PREFRONTAL CORTEX AND WORKING MEMORY PROCESSES

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Abstract—Working memory is a mechanism for short-term active maintenance of information as well as for processing maintained information. The dorsolateral prefrontal cortex has been known to participate in working memory. The analysis of task-related dorsolateral prefrontal cortex activity while monkeys performed a variety of working memory tasks revealed that delay-period activity is a neural correlate of a mechanism for temporary active maintenance of information, because this activity persisted throughout the delay period, showed selectivity to a particular visual feature, and was related to correct behavioral performances. Information processing can be considered as a change of the information represented by a population of neural activities during the progress of the trial. Using population vectors calculated by a population of task-related dorsolateral prefrontal cortex activities, we demonstrated the temporal change of information represented by a population of dorsolateral prefrontal cortex activities during performances of spatial working memory tasks. Cross-correlation analysis using spike firings of simultaneously isolated pairs of neurons reveals widespread functional interactions among neighboring neurons, especially neurons having delay-period activity, and their dynamic modulation depending on the context of the trial. Functional interactions among neurons and their dynamic modulation could be a mechanism of information processing in the dorsolateral prefrontal cortex. © 2005 Published by Elsevier Ltd on behalf of IBRO.

Key words: prefrontal cortex, delayed response, delay-period activity, functional interaction, information processing.

Working memory has been described as a system that provides temporary active maintenance of information and also enables manipulation and processing of information (Baddeley, 1986; Baddeley and Hitch, 1974). Working memory has been thought to participate significantly in higher cognitive functions such as thinking, planning, reasoning, decision-making, and language comprehension. Therefore, it is expected that understanding neural mechanisms of working memory could provide important clues to understand mechanisms of these cognitive functions.

Several models of working memory have been proposed (Miyake and Shah 1999). Among these, the most well-known and influential model of working memory is the one proposed by Baddeley and Hitch (1974) and Baddeley (1986, 2000). Baddeley’s model of working memory includes one master component (the central executive) and three slave components (the visuospatial sketchpad, the phonological loop, and the episodic buffer). Among slave components, the phonological loop is a system for performing speech perception and language comprehension and includes a mechanism for temporarily maintaining speech-based information by subvocal rehearsal. The visuospatial sketchpad is a system for processing visuospatial information as well as information that cannot be expressed by language and includes a mechanism for temporarily maintaining information as visuo-spatial images by a rehearsal system. The episodic buffer is a temporary storage system with a limited capacity of memory for integrating information as “chunks” from a variety of sources including long-term memory. The central executive acts to the master component and considered to be an attentional system with a limited memory capacity. The central executive is to select control processes or strategies and operate selected control processes to perform necessary behavior adequately and appropriately. Thus, the central executive supervises the performance of the three slave components.

The model of working memory proposed by Baddeley is a conceptual model, not a structure-based model. Therefore, as Baddeley (1986) himself stated, none of four working memory components correspond to any particular brain structure, although the function of the central executive is thought to be related to the function of the dorsolateral prefrontal cortex (DLPFC) (Baddeley, 1986; D’Esposito et al. 1995). However, a structure-based model or a process-based model would be useful when we consider how working memory is actually performed in the brain, how each component operates its function, and how the central executive controls three slave components. For example, from a functional point of view, all three slave components have common neural processes, such as a process for active maintenance of information and a process for dynamic information processing. In addition, the central executive also needs to have a neural process for dynamic information processing. Therefore, one way to understand how working memory is performed in the brain is to elucidate neural processes to achieve the active maintenance of information in the nervous system, to perform dynamic information processing, and to integrate different operations occurring in different brain areas.

In the late 1980s, Goldman-Rakic (1987, 1998) proposed that working memory is an important concept for understanding prefrontal functions, especially the functions of DLPFC. Since then, the DLPFC has been known to be an important area to understand working memory. This
notion has been supported by a variety of experiments including lesion studies (see reviews by Fuster, 1997; Goldman-Rakic, 1987; Petrides, 1994) and neurophysiological studies using non-human primates (see reviews by Funahashi and Kubota, 1994; Funahashi and Takeda, 2002; Fuster, 1997; Goldman-Rakic, 1999), and non-invasive brain activation studies using human subjects (see reviews by Stuss and Knight, 2002). The close relationships between working memory and functions of the DLPFC indicate that neurophysiological investigations of DLPFC neurons could provide important clues for basic neural mechanisms of working memory, such as how the active maintenance of information is achieved by DLPFC neurons and how dynamic information processing is performed in the DLPFC. In this article, we will describe some basic neural mechanisms of working memory based on the results obtained by neurophysiological investigations in the primate DLPFC.

Oculomotor delayed-response (ODR) task

It has long been known that monkeys having bilateral DLPFC lesions show impairment in performing the delayed-response task. Since C. F. Jacobsen (1936) first reported this evidence in 1936, a large number of studies support this finding. In the delayed-response task, the experimenter first puts the reward at one of two possible baiting places, and covers these places with identical opaque plates. Then, an enforced delay of several seconds or minutes is introduced. After the end of the delay period, the subject is required to select the place where the reward was baited. To perform the delayed-response task correctly, the subject is required to remember where the reward was baited during the delay period and to utilize remembered information for selecting a correct place. In addition, since the experimenter randomly changes the place where the reward is baited, the subject is required to update the memory of the reward-baited place trial by trial. Thus, to perform the delayed-response task correctly, the subject needs to use spatial working memory. It has been shown that the performance of the delayed-response task is closely related to the functions of the DLPFC. Therefore, an analysis of task-related activity observed in the DLPFC while the subject performs the delayed-response task could provide important clues to understand basic neural mechanisms of working memory operating in the brain.

We have used oculomotor versions of the delayed-response task (ODR task) (Bruce and Goldberg, 1985; Funahashi et al., 1989, 1991, 1993a,b; Hikosaka and Wurtz, 1983; Takeda and Funahashi, 2002). In this task, the monkey sat quietly in a primate chair in a dark, sound-attenuated room. The monkey faced a 21-inch color TV monitor, on which a fixation point (FP) and visual cues were presented. The monkey’s eye positions were monitored by a magnetic search coil technique. In the ODR task (Fig. 1A), the monkey was required to make a memory-guided saccade to the location where the visual cue had been presented. After a 5-s intertrial interval, a FP (a small white circle) was presented at the center of the TV monitor. If the monkey continued to look at the FP for 1 s (fixation period), a visual cue (a white circle) was presented for 0.5 s (cue period) randomly at one of eight predetermined locations around the FP. The monkey was required to maintain fixation at the FP throughout the 0.5-s cue period and subsequent 3-s delay period. At the end of the delay period, the FP was extinguished. This was the go signal for the monkey to make a saccade within 0.4 s (response period) to the location where the visual cue had been presented. If the monkey performed the correct eye movement, a drop of liquid reward was given.

Previously, it has been shown that bilateral lesions of the DLPFC are necessary to produce an impairment of the delayed-response task in monkeys (Butters et al., 1971). However, Funahashi et al. (1993a) showed that the monkey having even unilateral small lesion in the DLPFC exhibited a specific deficit in ODR performances (mnemonic scotomas), such that the monkey showed many incorrect saccades only when the visual cues were presented within the visual field contralateral to the lesioned hemisphere.
Task-related activity

Several types of neural activities have been recorded from the DLPFC while monkeys performed the ODR task. One type of task-related activity is cue-period activity, which is a phasic excitatory response occurring just after the visual cue presentation. Most cue-period activity exhibited spatial selectivity, such that cue-period activity was observed only when the visual cues were presented within a certain area of the visual field (Funahashi et al., 1990). The same response was also observed in a visual probe task, in which visual stimuli were presented but had no behavioral meaning. Therefore, cue-period activity has been thought to be a visual response.

Another type of activity observed in the ODR task is response-period activity (Funahashi et al., 1991). Since saccadic eye movements were performed during the response-period in the ODR task, this activity can be considered saccade-related activity. Response-period activity observed in the DLPFC has been classified into two groups (pre-saccadic and post-saccadic) based on whether response-period activity started before the initiation of the saccadic eye movement or not. In the DLPFC, the great majority of response-period activity was post-saccadic (Funahashi et al., 1991). Almost all of both pre- and post-saccadic activities exhibited directional selectivity, such that pre- and post-saccadic activity was observed only when the monkey performed saccadic eye movements toward a certain direction, mainly contralateral to the hemisphere where the neuron was located.

Delay-period activity

When we consider a neural mechanism of working memory, the most important task-related activity is delay-period activity. Delay-period activity is a tonic sustained activation during the delay period (Fig. 2A). Delay-period activity was often initiated several hundred ms after the onset of the visual cue, maintained during the delay period, and usually ended just after the saccadic eye movement was initiated. Delay-period activity was prolonged or shortened depending on the length of the delay period (Funahashi et al., 1989; Fuster, 1973; Kojima and Goldman-Rakic, 1982) and was observed only when the monkey performed correct responses (Funahashi et al., 1989; Fuster, 1973). When the monkey made an error, delay-period activity was not observed or it was truncated. The most important feature of delay-period activity is that a great majority of this activity exhibited directional preferences (Funahashi et al., 1993b) by (Rainer et al., 1998). Thus, using spatial working memory tasks such as the ODR task, directional delay-period activity observed in DLPFC neurons has been shown to be a neural correlate of the mechanism for temporary active maintenance of information (Funahashi and Kubota, 1994; Funahashi and Takeda, 2002; Fuster, 1997; Goldman-Rakic, 1998).

What information does delay-period activity represent?

If delay-period activity is a neural correlate of the mechanism for temporary active maintenance of information, the next question would be what information delay-period activity maintains. To answer this question, Funahashi et al. (1993b) examined characteristics of delay-period activity using two kinds of the ODR tasks (the delayed pro-saccade task and the delayed anti-saccade task). The delayed pro-saccade task was the same as the ODR task. In the delayed anti-saccade task, the monkey was required to make a memory-guided saccade to the direction opposite to the visual cue direction. Funahashi et al. (1993b) showed that a great majority (about 70%) of delay-period activity represented information regarding visual cue position, whereas a minority represented information regarding the direction of the saccade. Similar results were recently obtained by Takeda and Funahashi (2002). They used the ODR task and a rotatory oculomotor delayed-response (R-ODR) task, in which monkeys were required to perform memory-guided saccades to the direction 90° clockwise from the visual cue direction (Fig. 1B). They showed that most (86%) of DLPFC neurons exhibiting directional delay-period activity maintained information regarding the visual cue position, whereas a small proportion (13%) of neurons maintained information regarding the direction of the saccade. Thus, both studies showed that the majority of DLPFC neurons having directional delay-period activity maintained information regarding where the visual cue was presented. In addition, both studies showed that preferred directions of delay-period activity differed from neuron to neuron. Based on these observations Funahashi et al. (1989) proposed that DLPFC neurons exhibiting directional delay-period activity have mnemonic receptive fields (memory fields) in the visual field. This idea was supported by (Rainer et al., 1998).

Thus, using spatial working memory tasks such as the ODR task, directional delay-period activity observed in DLPFC neurons has been shown to be a neural correlate of the process for maintaining information temporarily in working memory. In addition, it has been shown that, in the DLPFC, the majority of directional delay-period activity represents retrospective information (e.g. visual cue directions), whereas the minority represents prospective information (e.g. directions of impending movements).

Experiments using non-spatial working memory tasks, such as delayed matching-to-sample tasks and delayed conditional tasks, have also revealed that delay-period
A. Delay-period activity in the ODR task

B. Tuning curve

C. Best directions

Fig. 2. Characteristics of delay-period activity observed in DLPFC neurons. (A) An example of directional delay-period activity. (B) An example of a tuning curve of directional delay-period activity. (C) Polar distribution of the best directions of delay-period activity. A majority of the best directions were directed toward the contralateral visual field.

activity is a neural correlate of a process for maintaining non-spatial information, such as faces (O'Scalaidhe et al., 1999; Wilson et al., 1993), and object shapes, patterns, or colors (Freedman et al., 2001; Lauwereyns et al., 2001;
Miller et al., 1996; Quintana et al., 1988; Rainer et al., 1999; Rainer and Miller, 2002; Rao et al., 1997; Sakagami and Niki, 1994; Sakagami et al., 2001; Watanabe 1990, 1992; Yajeya et al., 1988). In these experiments, delay-period activity of different DLPFC neurons exhibited different preference in stimulus modality and quality, indicating that delay-period activity of different neuron represents different stimulus modality or quality. However, Romo et al. (1999) showed that discharge rates of delay-period activity observed in the DLPFC varied as a monotonic function of the base stimulus frequency in a somatosensory discrimination task, in which monkeys were required to discriminate the difference in frequency between two mechanical vibrations applied to the fingertips. Based on this result, they concluded that this monotonic stimulus encoding could be a basic representation of one-dimensional sensory stimulus quality in working memory. In addition, White and Wise (1999) found rule-dependent neural activity in the DLPFC. Their reports indicate that DLPFC neurons maintain rules of behavioral tasks by modulating the magnitude of task-related activity. Similar results have been reported by Wallis et al. (2001) and Wallis and Miller (2003).

In summary, delay-period activity observed in DLPFC neurons can be considered a neural correlate of the process for maintaining information temporarily in working memory (Funahashi and Kubota, 1994; Funahashi and Takeda, 2002; Fuster, 1997; Goldman-Rakic, 1998). A wide range of information can be temporarily maintained in DLPFC neurons, including visuospatial information, motor information, non-spatial visual features, quality differences in one stimulus modality, or task rules. Regional differences in processing information within the DLPFC have been proposed; e.g. the mid-DLPFC participates mainly in the visuo-spatial information processing, whereas the midventrolateral prefrontal cortex participates in the non-spatial visual information processing (Goldman-Rakic, 1998; O'Scalaidhe et al., 1999; Wilson et al., 1993). However, neurons encoding spatial information and non-spatial information can be observed within the same area in the DLPFC (Carlson et al., 1997; Quintana and Fuster, 1999; Rainer et al., 1999; Sakagami and Tsutui, 1999). Many DLPFC neurons exhibit similar task-related activity in both spatial and non-spatial working memory tasks (Rao et al., 1997). Therefore, these observations suggest that each DLPFC neuron could represent not just one modality of information, but could represent a range of modalities of information depending on the task condition.

Information processing in the DLPFC

Recent neurophysiological studies show that information represented by prefrontal activities changes with the progress of a trial. For example Quintana and Fuster (1999) observed neurons attuned to the cue color and those attuned to response directions in the DLPFC while monkeys performed working memory tasks using color cues. They found that the discharge of neurons attuned to the cue color tended to diminish with the progress of the delay period, whereas the discharge of those attuned to response directions tended to be accelerated. These results indicate that the temporal modulation of the firing pattern along the trial reflects the alteration of the information represented by a neuron. Therefore, the gradual alteration of information with the progress of the trial can be seen as the gradual alteration of the temporal pattern of firing observed in a neuron or an assembly of neurons. Rainer et al. (1999) observed that neurons whose activity encoded sample objects gradually decreased the magnitude of their activity during the delay period, whereas neurons whose activity encoded anticipating target objects gradually increased the magnitude of their activity during the delay period, while monkeys performed a delayed paired-associate task and a delayed matching-to-sample task. A population analysis of prefrontal activities revealed that a population of prefrontal activities tended to reflect information regarding the sample object during the sample presentation and the early part of the delay period. However, a population of prefrontal activities began to reflect information regarding the anticipated target object toward the end of the delay period. These results indicate that the information represented by a population of prefrontal activities changes with the progress of the trial. These results also indicate that the temporal change of the represented information can be seen more clearly by looking at the behavior of a population of neural activities than by looking at the behavior of each neuron. Similar change of the information in information processing has been observed in putative pyramidal neurons and interneurons in the prefrontal cortex (Rao et al., 1999). Therefore, this temporal change of the information represented by a population of neurons could correspond to the information processing occurring in the DLPFC.

A large number of DLPFC neurons exhibited the same task-related activity with similar temporal pattern, with similar magnitude of activity, and with similar stimulus or response preference, when the subjects performed ODR tasks (Funahashi et al., 1989–91). Therefore, it can be thought that a particular piece of information (e.g. a spatial position of a visual cue) is encoded by a population of DLPFC neurons. Therefore, to understand how information is processed in relation to working memory, we need to consider not only the information that each single-neuron activity represents but also the information that a population of neural activity represents and the temporal change of the information along the progress of the task performance.

Takeda and Funahashi (2002) had examined prefrontal single-neuron activity using the ODR task and the R-ODR task. In the ODR task, the monkey was required to make a saccade to the direction where the visual cue was presented, whereas, in the R-ODR task, the monkey was required to make a saccade 90° clockwise from the direction where the visual cue was presented. They showed that the majority of delay-period activity observed in the DLPFC encoded the location of the visual cue, whereas the minority of delay-period activity and the majority of response-period activity encoded the direction of the saccade. These results indicate that the transformation from
visual information to saccade information is in fact performed in the DLPFC and suggest that temporal changes of directional selectivity obtained by a population of DLPFC activities during ODR and R-ODR performances could visualize a process related to the transformation from visual information to saccade information.

Takeda and Funahashi (2004) used a population-vector analysis to illustrate the temporal change of the preferred direction of a population of DLPFC activities along a trial of the ODR task and the R-ODR task. The population-vector analysis was originally introduced for an analysis of information processing in the primary motor cortex (Georgopoulos, 1988; Georgopoulos et al., 1986, 1988; Kettner et al., 1988; Schwartz et al., 1988). To calculate a population vector in one task condition, first a “cell vector” is needed to be calculated from neural activity for every neuron. The length of the cell vector represents the neuron’s discharge rate at that task condition and the direction of the cell vector corresponds to the neuron’s preferred direction. Each neuron’s preferred direction is usually determined from the tuning curve obtained by fitting mean discharge rates across all examined directions on the cosine function or the Gaussian function. Then, a population vector is calculated by a weighted sum of cell vectors of all neurons calculated under one task condition. Takeda and Funahashi (2004) calculated multiple population vectors to illustrate the temporal change of preferred directions of a population of DLPFC activities with the progress of a trial of the ODR task and the R-ODR task. They set a 250 ms time-window along the trial, calculated the population vector using a population of activities occurred during this time-window, then moved this time-window in 50 ms time-steps from the cue onset to the end of the response period.

Fig. 3A shows population vectors calculated by a population of DLPFC activities at the 180° trial of the ODR task. Directions of population vectors were mostly directed toward the 180° direction, indicating that the same directional preference was maintained by a population of DLPFC activities during the delay period of the ODR task. To confirm this observation, the temporal change of mean differences between the direction of the population vector and the direction of the visual cue was calculated across all cue conditions (Fig. 3C). This result showed that the mean differences were close to 0° across all periods. In the ODR

![Figure 3](image-url)
task, the monkey was required to maintain information regarding either the direction of the visual cue or the direction of the saccade during the delay period. The direction of the visual cue and the direction of the saccade were the same in this task. Therefore, this result indicates that the same directional information is maintained along the delay period of each cue condition by a population of DLPFC neurons.

Fig. 3B shows population vectors calculated by a population of DLPFC activities at the 180° trial of the R-ODR task, in which the visual cue was presented at the 180° direction and the direction of the correct saccade was the 90° direction. Directions of population vectors were directed toward the 180° direction during the cue period and at the beginning of the delay period. However, directions of population vectors began to rotate in the middle of the delay period, continued to rotate slowly from the 180° direction to the 90° direction during the late half of the delay period, and finally directed toward the 90° direction at the response period. The mean differences between the directions of the population vectors and the directions of the visual cue gradually changed from close to 0° to almost 90° during the delay period (Fig. 3D). The vector began to rotate at approximately 2 s after the delay onset (1 s before the Go signal) and rotation was maintained at a constant speed (about 90°/s) until the vector was in a direction similar to that of the saccade target. This result indicates that the information represented by a population of DLPFC activities changes from visual information to motor information during the delay period while the monkey performed the ODR tasks. Fuster (1997) has proposed the mediation of cross-temporal contingency as an important function of the DLPFC. He considered the delay period of the task as the period for the cross-temporal bridging of sensory-motor information, which is a dynamic process of internal transfer as well as a process of cross-temporal matching. The present result that population vectors rotate gradually from a sensory information domain to a motor information domain during the delay period supports his notion that the DLPFC plays a significant role for mediating the cross-temporal contingency. This result also suggests that delay-period activity observed in DLPFC neurons during working memory performances plays a role for a dynamic process of internal information transfer.

Interactions among DLPFC neurons as a mechanism of information processing

Single-neuron recording studies showed that the information represented by a population of DLPFC activities changes with the progress of the trial. An analysis using the population vectors indicates that the information represented by a population of DLPFC activities changed from visual information to motor information during the delay period while the monkey performed the ODR tasks. These observations indicate that DLPFC neurons participate in the temporarily active maintenance of information as well as the processing of information. How do DLPFC neurons process and transform information?

A possible mechanism of information processing would be interactions among DLPFC neurons, each of which exhibits different kinds of task-related activity or the same task-related activity with different spatial or object preference. One such example is the presence of the interaction between neurons exhibiting delay-period activity and neurons exhibiting post-saccadic activity. Many DLPFC neurons exhibit saccade-related activity while the monkey performed saccade tasks (Boch and Goldberg, 1989; Funahashi et al., 1991; Takeda and Funahashi, 2002), although most saccade-related activity is post-saccadic (Funahashi et al., 1991; Takeda and Funahashi, 2002). A great majority of both pre- and post-saccadic activities show directional selectivity in the ODR tasks (Funahashi et al., 1991; Takeda and Funahashi, 2002). Since post-saccadic activity starts several tens of ms after the initiation of the saccade, this activity has been considered an activity feedback from oculomotor centers such as the frontal eye field or the superior colliculus (Funahashi et al., 1991). On the other hand, delay-period activity is usually ended soon after a saccade was performed in the ODR tasks. Histogram displays constructed by a population of delay-period activities and post-saccadic activities aligned at the initiation of the saccade reveal that the termination of delay-period activity coincided with the initiation of post-saccadic activity (Goldman-Rakic et al., 1990). Removing or replacing unnecessary information that is maintained in the temporary storage buffer is an important process for working memory. Delay-period activity is no longer necessary once response behavior is performed, regardless of whether the response is correct or wrong. Therefore, by functional interactions between neurons exhibiting delay-period activity and neurons exhibiting post-saccadic activity, post-saccadic activity could play a role in the termination of delay-period activity.

A cross-correlation analysis between simultaneously recorded pair of single-neuron activities has been used to examine whether functional interactions are present between these two neurons (Perkel et al., 1967a,b). Rao et al. (1999) and Constantinidis et al. (2001) used the cross-correlation analysis to examine functional interactions between pyramidal and non-pyramidal neurons in the DLPFC and found feed-forward excitatory interactions as well as inhibitory interactions between putative pyramidal neurons and adjacent putative interneurons. Funahashi and Inoue (2000) also applied the cross-correlation analysis to simultaneously isolated DLPFC activities while monkeys performed the ODR task. Among 168 pairs of simultaneously isolated single-neuron activities, 18% showed an excitatory sharp and symmetrical peak at time 0 (central peak). Since these pairs of neurons tend to fire simultaneously, it is expected that functional interactions are present between these pairs of neurons. On the other hand, 23% had an excitatory sharp but asymmetrically distributed peak displaced from time 0 (displaced peak), indicating that one of the paired neurons sends excitatory signals to another neuron of the pair, as shown also by Rao et al. (1999).

Further, the cross-correlation analysis of simultaneously isolated DLPFC activities showed the presence of the infor-
mation flow from neurons having cue-period activity to
neurons having pre-saccadic activity through neurons hav-
ing delay-period activity. In addition, pairs of neurons both
of which exhibited delay-period activity tended to have
either significant excitatory central or displaced peaks,
indicating that extensive interactions between neurons
having delay-period activity are present in the DLPFC. In
neuron pairs that had central peaks in cross-correlograms,
best directions of task-related activity were identical or
similar between two neurons, and the similarity of best
directions was strongest in pairs of neurons both of which
exhibited cue-period activity. In neuron pairs that had dis-
placed peaks in cross-correlograms, best directions of
task-related activity were also similar between two neu-
rons, and the similarity of best directions was also stron-
gest in pairs of neurons both of which exhibited cue-period
activity. Interactions between neurons that exhibited differ-
ent directional preferences were more often observed in
neuron pairs both of which exhibited delay-period activity
than neuron pairs having other task-related activity. These
results suggest that the interactions among neurons hav-
ing different task-related activity and different directional
preference play an important role for processing informa-
tion. Frequently observed interactions among neurons
having delay-period activity suggest that these interactions

**Prefrontal model of working memory**

Working memory has been considered a neural system
that provides temporary active maintenance of necessary
information and also that enables dynamic processing,
integrating, and updating of temporarily maintained infor-
mation to perform a variety of cognitive tasks. Neurophys-
iological studies in the DLPFC indicate that delay-period
activity observed during working memory tasks is a neural
correlate of the mechanism for temporarily active mainte-
nance of information, that information processing can be
observed as a temporal change of the information repre-
sented by a population of neural activities, and that this
temporal change of the information could occur by the
interactions among neurons having different kinds of task-
related activity or neurons having same task-related activ-
ity with different preferences. Based on these findings, we
had proposed a model for understanding how working
memory is operated in the DLPFC (Funahashi, 2001).

As is shown in Fig. 4, our model includes four neural
processes: a selection process, a temporary information-
storage process, an output process, and modulatory in-
puts. The DLPFC is a multimodal association area (Mesu-

![Fig. 4. A model for explaining working memory processes in the prefrontal cortex.](image-url)
lam, 2000) and the DLPFC receives a variety of information including sensory, motor, motivational, and emotional information from other cortical and subcortical areas. Therefore, it can be considered that neural mechanisms of working memory operated in the DLPFC could participate in not just visuo-spatial or linguistic information processing, but also any kind of multimodal information processing. Although the DLPFC could participate in a variety of information processing, the information maintained and processed in the neural mechanisms of working memory operated in the DLPFC could be the information necessary for performing the current task or behavior. To maintain and process necessary information, the process for selecting information (the selection process) is needed. The selection process selects necessary information from the internal or external environment or long-term memory, and sends this information to the temporary information-storage process. The temporary information-storage process is an essential component of the neural mechanism of working memory in the DLPFC. This process temporarily maintains the information which is received from the selection process or other temporary information-storage processes. By extensive interactions among temporary information-storage processes, temporarily maintained information on this process could be processed, integrated, and updated. Then, new information could be created on this process. Extensive interactions among temporary information-storage processes can be considered a mechanism for dynamic information processing. The information maintained by the temporary information-storage process would eventually pass on to the output process. The output process outputs the information to the brain areas where it is utilized or where it controls their operations. The modulatory input is a signal or a trigger to modify, replace, or update the information maintained by the temporary information-storage processes. The modulatory inputs can be generated within the DLPFC or provided from other brain areas. The modulatory inputs include inputs from posterior association cortices, feedback signals from motor centers, motivational or emotional inputs from the limbic areas (Barbas, 1992; Pandya and Barnes, 1987), or modulatory signals by catecholaminergic and monoaminergic inputs (Arnsten, 1998; Luciana et al., 1998; Muly et al., 1998; Sawaguchi and Goldman-Rakic, 1994; Sawaguchi, 1998; Wang et al., 2004; Watanabe et al., 1997; Williams and Goldman-Rakic, 1995).

It is important to note that we hypothesize dynamic and flexible modulation of interactions among different processes as well as among temporary information-storage processes. The strength of functional interactions between neurons or assemblies of neurons would be modified dynamically and flexibly depending on the context of the behavioral task or external and internal states. By modifying the strength of neuronal interaction depending on these factors, information represented by a neuron or an assembly of neurons would change. Evidence for such dynamic and flexible modulation of the strength of neuronal interactions has been observed in DLPFC neurons (Funahashi, 2001; Vaadia et al., 1995). In addition to the interactions among temporary information-storage processes, modulatory inputs coming from other brain areas could also play a significant role to modify or update the information stored in temporal information-storage processes. Thus, information processing in relation to working memory could be explained as a change of the information represented by a neuron or a population of neurons caused by dynamic interactions among temporal information-storage processes as well as the interactions between modulatory inputs and temporal information-storage processes.

CONCLUSIONS

Working memory is a neural system for short-term active maintenance of information as well as for processing maintained information. By examining task-related single-neuron activity in the DLPFC while monkeys performed various working memory tasks, delay-period activity has been considered to be a neural correlate of the mechanism for short-term active maintenance of information. It has been known that a variety of information including spatial and non-spatial visual features, forthcoming behavioral responses, the quality as well as the quantity of expected reward, the difference of the tasks, or the rule of the task can be encoded as delay-period activity.

On the other hand, little is known about neural mechanisms for processing information. To understand neural mechanisms for processing information, we need to know what information is represented by the activity and how information represented by the activity changes with the progress of the trial. We used two ODR tasks (ODR task and R-ODR task) and identified what information each task-related activity represented. In addition, using the population vector analysis, we could not only visualize information represented by a population of prefrontal activity, but also visualize the temporal change of information represented by a population of prefrontal activity during the delay period. Neural mechanisms responsible for changing the information represented remain unresolved. However, extensive functional interactions among neighboring neurons and dynamic modulation of these interactions depending on the context of the trial would be a mechanism of information processing (Constantinidis et al., 2001; Funahashi, 2001; Funahashi and Inoue, 2000). Therefore, further analyses of dynamic and flexible interactions among prefrontal neurons and its temporal modulation are needed to understand neural mechanisms of processing information.

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