Thalamic mediodorsal nucleus and working memory

Yumiko Watanabe [1) 2)] and Shintaro Funahashi [2) 3)]

1 Human Technology Research Institute, National Institute of Advanced Industrial Science and Technology, Tsukuba 305-8568, Japan.

2 Department of Behavioral and Cognitive Sciences, Graduate School of Human and Environmental Studies, Kyoto University, Sakyo-ku, Kyoto 606-8501, Japan.

3 Kokoro Research Center, Kyoto University, Sakyo-ku, Kyoto 606-8501, Japan.

Correspondence should be sent to:

Shintaro Funahashi

Kokoro Research Center

Kyoto University

Sakyo-ku, Kyoto 606-8501, Japan.

Phone & Fax: (+81) 75-753-9674

E-mail: funahashi.shintaro.2z@kyoto-u.ac.jp

Abstract

Working memory is a dynamic neural system for temporarily maintaining and processing information. The prefrontal cortex (PFC) plays an important role in working memory. However, several evidences indicate that the thalamic mediodorsal nucleus (MD) also participates in working memory. Neurophysiological studies revealed that MD neurons exhibit sustained delay activity, which is considered to be a neural correlate of the temporary maintenance of information. Most MD neurons with delay activity represented information regarding motor responses, whereas some represented information regarding visual cues, suggesting that the MD participates more in prospective aspects of working memory, in contrast to the PFC, in which a minority participates in prospective aspects of working memory. A population vector analysis revealed that the transformation of sensory-to-motor information occurred during the earlier phase of the delay period in the MD compared with the PFC. These results indicate that reverberating neural circuits constructed by reciprocal connections between the MD and the PFC could be an important component for constructing prospective information in the PFC.

Key words: thalamic mediodorsal nucleus, prefrontal cortex, spatial working memory, delayed-response, retrospective information, prospective information.

1. Introduction

Working memory is an important concept for understanding the mechanisms of higher cognitive functions such as thinking, planning, reasoning, decision-making, and language comprehension (Baddeley and Hitch 1974; Baddeley 2000). 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." 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 a dynamic neural system that includes mechanisms for temporarily maintaining information as well as processing the maintained information.

The dorsolateral prefrontal cortex (DLPFC) has been shown to play significant roles in working memory (Goldman-Rakic 1987; Funahashi and Kubota 1994; Petrides 1994; Funahashi 2001; Funahashi and Takeda 2002; Fuster 2008). Brain imaging studies in human subjects have revealed that the DLPFC is activated whenever the subjects perform behavioral tasks that require working memory (e.g., n-back tasks) (Owen et al. 2005). Neuropsychological studies have also revealed that damage to the DLPFC impairs the performance of working memory tasks (Stuss and Levine 2002; Stuss et al. 2002). In animal studies, lesion of the DLPFC impaired performance in behavioral tasks that included an imposed delay period between cue presentation and response generation (e.g., delayed-response, delayed alternation, delayed matching-to-

sample task) (Fuster 2008). In addition, tonic sustained excitatory activity during the delay period has been observed in the DLPFC while monkeys performed tasks with a delay (Funahashi et al. 1989). These findings support the notion that the DLPFC plays an important and essential role in working memory.

However, the DLPFC is not only the brain area that participates in working memory processes. Other brain areas, including the parietal cortex (Gnadt and Andersen 1988; Chafee and Goldman-Rakic 1998), the temporal cortex (Fuster and Jervey 1982; Fuster et al. 1985; Miller et al. 1991, 1993), and the basal ganglia (Hikosaka and Sakamoto 1986; Hikosaka et al. 1989), also play important roles in working memory. It has been shown that these brain areas include neurons that exhibit tonic sustained excitatory activity during the delay period. All of these brain areas have anatomical connections to the DLPFC (Fuster 2008). Therefore, these brain areas, together with the DLPFC, might make specific neural circuitries for working memory.

The mediodorsal nucleus (MD) of the thalamus has been shown to have reciprocal connections with the prefrontal cortex (Kievit and Kuypers 1977; Goldman-Rakic and Porrino 1985; Giguere and Goldman-Rakic 1988; Ray and Price 1993). Several lines of evidences (Fuster and Alexander 1971, 1973; Kubota et al. 1972; Tanibuchi and Goldman-Rakic 2003) indicate that the MD also participates in working memory. In this review, we present findings which indicate that the MD participates in working memory and discuss neural mechanisms of working memory by comparing neurophysiological observations in the MD and the DLPFC.

2. Anatomical interactions between the MD and the prefrontal cortex

The mediodorsal nucleus (MD) is located at the midline of the diencephalon and one of the major parts of the thalamus in primate species. Thalamic neurons mainly project to the layer IV of the cerebral cortex and receive cerebral inputs mainly from neurons in the layer VI of the cerebral cortex. Thus, the thalamus has reciprocal connections with the cerebral cortex. Therefore, the thalamus is generally considered to provide gating functions for information flow to and from the cerebral cortex (Sherman and Guillery 2002). The thalamus consists of several thalamic nuclei and each thalamic nucleus has specific and reciprocal connections with the particular area of the cerebral cortex. Because of specific and reciprocal connections between a specific thalamic nucleus and a specific area of the cerebral cortex, functional similarities have been observed between these two regions (e.g., the motor thalamus has connections with the motor areas in the cerebral cortex). The MD has specific and reciprocal anatomical connections to the prefrontal cortex. Therefore, reciprocal connections between the MD and the prefrontal cortex suggest that the MD also participates in some important cognitive functions that the prefrontal cortex participates in.

The MD is divided into three sectors based on differences in anatomical characteristics: magnocellular sector (MDmc), parvocellular sector (MDpc), and multiform sector (MDmf). Since these sectors have specific anatomical connections with specific cortical and subcortical structures, they have been considered to play different functional roles. The MDmc is located in the medial part of the MD and has reciprocal connections with the orbitofrontal cortex (Kievit and Kuypers 1977; Giguere and Goldman-Rakic 1988). The MDmc also receives major inputs from the amygdala (Porrino et al., 1981). Therefore, the MDmc has been considered to participate mainly in emotional and motivational functions. The MDmf is located in the lateral part of the

MD and faces the intralaminar nucleus. Since the MDmf has anatomical connections to the frontal eye field (Kievit and Kuypers 1977; Goldman-Rakic and Porrino 1985), and since many neurons with eye movement-related activity have been observed in the intralaminar nucleus of the thalamus (Schlag-Rey and Schlag 1984; Schlag and Schlag-Rey 1984; Tanaka 2007), the MDmf and intralaminar nucleus are considered part of the oculomotor control system.

The MDpc is located in the region between the MDmc and the MDmf. The MDpc has reciprocal connections to the lateral portion of the prefrontal cortex (Kievit and Kuypers 1977; Goldman-Rakic and Porrino 1985; Barbas et al. 1991; Ray and Price 1993). The MDpc also receives inputs from both the substantia nigra pars reticulata (Ilinsky et al. 1985; Velayos and Reinoso-Suarez 1985; Tanibuchi et al. 2009) and the superior colliculus (Lynch et al., 1994). Therefore, the MDpc has been thought to participate in the same cognitive functions as the DLPFC.

3. Effects of lesions in the MD on working memory performance

The capacity of working memory has been examined using tasks with a delay, such as the delayed-response task, delayed alternation task, and delayed matching-to-sample task, in the DLPFC (Goldman-Rakic 1987; Fuster 2008). The creation of lesions in the MD of monkeys produces deficits in the performance of these delay tasks (Isseroff et al. 1982), indicating that the MD also participates in working memory processes. For example, Isseroff et al. (1982) examined the behavioral effects of MD lesions in 14 rhesus monkeys using a spatial delayed alternation task, a delayed-response task, an object reversal task, and a visual pattern discrimination task. The

performances of these tasks are known to be sensitive to damage of the prefrontal cortex. They found that lesions in the MD caused impairment in the spatial delayed alternation task and the delayed-response task, both of which are considered spatial working memory tasks. However, monkeys with MD lesions exhibited no impairment in the object reversal task and the visual pattern discrimination task. Neither of these tasks is considered a working memory task. Instead, the former requires associative memory and the latter requires long-term memory. Thus, lesions of the MD produce a specific deficit in spatial working memory tasks, which is similar to the deficit observed after damage to the DLPFC.

The MD has also been shown to participate in non-spatial working memory processes. Lesion of the MD impaired performance in the delayed matching-to-sample task (Aggleton and Mishkin 1983a, b; Parker et al. 1997) and the delayed non-matching-to-sample task (Zola-Morgan and Squire 1985) in monkeys. Parker et al. (1997) preoperatively trained a delayed matching-to-sample task with large or small stimulus sets to monkeys. Then, they examined the behavioral effects of bilateral ablations made in the medial sector of the MD. They found that bilateral ablation impaired performance of this task with large stimulus sets, but had no effect on performance with small stimulus sets. These results indicate that, although lesion of the MD impairs non-spatial working memory performance, more severe impairment is observed if the task difficulty is increased.

Although lesion of the MD produces working memory deficits in monkeys, it also produces deficits in other types of memory. Gaffan and Parker (2000) examined the effect of bilateral ablations of the MDmc on scene memory and object-reward association memory, and found that this ablation impaired both types of memory.

Mitchell et al. (2007) taught monkeys to perform both an object-in-place scene memory task and a strategy implementation task. The strategy implementation task was impaired by disconnecting the frontal cortex in one hemisphere from the contralateral inferotemporal cortex. They then made selective lesions in the MDmc by injecting a mixture of ibotenate and NMDA. They found that, although lesion of the MDmc had no effect on pre-learned strategy implementation performance, new learning in the object-in-place scene memory task was strongly impaired. These results indicate that the interconnections between the MD and the prefrontal cortex are important during new learning, but are not necessary for the implementation of pre-learned strategies. Based on these observations, they suggested that the involvement of the MD in prefrontal function is limited to situations in which new learning occurs. Recently, Mitchell and Gaffan (2008) showed that the MDmc participates in memory acquisition, but not in memory retrieval. In their experiment, rhesus monkeys learned 300 unique scene discriminations. Retention of these scenes was examined using a one-trial retrieval test. After bilateral neurotoxic lesion of the MDmc, they found no effect on performance in the one-trial retrieval task. However, new learning of 100 novel scene discriminations was severely impaired. Further, Mitchell et al. (2008) recently suggested that subcortical damage, such as lesions to the MD, has greater effects on new learning (or acquisition), whereas cortical damage has greater effects on retention.

Thus, lesions in the MD produce impairments in working memory performance as well as other types of memory performance, suggesting that the MD significantly participates in memory functions in general. This notion agrees with the observations that lesion in the MD produces severe memory impairment in humans and that the MD is one of the responsible brain structures for Korsakoff's syndrome. In addition, it is

interesting that the involvement of the MD in prefrontal function is limited when new learning occurs and that lesions in the MD have greater effects on the acquisition phase, whereas cortical damage has greater effects on the retention phase.

4. Human studies in the MD on working memory

Damage to the medial thalamus, including the MD, often produces syndromes similar to "prefrontal" syndromes in humans (Daum and Ackermann 1994; Van der Werf et al. 2000, 2003). "Prefrontal" syndromes observed in human subjects include impairment of executive abilities, inappropriate control of attention, loss of positive attitude, inability to inhibit unnecessary responses, and a deficit in the temporal organization of behavior (Fuster 2008). Van der Werf et al. (2003) used neuropsychological tests to examine the performance of 22 patients with thalamic infarction, the loci of which were identified by MRI. They used four neuropsychological tests (Wisconsin card sorting test, Tower of London test, verbal category fluency test, and Stroop test) to assess the patients' executive functions. They found that patients who had damage to the MD exhibited impairment in the performance of all these tasks, indicating that the MD participates in executive functions. They found that other thalamic structures, such as the midline nuclei and/or intralaminar nuclei, also contribute to executive functions. Working memory is an important fundamental process for executive function (Funahashi 2001). The neuropsychological tests that Van der Werf et al. (2003) used require working memory to perform correctly. Therefore, these results suggest that damage to the MD produces an impairment of working memory.

Zoppelt et al. (2003) showed that executive dysfunction is associated with damage in the lateral part of the MD. They examined 9 patients with thalamic infarction identified by MRI and 9 healthy control subjects. Among 5 patients who had damage in the MD, 2 had damage predominantly in the medial part of the MD and 3 had damage predominantly in the lateral part of the MD. Executive function was assessed by the Stroop test, a verbal fluency task, and digit span tests (forward and backward reproduction). They found that patients with damage in the lateral part of the MD exhibited more severe impairments in the digit span test with backward reproduction and in the phonemic condition of the verbal fluency test, whereas patients with damage in the medial part of the MD did not exhibit impairments in these tests. These results indicate that the lateral part of the MD is important for executive function. They also showed that, although patients with MD damage showed impaired memory processes such as recollection and familiarity, these memory impairments were more apparent when the medial part of the MD was included in the damaged area. These results agreed with observations that the medial part of the MD is one of the responsible brain structures for diencephalic amnesia (Bentivoglio et al., 1997). Thus, the medial part of the MD plays an important role in long-term memory, whereas the lateral part of the MD plays an important role in executive functions.

Functional brain imaging studies using humans have demonstrated activation in the MD while subjects performed delayed matching-to-sample tasks and delayed non-matching-to-sample tasks (Elliott and Dolan 1999; de Zubicaray et al. 2001). Monchi et al. (2001) examined thalamic activation using fMRI while 11 subjects performed the Wisconsin card sorting test and control tasks that included the matching of two identical cards. They found an increase in activity in the MD specifically when the subjects

received negative feedback. In the Wisconsin card sorting test, negative feedback signals the subject to shift the stimulus category from that used in the preceding trial to a new one. Therefore, this result indicates that the MD is important for replacing the content of working memory with new information.

Schizophrenia patients exhibit deficits in working memory (Goldman-Rakic 1994) and postmortem studies and brain imaging studies have indicated that the MD is involved in schizophrenia (Alelú-Paz and Giménez-Amaya 2008; Byne et al. 2009). For example, postmortem studies have generally shown a significant reduction in the cell number and volume of the MD in schizophrenia patients (Pakkenberg 1990, 1992; Popken et al. 2000; Young et al. 2000; Byne et al. 2001), although some studies did not find a volume reduction of the MD (Cullen et al. 2003). Recently, two groups assessed the volume of the MD by MRI and showed that the volume of the MD in schizophrenia patients was significantly smaller than that in healthy controls (Kemether et al. 2003; Shimizu et al. 2008). The reduction in the cell number as well as the volume of the MD may contribute to the deficits in working memory observed in schizophrenia patients.

5. Activity related to working memory in the DLPFC

Neurophysiological studies have been performed in the DLPFC to understand the neural mechanisms of spatial working memory using delayed-response tasks in primates (Fuster 1973; Funahashi et al. 1989). These studies have reported tonic sustained activation during the delay period (delay-period activity). This delay-period activity exhibited several features, which support the idea that delay-period activity is the neural correlate of the mechanism for temporarily maintaining information in

working memory. First, most of the delay-period activity exhibited directional selectivity (Funahashi et al. 1989; Takeda and Funahashi 2002). Delay-period activity was observed only when the visual cues were presented within a particular area of the visual field (Funahashi et al., 1989; Rainer et al. 1998a). The characteristics of this directional selectivity of delay-period activity (e.g., preferred direction and tuning width) can be determined by constructing a tuning curve using discharge rates during the delay period across all cue directions. Both the preferred direction and tuning width of delay-period activity differ from neuron to neuron (Funahashi et al. 1989). Second, most of the delay-period activity observed in DLPFC neurons represented the direction of the visual cue (i.e., representing retrospective information), whereas some delay-period activity represented the response direction (i.e., it represented prospective information) (Niki and Watanabe 1976; Funahashi et al. 1993; Takeda and Funahashi 2002). Third, the duration of delay-period activity depended on the length of the delay period. The duration of delay-period activity was either prolonged or shortened depending on the length of the delay period (Fuster 1973; Funahashi et al. 1989). Fourth, delay-period activity was observed only during correct trials. When the subject made an error in the response period, either delay-period activity was not observed during the delay period or the magnitude of delay-period activity was significantly reduced (Fuster 1973; Funahashi et al. 1989). Fifth, delay-period activity was observed not only during the performance of spatial working memory tasks but also during the performance of non-spatial working memory tasks including delayed matching-to-sample tasks (Miller et al. 1996; Rainer et al. 1998b) and visual association tasks (Asaad et al. 1998; Rainer et al. 1999). In these tasks, delay-period activity encoded non-spatial information. Based on these characteristics of delay-period activity, this activity has been considered to be a

neural correlate of the mechanism for temporarily maintaining information in working memory processes (Goldman-Rakic 1987; Funahashi 2001; Funahashi and Takeda 2002; Fuster 2008).

6. Neural activity observed during working memory performance in the MD

6.1 Activity related to working memory in the MD

Kubota et al. (1972) recorded single-neuron activity from the MD while monkeys performed a delayed alternation bar-pressing task and found that some neurons were activated before bar-pressing behavior, while none of the neurons were active during the delay period. However, Fuster and Alexander (1971, 1973) first examined single-neuron activity in the MD while monkeys performed a manual version of the delayed-response task. They found 6 types of task-related activities, similar to those observed in the DLPFC (Fuster 1973). About half of the MD neurons exhibited sustained excitatory activity during the delay period. In addition, Alexander and Fuster (1973) examined functional interactions between the DLPFC and the MD by cooling the DLPFC. They found that most (63%) MDpc neurons were affected by cooling of the DLPFC. The magnitude of delay-period activity was attenuated in some neurons. In other neurons, the duration of this activity was truncated or excitatory delay-period activity became inhibitory with cooling. Tanibuchi and Goldman-Rakic (2003) examined single-neuron activity in the MD while monkeys performed an oculomotor version of the delayed-response task. They found neurons that exhibited spatially tuned activity during the cue, delay, and/or response periods. Neurons that exhibited spatially

tuned activity were observed mainly in the MDpc, where neurons preferentially interconnected with neurons in the DLPFC. Thus, these results indicate that neurons in the MD exhibit activity similar to that observed in the DLPFC while monkeys performed working memory tasks. Although neural activity related to working memory has been observed in the MD, the characteristics of working memory-related activity have not been compared in detail with those observed in the DLPFC. In addition, neural activity in rather limited parts of the MD, such as the MDpc and the MDmf, has been examined in previous studies (Tanibuchi and Goldman-Rakic 2003; Sommer and Wurtz 2004). Therefore, a comparison of the response characteristics of neurons throughout the MD and a comparison of the response characteristics of MD neurons and DLPFC neurons are necessary to understand the participation of the MD in working memory processes.

6.2 Characteristics of working memory-related activity in the MD

Watanabe and Funahashi (2004a) analyzed the characteristics of task-related activity recorded homogeneously within the MD while monkeys performed an oculomotor version of the delayed-response task (ODR task). In this task, a visual cue was randomly presented for 0.5 s at one of 8 pre-determined peripheral positions while the monkey maintained fixation at a central fixation target. Monkeys were required to make a memory-guided saccade to the position where the visual cue had been presented after a 3-s delay period. Among 141 neurons recorded from throughout the entire MD, 26%, 53%, and 84% exhibited cue-, delay-, and response-period activity, respectively. In the DLPFC, similar proportions of task-related activity were observed, although more

response-period activity was observed in the MD than the DLPFC (Funahashi et al. 1989; Takeda and Funahashi 2002). Most of the cue- and response-period activity was phasic excitation, while most of the delay-period activity was tonic sustained activation in the MD. This tendency was similar to that in the DLPFC (Funahashi and Takeda 2002). Among MD neurons that exhibited response-period activity, 74% showed pre-saccadic activity which started before the initiation of the saccade, while the remaining 26% showed post-saccadic activity which started at the same time as or after the initiation of the saccade. In contrast, in the DLPFC, a great majority of response-period activity (84%) was post-saccadic and relatively little of this activity was pre-saccadic (Takeda and Funahashi 2002).

Most of the task-related activity observed in the MD showed directional selectivity (Watanabe and Funahashi 2004a). We considered that task-related activity showed directional selectivity if statistically significant task-related activity was observed when the visual cue was presented at a particular area of the visual field or when monkeys made saccades toward particular directions. Based on these criteria, all cue-period activity, 76% of delay-period activity, and 64% of response-period activity showed directional selectivity. Among response-period activities, 78% of pre-saccadic activity and 26% of post-saccadic activity showed directional selectivity (Watanabe and Funahashi 2004a). The proportion of directionally selective task-related activity was basically similar between MD neurons and DLPFC neurons (Funahashi et al. 1989, 1990, 1991; Takeda and Funahashi 2002).

A statistically significant contralateral bias in the preferred direction was present in both cue-period activity and pre-saccadic activity (Watanabe and Funahashi 2004a). However, significant contralateral bias was not observed in delay-period

activity, although most of the MD neurons with delay-period activity had preferred directions toward the contralateral visual field. On the other hand, most post-saccadic activity exhibited omni-directional selectivity. Neurons with directionally selective delay-period activity or response-period activity were observed mostly in the lateral part of the MD, whereas neurons with omni-directional delay-period activity or response-period activity were frequently observed in the medial part of the MD. In the DLPFC (Funahashi et al. 1989, 1990, 1991; Takeda and Funahashi 2002), a statistically significant contralateral bias of preferred directions was observed in cue-period activity, delay-period activity, and pre-saccadic activity. However, significant contralateral bias was not observed in post-saccadic activity. Delay-period activity was observed in the orbitofrontal cortex while a monkey performed the ODR task and most of the delay-period activity showed omni-directional selectivity (Ichihara-Takeda and Funahashi 2007). Anatomical studies have shown that the lateral part of the MD interconnects with the lateral part of the PFC, while the medial part of the MD interconnects with the orbitofrontal cortex (Kievit and Kuypers 1977). The spatial distributions of directional and omni-directional delay-period activities in the MD agree with the characteristics of the anatomical relation between the MD and the PFC.

These results indicate that, while monkeys performed the ODR task, similar types of task-related activity, and in similar proportions, were observed in both the MD and the DLPFC. Especially, directional delay-period activity was observed in the MD with similar characteristics and a similar proportion as in the DLPFC. Therefore, together with the results of behavioral studies, these findings suggest that the MD participates in spatial working memory processes. However, there are some differences in the manner in which the MD and the DLPFC participate in working memory

processes. The MD seems to participate more in motor aspects compared with the DLPFC, since response-period activity was more frequently observed in the MD (84%) than in the DLPFC (56%) and because the proportion of pre-saccadic activity was higher in the MD (74%) than in the DLPFC (22%).

6.3 Information encoding by MD neural activity

Previous studies (Fuster and Alexander 1971; Kubota et al. 1972; Tanibuchi and Goldman-Rakic 2003; Watanabe and Funahashi 2004a) have shown that MD neurons exhibited directionally selective delay-period activity while monkeys performed spatial working memory tasks. However, the information that is encoded by delay-period activity in MD neurons has not been examined. To perform the ODR task correctly, monkeys must maintain either the position of the visual cue (sensory or retrospective information) or the direction of the saccade (motor or prospective information) during the delay period. In the DLPFC, Niki and Watanabe (1976), Funahashi et al. (1993), and Takeda and Funahashi (2002) examined whether delay-period activity encoded the position of the visual cue or the direction of the response. For example, Takeda and Funahashi (2002) used two types of ODR tasks to examine this issue. In an ordinary ODR task, monkeys were required to make a memory-guided saccade to the location at which a visual cue had been presented after a 3-s delay period, while in a rotatory ODR task (R-ODR task), monkeys were required to make a memory-guided saccade 90 degrees clockwise from the cue direction after a 3-s delay period. By comparing the best directions of the same task-related activity between two task conditions in the same neuron, they found that a great majority of delay-period activity

(86%) encoded the position of the visual cue, while some delay-period activity (13%) encoded the direction of the saccade. Niki and Watanabe (1976) and Funahashi et al. (1993) reported results similar to those obtained by Takeda and Funahashi (2002). These results indicate that, although the DLPFC participates in working memory processes, DLPFC neurons mainly maintain sensory or retrospective information during the delay period.

Watanabe and Funahashi (2004b) used the same two types of ODR tasks as Takeda and Funahashi (2002) and examined the information that was encoded by MD activity during the delay period. By comparing the best directions of the same task-related activity between two task conditions in the same neuron, they found that 56% of delay-period activity encoded the position of the visual cue, while 41% encoded the direction of the saccade. Thus, more delay-period activity encoded the direction of the saccade in MD neurons compared with the activity in DLPFC neurons, indicating that more MD neurons participate in prospective information processing than DLPFC neurons. All cue-period activities encoded the position of the visual cue and most of the response-period activity encoded the direction of the saccade in the MD, suggesting that the MD participates in the transformation of sensory-to-motor information. A greater proportion of delay- and response-period activities encoded the direction of the saccade in the MD compared with the DLPFC. Therefore, the MD participates more in motor aspects of information processing in working memory processes compared with the DLPFC, and could provide impending motor information (prospective information) to the DLPFC.

6.4 Contribution of the MD to information processing

6.4.1 Population vector analysis in the DLPFC

Takeda and Funahashi (2002) showed that most delay-period activity in the DLPFC encoded the position of the visual cue (retrospective information), although a small proportion of delay-period activity encoded the direction of the saccade (prospective information). In addition, they showed that most response-period activity encoded the direction of the saccade. Based on these results, they hypothesized that the transformation of sensory-to-motor information (construction of impending motor information based on retrospective sensory information) occurs during the delay period in the DLPFC. To test this hypothesis, Takeda and Funahashi (2004) used a population vector analysis to examine how the information represented by a population of DLPFC activities altered during the progress of ODR and R-ODR trials.

The population vector analysis was originally proposed and advanced by Georgopoulos and his group (Georgopoulos et al. 1983, 1986, 1988, 1989, 1993; Georgopoulos 1988; Kettner et al. 1988; Schwartz et al. 1988; Lurito et al. 1991; Smyrnis et al. 1992). Georgopoulos and his group showed that population vectors calculated from a population of motor cortical activities can predict the direction of ~~the~~ hand-reaching movement (Georgopoulos et al. 1983, 1986, 1988; Kettner et al. 1988; Schwartz et al. 1988). In the population vector analysis, first, a 'cell vector' is calculated for every neuron under a particular direction of hand-reaching movement. The length of the cell vector corresponds to the neuron's discharge rate during the movement toward a particular direction and the direction of the cell vector corresponds to the neuron's preferred direction. A population vector is then calculated from the

weighted sum of cell vectors of all neurons under a particular direction of movement.

Using the population vector analysis, Takeda and Funahashi (2004) showed that the transformation of sensory-to-motor information occurred during the delay period in the DLPFC (Fig. 1). While monkeys performed the R-ODR task, in which the direction of the saccade in the response period was 90 degrees clockwise from the direction of the visual cue, the direction of the population vector was initially directed toward the direction of the visual cue. However, the direction of the population vector gradually rotated toward the direction of the saccade during the later half of the delay period and was eventually directed toward the direction of the saccade. Thus, Takeda and Funahashi (2004) visualized information processes that occurred in the DLPFC during the delay period using a population vector analysis.

6.4.2 Population vector analysis in the MD

Similar to DLPFC neurons, many MD neurons exhibit directional selectivity in task-related activity during ODR task performance. Therefore, a population vector analysis was applied to MD activities to examine information processes that occur in the MD while monkeys perform spatial working memory tasks (ODR and R-ODR tasks). Watanabe et al. (2009) calculated population vectors using a population of MD activities recorded during the ODR task and the R-ODR task. Initially, they examined the directions of the population vectors calculated using a population of cue-period activity and a population of response-period activity to confirm that the directions of the population vectors corresponded to the directions of the visual cue and the saccade, respectively. After they confirmed that calculated population vectors correctly

represented information regarding the directions of the visual cue and the saccade, they calculated population vectors of MD activities during a 250-ms window which slid a 50 ms step from the onset of the visual cue until 500 ms after the initiation of the response period (Fig. 1). In the ODR task, directions of population vectors were maintained mostly toward the direction of the visual cue throughout the entire delay period, since the direction of the visual cue was the same as the direction of the saccade in the ODR task. In the R-ODR task, the direction of the population vector was initially directed toward the direction of the visual cue. However, the direction of the population vector began to rotate toward the direction of the saccade in the early phase of the delay period and gradually pointed toward the direction of the saccade as the trial progressed. These results indicate that the transformation from visual information to saccade information occurs during the delay period in the MD. In addition, compared with the population vector analysis in the DLPFC (Takeda and Funahashi 2004), the rotation of the population vector started earlier in the MD than in the DLPFC. More delay-period activity encoded the direction of the saccade and more response-period activity exhibited pre-saccadic activity in the MD compared with the DLPFC. In addition, the MD has strong anatomical connections with the PFC. Therefore, these results indicate that the MD is the major area that provides information regarding impending behavioral information to the DLPFC.

Sommer and Wurtz (2004) examined neural signals conveyed through an ascending pathway from the superior colliculus (SC) to the frontal eye field (FEF) via the MD. They used antidromic and orthodromic responses generated by electrical stimulation of the FEF to identify relay neurons in the MD. They examined the nature of the information that was transferred from the SC to the FEF while monkeys

performed delayed-saccade tasks. They found that the SC sent visual as well as saccade signals to the FEF via the MD and that pre-saccadic activity was prominent in the MD. Based on these results, they hypothesized that a major signal conveyed by the ascending pathway to the FEF is the corollary discharge representing information regarding the direction and ~~the~~ amplitude of an impending saccade (Sommer and Wurtz 2002, 2004).

Thus, most MD neurons with delay-period activity encoded impending saccade information. A population vector analysis revealed that impending saccade information was generated during the earlier phase of the delay period in the MD, while the same information was generated during the later phase of the delay period in the DLPFC. More pre-saccadic activity was observed in the MD than in the DLPFC. In addition, the MD received corollary discharge representing information regarding the direction and amplitude of an impending saccade from the SC and sent this signal to the PFC. These results indicate that the MD is the brain structure that provides information regarding forthcoming saccade information (or prospective motor information) to the DLPFC. Although it is not fully understood how prospective motor information is generated, or which brain structure participates in this process, retrospective sensory information that is maintained during the delay period in the DLPFC could play an important role in generating prospective motor information, and cortical and subcortical structures that receive signals from the DLPFC could play an essential role.

7. Model of working memory processes

Funahashi (2006) proposed a model based on neural activities observed in the DLPFC. He proposed 4 components: a *selection process*, a *temporary information-*

storage process, an *output process*, and *modulatory inputs*. To achieve a specific goal, the subject is required to acquire necessary information from a variety of information. Therefore, the working memory system needs a neural component to select specific information to achieve the goal (*selection process*). Working memory is a mechanism for the temporary active maintenance of information. Therefore, this system needs a *temporary information-storage process* to actively maintain selected information. Delay-period activity observed in both the DLPFC and the MD is a neural correlate of this temporary information-storage process. However, the information maintained in the temporary information storage component needs to be sent to the brain areas where this information is utilized. Therefore, this system requires an *output process* to send maintained information to other brain areas. Since most of the neurons that exhibit delay-period activity are considered to be pyramidal neurons in the DLPFC (Constantinidis et al. 2001), these neurons also participate in the output process. In addition, information maintained in temporary information-storage should be deleted, replaced or updated depending on the change in the task requirements as the trial progresses. The *modulatory inputs* are signals from motor centers (Sommer and Wurtz 2004) or emotional or motivational centers (Barbas 1992) that play a role in deleting, replacing or updating the information stored in temporary storage.

In this model, we hypothesized that temporarily maintained information is processed by interaction among temporary information-storage processes. Excitatory as well as inhibitory interactions have been observed among task-related neurons in the DLPFC (Funahashi and Inoue 2000; Constantinidis et al. 2001). Dynamic and flexible interactions among neurons have been observed in the DLPFC (Vaadia et al. 1995; Funahashi 2001). Therefore, we hypothesized that dynamic and flexible interactions

among processes and modulatory signals play an essential role in information processing. To understand information flow during spatial working memory performance in the DLPFC and how each task-related DLPFC neuron contributes to this process, Takeda and Funahashi (2007) first determined which task-related activity each DLPFC neuron exhibited and what information (*cue direction* or *saccade direction*) each task-related activity represented, and then compared preferred directions of task-related activities for each neuron. In DLPFC neurons with both cue- and delay-period activities, the preferred directions of both activities were always similar. Since all cue-period activities represented visual information, this result indicates that the directional selectivity of delay-period activity is affected by the directional selectivity of cue-period activity. Therefore, in neurons with both cue- and delay-period activities, both activities represent visual information. Similarly, in DLPFC neurons with both delay- and response-period activities, the preferred directions of both activities were also similar, indicating that both activities represented motor information in these neurons.

As we mentioned before, all neurons with only cue-period activity represent visual information and most neurons with only response-period activity represent motor information in the DLPFC. Therefore, based on these observations, an outline of the possible information flow during spatial working memory performance in the DLPFC is shown in Fig. 2. Visual inputs first activate DLPFC neurons that only have cue-period activity (C*cue*). This activation is transferred to DLPFC neurons that have both cue- and delay-period activity (C*cue*D*cue*) and then to DLPFC neurons that have only delay-period activity (D*cue*). Since all of these DLPFC neurons receive visual inputs, both cue- and delay-period activities represent visual information. However, during the delay period, prospective motor information is generated and this information is maintained in

DLPFC neurons that only have delay-period activity (D*resp*). This information is transferred to DLPFC neurons with both delay- and response-period activities (D*resp*R*resp*) and then to DLPFC neurons with only response-period activity (R*resp*). A comparison of the directional selectivity of delay-period activity between the ODR and R-ODR tasks revealed that delay-period activity encoded either visual information or saccade information in the DLPFC. No delay-period activity encoded both visual and saccade information simultaneously. Therefore, prospective motor information is necessary to generate delay-period activity that encodes saccade information in the DLPFC. In this sense, the MD can be considered a possible candidate of brain structures that provide information regarding prospective motor information to the DLPFC. The characteristics of the activities of MD neurons support this idea.

8. General Conclusions

Working memory is a dynamic neural system that includes mechanisms for the temporary active maintenance of information as well as for processing information. The DLPFC is an important brain structure for working memory. However, the MD also plays an important role in working memory itself as well as in supporting working memory functions that occur in the DLPFC. Neurophysiological studies have revealed that same task-related activities were observed in both the MD and the DLPFC while monkeys performed spatial working memory tasks. However, more neurons exhibited response-period activity in the MD and more response-period activity was pre-saccadic in the MD. More neurons with delay-period activity encoded prospective motor information in the MD while few neurons with delay-period activity encoded motor

information in the DLPFC. Furthermore, a population vector analysis revealed that the rotation of population vectors started earlier in the MD than in the DLPFC. These results indicate that the MD participates more in motor aspects of information processing than the DLPFC. An analysis of information flow during spatial working memory performance in the DLPFC revealed that prospective motor information must be generated somewhere in the brain and that this information could be provided to the DLPFC to generate delay-period activity encoding saccade information. An analysis of MD neuron activity shows that the MD is an important brain structure that provides information regarding prospective motor information to the DLPFC. Further studies are needed to identify which brain area generates prospective motor information, how this information is generated in that brain area, and how retrospective sensory information contributes to this process.

Acknowledgment

This work was supported by Grant-in-Aid for Scientific Research from the Japanese Ministry of Education, Science, Sports, Culture, and Technology (MEXT) (18020016, and 21240024 to S.F. and 18730481 to Y.W.). This work was also supported by JSPS Postdoctoral Fellowships for Research Abroad to Y.W.

References

Aggleton, J.P. and Mishkin, M. (1983a) Memory impairments following restricted medial thalamic lesions in monkeys. Exp. Brain Res., 52: 199-209.

Aggleton, J.P. and Mishkin, M. (1983b) Visual recognition impairment following medial thalamic lesions in monkeys. Neuropsychologia, 21: 189-197.

Alelú-Paz, R. and Giménez-Amaya, J.M. (2008) The mediodorsal thalamic nucleus and schizophrenia. J. Psychiatry Neurosci., 33: 489-498.

Alexander, G.E. and Fuster, J.M. (1973) Effects of cooling prefrontal cortex on cell firing in the nucleus medialis dorsalis. Brain Res., 61: 93-105.

Asaad, W.F., Rainer, G., and Miller, E.K. (1998) Neural activity in the primate prefrontal cortex during associative learning. Neuron, 21: 1399-1407.

Baddeley, A. (2000) The episodic buffer: a new component of working memory? Trends Cogn. Sci., 4: 417-423.

Baddeley, A.D. and Hitch, G.J.L. (1974) Working Memory, In Bower, G.A. (ed.) The Psychology of Learning and Motivation: Advances in Research and Theory. Vol. 8 Academic Press, New York; p. 47-89.

Baddeley, A. and Logie, R.H. (1999) Working memory: the multiple-component model. In: Miyake, A. and Shah, P. (eds.), Models of Working Memory: Mechanisms of Active Maintenance and Executive Control, Cambridge University Press, Cambridge; p. 28–61.

Barbas, H. (1992) Architecture and cortical connections of the prefrontal cortex in the rhesus monkey. In Advances in Neurology, Vol. 57, (P. Chauvel and A.V. Delgado-Escueta, eds.), Raven Press, New York, p. 91-115.

Barbas, H., Henion, T.H.H., and Dermon, C.R. (1991) Diverse thalamic projections to the prefrontal cortex in the rhesus monkey. J. Comp. Neurol., 313: 65-94.

Bentivoglio, M., Aggleton, J.P., and Mishkin, M. (1997) The thalamus and memory formation. In: Striade, M., Jones, E.G., and McCormic, D.A. (eds.) Thalamus, Vol.2 Elsevier: Amsterdam; p. 689-720.

Byne, W., Buchsbaum, M.S., Kemether, E., Hazlett, E.A., Shinwari, A., Mitropoulou, V., and Siever, L.J. (2001) Magnetic resonance imaging of the thalamic mediodorsal nucleus and pulvinar in schizophrenia and schizotypal personality disorder. Arch. Gen. Psychiatry, 58: 133-140.

Byne, W., Hazlett, E.A., Buchsbaum, M.S., and Kemether, E. (2009) The thalamus and schizophrenia: current status of research. Acta Neuropathol., 117: 347-368.

Chafee, M.V. and Goldman-Rakic, P.S. (1998) Matching patterns of activity in primate prefrontal area 8a and parietal area 7ip neurons during a spatial working memory task. J. Neurophysiol., 79: 2919-2940.

Constantinidis, C., Franowicz, M.N., and Goldman-Rakic, P.S. (2001) Coding specificity in cortical microcircuits: a multiple-electrode analysis of primate prefrontal cortex. J. Neurosci., 21: 3646-3655.

Cullen, T.J., Walker, M.A., Parkinson, N., Craven, R., Crow, T.J., Esiri, M.M. and Harrion, P.J. (2003) A postmortem study of the mediodorsal nucleus of the thalamus in schizophrenia. Schizophr. Res., 60: 157-166.

Daum, I. and Ackermann, H. (1994) Frontal-type memory impairment associated with thalamic damage. Int. J. Neurosci., 77: 187–198.

Elliott, R. and Dolan, R.J. (1999) Differential neural responses during performance of matching and nonmatching to sample tasks at two delay intervals. J. Neurosci., 19:

5066-5073.

Funahashi, S. (2001) Neuronal mechanisms of executive control by the prefrontal cortex. Neurosci. Res., 39: 147-165.

Funahashi, S. (2006) Prefrontal cortex and working memory processes. Neuroscience, 139: 251-261.

Funahashi, S. and Inoue, M. (2000) Neuronal interactions related to working memory processes in the primate prefrontal cortex revealed by cross-correlation analysis. Cereb. Cortex, 10: 535-51.

Funahashi, S., Bruce, C.J., and Goldman-Rakic, P.S. (1989) Mnemonic coding of visual space in the monkey's dorsolateral prefrontal cortex. J. Neurophysiol., 61: 331-349.

Funahashi, S., Bruce, C.J., and Goldman-Rakic, P.S. (1990) Visuospatial coding in primate prefrontal neurons revealed by oculomotor paradigms. J. Neurophysiol., 63: 814-831.

Funahashi, S., Bruce, C.J., and Goldman-Rakic, P.S. (1991) Neuronal activity related to saccadic eye movements in the monkey's dorsolateral prefrontal cortex. J. Neurophysiol., 65: 1464-1483.

Funahashi, S., Chafee, M.V., and Goldman-Rakic, P.S. (1993) Prefrontal neuronal activity in rhesus monkeys performing a delayed anti-saccade task. Nature, 365: 753-756.

Funahashi, S. and Kubota, K. (1994) Working memory and prefrontal cortex. Neurosci. Res., 21: 1-11.

Funahashi, S. and Takeda, K. (2002) Information processes in the primate prefrontal cortex in relation to working memory processes. Rev. Neurosci., 13: 313-345.

Fuster, J.M. (1973) Unit activity in prefrontal cortex during delayed-response

performance: neuronal correlates of transient memory. J. Neurophysiol., 36: 61-78.

Fuster, J.M. (2008) The Prefrontal Cortex, Fourth Edition. Academic Press, New York.

Fuster, J.M. and Alexander, G.E. (1971) Neuron activity related to short-term memory. Science, 173: 652-654.

Fuster, J.M. and Alexander, G.E. (1973) Firing changes in cells of the nucleus medialis dorsalis associated with delayed response behavior. Brain Res., 61: 79-91.

Fuster, J.M., Bauer, R.H., and Jervey, J.P. (1985) Functional interactions between inferotemporal and prefrontal cortex in a cognitive task. Brain Res., 330: 299-307.

Fuster, J.M. and Jervey, J.P. (1982) Neuronal firing in the inferotemporal cortex of the monkey in a visual memory task. J. Neurosci., 2: 361-375.

Gaffan, D. and Parker, A. (2000) Mediodorsal thalamic function in scene memory in rhesus monkeys. Brain, 123: 816-827.

Georgopoulos, A.P. (1988) Neural integration of movement: role of motor cortex in reaching. FASEB J., 2: 2849–2857.

Georgopoulos, A.P., Caminiti, R., Kalaska, J.F., and Massey, J.T. (1983) Spatial coding of movement: a hypothesis concerning the coding of movement direction by motor cortical populations. Exp. Brain Res., 7: 327–336.

Georgopoulos, A.P., Kettner, R.E., and Schwartz, A.B. (1988) Primate motor cortex and free arm movements to visual targets in three-dimensional space. II. Coding of the direction of movement by a neuronal population. J. Neurosci., 8: 2928–2937.

Georgopoulos, A.P., Lurito, J.T., Petrides, M., Schwartz, A.B., and Massey, J.T. (1989) Mental rotation of the neuronal population vector. Science, 243: 234–237.

Georgopoulos, A.P., Schwartz, A.B., and Kettner, R.E. (1986) Neuronal population coding of movement direction. Science, 233: 1416–1419.

Georgopoulos, A.P., Taira, M., and Lukashin, A. (1993) Cognitive neurophysiology of the motor cortex. Science, 260: 47–52.

Giguere, M. and Goldman-Rakic, P.S. (1988) Mediodorsal nucleus: areal, laminar, and tangential distribution of afferents and efferents in the frontal lobe of rhesus monkeys. J. Comp. Neurol., 277: 195-213.

Gnadt, J.W. and Andersen, R.A. (1988) Memory related motor planning activity in posterior parietal cortex of macaque. Exp. Brain Res., 70: 216-220.

Goldman-Rakic, P.S. (1987) Circuitry of primate prefrontal cortex and regulation of behavior by representational memory. In: Handbook of Physiology: The Nervous System: Higher Functions of the Brain, (F. Plum, ed.), Vol. 5, Sect. 1, American Physiological Society, Bethesda, MD; p. 373-417.

Goldman-Rakic, P.S. (1994) Working memory dysfunction in schizophrenia. J. Neuropsychiatr. Clin. Neurosci., 6: 348-357.

Goldman-Rakic, P.S. and Porrino, L.J. (1985) The primate mediodorsal (MD) nucleus and its projection to the frontal lobe. J. Comp. Neurol., 242: 535-560.

Hikosaka, O. and Sakamoto, M. (1986) Cell activity in monkey caudate nucleus preceding saccadic eye movements. Exp. Brain Res., 63: 659-662.

Hikosaka, O., Sakamoto, M., and Usui, S. (1989) Functional properties of monkey caudate neurons. I. Activities related to saccadic eye movements. J. Neurophysiol., 61: 780-798.

Ichihara-Takeda, S. and Funahashi, S. (2007) Activity of primate orbitofrontal and dorsolateral prefrontal neurons: task-related activity during an oculomotor delayed-response task. Exp. Brain Res., 181: 409-425.

Ilinsky, I.A., Jouandet, M.L., and Goldman-Rakic, P.S. (1985) Organization of the

nigrothalamocortical system in the rhesus monkey. J. Comp. Neurol., 236: 315-330.

Isseroff, A., Rosvold, H.E., Galkin, T.W., and Goldman-Rakic, P.S. (1982) Spatial memory impairments following damage to the mediodorsal nucleus of the thalamus in rhesus monkeys. Brain Res. 232: 97-113.

Kemether, E.M., Buchsbaum, M.S., Byne, W., Hazlett, E.A., Haznedar, M., Brickman, A.M., Platholi, J., and Bloom, R. (2003) Magnetic resonance imaging of mediodorsal, pulvinar, and centromedian nuclei of the thalamus in patients with schizophrenia. Arch. Gen. Psychiatry, 60: 983-991.

Kettner, R.E., Schwartz, A.B., and Georgopoulos, A.P. (1988) Primate motor cortex and free arm movements to visual targets in three-dimensional space. III. Positional gradients and population coding of movement direction from various movement origins. J. Neurosci., 8: 2938–2947.

Kievit, J. and Kuypers, H.G.J.M. (1977) Organization of the thalamo-cortical connexions to the frontal lobe in the rhesus monkey. Exp. Brain Res., 29: 299-322.

Kubota K., Niki H., and Goto A. (1972) Thalamic unit activity and delayed alternation performance in the monkey. Acta Neurobiol. Exp., 32: 177-192.

Lurito, J.T., Georgakopoulos, T., and Georgopoulos, A.P. (1991) Cognitive spatial-motor processes. 7. The making of movements at an angle from a stimulus direction: studies of motor cortical activity at the single cell and population levels. Exp. Brain Res., 87: 562–580.

Lynch, J.C., Hoover, J.E., and Strick, P.L. (1994) Input to the frontal eye field from the substantia nigra, superior colliculus, and dentate nucleus demonstrated by transneuronal transport. Exp. Brain Res., 100: 181-186.

Miller, E.K., Erickson, C.A., and Desimone, R. (1996) Neural mechanisms of visual

working memory in prefrontal cortex of the macaque. J. Neurosci., 16: 5154-5167.

Miller, E.K., Li, L., and Desimone, R. (1991) A neural mechanism for working and recognition memory in inferior temporal cortex. Science, 254: 1377-1379.

Miller, E.K., Li, L., and Desimone, R. (1993) Activity of neurons in anterior inferior temporal cortex during a short-term memory task. J. Neurosci., 13: 1460-1478.

Mitchell, A.S., Baxter, M.G., and Gaffan, D. (2007) Dissociable performance on scene learning and strategy implementation after lesions to magnocellular mediodorsal thalamic nucleus. J. Neursci., 27: 11888-11895.

Mitchell, A.S., Browning, P.G.F., Wilson, C.R.E., Baxter, M.G., and Gaffan, D. (2008) Dissociable roles for cortical and subcortical structures in memory retrieval and acquisition. J. Neurosci., 28: 8387-8396.

Mitchell, A.S. and Gaffan, D. (2008) The magnocellular mediodorsal thalamus is necessary for memory acquisition, but not retrieval. J. Neurosci., 28: 258-263.

Miyake, A. and Shah, P. (1999) Toward unified theories of working memory: emerging general consensus, unresolved theoretical issues, and future research directions. In: Models of Working Memory: Mechanisms of Active Maintenance and Executive Control. (A. Miyake and P. Shah, eds.), Cambridge University Press, UK, p. 442-481.

Monchi, O., Petrides, M., Petre, V., Worsley, K., and Dagher, A. (2001) Wisconsin card sorting revisited: distinct neural circuits participating in different stages of the task identified by event-related functional magnetic resonance imaging. J. Neurosci., 21: 7733-7741.

Niki, H. and Watanabe, M. (1976) Prefrontal unit activity and delayed response: relation to cue location versus direction of response. Brain Res., 105: 79-88.

Owen, A.M., McMillan, K.M., Laird, A.R., and Bullmore, E. (2005) N-back working memory paradigm: a meta-analysis of normative functional neuroimaging studies. Human Brain Mapping, 25: 46-59.

Pakkenberg, B. (1990) Pronounced reduction of total neuron number in mediodorsal thalamic nucleus and nucleus accumbens in schizophrenics. Arch. Gen. Psychiatry, 47: 1023-1028.

Pakkenberg, B. (1992) The volume of the mediodorsal thalamic nucleus in treated and untreated schizophrenics. Schizophrenia Res., 7: 95-100.

Parker, A., Eacott, M.J., and Gaffan, D. (1997) The recognition memory deficit caused by mediodorsal thalamic lesion in non-human primates: a comparison with rhinal cortex lesion. Eur. J. Neurosci., 9: 2423-2431.

Petrides, M. (1994) Frontal lobes and working memory: evidence from investigations of the effects of cortical excisions in nonhuman primates. In: Handbook of Neuropsychology, Vol. 9, (F. Boller and J. Grafman, eds.), Elsevier, Amsterdam, p. 59-82.

Popken, G.J., Bunney, W.E., Potkin, S.G., and Jones, E.G. (2000) Subnucleus-specific loss of neurons in medial thalamus of schizophrenics. Proc. Natl. Acad. Sci. USA, 97: 9276-9280.

Porrino, L.J., Crane, A.M., and Goldman-Rakic, P.S. (1981) Direct and indirect pathways from the amygdala to the frontal lobe in rhesus monkeys. 198: 121-136.

Rainer, G., Asaad, W.F., and Miller, E.K. (1998a) Memory fields of neurons in the primate prefrontal cortex. Proc. Natl. Acad. Sci. USA, 95: 15008-15013.

Rainer, G., Asaad, W.F., and Miller, E.K. (1998b) Selective representation of relevant information by neurons in the primate prefrontal cortex. Nature, 393: 577-579.

Rainer, G., Rao, S.C., and Miller, E.K. (1999) Prospective coding for objects in primate prefrontal cortex. J. Neurosci., 19: 5493-5505.

Ray, J.P. and Price, J.L. (1993) The organization of projections from the mediodorsal nucleus of the thalamus to orbital and medial prefrontal cortex in macaque monkeys. J. Comp. Neurol., 337: 1-31.

Schlag, J. and Schlag-Rey, M. (1984) Visuomotor functions of central thalamus in monkey. II. Unit activity related to visual events, targeting, and fixation. J. Neurophysiol., 51: 1175-1195.

Schlag-Rey, M. and Schlag, J. (1984) Visuomotor functions of central thalamus in monkey. I. Unit activity related to spontaneous eye movements. J. Neurophysiol., 51: 1149-1174.

Schwartz, A.B., Kettner, R.E., and Georgopoulos, A.P. (1988) Primate motor cortex and free arm movements to visual targets in three-dimensional space. I. Relations between single cell discharge and direction of movement. J. Neurosci., 8: 2913–2927.

Sherman, S.M. and Guillery, R.W. (2002) The role of the thalamus in the flow of information to the cortex. Phil. Trans. R. Soc. Lond. B, 357: 1695-1708.

Shimizu, M., Fujiwara, H., Hirao, K., Namiki, C., Fukuyama, H., Hayashi, T., and Murai, T. (2008) Structural abnormalities of the adhesio interthalamica and mediodorsal nuclei of the thalamus in schizophrenia. Schizophr. Res., 101: 331-338.

Smyrnis, N., Taira, M., Ashe, J., and Georgopoulos, A.P. (1992) Motor cortical activity in a memorized delay task. Exp. Brain Res., 92: 139–151.

Sommer, M.A. and Wurtz, R.H. (2002) A pathway in primate brain for internal monitoring of movements. Science, 296: 1480-1482.

Sommer, M.A. and Wurtz, R.H. (2004) What the brain stem tells the frontal cortex. I. Oculomotor signals sent from superior colliculus to frontal eye field via mediodorsal thalamus. J. Neurophysiol., 91: 1381-1402.

Stuss, D.T. and Levine, B. (2002) Adult clinical neuropsychology: lessons from studies of the frontal lobes. Annu. Rev. Psychol., 53: 401-433.

Stuss, R.T., Alexander, M.P., Floden, D., Binns, M.A., Levine, B., McIntosh, A.R., Rajah, N., and Hevenor, S.J. (2002) Fractionation and localization of distinct frontal lobe processes: evidence from focal lesions in humans. In Principles of Frontal Lobe Function, (D.T. Stuss and R.T. Knight, eds.), Oxford University Press, New York, p. 392-407.

Takeda, K. and Funahashi, S. (2002) Prefrontal task-related activity representing visual cue location or saccade direction in spatial working memory tasks. J. Neurophysiol., 87: 567-588.

Takeda, K. and Funahashi, S. (2004) Population vector analysis of primate prefrontal activity during spatial working memory. Cereb. Cortex, 14: 1328-1339.

Takeda, K. and Funahashi, S. (2007) Relationship between prefrontal task-related activity and information flow during spatial working memory performance. Cortex, 43: 38-52.

Tanaka, M. (2007) Spatiotemporal properties of eye position signals in the primate central thalamus. Cereb. Cortex, 17: 1504-1515.

Tanibuchi, I. and Goldman-Rakic, P.S. (2003) Dissociation of spatial-, object-, and sound-coding neurons in the mediodorsal nucleus of the primate thalamus. J. Neurophysiol., 89: 1067-1077.

Tanibuchi, I., Kitano, H., and Jinnai, K. (2009) Substantia nigra output to prefrontal

cortex via thalamus in monkeys. I. Electrophysiological identification of thalamic relay neurons. J. Neurophysiol., 102: 2933-2945.

Vaadia, E., Haalman, I., Abeles, M., Bergman, H., Prut, Y., Slovin, H., and Aertsen, A. (1995) Dynamics of neuronal interactions in monkey cortex in relation to behavioural events. Nature, 373: 515-518.

Van der Werf, Y.D., Scheltens, P., Lindeboom, J., Witter, M.P., Uylings, H.B.M., and Jolles, J. (2003) Deficits of memory, executive functioning and attention following infarction in the thalamus; a study of 22 cases with localised lesions. Neuropsychologia, 41: 1330-44.

Van der Werf, Y.D., Witter, M.P., Uylings, H.B.M., and Jolles, J. (2000) Neuropsychology of infarctions in the thalamus: a review. Neuropsychologia, 38: 613-627.

Velayos, J.L. and Reinoso-Suarez, F. (1985) Prosencephalic afferents to the mediodorsal thalamic nucleus. J. Comp. Neurol., 242: 161-181.

Watanabe, Y. and Funahashi, S. (2004a) Neuronal activity throughout the primate mediodorsal nucleus of the thalamus during oculomotor delayed-responses. I. Cue-, delay-, and response-period activity. J. Neurophysiol., 92: 1738-1755.

Watanabe, Y. and Funahashi, S. (2004b) Neuronal activity throughout the primate mediodorsal nucleus of the thalamus during oculomotor delayed-responses. II. Activity encoding visual versus motor signal. J. Neurophysiol., 92: 1756-1769.

Watanabe, Y., Takeda, K., and Funahashi, S. (2009) Population vector analysis of primate mediodorsal thalamic activity during oculomotor delayed-response performance. Cereb. Cortex, 19: 1313-1321.

Young, K.A., Manaye, K.F., Liang, C.-L., Hicks, P.B., and German, D.C. (2000)

Reduced number of mediodorsal and anterior thalamic neurons in schizophrenia. Biol. Psychiatry, 47: 944-953.

Zola-Morgan, S. and Squire, L.R. (1985) Amnesia in monkeys after lesions of the mediodorsal nucleus of the thalamus. Ann. Neurol., 17: 558-564.

Zoppelt, D., Koch, B., Schwarz, M., and Daum, I. (2003) Involvement of the mediodorsal thalamic nucleus in mediating recollection and familiarity. Neuropsychologia, 41: 1160-1170.

de Zubicaray, G.I., McMahon, K., Wilson, S.J., and Muthiah, S. (2001) Brain activity during the encoding, retention, and retrieval of stimulus representations. Learn. Mem., 8: 243-251.

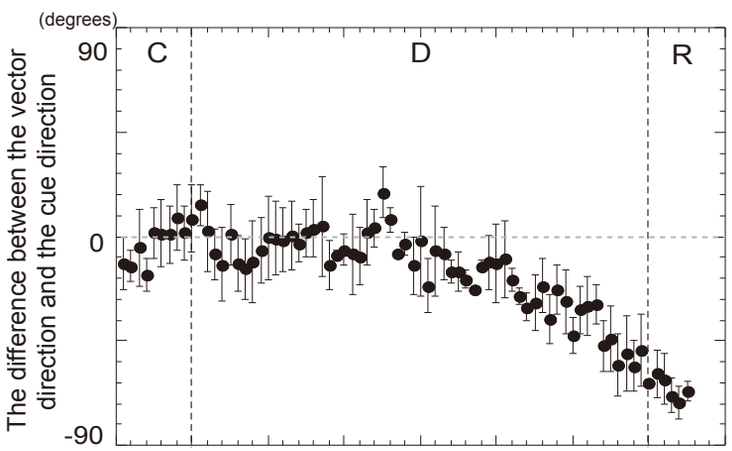
Figure legends

Figure 1: Temporal changes in the differences between the directions of population vectors and the direction of the visual cue in the R-ODR task. Each point represents the mean and standard error. The upper figure is based on DLPFC activity and is modified from Takeda and Funahashi (2004). The bottom figure is based on MD activity and is modified from Watanabe et al. (2009).

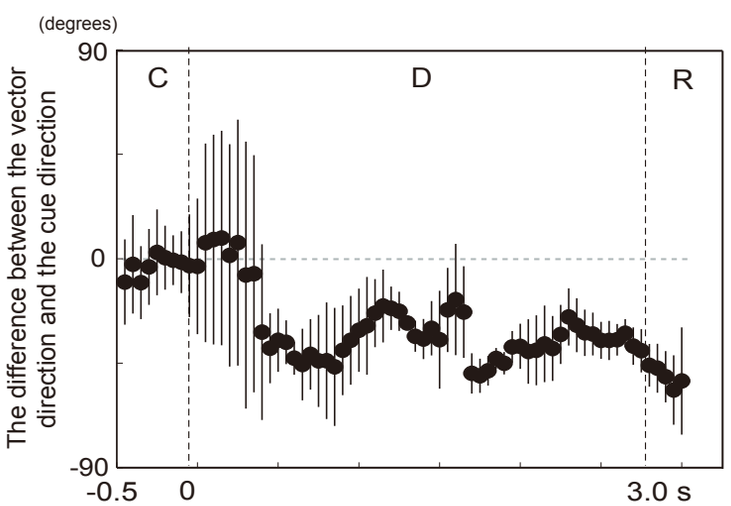
Figure 2: Left, schematic drawings of temporal profiles of activity for six groups (D*cue*, D*sac*, CD*cue*, D*cue*R*cue*, D*sac*R*sac*, and CD*cue*R*cue*) of DLPFC neurons. Right, schematic drawing of information flow during delayed-response performance based on the characteristics of activities in the DLPFC and MD.

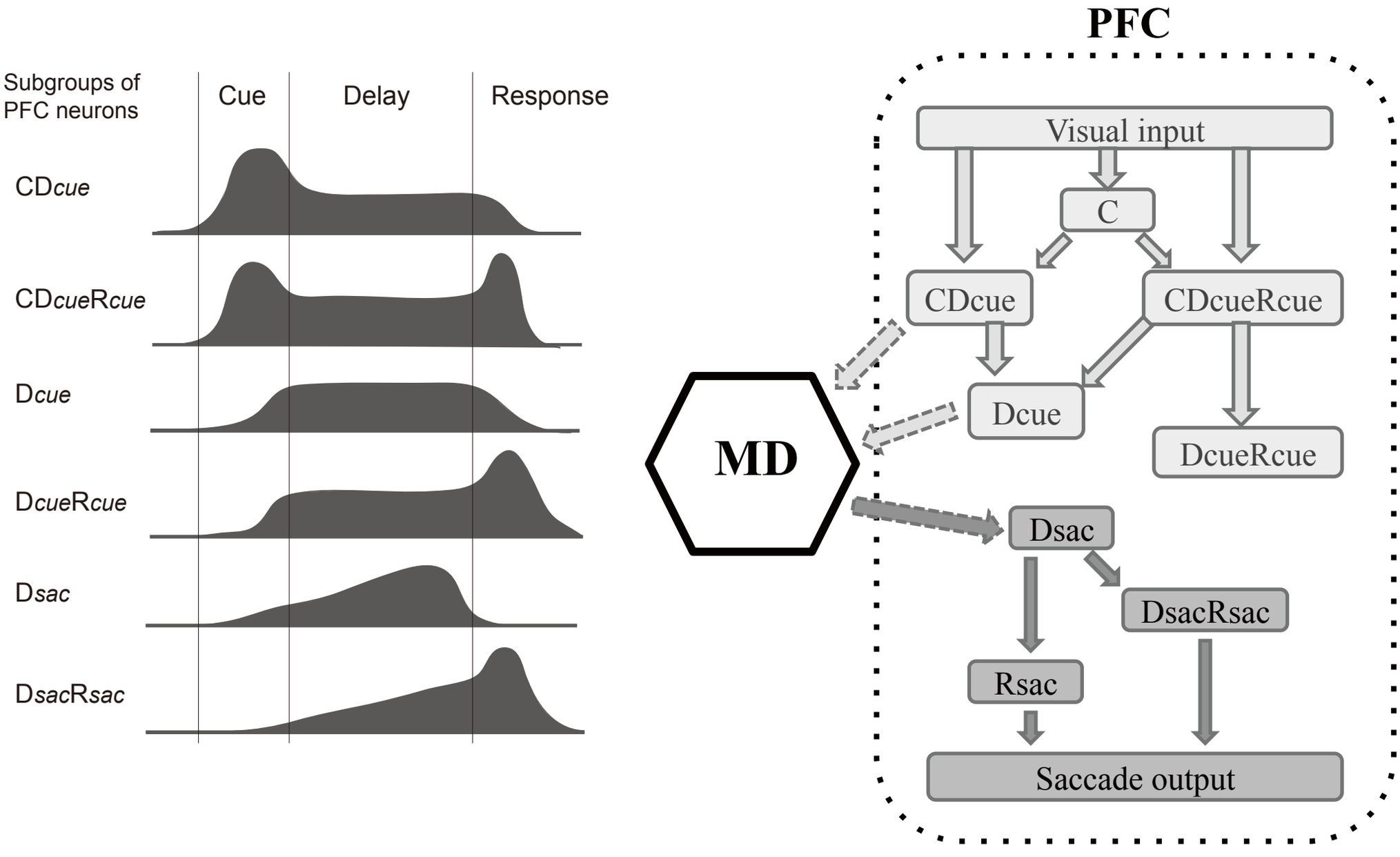
Population vector analysis during R-ODR performance

DLPFC neurons



MD neurons




Subgroups of
PFC neurons
Cue
Delay
Response
CDcue
CDcueRcue
Dcue
DcueRcue
Dsac
DsacRsac
MD
PFC
Visual input
C
CDcue
CDcueRcue
Dcue
DcueRcue
Dsac
DsacRsac
Rsac
Saccade output