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Spatiotemporal characteristics of hemodynamic changes in the human lateral prefrontal cortex during working memory tasks

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Abstract

The prefrontal cortex (PFC) is widely believed to subserve mental manipulation and monitoring processes ascribed to the central executive (CE) of working memory (WM). We attempted to examine and localize the CE by functional imaging of the frontal cortex during tasks designed to require the CE. Using near-infrared spectroscopy, we studied the spatiotemporal dynamics of oxygenated hemoglobin (oxy-Hb), an indicator of changes in regional cerebral blood flow, in both sides of lateral PFC during WM intensive tasks. In most participants, increases in oxy-Hb were localized within one subdivision during performance of the n-back task, whereas oxy-Hb increased more diffusely during the random number generation (RNG) task. Activation of the ventrolateral PFC (VLPFC) was prominent in the n-back task; both sustained and transient dynamics were observed. Transient dynamics means that oxy-Hb first increases but then decreases to less than 50% of the peak value or below the baseline level before the end of the task. For the RNG task sustained activity was also observed in the dorsolateral PFC (DLPFC), especially in the right hemisphere. However, details of patterns of activation varied across participants: subdivisions commonly activated during performance of the two tasks were the bilateral VLPFCs, either side of the VLPFC, and either side of the DLPFC in 4, 2, and 4 of the 12 participants, respectively. The remaining 2 of the 12 participants had no regions commonly activated by these tasks. These results suggest that although the PFC is implicated in the CE, there is no stereotyped anatomical PFC substrate for the CE.

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Working memory (WM) is a neural mechanism that provides and supports temporary storage and manipulation of information used in complex cognitive tasks like learning and reasoning (Baddeley, 1986). Baddeley and Hitch (1974) proposed the multicomponent model of working memory, which comprises the central executive (CE) and two slave systems as a theoretical framework. Although the slave systems have been profitably studied by functional imaging (using PET and fMRI), much of the evidence on the neural

basis of working memory—especially the CE—comes from animal studies. These studies demonstrate that the prefrontal cortex (PFC) subserves executive control functions and that distinct subdivisions in the lateral PFC subserve different aspects of working memory (Goldman-Rakic, 1987; Petrides, 1989; Watanabe, 1996). There are several models for specialization of PFC subregions. For example, Goldman-Rakic proposed a “domain-specific” modularity in monkeys: a dorsal region of the lateral PFC is thought to be specialized for visual-spatial processing, while a more ventral region is involved in nonspatial visual processing within WM (Goldman-Rakic, 1987). Conversely, Petrides posits segregation within PFC based on the nature of processing within WM: the middle portion of the

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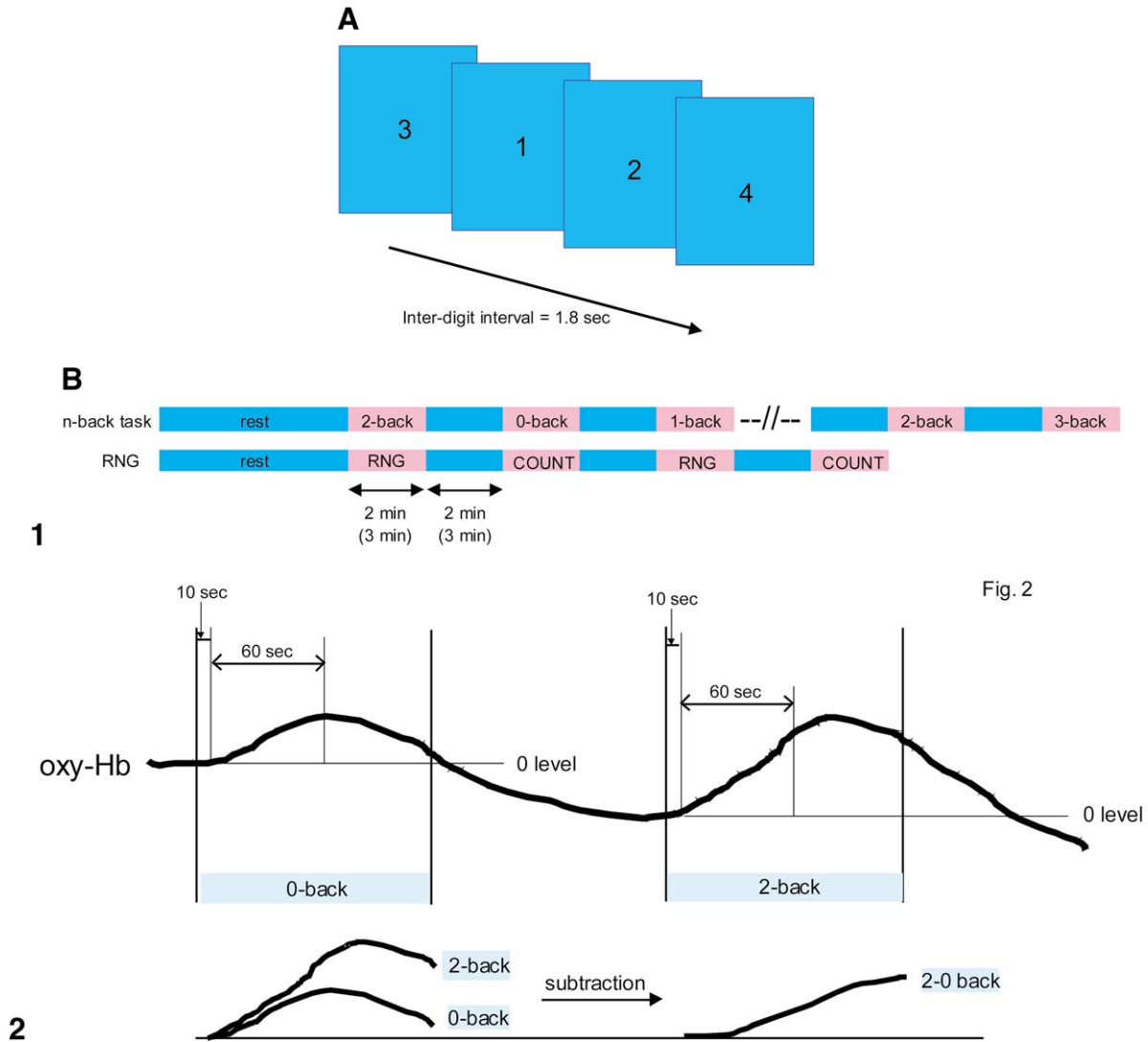


Fig. 1. (A) The *n*-back task; (B) an example of the experimental design.
 Fig. 2. Analysis of NIRS data.

ventrolateral prefrontal cortex (VLPFC) is the initial recipient of information from posterior association areas and the locus of the initial interaction of executive processing with short-term and long-term memory; the middle portion of the dorsolateral prefrontal cortex (DLPFC) is recruited only when active manipulation and monitoring of information in WM by executive processes is required (Petrides, 1989). Fuster posits another model of DLPFC functional organization: the DLPFC is a unitary association cortex that integrates information in a supramodal fashion (Fuster, 2000).

It is now widely accepted that the PFC plays a critical role in the neural network subserving WM and executive control operations in humans. Recent neuroimaging studies have demonstrated that there is also segregation of WM functions within the human lateral PFC and this segregation is based on the type or nature of the processes that are

carried out by the lateral PFC (Cohen et al., 1997; Courtney et al., 1998; Owen et al., 1999). The VLPFC is concerned with the active organization of sequences of responses based on conscious, explicit retrieval of information from posterior association systems, with some theorists also positing that the VLPFC guides active online maintenance of the accessed representations. By contrast, the DLPFC subserves active manipulation or monitoring. However, the neural correlate of the CE remains largely unknown. This is mainly due to the fact that the operational definition of the CE is vague. The CE is generally assumed to be an attentional control system over all other processes presumed to constitute WM, thus emphasizing the uniform nature of the CE. Reviewing neuropsychological and neuroradiological experiments, however, Parkin has demonstrated that there is no localization evidence for the CE, and different executive

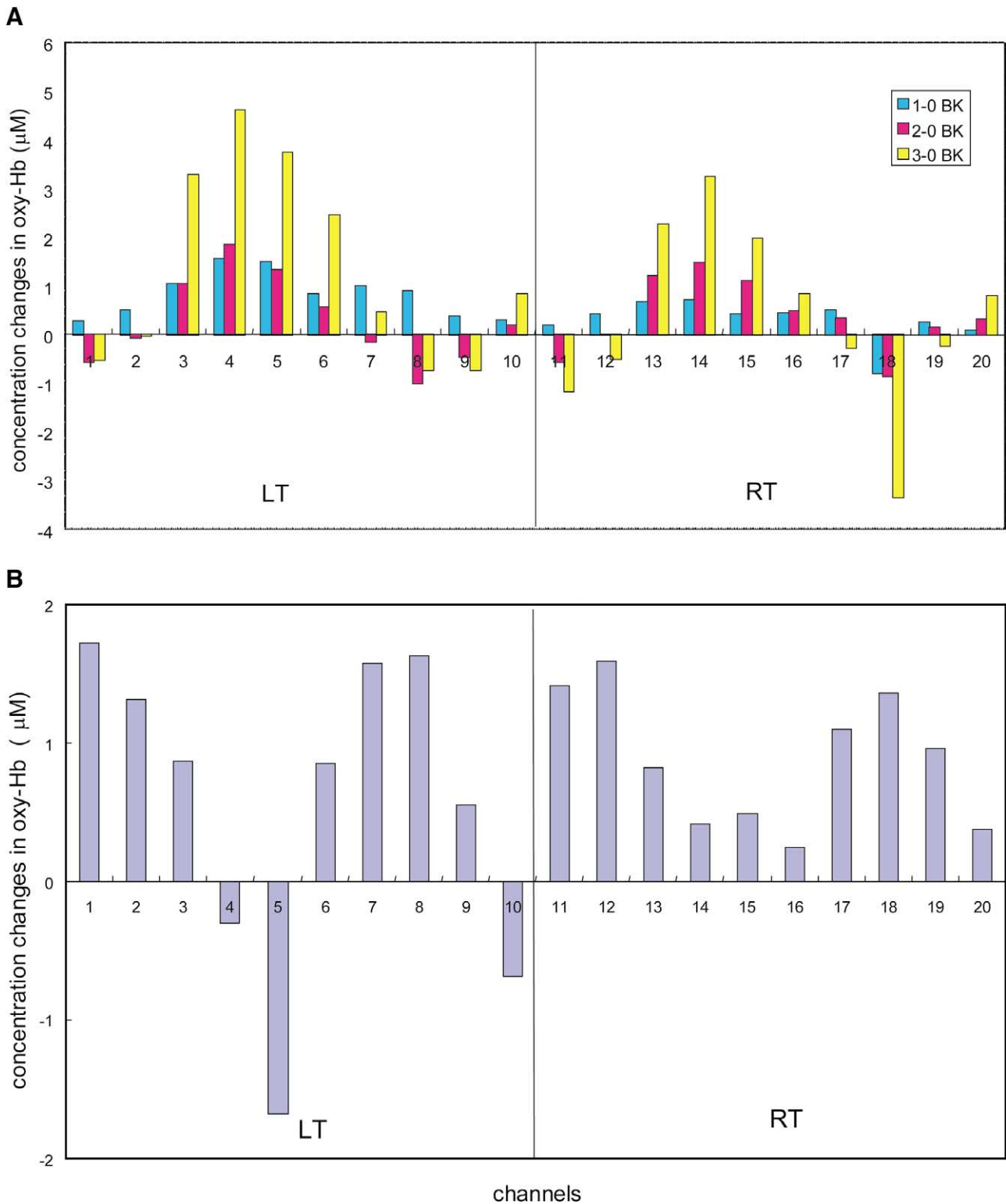


Fig. 3. An example of oxy-Hb concentration changes in each channel during n-back (A) and RNG tasks (B) obtained from participant 8. LT, left; RT, right.

tasks involve different neural substrates, from which he has concluded that the idea of the CE should be abandoned (Parkin, 1998). Meanwhile, Baddeley, who suggested that

Parkin's criticisms of the CE were based on a series of misconceptions, has argued that the CE is a collection of various subsystems, although how the subsystems interact

and how they map onto the anatomical substrate are empirical questions (Baddeley, 1998). A wide range of cognitive functions, such as manipulation and selection, has been ascribed to the CE and the cerebral substrates of these executive functions have been explored in neuroimaging studies, which have demonstrated that different executive functions recruit various frontal areas (Collette et al., 2002). Thus, much recent work favors—or is consistent with—some specialization within frontal functions. However, the fundamental question has not yet been definitely answered: Is the CE a unitary anatomical substrate with multiple functions or an agglomeration of independent but interacting control processes that are dependent on the VLPFC and the DLPFC? If the CE could be localized as a unitary system, then it is postulated that there would be common sustained regional brain activation within the PFC throughout the WM task. On the other hand, if the CE is not based on a unitary anatomical substrate, either or both the VLPFC and the DLPFC would be activated. Furthermore, the activity in either brain region can vary with time depending on the precise executive processes that are recruited by the task being performed. Thus, it is expected that dynamic recording of changes in regional cerebral blood flow (rCBF) associated with multiple regions of the lateral PFC can help clarify the concept of the CE.

Near-infrared spectroscopy (NIRS), a noninvasive optical technique, can measure changes in the hemoglobin (Hb) oxygenation state in the human brain (Jöbsis, 1977). Most commercially available NIRS instruments use continuous wave light as a light source and measure transmitted intensity at fixed spacing (CW-type NIRS instrument). With a CW-type instrument, we can see the successive changes in Hb concentration associated with changes in rCBF coupled to those in neuronal activity in real time (Hoshi and Tamura, 1993; Kato et al., 1993; Villringer et al., 1993). In addition, unlike functional magnetic resonance imaging (fMRI), NIRS allows studies outside of specific institutions. Since CW-type instruments cannot determine the optical path length in the head, however, obtained values are expressed as a product of concentration changes and the optical path length. In contrast, time-resolved measurement with ultrashort laser pulses enables us to determine the mean optical path length (Delpy et al., 1988), which is a summation of partial optical path lengths within the cerebral and extracerebral tissues (the scalp and the skull). In this study, using a 20-channel CW-type NIRS instrument to measure the spatiotemporal characteristics of oxy-Hb changes and a single-channel TRS instrument to estimate the mean optical path length in each channel, we examined changes in rCBF during performance of two working memory tasks—*n*-back and random number generation (RNG) tasks. The two tasks involve different subsystems of the CE and nonexecutive functions: the *n*-back task involves updating, encoding, rehearsal, maintenance, and retrieval, whereas suppression of habitual responses, self-monitoring, internal generation, and

sequencing behavior are involved in the RNG task. It is expected that the two tasks activate different brain regions, while there can also be overlaps in brain activations, not only because both the tasks require the same functions, such as sustained attention, but also selected frontal regions are involved in broad functions (Duncan, 2001). For example, encoding (D'Esposito et al., 2000) and suppression of habitual responses (Jahanshahi et al., 2000) are associated with activation of the left DLPFC. Thus, the existence of common sustained regional brain activation across subjects and tasks does not necessarily mean that the CE is unitary. In contrast, if such brain activation does not exist, it is concluded that the CE is not the unitary localized system.

Methods

Participants

Twelve right-handed paid volunteers (age range, 21–29, male 11, female 1) participated in this study. None had a history of neurological illness, head injury, or substance abuse. Prior to each study, written informed consent was obtained from all participants. All participants were given practice with the tasks.

Near-infrared spectroscopy instruments

A multichannel NIRS imaging system (OMM-2000, Shimadzu Co.) and a single-channel time-resolved spectroscopy instrument (TRS-10, Hamamatsu Photonics KK) were employed. Three wavelengths (780, 805, and 830 nm) were used in both the instruments. Four pairs of illuminating and detecting light guides were symmetrically placed on the lateral PFC region of both sides with an illuminating and detecting light guide separation of 3 cm (Fig. 3A). Measurement by the OMM-2000 was started about 5 min before the first task and was continued until the end of the last task. After the measurement by the OMM-2000, the mean optical path length was determined using the TRS-10 at each light guide pair. Although theoretically the optical path is not changed by activation because it is dependent on scattering but not absorption (Furutsu and Yamada, 1994), the optical path length determined by TRS varies with absorption change. However, the degree of change in the optical path length is less than 4% (unpublished data). Thus, we used the optical path length measured at the resting state for calculation. Upon completion of the study, participants underwent MRI measurement to confirm the brain region beneath each light guide.

Working memory tasks

The n-back task (Fig. 1A)

Participants viewed a sequence of single random digits on a computer display. The digits were limited to the values

1, 2, 3, and 4 that were shaped on a 8×8 cm matrix of 400 pixels. The interdigit interval was 1.8 s. Prior to a digit series, participants were instructed to remember the “target” digit that was n-back (0, 1, 2, or 3 digits back in the sequence). Using their left hand, participants responded by pressing the buttons that corresponded to the target digit. The 0-back task was used as the control task.

The RNG task

Participants were asked to recite a sequence of random digits between 0 and 9 to a 1-Hz pacing tone (RNG). As the control task, they were asked to repeatedly count out softly in order from 0 to 9 (COUNT).

Seven participants performed each task for 3 min, while 5 performed for 2 min. The order of n-back and RNG tasks was randomized. All tasks were repeated twice in a counterbalanced fashion, with a 2 or 3-min resting period in between (Fig. 1B).

Analysis of NIRS data (Fig. 2)

Concentration change (μM) in oxy-Hb was chosen for analysis, because it is the best indicator of changes in rCBF (Hoshi et al., 2001). The value at the point 10 s after the beginning of each task was taken as 0 (the baseline) for each channel, and then concentration changes in oxy-Hb were recalculated for 60 s from this point. Combining data obtained from the first and second trials changes during each test task were compared with those during the corresponding control task (the 0-back task, COUNT) using the Student *t* test. $P < 0.001$ was taken as a significant level. The mean value of concentration change in oxy-Hb for the 60 s in each task was calculated, and then the value for the corresponding control task was subtracted from those for test tasks (1 – 0 back, 2 – 0 back, 3 – 0 back, RNG-COUNT) (Figs. 3A and B). The values obtained here were used for reconstruction of topographical images, which were mapped by using linear interpolation of changes in oxy-Hb for all the channels. These subtraction images were superimposed on the 3-D MRI pictures. Because of the poor spatial resolution of NIRS, the measured area was roughly divided into four subdivisions: the DLPFC (Brodmann area (BA) 9/46), the VLPFC (BA44/45/47), BA 6, and BA 8. When significant increases in oxy-Hb were observed in two or more subdivisions, correlation analysis was performed between these subdivisions. If the values for a pair of subdivisions were not strongly correlated ($P > 0.001$), they were considered to be independently activated. If the values for two subdivisions were strongly correlated, the subdivision with larger increases in oxy-Hb was considered to be primarily activated. To quantify the asymmetry in functional activation, the laterality index (LI), which was based on the LI for fMRI (Binder et al., 1996), was calculated. The LI was defined as $LI = [100 \times (\Delta[\text{oxy-Hb}]_L - \Delta[\text{oxy-Hb}]_R) / (\Delta[\text{oxy-Hb}]_L + \Delta[\text{oxy-Hb}]_R)]$, where $\Delta[\text{oxy-Hb}]_L$ and $\Delta[\text{oxy-Hb}]_R$ are concentration changes in oxy-Hb that reached the significant level in the left and right sides, respectively. The value of the LI can range from +100 to –100%. A negative value indicates right-hemispheric dominance; a positive value indicates left-hemispheric dominance; and a value near 0 indicates no dominant hemisphere.

The period between 10 s after the beginning of each task and the end of the task (or 50 s before the end of the task for the participants who performed tasks for 3 min) was selected for examination of the time course of changes. Averaging traces in the first and second trials for each channel, the trace during the corresponding control task was subtracted from that in each test task (Fig. 2).

Results

Results

Task performance

As is typical with simple cognitive tasks, the mean responses accuracy was high and the distribution of scores was negatively skewed. Accuracies for the 1-, 2-, and 3-back tasks were 98 ± 4.01 (mean \pm SD), 93 ± 8 , and $83 \pm 24\%$, respectively, while two participants showed extremely poor task performance in the 3-back task (Table 2). Randomness was evaluated by counting bias (CA, the tendency to count in ascending or descending series in steps of 1), interval bias (IB, the tendency to produce digit series with particular interdigit intervals), and repetition bias (RB, the tendency to repeat the same digit) (Shinba and Ebata, 2000). There were no participants who showed higher scores in all the three biases compared with the standard values of our institute obtained from healthy adult volunteers.

Spatial characteristics of hemodynamic changes during performance of the n-back and RNG tasks

Fig. 4B shows an example of topographical subtraction images of oxy-Hb superimposed on 3-D MRI images between the 1-, 2-, or 3-back tasks and the 0-back task. In this case the largest increase in oxy-Hb was observed in the bilateral VLPFC and the degree of increases in oxy-Hb showed a positive correlation with the task difficulty. Such a positive correlation was observed in 8 of the 12 participants, including 2 participants who showed poor task performance in the 3-back task (participants 7 and 11). Thus, further analysis was performed on the 3-back task.

In most participants, increases in oxy-Hb were localized within one subdivision during performance of the n-back task, whereas oxy-Hb increased more diffusely during the RNG task. Table 1 summarizes activation areas during the

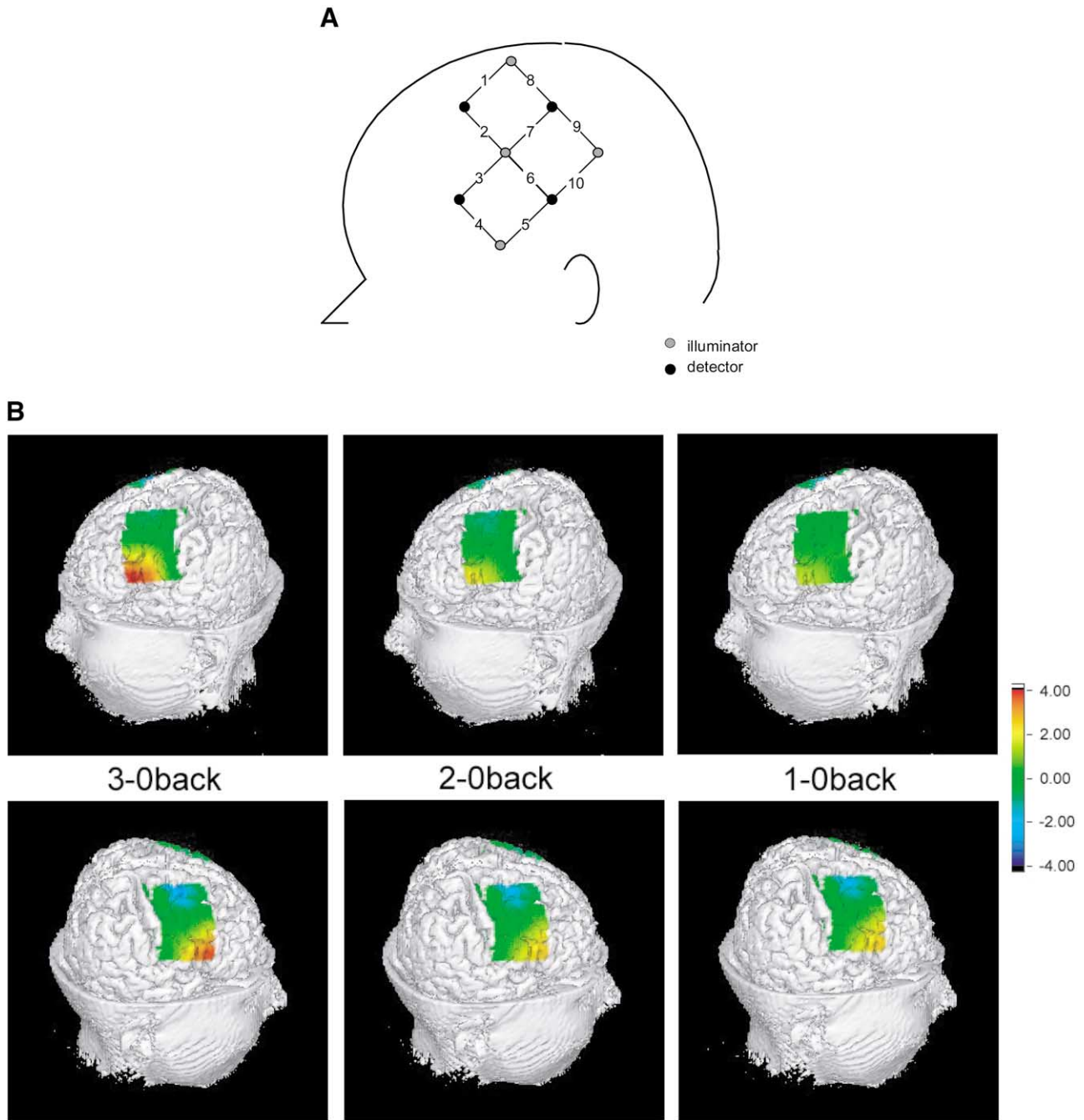


Fig. 4. (A) Positions of light guides. (B) Subtraction topographical images of oxy-Hb between n-back ($n = 1, 2,$ and 3) and 0-back tasks. Color scale denotes concentration changes (μM).

n-back and RNG tasks. Activation from the VLPFC was prominent with the n-back task, but hemispheric dominance was not clearly observed. For the RNG task, activation was observed in the DLPFC as well as the VLPFC and was more right hemisphere dominant. There was no relationship between activated areas and task performance in either of the tasks. Subdivisions commonly activated during performance of the two tasks were the bilateral VLPFCs, either side of the VLPFC, and either side of the DLPFC in 4, 2, and 4 of the 12 participants, respectively. No commonly

activated subdivisions were observed in the remaining two (participants #3 and #8).

Temporal characteristics of hemodynamic changes during performance of the n-back and the RNG tasks

Examination of the time course of changes in oxy-Hb in activated subdivisions demonstrated that activation of the VLPFC was nonsustained (Fig. 5A) as well as sustained (Fig. 5B). Nonsustained activation means that oxy-Hb first

Table 1
Foci of significant increase in rCBF associated with 3-back and RNG tasks

Subjects	3 – 0 Back			RNG-count		
	LT	RT	Laterality index	LT	RT	Laterality index
1	V	V, BA6	61.1	V/D	V	24.7
2	D	V	–68.7	D	D	–57.3
3	V	V	4.8	—	BA8	–100
4	V	V	–39.2	D/V	D/BA6/V	–26.4
5	D, BA8	V	59.6	V/D	V/D	–39.9
6	V, BA6	V/BA6	–54.1	V/BA6	V/BA6	–28.8
7	V	V	–33.8	V	V/D	–54.3
8	V	V	–5.2	D	D	–4.9
9	D/BA6/V	BA8/6	52.0	D/BA6	V	74.8
10	V, BA6/8	V/BA6	–47.6	D/BA6	V	–65.7
11	V, BA6	V/BA6	–25.8	V	V/D	–71.3
12	V	D	18.0	D/V	D/BA8	32.1

Note. V/BA6 denotes that the VLPFC was primarily activated. V, VLPFC; D, DLPFC; BA6, Brodmann area 6; BA8, Brodmann area 8.

increases but then decreases to less than 50% of the peak value or below the baseline level before the end of the task. In contrast, activation of the DLPFC was sustained with one exceptional case (participant 6). In the participants who showed nonsustained activation, oxy-Hb remained high in the opposite side or increased in other subdivisions (Fig. 6A). For participant 5, three subdivisions were independently activated during performance of the n-back task, in which the time courses of change in oxy-Hb were different and it appeared that these subdivisions had worked in a complementary manner (Fig. 6B). Table 2 summarizes the time courses of change in oxy-Hb during the tasks. The type of activation (sustained or nonsustained) was not related to task performance.

When the homologous lateral PFC in both hemispheres was activated, synchronous changes in oxy-Hb, in which the correlation coefficient was larger than 0.9, were observed in both of the tasks (Fig. 7). Such synchronous changes were more often observed in the n-back than the RNG task.

Discussion

Spatial characteristics

It is thought that the n-back task requires manipulations and monitoring in addition to active maintenance, and it has been reported that both the VLPFC and the DLPFC are activated during performance of the verbal n-back task (Braver et al., 1997; D'Esposito et al., 1998). However, the present study has demonstrated that the VLPFC mainly contributes to the n-back task. This might be explained by the fact that once participants find a strategy, they can automatically perform even the 3-back task, in which little manipulation or monitoring is required. Meanwhile, two participants whose task performance was poor (participants 7 and 11) also showed activation of the bilateral VLPFC.

Since these two participants reported that they had not been able to find any strategies, it is supposed that their VLPFC was mainly engaged in receiving information from posterior cortical regions but less in executive processing during performance of the n-back task.

It is plausible that the RNG task requires more manipulation and monitoring than the n-back task because it involves not only WM processes but also other cognitive processes, such as the suppression of habitual responses and internally driven response generation (Jahanshahi et al., 2000). The functional anatomical substrates of various random generation responses, such as random selection of four joystick movements, have been examined in some PET studies (Deiber et al., 1991; Frith et al., 1991), which demonstrated that generating random responses engages the prefrontal cortex, mainly the DLPFC, though the functional role played by the DLPFC remained to be clarified. In a recent PET study of the RNG task by Jahanshahi et al. (2000) it was reported that compared with counting from 1 to 9, random generation of numbers from 1 to 9 was associated with increased rCBF in the left DLPFC, the anterior cingulate, the posterior parietal cortex bilaterally, the right VLPFC, and the cerebellum. They proposed that the role of the DLPFC in RNG is suppression of habitual counting through the inhibitory influence of the left DLPFC over a number associative network distributed in the superior temporal cortex and explained that the right VLPFC activation was related to vigilance and might be related to selection of appropriate production strategies and switching of modification of such strategies (Jahanshahi et al., 2000). The present study also demonstrated that the left DLPFC or the right VLPFC was activated in the RNG task; however, simultaneous activation of the left DLPFC and the right VLPFC was observed in only five participants. This discrepancy might be related to the fact that the PET study employed group analyses, whereas the NIRS study employed individual analyses.

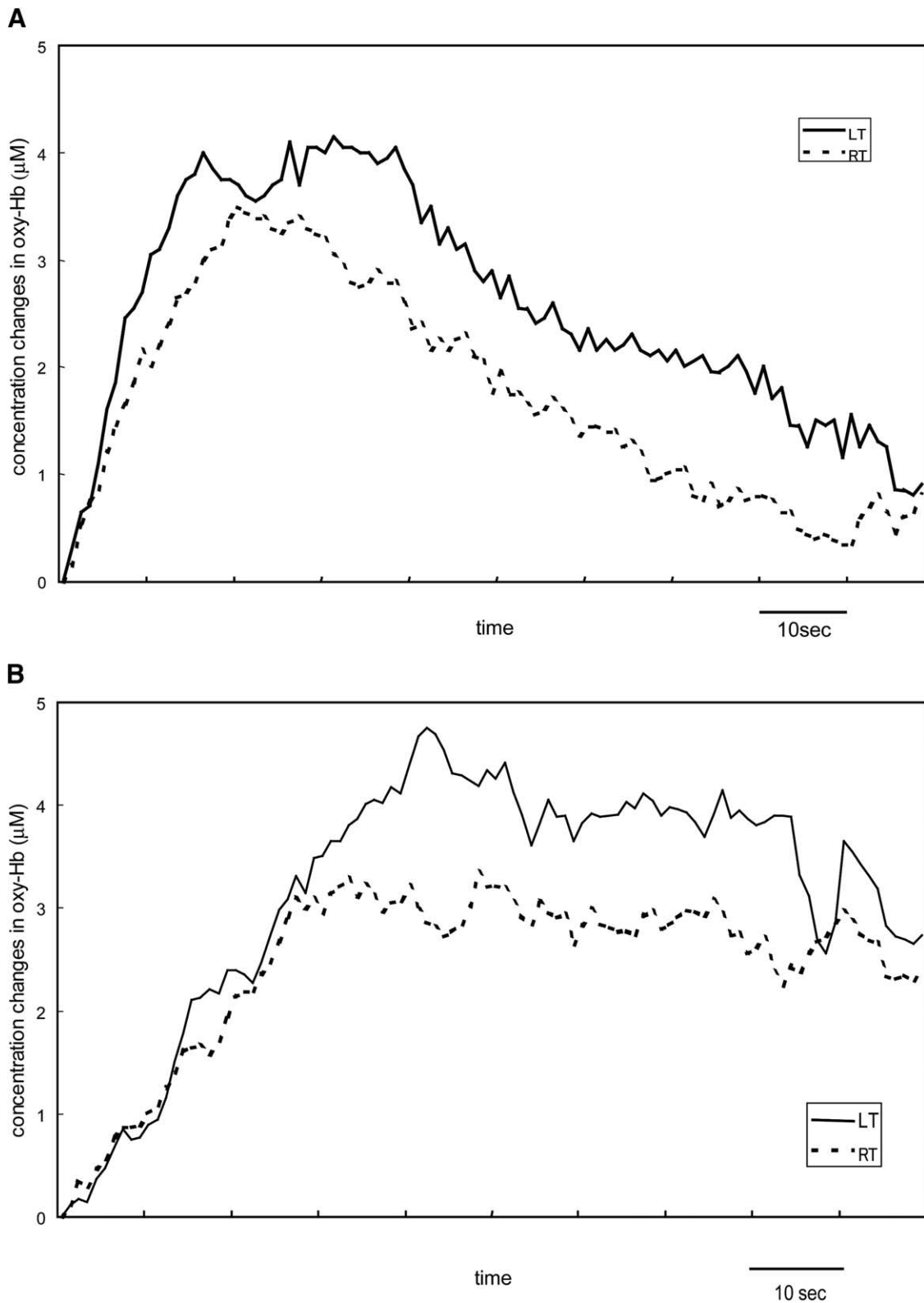


Fig. 5. Nonsustained (A) and sustained (B) oxy-Hb increases during the 3 – 0 back task in bilateral VLPFs.

Recent neuroimaging studies have provided evidence of commonalities in the patterns of frontal activity associated with many quite different cognitive demands (Duncan and

Owen, 2000). Such commonalities were also observed in this study. However, brain subdivisions that were commonly activated during performance of the two tasks varied with

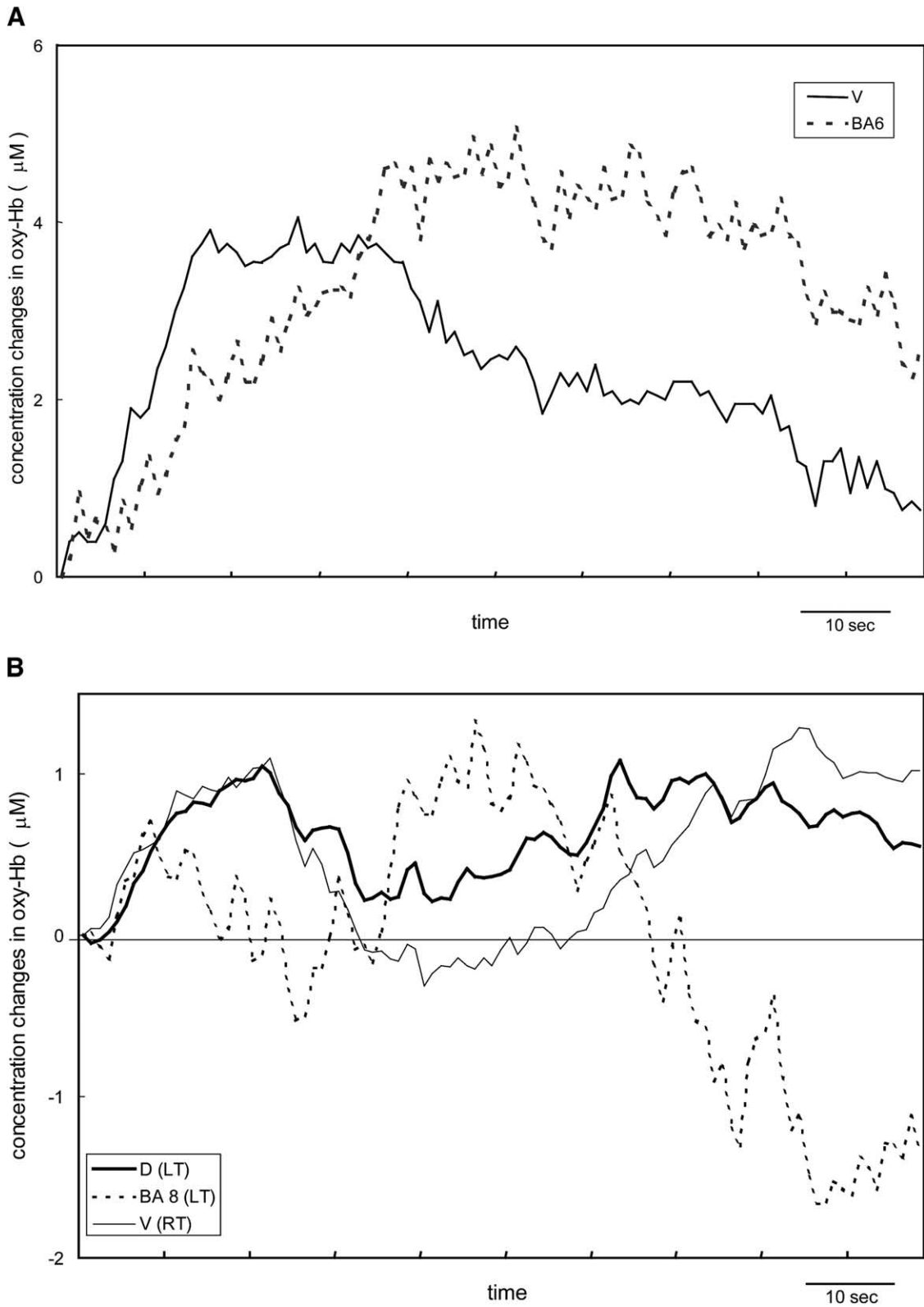


Fig. 6. Dynamic oxy-Hb changes during the 3 – 0 back task in different brain subdivisions; (A) left side in participant 6; (B) participant 5.

each participant and there were no commonly activated subdivisions in two participants. Thus, it is unlikely that the CE is localized as a unitary system in the measured areas of

the PFC, although it might be localized in other frontal areas, such as BA 10 (Collette et al., 1999), which were not measured in the present study.

Table 2
Temporal characteristics of increase in rCBF and task performance

Subjects	3-Back			RNG		
	LT	RT	Task performance (%)	LT	RT	Task performance (observed bias)
1	V↓	V↓, BA6(↓)	86.5	V/D	V	–CB
2	D	V(↓)	93.5	D	D	CB, –CB, IB
3	V(↓)	V(↓)	97.5	—	BA8	RB, –CB
4	V	V	88.0	D/V	D/BA6/V	–CB
5	D(↓), BA8↓	V(↓)	95.0	V/D	V/D	
6	V↓, BA6	V/BA6↓	80.5	V/BA6(↓)	V/BA6↓	
7	V	V	62.5	V	V/D	
8	V(↓)	V	96.0	D	D	
9	D/BA6/V	BA8/6	89.5	D/BA6	V	
10	V↓, BA6/8	V/BA6↓	88.0	D/BA6	V	
11	V↓, BA6	V/BA6↓	14.0	V	V/D	CB
12	V	D	99.0	D/V	D/BA8	

Note. ↓, oxy-Hb first increased and then decreased to less than 30% of the peak value before the end of the task; (↓) oxy-Hb decreased but remained higher than 30% of the peak value. CB, counting bias (ascending series); –CB, counting bias (descending series); IB, interval bias; RB, repetition bias.

Temporal characteristics

We found that the temporal course of VLPFC activation had both sustained and transient components, whereas DLPFC activation was sustained. This is consistent with segregation of WM functions within the lateral PFC. In addition, activation for the RNG task is more sustained than that for the n-back task. Some theoretical models of PFC function might explain this unsustained activation. Fuster (2000) has posited that none of the cognitive functions is localized in the PFC, and only parts of the networks of

executive memory are localized there: being at the top of the perception–action cycle, the PFC plays a critical role in the mediation of contingencies of action across time, which is based on the interplay of sensory and motor processing. In Fuster’s model the part of the PFC that is involved varies with the strategy participants select. Thus, unsustained activation might reflect alterations in strategy, which is supported by the fact that decreasing rCBF was often accompanied by increases in rCBF in other regions. By contrast, Miller and Cohen have posited that the PFC units themselves are not responsible for carrying out input–output

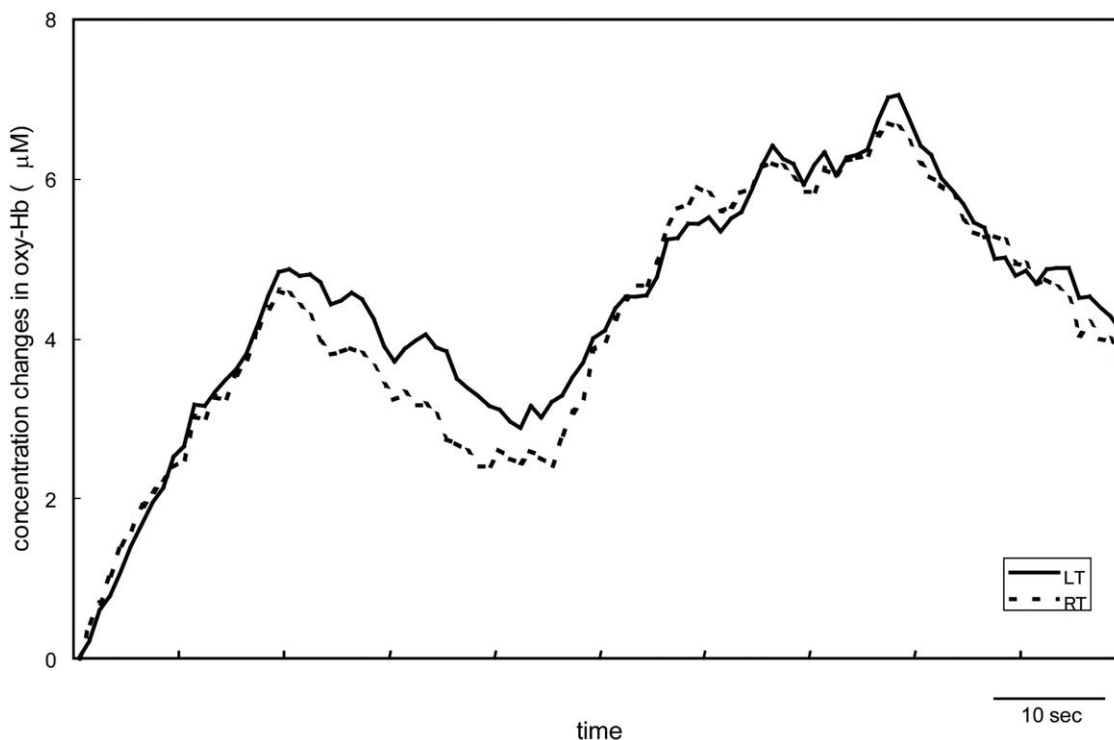


Fig. 7. Synchronous oxy-Hb changes during the 3 – 0 back task in bilateral VLPFCs.

mapping needed for performance, but rather they influence the activity of other units whose responsibility is making the needed mapping. In their model, the pathway from input to output does not run through the PFC, and over time, the circuits that are repeatedly selected by PFC bias signals can function independently of the PFC, and performance of the task becomes more automatic (Miller and Cohen, 2001). This concurs with the findings obtained from neuroimaging and neurophysiological studies that greater PFC activation occurs during initial learning and weaker activity as a task becomes more practiced (Petersen et al., 1998; Schadmehr and Holcomb, 1997). Such automatic response might account for the unsustained activation observed, especially in participants with high task performance. A third explanation is that the unsustained activation might have been due to uncoupling between neuronal activity and CBF, although there is no direct evidence. Although further studies are required to explain unsustained activation, the temporal characteristics also suggest that the CE is not localizable, but stems from neural pathways needed for task performance.

When the homologous lateral PFC in both hemispheres was activated, synchronous changes in oxy-Hb were observed. This synchronous activation was not related to task performance. This suggests that activation in one side can be passively transferred to the other side through the corpus callosum. Only one side might have been essential for performing the task.

Conclusion

Much theoretical and experimental work has combined to suggest specific loci and roles for working memory processes in the frontal cortex. Although our study supports some functional segregation, two different working memory tasks selectively activated different regions in the PFC, it also demonstrated that there are overlaps in brain activations across the tasks in each participant. However, our data on nonsustained activation and differences in commonly activated areas between participants suggest that such processing, especially with regard to the CE, are not rigidly stereotyped and therefore cannot be localized.

Acknowledgments

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