** 225–241.
24. Homan, R. W., Herman, J. & Purdy, P. (1987) *Electroencephalograph. Clin. Neurophysiol.* **66,** 376–382.
25. Nakamura, K., Mikami, A. & Kubota, K. (1992) *NeuroReport* **3,** 177–120.
26. Chelazzi, L., Miller, E. K., Duncan J. & Desimone, R. (1993) *Nature (London)* **363,** 345–347.
27. Buzsaki, G. (1996) *Cereb. Cortex* **6,** 81–92.
28. Miller, R. (1991) *Cortico-Hippocampal Interplay and the Representation of Contexts in the Brain* (Springer, Berlin).
29. Makeig, S. & Jung, T-P. (1996) *Cognit. Brain Res.* **4,** 15–25.
30. Lisman, J. E. & Idiart, M. A. (1995) *Science* **267,** 1512–1515.
31. Lopes da Silva, F. H. (1992) in *Induced Rhythms in the Brain* eds. Basar, E. & Bullock, T. H. (Birkhaeuser, Boston).