# Chapter 6 Optical Imaging of Short–Term Working Memory in Prefrontal Cortex of the Macaque Monkey

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**Abstract** Prefrontal cortex is an area critical for cognitive functions such as planning, decision-making, and reasoning. Working memory is a key aspect to the execution of these functions and has been strongly associated with prefrontal function. This chapter reviews the functional organization of a prefrontal area, area 46, that has been associated with working memory in monkeys. Anatomical and optical imaging studies indicate the presence of a clustered organization within area 46, similar in nature to clustered organizations found in sensory cortical areas. Although the relationship of these clusters to working memory function is unknown, optical imaging studies suggest a spatial organization for mnemonic function. This 'spatial memory map' is topographically consistent with electrophysiologically established maps for visual and eye movement response. Interestingly, in trials in which response suppression is required, optical imaging reveals a possible suppressive signal; lack of this signal may underly the perseveration seen in diseases such as schizophrenia. In sum, I suggest that clustered organization in prefrontal cortex provides a scaffold upon which visual, mnemonic, and motor response are organized.

### 6.1 Introduction

Since a number of cognitive functions such as planning, decision-making, and reasoning require working memory, understanding the neural basis of cognitive function centers on the organization and encoding of working memory. Disruption of such processes has been associated with cognitive dysfunction (such as dissociation and perseveration) characteristic of mental diseases such as schizophrenia. Thus, understanding the neural basis underlying the working memory is important for a broad range of cognitive functions and for the development of clinical therapies that may lead to treatment of prefrontal dysfunctions.

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## 6.2 Prefrontal Delay Period Activity Encodes Short–Term Working Memory

**Editor's Proof** 

A significant literature suggests that the dorsolateral prefrontal cortex (dlPFC) or area 46 plays an important role in attention and working memory (Goldman-Rakic 1987; Petrides 1994; Fuster 1997; Inoue et al. 2004). It is well known that lesions to the dIPFC impair short-term working memory and the ability to suppress responses. In the macaque monkey (Fig. 6.1a), area 46 surrounds the principle sulcus and lies anterior to the arcuate sulcus (Fig. 6.1b, Walker 1940). (Note that this area has also been subdivided, based on histological and connectional evidence, into area 46 and area 9/46, Petrides and Pandya (1999).) A number of studies have examined the role of dIPFC in short-term working memory using delay match to sample paradigm. In the oculomotor delay response task (Fig. 6.2), monkeys are presented a cue (a), remember the cued location during the delay period (b), and, upon extinction of the fixation dot, subsequently perform an eye saccade to the remembered location (c). During the delay period, activity of many single neurons in area 46 is elevated, often exhibiting a sustained increase in spike firing. Furthermore, the delay period activity of single neurons has also been shown to be spatially tuned; that is, the delay activity is only elevated for the memory of certain spatial locations and not others (Fig. 6.3, Funihashi et al. 1989). Evidence further suggests that, analogous to population coding in motor cortex (Georgopoulos et al. 1988), location or direction of remembered location results from vector summation of many single unit responses (Takeda and Funihashi 2004). Furthermore, Takeda and Funihashi show that, in monkeys trained to perform a saccade 90° from the remembered location, during the delay period the population response shifts from the remembered location to the intended saccadic location, thereby suggesting a dynamic encoding of such population response. In sum, dIPFC delay period activity, both at the single cell and the population level, is consistent with the short-term storage of information and is regarded as a neuronal correlate of a short-term working memory. Such short-term storage is probably dynamic in nature.



Fig. 6.1 Location of dorsolateral prefrontal cortex in macaque monkey. (a) Location of arcuate and principal sulci. (b) Area 46 surrounds the principle sulcus and lies anterior to the arcuate sulcus (adapted from Walker 1940). (b) Based on histological and connectional study, this area is also referred to as 46 and 9/46 (Petrides and Pandya 1999)



Fig. 6.2 Oculomotor delay response task. Monkeys are trained to visually fixate a central fixation dot (*small circle*) on a monitor continuously throughout this task. They are presented a cue (*red square* in **a**) at one of several possible locations (locations indicated by *empty squares*), the cue disappears and they are required to remember the cued location during the delay period (**b**). Upon extinction of the fixation dot, they subsequently perform an eye saccade to the remembered location (**c**). Correct performance is rewarded with a drop of juice



**Fig. 6.3** Memory fields are spatially tuned. Delay period activity of prefrontal neuron in a monkey performing oculomotor delay response task. **a** Post-stimulus time histograms (*PSTH*) for activity during oculomotor delay response task to each of 8 directions. Prominent delay period activity is seen only for the DOWN direction (bottom *PSTH*). Resulting delay period tuning curve is shown *below* (from Funihashi et al. 1989). This indicates neurons in area 46 maintain memory trace of stimulus at specific spatial locations. (**b**) Shifting spatial selectivity during a mnemonic task via population vector coding of delay period activity. Direction of vector shifts during delay period reflecting initial representation of visual spatial code to one representing the encoding of intended saccade direction (visual input to motor output) (from Takeda and Funihashi 2004)

## 6.3 Does Prefrontal Cortex Contain Clustered Functional Organization?

**Editor's Proof** 

One approach for studying prefrontal activity is optical imaging. This approach is useful only if activity within prefrontal areas is organized in a modular or clustered fashion. A number of cortical areas exhibit functional organizations consisting of repeated modules, typically 200–500  $\mu$ m in size (terms such as domains, clusters, patches, puffs, and columns have also been used). Evidence from both anatomical and functional studies indicate the presence of clustered organization in sensory, motor, and association cortices (in V1 and V2 (for review see Roe 2003), V4 (Ghose and Ts'o 1997; Tanigawa et al. 2008; Roe 2008), IT (Tsunoda et al. 2001), Area 7 (Siegel et al. 2003; Raffi and Siegel 2005)). Whether regions such as pre-frontal cortex contain clustered organizations is controversial (cf. Goldman-Rakic 1987, 1999). However, given the breadth of areas from which clustered organization has been observed, one could argue that the basic organization of prefrontal cortex is not dissimilar from other cortical areas.

Some evidence does point to the presence of clustered organization in prefrontal cortex. In dlPFC, tracer injections lead to a characteristic local network of labeled patches (Lund et al. 1993; Kritzer and Goldman-Rakic 1995). The pattern of label in principal sulcus following injections into other areas such as inferior parietal cortex appear patchy or columnar in nature (Cavada and Goldman-Rakic 1989). In fact, parietally-derived patches are observed to interdigitate with those from callosal sources (Goldman-Rakic and Schwartz 1982). 2-Deoxyglucose labeling of prefrontal activation during a spatial mnemonic task also suggest a columnar or patchy organization (Friedman and Goldman-Rakic 1994). These patches measure on average a few hundred microns in size and are not dissimilar to patchy label seen in other sensory areas.

Functional evidence for columnar organization can also be found from optical imaging studies of cortical response to microstimulation (Fig. 6.4). Sawaguchi (1994, 1996) used voltage sensitive dye imaging methods to record prefrontal cortical response to local electrical microstimulation in the anesthetized monkey. Such stimulation produced focal, interdigitated regions of activation and suppression, ranging in size from 200 to 1,000 µms. The enhanced and suppressed activity in these optically detected regions were confirmed by electrophysiological recording. The optical signal at these sites followed the stimulation 3-6 ms after microstimulation, peaked at 70-80 ms, and lasted for 130-150 ms. Hirata and Sawaguchi (2008) also demonstrated the presence of columnar activation in prefrontal brain slices with voltage sensitive dye techniques. These studies demonstrating focal activation support the presence of functional clustering within prefrontal cortex. Although such clustered activation was not observed in another study of macaque prefrontal cortex using voltage sensitive dye recording methods (Seidemann et al. 2002), there were significant differences in the preparation (awake monkey), the stimulation parameters, and locations of stimulation (FEF) and imaging (FEF and 8Ar).





**Fig. 6.4** Local activation of clustered activity in prefrontal cortex in response to microstimulation. Intracortical microstimulation (ICMS) at one site leads to focal activation at some nearby sites (1–4) and suppression at other sites (*white outlines*). These sites measure a few hundred microns in size. (Adapted from Sawaguchi (1994, 1996).)

# 6.4 Topographic Organization of Prefrontal Cortex

Prefrontal cortex contains cells with different response functions. In dIPFC, spike firing has been associated with sensory stimulation, mnemonic response, premotor response, and motor response. Do these response functions have any topographic organization and, if so, do these organizations have any predictable relationship to each other? With respect to visual response, the dIPFC is organized such that the central visual locations are represented ventral and posterior on the arcuate convexity and eccentric locations more dorsal and anterior (Fig. 6.5a, Suzuki and Azuma 1983). Although different studies differ in detail, most studies find a ventral to dorsal topographic map in the PFC. Saccadic responses in the frontal eye fields have an organization such that microstimulation of ventral sites lead to small eye saccades and that of dorsal sites lead to larger saccades (Fig. 6.5b, Bruce and Goldberg 1985).

Since both visual and motor-related responses have a ventral (central, small saccades) to dorsal (peripheral, large saccades) organization in PFC, it is possible that a spatial map for delay period activity may bear a similar organization. Alternatively, as working memory is a dynamic process in which information must be constantly updated, manipulated, and integrated, it is possible that such spatial information changes by the moment or that no spatial organization for mnemonic information exists in prefrontal cortex.







**Fig. 6.5** (a) Topography of visual response in prefrontal cortex (Suzuki and Azuma 1984). (b) Topography of saccadic response to microstimulation at different locations along the arcuate sulcus (frontal eye fields) (Bruce and Goldberg 1985)

#### 6.5 Is There Spatial Organization for Memory Location?

In a series of studies on the functional organization of prefrontal cortex, Sawaguchi and his colleagues (Sawaguchi et al. 1988, 1989; Sawaguchi and Goldman-Rakic 1991, 1994) injected pharmacological agents (such as bicuc-



ulline or dopamine antagonists) into restricted regions of prefrontal cortex near the principal sulcus. While monkeys retained their ability to saccade to cued spatial locations, they lost their ability to accurately saccade to remembered locations. These effects were spatially specific, as injection at a site a few millimeters away resulted in a change in the visual location of the deficit. Upper fields were more affected by injections into caudal regions of the dlPFC and amd lower fields by injections into more rostral regions. These studies provided evidence that some spatial map for mnemonic function exists in dlPFC.

One way to directly examine the possible existence of a spatial mnemonic map is to use the intrinsic optical imaging approach. Intrinsic cortical signals are activity-dependent reflectance changes of cortical tissue due to changes in oxygenation of the blood in the microvasculature (Grinvald et al. 1986; Ts'o et al. 1990; Vanzetta et al. 2004) and have both spiking and subthreshold contributions (Roe and Ts'o 1995, 1999; Issa et al. 2000; Ramsden et al. 2001; Dragoi and Sur 2000; Schwartz and Bonhoeffer 2001; Devor et al. 2003; Thompson et al. 2003). This hemodynamic signal consists of a decrease in reflectance (so-called "initial dip") due to an initial deoxygenation of the tissue (caused by neuronal activity induced increase in oxygen consumption) followed by an increase in reflectance presumably due to the inrush of freshly oxygenated blood (BOLD signal) (see Fig. 6.6a). In sensory cortices, the typical timecourse under 600-630 nm illumination exhibits a time to peak of 2-3 s. The magnitude of reflectance change is typically in the 0.1-1.0%range. Similar signals have been recorded in awake and anesthetized animals (Grinvald et al. 1991; Vnek et al. 1999). By presenting appropriate stimuli during optical imaging, the functional organizations of the sensory cortices can be mapped at high spatial (50-100 µm) resolution.

The intrinsic signal imaging method was used to map mnemonic prefrontal activity in macaque monkeys trained to perform a delay match to sample task (Roe et al. 2004). During this task (cf. Fig. 6.2), monkeys maintained fixation throughout the imaging period. After presentation of a visual cue (0.5 s), monkeys were required to remember the location of the cue during the delay period (2 s, fixation maintained). Upon offset of the fixation spot, they performed an eye saccade to the previously cued location, indicating they had remembered the correct location. During this task, single condition images were obtained by summing imaged frames acquired during the delay period (see Fig. 6.7, frames 6–15) and subtracting a sum of prestim frames (frames 1–2, first-frame subtraction). During each block of trials, the set of cued locations were presented in an interleaved fashion. Blank trials, during which no cue was presented, were also interleaved.

To explore the presence of a spatial map, imaged delay period activity for eight different locations of identical eccentricity were compared (Fig. 6.6b, inset above). In this task, while the monkey maintained fixation, a cue (Cue) was flashed at one of the eight locations. Memory for this location was maintained through the delay period (Delay) and was indicated by saccade to the correct remembered location (Resp).





**Fig. 6.6** Differential timecourses in dlPFC for remembered location. (a) Standard intrinsic signal timecourse. Neural activation is accompanied by a decrease in cortical reflectance (dR/R). (b) The intrinsic signal recorded from dlPFC location with strong delay activity for *left (pink)*, weaker response for *up (dark blue)* and *right (yellow)*, and even weaker (or perhaps suppressive) for *down (light blue)* and *blank (white)* 

Examination of intrinsic signal timecourses suggested spatial specificity. As shown in Fig. 6.6b, cortical response timecourses were sampled from a region responsive to memory for the left location. Delay period activity during memory for up, left, right, down, and blank locations produced different magnitude responses. In this location, response was greatest for the left (pink curve) location, weaker for the up (blue curve) and the right (yellow curve) locations, and weakest (perhaps suppressed?) for the down (light blue curve) and blank





**Fig. 6.7** Imaged maps in dIPFC in a delay match to sample task. Each image was obtained by summing the reflectance response during delay period (frames 6–15) and subtracing precue activity (frames 1–2) and represents the delay activity associated with memory for one of the eight locations (see *upper left inset*). *Upper right inset* indicates location imaged in dIPFC. *Ps* principal sulcus; *As* arcuate sulcus; *A* anterior; *M* medial. Central schematic summarizes the activations: from posterior to anterior, mapping progresses from horizontal axis (*red*), to 45° clockwise axis (*magenta*), to vertical (*light blue*), to 45° counterclockwise axis (*green*)

(white curve) conditions. This suggests that each location of dlPFC exhibits maximal delay period activity for one particular remembered location and not for others.

This impression was further supported by examining images of delay activity. Images of prefrontal delay activity revealed that memory for different locations led to different prefrontal activations. Within the region representing a single eccentricity (Fig. 6.7, upper right inset), memory for locations on the vertical axis (locations 1

and 5) appeared central most in the image (light blue pixels). Those on axis  $45^{\circ}$  clockwise (locations 2 and 6) fell more caudal (magenta pixels), and those on axis tilted  $45^{\circ}$  counterclockwise (locations 4 and 8) fell more anteriorly (green pixels). Activations to locations on the horizontal axis (locations 3 and 7) produced the least activation (red pixels). Thus, although the topography is crude, this data does suggest that, within a local region in dlPFC, there is a differential mapping with respect to spatial mnemonic location.

How does this activation relate to the dorsal–ventral map observed for visual and eye movement response? To address this question, a second paradigm compared delay period response for more peripheral ( $10^\circ$  eccentricity) vs. more central ( $5^\circ$  eccentricity) locations (Fig. 6.8, left). Results showed that activation for more central locations (Fig. 6.8d,  $5^\circ$ ) were located ventral to those of more eccentric (Fig. 6.8c,  $10^\circ$ ) locations, consistent with the topographic maps for visual stimulation (Suzuki and Azuma 1983) and for location of eye saccades elicited by microstimuation (Bruce and Goldberg 1985).

Although preliminary, these data together suggest that PFC in monkeys trained for spatial oculomotor delay response tasks contain some global spatial topography (Fig. 6.9, dashed isoeccentricity lines) and a local topography within each spatial location which is based on different axes of spatial memory (Fig. 6.9, colored arrows). Combining previous studies on topography with these results suggests a possible organization as depicted in Fig. 6.9. However, one must bear in mind that, given the dynamic nature of working memory demands, such a topography may not be static and may simply be one instantiation of many possible organizations



**Fig. 6.8** Imaging global organization of central and peripheral mnemonic representation. *Left*: Schematic of mnemonic task for small vs. large eccentricities. (a) Diagram of imaged location in dlPFC (*dotted rectangle*). (b) Summary overlay of activations seen in (c) and (d). (c) and (d) Activation for more central locations ((d),  $5^{\circ}$ ) were located ventral to those of more eccentric ((c),  $10^{\circ}$ ) locations, consistent with the topographic maps for visual stimulation (Suzuki and Azuma 1984) and for location of eye saccades elicited by microstimuation (Bruce and Goldberg 1985)





Fig. 6.9 Summary for spatial topography of delay activity in PFC

established in different tasks. Although speculative, we would like to forward the possibility that prefrontal cortex may have a native spatial organization that is then assumed by current task demands.

# 6.6 Is There a Signal for Suppression in Prefrontal Cortex?

One of the hallmarks for prefrontal function is the ability to appropriately suppress actions. Diseases involving prefrontal dysfunction are often accompanied by inability to appropriately cease or adapt to changing task demand.

To test whether such dysfunction might be detected with imaging methods, during delay match to sample tasks, we presented blank trials interleaved with cued trials. During the blank trials, the monkey visually acquires the fixation spot but is presented no cue. He thus awaits the cue and expects it at a certain time. However, when none is presented he must suppress his characteristic behavior and NOT perform an eye saccade (see Fig. 6.10, schematic at left). During these blank trials, since there is no visual cue and thus nothing to remember, one might expect the lack of any detectable response (no reflectance change). However, a consistent and robust signal was observed during these blank trials. Surprisingly, the observed optical signal was opposite in sign (i.e., increase in reflection) to the normal decrease in reflectance (Fig. 6.10, right; see also Fig. 6.6 white curve). The magnitude of this upward deflection was quite large, in fact equal in magnitude to the downward mnemonic response (Fig. 6.6). This



Fig. 6.10 Delay period activity during blank trials. During blank trials, no cue appeared and the monkey was required to maintain fixation at the central fixation spot and not to perform any saccade. (a) Eight location task; (b) small vs. big eccentricity task. For both tasks, reflectance signal exhibits upwards deflection during the period of task corresponding to the delay period in cued trials

signal, furthermore, was not a general response of the task, but rather followed the timing of the delay period. As seen in the graphs in Fig. 6.10, the upward deflection begins at onset of delay period (left red line: at frame 6 in Fig. 6.10a, at frame 8 in Fig. 6.10b) and falls by the end of the delay period (second red line: at frame 15 in Fig. 6.10a and at frame 17 in Fig. 6.10b).

How should this increase in reflectance be interpreted? It is unlikely to be cue related since it is seen only during delay periods. It is also unlikely to be a mnemonic response since there was no cue to remember. One possibility is that this positive signal deflection could be interpreted as a suppressive signal, one which is needed to suppress the saccadic response. Electrophysiological recording would be required to evaluate the neuronal response (e.g., decrease in neuronal firing) underlying the increase in optical reflectance. We suggest one possible corollary of this finding. If this signal arises due to an active suppressive response would result in inappropriate saccade behavior. In other words, lack of such a suppressive signal could underly perseveration behavior characteristic of prefrontal dysfunction (cf. Gusnard et al. 2003). This is an exciting possibility that could have significant clinical implications.



#### 6.7 Summary

The experiments described here summarize some of the initial attempts at elucidating the functional organization of dorsolateral prefrontal cortex in the macaque monkey. While such studies are still in their early stages, they are important for guiding future studies on prefrontal organization. The key observation that delay period activity in dIPFC is tuned was highly instrumental in driving investigations into spatial organization of mnemonic representation. In principal, such tuning could be viewed as analogous to orientation tuning in visual cortex. As demonstrated in visual cortex, such tunings can self-organize to form systemic maps (cf. Swindale 2004). Similarly, prefrontal areas may share such structural framework. The studies described here have introduced the idea that such tuning can, at least at the population level, form crude spatial organizations in prefrontal cortex. Some important directions that remain for future studies include: (1) What are the dynamics of such maps, especially as they relate to task demand? (2) Is there differential localization for different types of mnemonic activity, such as spatial vs. nonspatial memory (McCarthy et al. 1996; Rainer et al. 1998; Kojima et al. 2007)? and (3) How does the organization of mnemonic function relate to other prefrontal functions such as active suppression of persistent behavior? Advances in neuroimaging and electrophysiological approaches, both at the cellular, population, and behavioral levels, will undoubtedly elucidate these questions in the near future.

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