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Review Article

Neuronal mechanisms of executive control by the prefrontal cortex

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Abstract

Executive function is considered to be a product of the coordinated operation of various processes to accomplish a particular goal in a flexible manner. The mechanism or system responsible for the coordinated operation of various processes is called executive control. Impairments caused by damage to the prefrontal cortex are often called dysexecutive syndromes. Therefore, the prefrontal cortex is considered to play a significant role in executive control. Prefrontal participation to executive control can be partly explained by working memory that includes mechanisms for temporary active storage of information and processing stored information. For the prefrontal cortex to exert executive control, neuronal mechanisms for temporary storage of information and dynamic and flexible interactions among them are necessary. In this article, we present the presence of dynamic and flexible changes in the strength of functional interaction and extensive functional interactions among temporal information-storage processes in the prefrontal cortex. In addition, recent imaging studies show dynamic changes in functional connectivity between the prefrontal cortex and other cortical and subcortical structures depending upon the characteristics or the temporal context of the task. These observations indicate that the examination of dynamic and flexible modulation in neuronal interaction among prefrontal neurons as well as between the prefrontal cortex and other cortical and subcortical areas is important for explaining how the prefrontal cortex exerts executive control.

Keywords: Prefrontal cortex; Working memory; Executive control; Dynamic changes for representing information; Dynamic interaction

1. Introduction

Reliable planning, judgement, decision-making, anticipation, and reasoning are essential processes in our daily lives, since we often face problems that need to be solved immediately or make decisions quickly and appropriately. To perform these processes efficiently and successfully, we need to monitor the external world continuously, pay attention to necessary information, input wanted information, retrieve related information from long-term memory, manipulate and integrate information, and then output appropriate information to particular brain areas. We also need to suppress unnecessary output to inappropriate brain areas and inhibit inappropriate actions to perform temporally coordinated sequential actions. The functions produced by these processes have been called higher cognitive functions, or more specifically ‘executive function’ (Roberts, 1998; Miyake and Shah, 1999; Shah and Miyake, 1999). Executive function is considered to be a product of the coordinated operation of various processes to accomplish a particular goal in a flexible manner. The mechanism or system responsible for the coordinated operation of various processes is called ‘executive control’. The prefrontal cortex has been considered to be an important structure for executive control, since it has been reported that damage of the prefrontal cortex produces poor judgment, planning, and decision-making (Stuss and Benson, 1986; Fuster, 1997; Goldman-Rakic, 1998). These deficits were thought to be caused by the degradation of executive control. Therefore, syndromes caused by prefrontal damage are called ‘dysexecutive syndromes’ (Stuss and Benson, 1986). How-

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ever, neither executive function nor executive control has been well defined. Therefore, to understand the importance of prefrontal operations in higher cognitive processes such as judgement, planning, and decision-making, it is important to consider the characteristics of executive control, how executive control operates, the neuronal mechanisms of executive control, and how the prefrontal cortex participates in executive control.

In this article, we first consider the definition and examples of executive control. Next, since working memory is an important concept to understand executive function, we will present a functional model of working memory, which is a model modified from our earlier proposed model (Funahashi and Kubota, 1994), and its neuronal interpretation to explain how the nervous system achieves executive control. To consider the characteristics of executive control, it is essential to understand neuronal mechanisms for temporary information-storage processes and their flexible and dynamic interactions. Therefore, we will discuss neuronal mechanisms for temporary information-storage processes and their flexible and dynamic interaction. Neuronal mechanisms for executive control cannot be explained by the mechanism within the prefrontal cortex. It is important to understand the mechanism of the dynamic interaction between the prefrontal cortex and other cortical and subcortical areas. Therefore, we will also discuss evidence regarding dynamic interaction between the prefrontal cortex and other cortical and subcortical areas.

2. Executive control and the prefrontal cortex

Adequate planning, judgement, decision-making, anticipation or reasoning, and monitoring external as well as internal states are higher cognitive functions, or more specifically, functions under executive control, i.e. executive functions. Executive function refers to the function of a multi-operational system, and is thought to be mediated by the prefrontal cortex. Many authors have shown that the prefrontal cortex significantly contributes to executive processes (e.g. Baddeley, 1986; Stuss and Benson, 1986; Fuster, 1995; Kolb and Whishaw, 1996; Fuster, 1997). Patients with prefrontal cortical damage usually show normal IQs in most psychological tests, and have normal long-term memory functions, and exhibit normal perceptual and motor skills. ‘Old information and well-established processes appear to be unaffected by frontal lobe damage. However, when intellectual operations demand the creation of a program of action and a choice between several equally probable alternatives, the intellectual activity of patients with a marked ‘frontal syndrome’ is profoundly disturbed’ (Luria, 1969 and Stuss and Benson, 1986). This disturbance of intellectual activity is caused by poor judgment, planning, and decision-making (Stuss and Benson, 1986), and also by poor temporal organization of behavior (Fuster, 1997), as well as poor working memory (Goldman-Rakic, 1987; Petrides, 1994, 1998; Goldman-Rakic, 1998). The abilities of frontal patients have been examined by various behavioral tests including the Wisconsin card-sorting test (Milner, 1963 and Stuss et al., 2000), the tower of London puzzle (Shallice, 1982 and Owen et al., 1990), the self-ordered task (Petrides and Milner, 1982), word or item fluency tests (Milner, 1964; Jones-Gotman and Milner, 1977; Crowe, 1992; Jahanshahi et al., 1998; Jahanshahi and Dirnberger, 1999), and various other tests (Milner, 1964, 1982; Freedman and Oscar-Berman, 1986; Milner et al., 1991). Based on these observations, Stuss and Benson (1986) indicated that frontal patients exhibit a lack of insight and foresight, diminished capacity for planning, and decreased initiative. Similar impairments have also been reported in animals with prefrontal lesions (see reviews by Goldman-Rakic, 1987; Petrides, 1994; Fuster, 1997). These conditions are caused by a loss of recent memory or working memory, hyperactivity, increased distractibility, failure to make a prestarting synthesis and disturbance of the process of internal inhibition (Luria et al., 1964). All of these impairments, observed in prefrontal patients and prefrontal animals cannot be simply explained by the failure of a particular function such as perception, motor, or long-term memory, but rather by the failure of the coordinated operation of perceptual, motor and memory processes. Coordination of perceptual, motor and memory processes is essential for anticipation, planning, monitoring, and decision-making. Therefore, ‘disorders of the executive functions, if present, after focal brain damage, appear to be maximal after frontal lobe damage, suggesting that the frontal lobe is the executive center’ (Stuss and Benson, 1986).

3. What is executive control?

Although executive control is closely related to the function of the prefrontal cortex, executive processes and executive control have not been well defined. Perner and Lang (1999) defined executive processes as ‘processes responsible for higher-level action control that are necessary in particular for maintaining a mentally specified goal and for bringing it to fruition against distracting alternatives’. Pineda et al. (1998) included the following processes as executive processes — self-regulation, control of cognition, temporal organization of response to immediate stimuli, planning behavior, and control of attention. According to Baddeley and Della Sala (1998), executive control is the coordinated operation of multiple control systems, which operate simultaneously. Executive control is the main function of the central executive in their working memory model. Since it would be difficult for a defective central executive to oversee the simultaneous and coordinated operation of two slave systems (the visuospatial sketchpad and the phonological loop) in their model, they proposed that the executive control can be analyzed using a dual-task paradigm, in which the subject is required to perform two different tasks simultaneously. In addition to the coordinated operation of multiple control systems, they also included as functions of the central executive selective attention, the capacity to switch attention from one source to another, and the capacity to access and manipulate information in long-term memory (Baddeley and Della Sala, 1998). Rabbitt (1997) described seven features of the executive control. First, executive control is necessary to deal with novel tasks. Second, executive control extends beyond the current internal or external environment to restructure an interpretation of the past, as well as to attempt active control of the future. Third, executive control is necessary to initiate new sequences of behavior and also to interrupt other ongoing sequences of responses. Fourth, executive control is necessary to prevent inappropriate responses. Fifth, executive control can achieve rapid switching from one task to another. Sixth, executive control is necessary to monitor performance to correct errors, to alter plans, or recognize new opportunities. Seventh, executive control enables attention to be sustained continuously over long periods. Similarly, Smith and Jonides (1999) summarized five processes that can be considered executive processes — (1) focusing attention on relevant information or processes and inhibiting irrelevant ones (attention and inhibition); (2) scheduling processes in complex tasks (task management), which requires the switching of focused attention between tasks; (3) planning a sequence of subtasks to accomplish a goal (planning); (4) updating and checking the contents of working memory to determine the next step in a sequential task (monitoring); and (5) coding representations in working memory for time and place of appearance (coding).

Thus, executive control includes the control of attention (switching attention from one source to another or focusing attention on one source), temporal organization of a response, planning or scheduling complex tasks to accomplish a future goal, the capacity to access and manipulate information in long-term memory, and monitoring current internal and external states. These processes and functions are complex and have multiple subprocesses and subfunctions. Although the subprocesses and subfunctions that are used during a particular operation will vary depending upon the task conditions, the most significant role of the executive control is to coordinate the operation of multiple processes and control systems to accomplish a particular goal.

4. Examples of executive control

4.1. Control of attention

The attention–inhibition process (Smith and Jonides, 1999) or the capacity to switch attention from one source to another (Baddeley and Della Sala, 1998) can be best observed when two processes or stimuli are in conflict. Under these conditions, one needs to exert active inhibition or 'executive inhibition' (Perner and Lang, 1999) of inappropriate responses. The Stroop test can be used to examine this capacity. In the Stroop test, subjects are presented with the name of a color printed in a different color (e.g. the word 'green' is printed in red) and are required to report the name of the color of the printing (e.g. red). To perform this test successfully, subjects must pay attention to the relevant stimulus (the color of the printing) and inhibit the irrelevant but prepotent process of stating the printed word. In this test, subjects take more time to answer 'red' when the word 'green' is printed in red than when the word 'red' is printed in red. Lesion studies have suggested that lesions in the right dorsolateral prefrontal area cause more response errors (Vandrell et al., 1995). Although functional imaging studies have shown the activation of numerous brain areas in the Stroop test, the area that is commonly activated in the Stroop test is the anterior cingulate area (e.g. Peterson et al., 1999). Therefore, the anterior cingulate cortex is thought to play a role in monitoring competition between two conflicting processes during task performance (Carter et al., 1998 and Botvinick et al., 1999).

Another example to test this process is a version of Luria's hand game (Luria et al., 1964). In this task, the subject is required to perform a different behavior than the experimenter. For example, if the experimenter presents a pointed finger, the subject is required to make a fist, or if the experimenter taps once, the subject needs to tap twice, and vice versa. The subject's natural tendency is to imitate the experimenter. However, to perform this game correctly, the subject needs to pay attention to the experimenter's behavior, suppress irrelevant (imitating) behavior, and produce only relevant behavior. Luria et al. (1964) reported that a patient with a damaged left frontal lobe could not perform this task correctly even though she could repeat the experimenter's verbal instructions.

4.2. Inhibition

Inhibiting behavioral responses to inappropriate stimuli is an important role of executive control. Patients with damage in the posterior part of the prefrontal cortex (the frontal eye field) find it difficult to perform the anti-saccade task, in which subjects are required to make a saccade in the direction opposite the visual target presented (Guitton et al., 1985 and Pierrot-Deseilligny et al., 1991). Such patients cannot suppress unwanted saccadic eye movements to the salient visible target in the anti-saccade task. In addition, Müri et al. (1999) reported that transcranial magnetic stimulation of the dorsolateral prefrontal cortex produced a significant increase in contralateral express saccades. Express saccades are reflexive responses to salient visual stimuli, and the superior colliculus is related to the generation of these saccades. Based on these results, Müri et al. (1999) suggested that the dorsolateral prefrontal cortex usually inhibits output to the superior colliculus to suppress inappropriate saccades. Further, no-go dominant brain potentials have been observed in the dorsolateral prefrontal cortex while both monkeys and humans performed go/no-go discrimination tasks (Gemba and Sasaki, 1990 and Sasaki et al., 1993), suggesting that this brain area participates in the active inhibition of movement initiation. Similarly, Konishi et al., (1999b) found transient no-go dominant activation in the posterior part of the inferior frontal sulcus in the right hemisphere by transient fMRI analysis. These results indicate that the dorsolateral prefrontal cortex participates in the active suppression of inappropriate movement and behavior.

4.3. Task management

Task management is necessary, when the subject performs two cognitive tasks simultaneously (the dual-task condition). The dual-task condition has been used to analyze working memory processes, and especially to examine functions of the central executive (Baddeley, 1986). Baddeley and Hitch (1974) proposed a functional model of working memory. Their model includes an attention-based control process called the ‘central executive’. According to Logie (1995) and Baddeley and Della Sala (1998), executive control is the coordinated operation of multiple control systems, which occur simultaneously and executive control is the main function of the central executive of working memory. Therefore, task management function can be best analyzed under the dual-task condition (Baddeley, 1986; Azouvi et al., 1996; Vilkki et al., 1996). D’Esposito et al. (1995) used dual-task conditions and examined changes in regional blood flow by fMRI. In one task, the subject was required to determine whether the word presented was a vegetable, whereas in the other task, the subject had to decide whether two visual stimuli differed only with regard to rotation. In the dual-task condition, the subject was required to perform these two tasks concurrently. They found that only the frontal area, especially the dorsolateral prefrontal area (mainly area 46), was activated in the dual-task condition. This result suggests that the central executive is located in the dorsolateral part of the prefrontal cortex.

4.4. Set-shifting

Task management in complex tasks includes a scheduling process. This process requires the switching of focused attention depending upon tasks, conditions, or the context of the task. The Wisconsin card-sorting test requires the task management process to appropriately shift attention to a particular category of stimulus attributes (set-shifting) and to maintain this category in working memory. Konishi et al. (1998) and Konishi et al. (1999a) examined brain areas related to set-shifting ability during the performance of the Wisconsin card-sorting test by event-related fMRI methods. They found that set-shifting in the Wisconsin card-sorting test caused transient activation of the bilateral dorsolateral prefrontal cortex (Konishi et al., 1998). They also found that the same area was activated, even when the subjects were informed of the new correct category of stimulus attributes (i.e. working memory is needed, but not set-shifting) (Konishi et al., 1999a). Therefore, they concluded that set-shifting and working memory could act cooperatively in the same area in the dorsolateral prefrontal cortex (Konishi et al., 1999a). Konishi et al. (1999b) also found transient no-go dominant activation in the posterior part of the inferior frontal sulcus in the right hemisphere by transient fMRI analysis. This area spatially overlapped the area related to set-shifting in the Wisconsin card-sorting test (Konishi et al., 1998). Therefore, shifting attention from one stimulus attribute to another may be closely related to the inhibition of behavioral responses to inappropriate stimuli. These results indicate that the same area within the dorsolateral prefrontal cortex participates in task management as well as attention-inhibition processes.

5. How does the nervous system achieve executive control?

The functions of executive control include selective attention, inhibition, task management, planning, monitoring, coding, and manipulating information. Executive control can be considered to be the coordinated operation of various processes or functions to accomplish a particular goal in a flexible manner. However, to realize this function, executive control itself needs to have some common mechanisms and characteristics. Common mechanisms include a mechanism for the temporary active storage of information and a mechanism for processing information. Working memory has these features.

5.1. Working memory

In cognitive psychology, working memory refers to a system for maintaining task-relevant information during the performance of a cognitive task. In general, working memory has been described as a system that provides not only temporary active storage of information but also enables the manipulation and processing of information (Baddeley, 1986 and Baddeley, 1992). For example, Baddeley and Logie (1999) described working memory as a mechanism to 'allow humans to comprehend and mentally represent their immediate environment, to retain information about their immediate past experience, to support the acquisition of new knowledge, to solve problems, and to formulate, relate, and act on current goals'. Kieras et al. (1999) described working memory as a mechanism to 'encompass the entire ensemble of temporary stored codes, knowledge representations, and procedures, whereby, information is maintained, updated, and applied for performing perceptual-motor and cognitive tasks'. Further, Miyake and Shah (1999) described working memory as 'mechanisms or processes that are involved in the control, regulation, and active maintenance of task-relevant information in the service of complex cognition, including novel as well as familiar, skilled tasks'. Thus, working memory is an important concept for considering the mechanisms of the temporary storage of information and its processing, which are common mechanisms for executive processes.

5.2. Two types of temporary storage peocesses of information

Temporary active information storage is necessary for executive control to operate various processes or functions in a coordinated manner. This mechanism can be best understood by the concept of working memory. However, a similar temporary active storage of information is also necessary for processing perceptual, linguistic, and motor information. Baddeley (1986) originally proposed two slave systems (the phonological loop and the visuospatial sketch pad) in the working memory model, each of which had a temporary storage mechanism for linguistic and visuospatial information, respectively. In neurophysiological studies, tonic sustained activation during the delay period of memory tasks (e.g. a delayed matching-to-sample task, a delayed response task) is considered to be a neuronal correlate for the internal representation and storage of perceptual or motor information. This delay period activity has been observed in inferior temporal neurons (Fuster and Jervey, 1982; Miyashita and Chang, 1988; Fuster, 1990; Miller et al., 1993), posterior parietal neurons (Gnadt and Andersen, 1988; Murata et al., 1996), and premotor neurons (Weinrich and Wise, 1982; Kurata and Wise, 1988). Delay-period activity observed in these areas was shown to encode sensory or motor information that is relevant to perform a particular sensory or motor task correctly. These observations suggest that neuronal mechanisms for temporary active storage of information can be divided into two types — a temporary storage mechanism for modality-specific information processing and a storage mechanism for general purpose, which could participate in more general processes or functions such as planning, judgement and monitoring.

5.3. Prefrontal working memory process as a mechanism for executive control

The prefrontal cortex is related to the executive function and could be the center for executive control. For executive control, it is important to operate various processes and functions operating in various brain regions in a coordinated manner. To accomplish this operation, anatomical connections with variety of brain areas and mechanisms for storing and processing various kinds of information are necessary. The information stored and processed in this mechanism includes the behavioral context for various cognitive tasks such as making a decision, solving a problem, or thinking and also includes control signals to regulate information flow between different cortical systems. The output from this mechanism could affect and regulate the operation of modality-specific information processing depending upon the context of the task or behavior and direct the information processing operating on the modality-specific cortical areas. Therefore, a hierarchial relation can be hypothesized between these two mechanisms, such that the output from the prefrontal cortex directs the information processing occurred in the modality-specific information processes.

A similar idea has been proposed by Cohen and co-workers (Cohen and Servan-Schreiber, 1992 and Cohen et al., 1996). They proposed a theory of prefrontal functions using a computational architecture within the connectionist framework or parallel distributed processing framework. Their central hypothesis is that the prefrontal cortex represents context information and that context representation is closely related to goal representations within a production system architecture. In their theory, context information is defined as information necessary to mediate an appropriate behavioral response, and includes a set of task instructions, a specific prior stimulus, or the result of processing a sequence of prior stimuli (Cohen et al., 1996). To accomplish an appropriate behavioral action associated with a particular goal, it is necessary for some structure to maintain an internal representation of the goal or goal-related knowledge for execution, to suppress unnecessary and competing behaviors and to coordinate series of behaviors temporally. Cohen et al. (1996) considered that the prefrontal cortex performs these functions. The prefrontal cortex represents and retains behavioral context, and modulates information flow by representing the context. In this regard, Cohen's idea for prefrontal function is similar to our model.

In general, working memory is considered to be a system that includes not only a mechanism for the temporary storage of information but also a mechanism for manipulating and processing stored information (Baddeley, 1986; Baddeley and Logie, 1999; Miyake and Shah, 1999). The internal and external states change depending upon the progress of a task or behavior, and the kind of information that needs to be stored in working memory would also change. Therefore, the information stored in working memory needs to be replaced, processed, or updated flexibly depending upon the internal and external states as well as the context of the task or the behavior. The necessary information is temporarily stored in the working memory buffer. However, at the same time, this information is processed in the very same working memory buffer. This indicates that working memory can be considered a workspace for information processing. The function as a workspace for information processing would be the most important aspect of working memory.

For the prefrontal mechanism related to working memory to operate as executive control, this requires at least three features; i.e. it must be able to (1) represent and process any kind of information; (2) access any kind of necessary information; and (3) provide information to various neuronal systems to direct information processing in these systems. Therefore, neuronal operations in working memory must be flexible. The prefrontal mechanism related to working memory must also have flexible and dynamic input–output relationships with miscellaneous brain systems.

6. Neuronal interpretation of working memory processes

We had proposed a model of working memory processes (Funahashi and Kubota, 1994). However, we modify and extend that model to explain the neuronal interpretation of executive control processes. A model of working memory is shown in Fig. 1, and includes four basic processes — a selection and input process, a temporal information-storage process, an output process, and modulatory signals. As in the earlier model, the selection and input process selects necessary information to perform a particular task and inputs the information to the temporal information-storage process. The temporal information-storage process is a

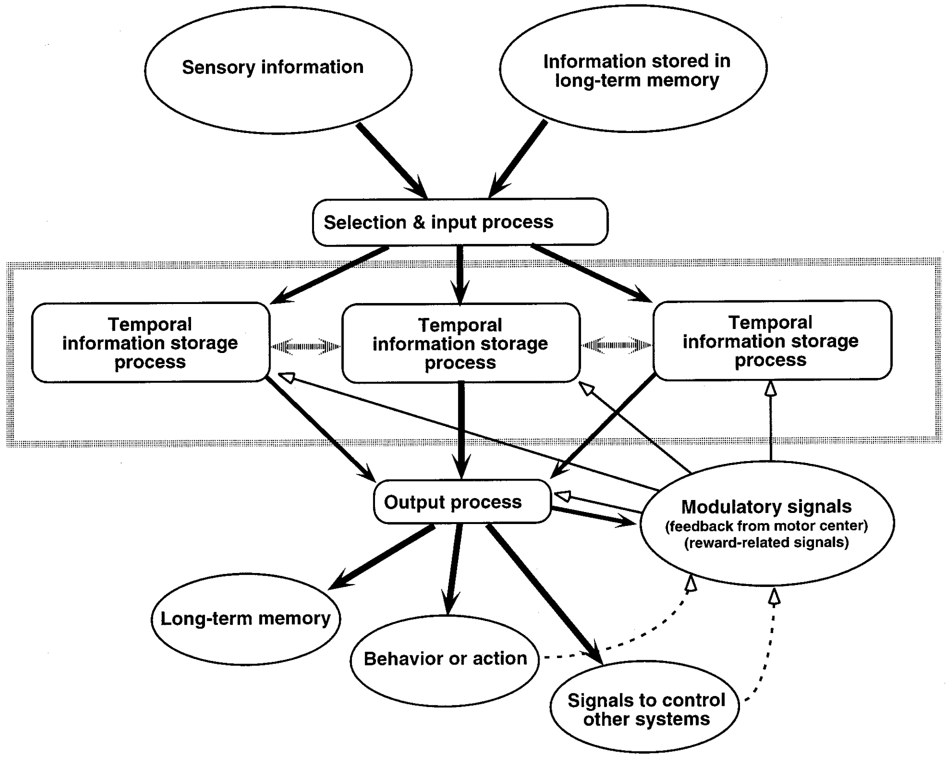


Fig. 1. A model for explaining how the prefrontal working memory processes participate in executive control. In this model, we emphasize the presence of dynamic interactions among different processes and dynamic interactions between storage processes.

basic component of working memory and an assembly of this process provides the workspace for information processing. The primary function of this process is to store information to be processed. The output process outputs processed information or control signals to cortical or subcortical systems for modality-specific information processing. Modulatory signals are feedback signals from the cortical or subcortical systems, where information has been provided. Modulatory signals also include emotional inputs from limbic systems (Barbas, 1992) and the orbitofrontal cortex (Pandya and Barnes, 1987), and catecholaminergic input (Sawaguchi and Goldman-Rakic, 1994; Williams and Goldman-Rakic, 1995; Watanabe et al., 1997; Luciana et al., 1998; Muly et al., 1998; Sawaguchi, 1998; Arnsten et al., 1999). These signals can be used as signals for modulating, manipulating, and updating information temporarily stored in the information-storage process.

Each process in this model might be defined as either a neuron or an assembly of neurons which exhibits a particular function such as the selection of necessary information, temporal storage of information and so on. Within each process, the function of a unit (a neuron or an assembly of neurons) may be different from other unit, such that one unit stores spatial information while other unit stores object information. Important differences from the earlier model are that the current model stresses dynamic and flexible interactions between different processes and extensive interactions among units of temporal information-storage processes. Although each unit of information storage process could store one particular kind of information at a time, active storage units within a certain cortical area might form a particular spatial pattern and this spatial pattern might be considered the representation of that information. Functional relations between neurons or assemblies of neurons can be modulated dynamically and flexibly depending upon the context of the behavioral task or external and internal states. By modulating the strength of neuronal interaction depending upon the behavioral context, information that a neuron or an assembly of neurons represents would change gradually or drastically. The temporal change in the spatial pattern of activated storage units might be considered the neuronal process of information processing. Since information processing can be considered as a neuronal process for modification or transformation of information from one kind of representation to another kind of representation, this dynamic and flexible modulation of the strength of neuronal interaction or functional connectivity between neurons must be the essence of information processing in working memory. Evidence for such dynamic and flexible modulation in neuronal interactions has been observed in prefrontal neurons (Vaadia et al., 1995; Funahashi, 1998a,b). Information processing in relation to working memory can be considered the dynamic and flexible modulation of interactions between temporal information-storage units, as well as the effect of modulatory signals on temporal information-storage processes.

In the following sections, we will consider the neuronal mechanisms of temporal information-storage processes, some evidence for dynamic interactions among prefrontal neurons, and evidence for dynamic and flexible interactions among various brain areas depending upon the context of the tasks.

7. Neuronal mechanisms of temporal information-storage processes

Delay-period activity, which is tonic sustained activation during an imposed delay period, has been considered to be a neuronal correlate of temporal information-storage processes (Goldman-Rakic, 1987; Funahashi and Kubota, 1994; Funahashi, 1996; Fuster, 1997; Miller, 1999). Neurophysiological studies using spatial working memory tasks such as the delayed-response task have revealed that many neurons in the prefrontal cortex exhibit delay-period activity (Fuster, 1973; Niki, 1974; Niki and Watanabe, 1976; Kojima and Goldman-Rakic, 1982, 1984; Funahashi et al., 1989; Watanabe, 1996; Carlson et al., 1997). Delay-period activity is prolonged or shortened depending upon the length of the delay period (Fuster, 1973; Kojima and Goldman-Rakic, 1982; Funahashi et al., 1989). Furthermore, this activity is observed only when monkeys perform correct responses (Fuster, 1973; Funahashi et al., 1989, 1997b). A great majority of delay-period activity exhibits a directional or positional preference (Funahashi et al., 1989; Carlson et al., 1997; Rao et al., 1997). In both delayed pro- and anti-saccade tasks, the great majority (about 70%) of prefrontal neurons that exhibited delay-period activity represented information regarding visual cue positions, whereas the remaining neurons represented information regarding the directions of saccades (Funahashi et al., 1993a). Similar results have been observed by Niki and Watanabe (1976) using a manual delayed-response task and a conditional position task and recently by Takeda et al. (1999) using conditional saccade paradigms with a delay. These results indicate that many prefrontal neurons with directional delay-period activity in spatial working memory tasks encode information regarding the visual cue positions. Furthermore, the preferred positions, where neurons exhibited the maximum delay-period activity, differed from neuron to neuron. Therefore, neurons with directional delay-period activity have been proposed to have mnemonic receptive fields (memory fields) of visual cues in the visual field (Funahashi et al., 1989 and Rainer et al., 1998b).

Although many prefrontal neurons with delay-period activity encoded retrospective information (e.g. visual cue positions), significant numbers of neurons encoded prospective information (e.g. directions of impending movements) (Niki and Watanabe, 1976 and Funahashi et al., 1993a). In addition to these observations, recently Hoshi et al. (2000) reported neuronal activity related to motor selection in the prefrontal cortex. These results indicate that delay-period activity representing motor information is present in the prefrontal cortex.

Experiments using non-spatial working memory tasks such as delayed matching-to-sample tasks and delayed conditional tasks have revealed that delay-period activity also reflects the active retention of non-spatial information, such as faces (Wilson et al., 1993 and O'Scalaidhe et al., 1997) and object shapes, patterns, or colors (Quintana et al., 1988; Yajeya et al., 1988; Watanabe, 1990, 1992; Sakagami and Niki, 1994; Miller et al., 1996; Rao et al., 1997; Rainer et al. 1998a). Recently, Romo et al. (1999) showed that discharge rates of delay-period activity 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 may be a basic representation of one-dimensional sensory stimulus quality in working memory. In addition, White and Wise (1999) found rule-dependent neuronal activity in the prefrontal cortex. They reported that between one-third and one-half of task-related neurons showed statistically significant differences in task-related activity depending upon the rule (a conditional rule or a spatial rule), indicating that these neurons retained rules of behavioral tasks by modulating the magnitude of their task-related activity.

Thus, delay-period activity observed in prefrontal neurons can be considered a neuronal correlate for the temporary active storage of information (Funahashi and Kubota, 1994; Funahashi, 1996; Fuster, 1997; Goldman-Rakic, 1998). A wide range of information is stored by neurons, including visuospatial information, motor information, non-spatial object features, quality differences in one stimulus modality, and task rules. Regional differences in information processing have been proposed for e.g. the mid-dorsolateral prefrontal cortex mainly participates in visuospatial information processing, whereas the mid-ventrolateral prefrontal cortex mainly participates in processing of information regarding non-spatial object features (Wilson et al., 1993; O'Scalaidhe et al., 1997; Goldman-Rakic, 1998; O'Scalaidhe et al., 1999). However, the cortical regions associated with various types of task-related activities during the performance of various tasks extensively overlap (Carlson et al., 1997; Quintana and Fuster, 1999; Rainer et al., 1999; Sakagami and Tsutsui, 1999), and even, number of neurons exhibit task-related activity in both spatial and non-spatial working memory tasks (Rao et al., 1997). In addition, since many prefrontal neurons exhibited task-related activity during multiple task events, these neurons are multi-functional. Fig. 2 summarizes examples of such activities recorded while monkeys performed an oculomotor delayed-response task. These observations support the notion that neurons in the dorsolateral prefrontal cortex can store and represent various types of information and, therefore, working memory processes in the dorsolateral prefrontal cortex could act as executive control.

8. Evidence for the manipulation or integration of information by interactions between storage processes

Several neurophysiological studies have offered evidence for the mechanism for manipulating or integrating information in the prefrontal cortex. One example is the interaction between neurons that exhibit delay-period activity and those that exhibit post-saccadic activity. Many prefrontal neurons exhibited saccade-related activity when saccadic eye movements were used as a behavioral response (Boch and Goldberg, 1989 and Funahashi et al., 1991). Most of these saccade-related activities were post-saccadic. But, they exhibited directional selectivity (Funahashi et al., 1991). Therefore, these post-saccadic activities could reflect feedback information from oculomotor centers. On the other hand, excitatory delay-period activity was usually terminated soon after the subject performed a response behavior. Comparison of the temporal characteristics of post-saccadic activity and delay-period activity revealed that the termination of delay-period activity coincided with the initiation of post-saccadic activity, suggesting that post-saccadic activity controls delay-period activity (Goldman-Rakic et al., 1990). Since erasing unnecessary information is an important process in working memory, feedback inputs from motor centers could serve to erase unnecessary information by terminating delay-period activity.

Evidence for the integration of information by interactions between neurons that exhibit delay-period activity has been suggested by experiments using delayed-response tasks with sequential movements. Delay-period activity whose selectivity was different from that earlier reported for directional delay-period activity has been observed in the prefrontal cortex in delayed-response tasks with sequential hand-reaching behavior or sequential saccades. These include delay-period activity representing a pair of different spatial positions, delay-period activity representing the temporal order of the presentation of multiple cues, and

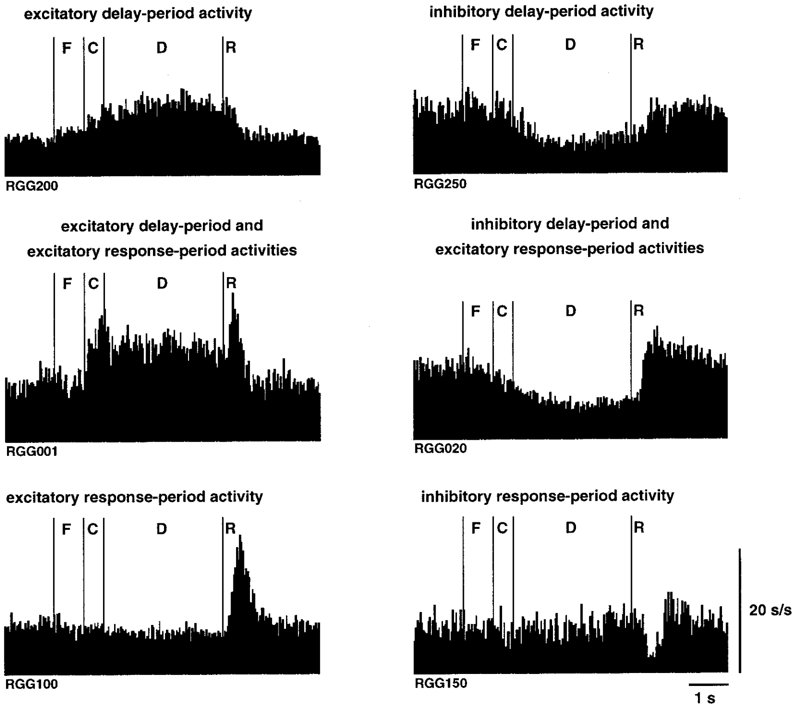


Fig. 2. Examples of neuronal activities exhibiting various task-related activities while monkeys performed an oculomotor delayed-response task. About a half of prefrontal neurons exhibited task-related activity during only one task event (see figures on the first and third rows), whereas the remaining half of neurons exhibited task-related activity during multiple-task events (see figures on the second row). F, C, D and R indicate fixation period, cue period, delay period, and response period, respectively.

delay-period activity representing a pair of different spatial positions as well as the temporal order of their presentation (Barone and Joseph, 1989; Funahashi et al., 1993b, 1997b). When activities were recorded during a conventional delayed-response task in which a single spatial cue was presented in each trial, most of these neurons exhibited delay-period activity with directional selectivity similar to that observed earlier (Funahashi et al., 1993b and Funahashi et al., 1997b). Therefore, delay-period activity representing a pair of different spatial positions, the temporal order of the presentation of multiple cues, or both, might be created by functional interactions between neighboring neurons, which represent different spatial selectivities.

Several recent studies have shown that the information represented by prefrontal activities changes with the temporal progression of the task. For example, using a delayed paired association task, Rainer et al. (1999) showed that shortly after sample presentation, prefrontal neuronal activity primarily reflected the characteristics of sample stimuli (sensory-related coding), whereas towards the end of the delay, prefrontal activity began to reflect the characteristics of anticipated targets (prospective coding). Similarly, using a spatial delayed matching-to-sample task, Sawaguchi and Yamane (1999) reported that, in the early phase of the delay period, prefrontal neurons with delay-period activity tuned spatial information broadly. However, in the later phase, the proportion of neurons with sharper spatial tuning and high spatial discriminability increased. In addition, Asaad et al. (1998) indicated that the prefrontal cortex is important for learning arbitrary cue-response associations for complex behavior and showed that neuronal activity conveyed the direction of impending eye movement progressively earlier within each successive trial while monkeys performed an associative learning paradigm. Quintana and Fuster (1999) observed cells attuned to the cue color and those attuned to response directions in the prefrontal cortex while monkeys performed working memory tasks using color cues and found that the discharge of cells attuned to the cue color tended to diminish in the course of the delay, whereas the discharge of those attuned to response directions tended to be accelerated. All these results indicate that modulation of the temporal pattern of neuronal firing reflects alteration of the information represented by the neuron and that information representing by firing of a neuron or an assembly of neurons alters gradually with the temporal progression of the trial.

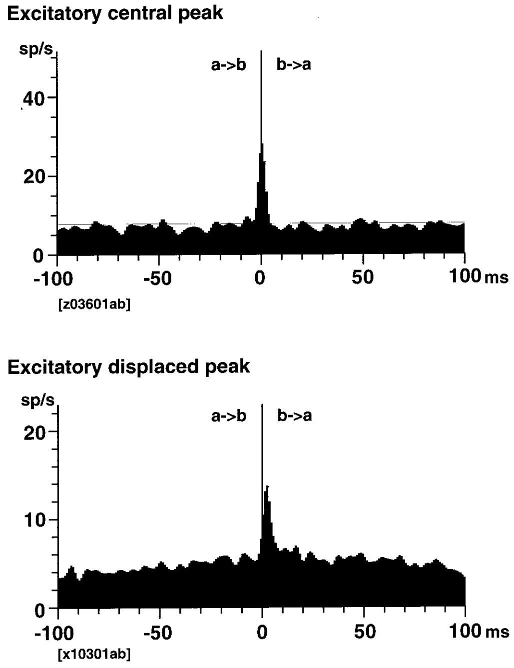
Thus, although there are not many evidences showing functional interactions between neurons with various types of task-related activity or various selectivities in task-related activity, without such functional interactions it is impossible to create such complex selectivity of prefrontal neurons and temporal changes in information represented by prefrontal activities. Therefore, these results suggest that the interactions among prefrontal neurons that exhibit various task-related activities with different directional preferences play an important role in integrating, manipulating and transforming information.

9. Evidence for dynamic changes in interactions among prefrontal neurons

Dynamic and flexible changes in functional interaction among temporal information-storage processes would be a key component for understanding neuronal mechanisms of information processing and executive control by the prefrontal cortex. To examine functional interaction between two cortical neurons, a cross-correlation analysis of the activities of a simultaneously isolated pair of single neurons is useful (Perkel et al., 1967a,b; Aertsen and Gerstein, 1985; Gerstein and Aertsen 1985). This analysis has been applied in various brain areas including the visual cortex (Toyama et al., 1981a; Toyama et al. 1981b; Tanaka 1983; Krüger and Aiple, 1988; Hata et al., 1991; Hata et al. 1993), the auditory cortex (Espinosa and Gerstein, 1988; Ahissar et al., 1992), the hippocampus (Sakurai, 1996, 1998), the motor cortex (Murphy et al., 1985a,b; Kwan et al., 1987), and the striatum (Bergman et al., 1998).

In the prefrontal cortex, Wilson et al. (1994) showed functional relationships between pyramidal cells and non-pyramidal cells, such that the types of responses (excitatory or inhibitory) of these neurons were often inverted (e.g. those of pyramidal cells were excitatory while those of non-pyramidal cells were inhibitory) and the timing of excitatory and inhibitory responses appear to be phased. This result suggests the presence of functional interactions between pyramidal and non-pyramidal neurons in the prefrontal cortex. Recently, Rao et al. (1999) used a cross-correlation analysis to examine functional interactions between pyramidal and non-pyramidal neurons in the prefrontal cortex and found dynamic inhibitory interactions between pyramidal neurons and adjacent non-pyramidal interneurons.

We also applied a cross-correlation analysis to prefrontal activities recorded during performance of an oculomotor delayed-response (ODR) task and examined functional interactions between prefrontal neurons with task-related activities at different task events (Funahashi et al., 1997a and Funahashi and Inoue, 2000). We recorded multiple-neuron activities from a single microelectrode that penetrated the dorsolateral prefrontal cortex while monkeys performed the ODR task, and isolated multiple single-neuron activities from multiple-neuron activities. Fig. 3 shows examples of the cross-correlograms (CCGs) we obtained. Among 168 pairs of single-neuron activities, 84 pairs had significant peaks at about time 0 in the CCG. Of these 84 pairs, 30 (36%) showed an excitatory sharp and symmetrical peak at time 0 (central peak, Fig. 3A), whereas 38 (45%) had excitatory sharp but asymmetrically distributed peaks displaced from time 0 (displaced peak, Fig. 3B). The remaining neuron pairs exhibited either asymmetrical positive and negative peaks displaced from time 0 (4%) or significant negative peaks at about time 0 (15%). Strong and significant peaks were observed in CCGs for many prefrontal neuron pairs that exhibited various task-related activity. The analysis using CCGs indicates that information flowed from prefrontal neurons with cue-period activity to neurons with oculomotor activity through neurons with delay-period activity. In addition, neuron pairs where both neurons exhibited delay-period activity tended to have significant excitatory peaks in CCGs, indicating that excitatory interactions between temporary information-storage processes are present in the prefrontal cortex. Further, neuron pairs that had excitatory central peaks in CCGs tended to have similar directional preferences in task-related activities, and this similarity was strongest in neuron pairs where both neurons exhibited cue-period activity. Neuron pairs that had displaced peaks in CCGs also showed similar directional preferences in task-related activities and this


Excitatory central peak

Excitatory displaced peak

Fig. 3. Two examples of cross-correlograms observed in prefrontal neuron pairs. The cross-correlograms were constructed using neuron activities collected simultaneously from a pair of prefrontal neurons while the monkey performed an oculomotor delayed-response task. Two major types of correlograms were observed. The correlogram with an excitatory central peak at time 0 suggests that both neurons receive a common excitatory input, whereas that with an excitatory peak displaced from time 0 suggests that one neuron sends excitatory outputs to the other. Bin width is 1 ms.

similarity was also stronger in neuron pairs where both neurons exhibited cue-period activity. However, interactions between neurons that exhibited task-related activity with different directional preferences increased with the temporal progression of the task. These results suggest that these functional interactions play an important role in information processing. Excitatory interactions among neurons with delay-period activity were frequently observed in the prefrontal cortex, suggesting that through these interactions, the information stored by temporary storage processes may be transformed from one form of representation to another or integrated to create a more complex representation, such as delay-period activity, representing a combination of visual cue positions and the temporal order of their presentation (Barone and Joseph, 1989 and Funahashi et al., 1997b).

Although about half of the neuron pairs examined exhibited either excitatory central peaks or displaced peaks in CCGs, the functional interactions drawn from these CCGs were overall interactions between particular neuron pairs, since these CCGs were calculated using activities recorded throughout the entire trial period. However, each neuron modulated its activity depending upon the trial conditions (e.g. the position where the visual cue was presented or the direction where the saccade was directed), the temporal context of the trial (e.g. cue period, delay period, or response period) and trial events. Therefore, the strength of functional interactions observed in CCGs may be modulated depending upon the trial conditions of the task or the temporal context of the trial. To examine this issue, we calculated CCGs of neuron pairs that exhibited excitatory central or displaced peaks for each cue condition in the ODR task (Funahashi et al., 1997a). Fig. 4 shows an example of CCGs calculated for neuron activities in every cue condition. The height of the central peak was modulated depending upon the cue conditions. In this particular case, strong central peaks were observed in trials in which the visual cues were presented at 90, 225 and 315° positions. This modulation of the peak height in CCGs was observed in most of the neuron pairs examined. These results suggest that, although many prefrontal neurons show functional interaction with neurons that exhibit the same or a different type of task-related activity, the strength of this interaction may change dynamically depending upon the conditions of the task.

The fact that the height of the excitatory peak in CCGs was modulated depending upon the trial conditions strongly suggests that the strength of the functional interaction between a pair of prefrontal neurons is also modulated depending upon the temporal context of the task. A correlation analysis called the joint peri-stimulus time histogram (jPSTH) analysis was developed by Gerstein and Perkel (1969, 1972) and Aertsen et al. (1989) to examine the temporal modulation of functional interaction between a pair of simultaneously recorded single-neuron activities. The jPSTH method has been shown to be useful for analyzing context-dependent changes or temporal changes in functional connectivity between two neurons during the temporal progression of a trial. The temporal change in functional connectivity can be shown as a histogram called a PST coincidence histogram (CH). The important features of this method are that the temporal change in functional connectivity between two neurons can be shown as a temporal change in the height of the PST coincidence histogram and that this change is independent of the task-related modulation of the neurons' firing rates during the trial (Aertsen et al., 1989). The validity of this method and the functional importance of a temporal change in the effective connectivity between cortical neurons have been demonstrated by Vaadia et al. (1995) using prefrontal activities. Although some caution is needed to interpret the results (Ito and Tsuji, 2000), the jPSTH method is useful for examining the temporal modulation of functional interaction between prefrontal neurons during the temporal progression of the trial. Therefore, we constructed jPSTHs and examined CHs for selected neuron pairs that were isolated from the same record (Funahashi, 1998a and Funahashi, 1998b). Fig. 5 shows examples of jPSTH and CH obtained from neurons x11302a and b recorded during performance of an ODR task. In this example, neuron x11302a exhibited tonic excitatory delay-period activity, whereas neuron x11302b exhibited excitatory cue-period activity. The CCG calculated from these two neurons' activities had an excitatory asymmetrical peak displaced from time 0 (Fig. 5). The temporal pattern of the CH indicates that the probability of coincidental firing changed during the temporal progression of the trial. Since the temporal pattern of CH can be thought to represent the strength of functional connectivity (Aertsen et al., 1989), this temporal pattern of CH suggests that functional connectivity between these two neurons was stronger during the early half of the delay period, but became weaker during the later half of the delay period. Although the temporal patterns of CHs varied from neuron pair to neuron pair, stronger functional connectivity was only observed during the cue-period or the response-period, during the entire delay period, during the early half of the delay period (Fig. 5), or during the late half of the delay period.

Thus, a large number of neuron pairs in the prefrontal cortex exhibited significant peaks around time 0 in CCGs, suggesting that a large number of prefrontal neurons have excitatory input–output relationships with neighboring neurons. A pair of neurons with a

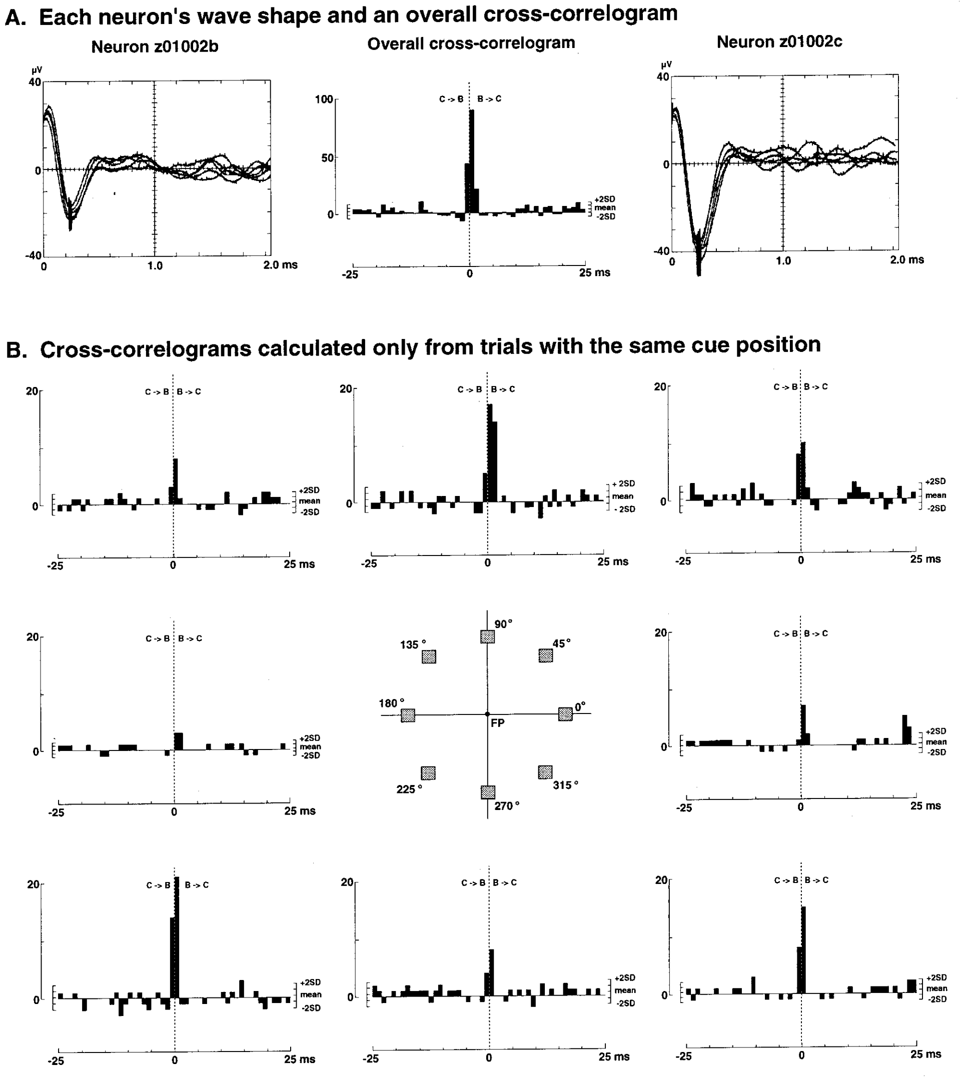


Fig. 4. Modulation of the peak amplitude in cross-correlograms depending upon the trial conditions. The center diagram indicates the locations of the visual cue used in an oculomotor delayed-response task. The cross-correlograms around the center diagram are those calculated by neuronal activities collected during the trials, in which the visual cue was presented at the corresponding position. High peaks in cross-correlograms were observed at the 90, 225 and 315° trials, suggesting that functional interaction between these two neurons was enhanced at the 90, 225 and 315° trials. Bin width is 1 ms.

significant peak in the CCG often had different types of task-related activities or different spatial selectivities in task-related activity, suggesting that information processing occurs in the prefrontal cortex through this input–output relationship between neighboring neurons. In addition, dynamic and flexible changes in functional interaction among temporal information-storage units are important for understanding neuronal mechanisms of information processing and executive control by the prefrontal cortex. The strength of functional interactions between neurons was modulated depending upon trial conditions and the temporal context of the trial, indicating that flexible and dynamic modulation of the strength of functional interaction among neurons is present in the prefrontal cortex and is likely to play a significant role in executive control.

10. Dynamic interactions between the prefrontal cortex and other cortical areas

To understand how the prefrontal cortex exerts executive control, it is important to consider dynamic and flexible functional interactions between the prefrontal cortex and other cortical and subcortical areas. Cortico-cortical and cortico-subcortical anatomical connections with the prefrontal cortex have been examined extensively (see reviews by Pandya and Barnes (1987) and Fuster (1997)). The dorsolateral prefrontal cortex has reciprocal cortico-cortical connections with the posterior parietal cortex, the inferior temporal cortex, the superior temporal polysensory areas, the anterior cingulate, the retrosplenial cortex, and the parahippocampal gyrus. The dorsolateral prefrontal cortex also has strong reciprocal connections with the mediodorsal nucleus of the thalamus. In addition, the prefrontal cortex has connections with the frontal eye field, the pre-supplementary motor area, the premotor cortex, and the caudate nucleus. Recently, Morris et al. (1999) reported that the mid-dorsolateral prefrontal cortex (areas 46 and 9) projects to the retrosplenial area 30 and the posterior presubiculum and suggested that this system could be the anatomical substrate of functional interaction between the dorsolateral prefrontal cortex and the hippocampus. Thus, the dorsolateral prefrontal cortex has anatomical connections with various cortical and subcortical areas, especially sensory and motor association areas and the limbic system. Most of these connections are reciprocal. These observations strongly suggest that the dorsolateral prefrontal cortex can input various kinds of information including sensory, motor, and emotional information as well as information stored in long-term memory, and is, therefore, in a good position to obtain any kind of information necessary. These observations also suggest that the dorsolateral prefrontal cortex can output various types of information and control signals to cortical and subcortical systems and is, therefore, again in a good position to manage information processing in other systems.

Recent non-invasive brain imaging studies have revealed these networks and dynamic changes in functional interactions between the prefrontal cortex and other cortical areas. With regard to episodic memory encoding and retrieval, it has been shown that episodic memory encoding is related to the left prefrontal cortex, whereas episodic memory retrieval is related to the right prefrontal cortex (Fletcher et al., 1998a,b; Duzel et al., 1999). For example Klingberg and Roland (1998) showed by a PET study that episodic encoding was related to the left prefrontal cortex in an association task in which subjects were required to make an association between abstract pictures and computer-generated sounds. However, they found no activation during episodic retrieval in the right prefrontal cortex. On the other hand, Wagner et al. (1998a) reported that, although retrieval-associated activation was observed in the right prefrontal cortex, this activation reflected attempted retrieval, not successful retrieval. The prefrontal cortex apparently plays a significant role in episodic memory retrieval as well as episodic memory encoding. However, many other cortical systems also participate in episodic memory retrieval (Kohler et al., 1998).

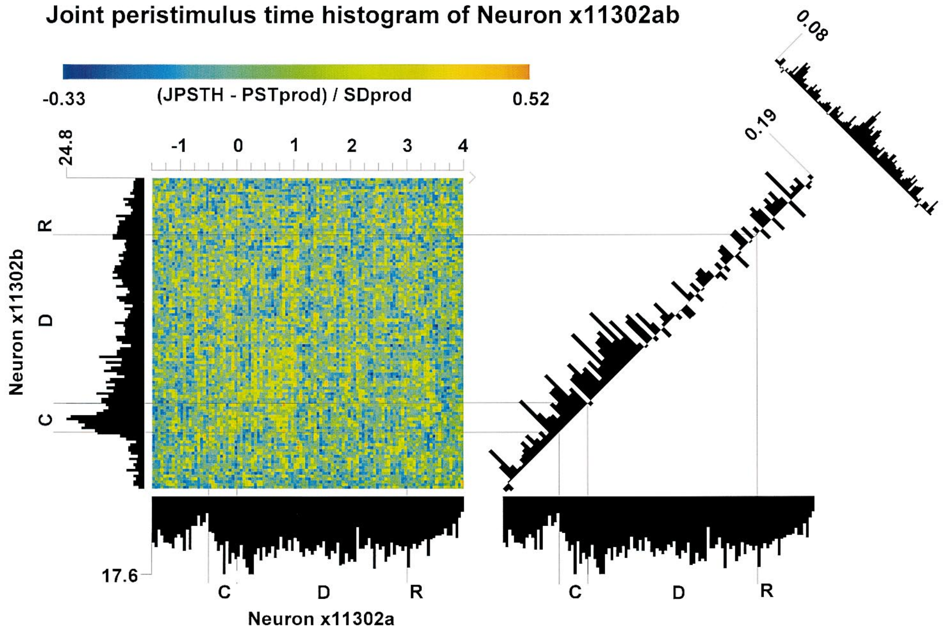


Fig. 5. An example of the temporal modulation of functional connectivity between two simultaneously isolated prefrontal neurons during the temporal progression of the task. The activities of both neurons were recorded while the monkey performed an oculomotor delayed-response task. Two histograms at the bottom indicate neuron x11302a's activity during the temporal progression of the task (starting at the left and ending at the right). The histogram on the left indicates neuron x11302b's activity during the temporal progression of the task (starting at the bottom and ending at the top). C, D and R indicate the cue, delay and response periods, respectively. In the cue period, a visual cue was presented randomly at one of the eight peripheral positions. The monkey needed to keep gazing at the central fixation point during the cue period (0.5 s) and the delay period (3 s). During the response period, the monkey had to make a saccade to the position, where the visual cue had been presented. The color map on the left is a joint-peristimulus time histogram, indicating strengths of correlated firings between two neurons. The diagonal histogram on the right is a coincidence histogram, indicating the temporal modulation of the probability of coincidental firing of two neurons. The shape of the coincidence histogram indicates the temporal modulation of the strength of functional connectivity between two neurons. In this example, functional connectivity is stronger during the early phase of the delay period. Both the joint-peristimulus time histogram (jPSTH) and the coincidence histogram were calculated using a program, TEMPO (Biographics, Inc.). Bin size is 25 ms.

Recently, Brewer et al. (1998) and Wagner et al. (1998b) showed that the magnitude of focal activation in the right prefrontal cortex and the parahippocampal cortex predicted whether photographs or words that were presented as items to remember were later remembered well or forgotten by the subjects. These results indicate that dynamic functional interactions and co-activation between the prefrontal cortex and other cortical areas are important for episodic memory functions.

In imaging studies, *n*-back tasks have often been used as a working memory task. Visuospatial *n*-back (0-back, 1-back, and 2-back) tasks have been shown to activate bilateral dorsolateral prefrontal areas (Cohen et al., 1997; Smith and Jonides, 1997, 1998). The magnitude of such activation in the prefrontal cortex depended on the memory load required to perform the task (Carlson et al., 1998 and Callicott et al., 1999). However, even simple working memory tasks like *n*-back tasks are composed of numerous elementary subsecond neuronal processes. Based on an analysis of evoked potentials, McEvoy et al. (1998) showed that, although some of these processes varied with the type of information (verbal or spatial), the processes reflected in the frontal and parietal slow waves were affected by the amount of information being retained, but not by the type of information. Therefore, they suggested that working memory emerges from a dynamic cortical network linking task-specific processes with non-specific, capacity-limited, higher-order attentional processes (McEvoy et al., 1998).

Dynamic cortical networks, which include the prefrontal cortex have been shown directly by correlation analysis in brain imaging studies as well as by covariance and correlation analysis of event-related potentials. Using a working memory task for faces, McIntosh et al. (1996) examined neural interactions among different cortical regions by an anatomically based covariance structural equation modeling. As a result, they found that different interactions among different cortical areas were observed in different task conditions (e.g. different delay lengths) and that a top-down interaction from the prefrontal cortex to the temporal and occipital cortices was observed with a long delay condition. In addition, McIntosh et al. (1999) have shown that the left prefrontal cortex exhibits learning-related modulations of brain activation only in aware subjects during an associative learning paradigm and a correlation analysis of this modulation revealed significant functional connectivity with the contralateral prefrontal cortex, the sensory association cortices and the cerebellum. In addition, evidence for homotopic interaction or co-activation of the left and right prefrontal cortices has been reported (McGuire et al., 1991; Klingberg et al., 1997). Klingberg et al. (1997) reported an increase in bilateral co-activation of the dorsolateral prefrontal cortex and the inferior parietal cortex with an increase in task difficulty by PET studies. They also found that the inferior parietal cortex was often co-activated with the dorsolateral prefrontal cortex in working memory tasks as well as tasks involving planning. Further, Gevins and his colleagues developed a method for calculating the covariance and correlation of event-related potentials recorded with a multi-channel, high-resolution EEG system, and showed temporal dynamics of interactions among various brain areas (Gevins et al. 1983 and Gevins, 1990). Using cognitive tasks, they showed that waves of covariance migrated from visual areas to the parietal area and eventually into the prefrontal cortex. Using this method, they indicated that large distributed areas in the brain were co-activated at a certain period and that the co-activated areas or the co-activated network changed with the behavioral context of the trial. All of these results indicate the importance of cortico-cortical and cortico-subcortical interactions and co-activation between the prefrontal cortex and other cortical areas for performing cognitive tasks. These results also indicate that cortico-cortical and cortico-subcortical interactions and co-activation are dynamic and flexible and show temporal modulation depending upon the context of the cognitive task.

Recently, top-down modulatory influences by the prefrontal cortex have been shown. Using a visual associative memory task, Hasegawa et al. (1998) showed that visual image retrieval from long-term memory was under the executive control of the prefrontal cortex, as revealed by a partial split-brain paradigm in monkeys. In addition, by neurophysiological experiments using monkeys with callosal resection, Tomita et al. (1999) showed that top-down signals from the prefrontal cortex regulated episodic memory retrieval in the temporal cortex. These observations indicate that the prefrontal cortex can manage information processing in other cortical areas using top-down signal pathways. Similarly, Lumer and Rees (1999) showed that, in bistable viewing conditions, covariation of activity was observed in multiple extrastriate areas, the parietal cortex, and the prefrontal cortex by fMRI. Coordinated activation of these areas was not linked to sensory or motor events, but rather reflected perceptual events or internal changes of perception. Therefore, they concluded that functional interactions between the visual and prefrontal cortex could contribute to conscious vision. On the other hand, enhancement or suppression of the visual response was observed in inferior temporal neurons when two visual stimuli (one preferred and the other, non-preferred) were presented simultaneously in the neuron's receptive field. Chelazzi et al. (1998) proposed that this phenomenon can be explained by a 'biased competition' model of attention, such that objects in the visual field compete for representation within the cortex and that this competition is biased by 'top-down' feedback from structures involved in working memory. Although this is just a model, according to the results of Hasegawa et al. (1998), Tomita et al. (1999) and Lumer and Rees (1999) top-down signal from the prefrontal cortex could bias the processes in the visual system.

These results indicate the presence and importance of a top-down modulatory effect by the prefrontal cortex in performing cognitive tasks. These results also suggest that the top-down modulatory influence of the prefrontal cortex may affect a wide variety of cognitive activities including sensory perception, attention, episodic memory encoding and retrieval through dynamic cortico-cortical and cortico-subcortical functional interactions.

11. Conclusions

Executive function is considered to be a product of the coordinated operation of various processes to accomplish a particular goal in a flexible manner. The mechanism or system responsible for the coordinated operation of various processes is called executive control. Since impairments caused by prefrontal damage have often been called dysexecutive syndromes, the prefrontal cortex is considered to play a significant role in executive control. Working memory processes observed in the prefrontal cortex, especially neuronal mechanisms for temporary storage of information and dynamic and flexible interactions among them, can explain how the prefrontal cortex exerts executive control. We showed the presence of extensive functional interactions among temporal information-storage processes and dynamic and flexible modulation of these interactions. Evidence for the dynamic and flexible modulation of neuronal interaction has been observed in prefrontal neurons by neurophysiological experiments. In addition, recent imaging studies have shown dynamic modulation of functional connectivity between the prefrontal cortex and other cortical and subcortical structures depending upon the characteristics of the task or the temporal context of the task.

Information processing in general can be considered a modification or transformation from one type of representation to another type of representation. The representation of particular information in the prefrontal cortex might be considered a spatial pattern of both active and inactive areas within the prefrontal cortex, or a differential temporal pattern of activity at a particular region within the prefrontal cortex, or a combination of both. Prefrontal neurons that exhibit one type of task-related activity are usually distributed in a wide area of the prefrontal cortex. There is a large overlap of spatial distributions among neurons that exhibit different types of task-related activities (Carlson et al., 1997; Quintana and Fuster, 1999; Rainer et al., 1999; Sakagami and Tsutsui, 1999). However, some topographic pattern in the distribution of task-related neurons within the prefrontal cortex has been suggested. For example, an experiment using local impairment through the injection of bicuculline revealed a topographic deficit in spatial working memory, such that impairment of the anterior part of the principal sulcal area produced spatial working memory deficits when the visual cues were presented in the lower visual field, whereas impairment of the posterior part produced deficits when the visual cues were presented in the upper visual field (Sawaguchi and Goldman-Rakic, 1994). In addition, each type of task-related activity also exhibits some specificities, such as directional selectivity observed in cue-, delay-, and response-period activities (Funahashi et al., 1989, 1990, 1991). Therefore, we might observe flexible and dynamic features of information processing by showing spatio-temporal change in the distribution of active and inactive areas within the prefrontal cortex along the temporal context of the task.

Acknowledgements

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