

Persistent Discharges in the Prefrontal Cortex of Monkeys Naïve to Working Memory Tasks

Neurons in the prefrontal cortex and a network of interconnected brain areas discharge in a persistent fashion after the offset of sensory stimulation. Such persistent discharges are thought to constitute a neuronal correlate of working memory. The information content of neuronal discharges and its anatomical localization across the surface of the prefrontal cortex has been a matter of debate. Discrepant results by different laboratories may be due to the effects of different training regimens and tasks used in memory tasks. In order to address how training in a memory task alters neuronal responses, we performed recordings in monkeys that were never trained in memory tasks, but passively viewed visual stimuli. We have found that a population of prefrontal neurons responded to visual stimuli and also exhibited significantly elevated responses during "delay" intervals of the task. For a population of these neurons, persistent discharges were selective for the location and feature of the preceding stimulus. These discharges were typically disrupted by the appearance of a subsequent stimulus. Our results suggest that some prefrontal neurons represent the location and identity of visual stimuli in a persistent fashion, even when the latter are not behaviorally important or required to be kept in memory.

Keywords: cognition, neurophysiology, principal sulcus, training

Introduction

Working memory, the ability to retain and integrate information over a time period of a few seconds, is a critical component of higher cognitive functions such as planning, language, and reasoning (Baddeley 1992). Understanding these complex operations that constitute the apex of human mental activity is therefore contingent on understanding the neural basis of working memory, a fact that explains the intense research interest that working memory has received over several decades. A first step in identifying neural correlates of working memory was the description of neurons that continue to discharge even after the end of sensory stimulation, while animal subjects were required to remember a stimulus during a behavioral task (Fuster and Alexander 1971). Subsequent work by Patricia Goldman-Rakic and her colleagues indicated that such persistent discharges of individual neurons vary depending on the properties of the stimuli held in memory, for example the position of a visual stimulus (Funahashi et al. 1989). This key finding offered a direct mechanism through which neurons could encode information held in memory. More recent research sought to address how information about different memoranda is organized in the primate brain. It is now well appreciated that persistent discharges are present in a network of cortical and subcortical areas interconnected with the prefrontal cortex (Goldman-Rakic 1988; Constantinidis and Procyk 2004). By some accounts,

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the neural pathways encoding information about the identity of stimuli and their location in space terminate at distinct subdivisions of the prefrontal cortex (Wilson et al. 1993; O Scalaidhe et al. 1997). However, such an organization has been disputed by other studies, suggesting instead that the prefrontal cortex is a zone of convergence between spatial and feature information (Rao et al. 1997; Rainer et al. 1998). The discrepancy between these studies may be explained by a difference in what the subjects in each experiment were actually trained to do. Integration of spatial and feature information may not be obvious unless animals are trained to perform a task that requires both (Rao et al. 1997; Miller 2000).

These results suggest that in order to address how mnemonic information is organized and represented in the primate cortex, it is essential to understand how training in a behavioral task alters neuronal activity, and how the cortex represents information in the experimentally naïve state, prior to training in any cognitive task. A related question has to do with how persistent discharges are altered when one intentionally tries to remember a stimulus. Working memory is often assumed to be an active process requiring conscious effort (Frith and Dolan 1996; Postle 2006). However, in our everyday experience we are able to recall stimuli even when not explicitly required to remember them, or cued about their potential importance. It is therefore possible that much of the activity present during the active maintenance of working memory is also generated in an automatic fashion, during passive exposure to sensory stimuli. In order to address this question we conducted neurophysiological recordings from the lateral prefrontal cortex of monkeys passively viewing visual stimuli and we characterized neuronal discharges during and after stimulus presentations. To ensure that the animals were not habitually trying to remember the stimuli even in the absence of a mnemonic requirement, we conducted experiments in subjects naïve to any type of working memory training. Our experiments therefore provided a baseline of neuronal activity, unaltered by behavioral training or willful execution of a memory task.

Materials and Methods

Two male, rhesus monkeys (*Macaca mulatta*) with no prior experimentation experience and weighing 6–10 kg were used in the experiments. Neural recordings were performed in areas 46, 8, 45, and 12 of the prefrontal cortex (Fig. 1). All animal experiments were performed in compliance with the guidelines set forth by the National Institutes of Health as reviewed and approved by the Wake Forest University Animal Care and Use Committee.

Behavior and Stimuli

Monkeys sat in a primate chair with their head fixed while viewing a monitor positioned 68 cm away under dim ambient illumination. To control for eye movements, animals were required to fixate a central

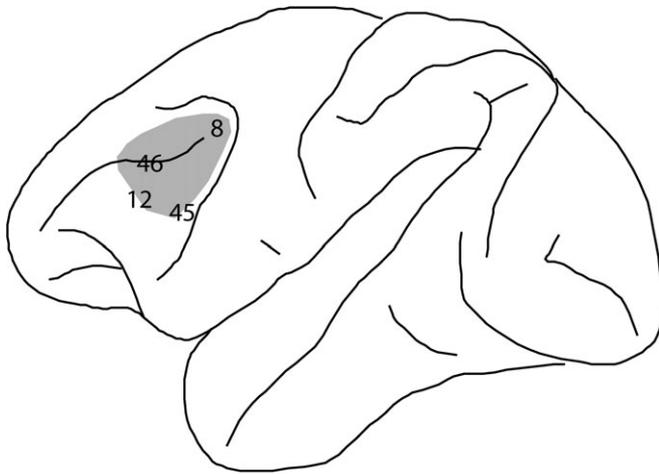


Figure 1. Schematic diagram of the monkey brain. Shaded region indicates the cortical surface that we sampled with our electrophysiological recordings, which included areas 46 and 8 of the dorsolateral prefrontal cortex, and areas 12 and 45 of the ventrolateral prefrontal cortex.

point consisting of a white square, 0.2° in size. The animals had to maintain fixation throughout the trial, while visual stimuli were presented on the screen, in order to receive a liquid reward. Eye position was monitored using an infrared eye position scanning system (model RK-716; ISCAN, Burlington, MA) that was capable of at least 0.3° resolution around the center of vision. Eye position was sampled at 240 Hz, digitized, and recorded. Breaks in fixation terminated the trial and resulted in no reward. The display of visual stimuli, online monitoring of eye position, and synchronizing stimuli with neurophysiological data were performed with the WaVE software (Meyer and Constantinidis 2005), developed in the laboratory, based on the Matlab environment (Mathworks, Natick, MA), and utilizing the psychophysics toolbox (Brainard 1997; Pelli 1997).

Visual stimuli were presented on the screen while the animal fixated. Two types of stimuli were used, a spatial and a feature set (Fig. 2). In the spatial set, stimuli consisted of a white, 2° square that appeared in one of 9 locations on a 3×3 grid, of 10° dimensions (Fig. 2A). The position of the stimulus varied randomly from trial to trial, so that the monkey could not anticipate its location. Following a 1 s fixation interval during which only the fixation point was visible, the stimulus was presented for 500 ms and was followed by a second stimulus presentation with an intervening, 1.5-s “delay” period between them, when only the fixation point was visible on the screen. The second stimulus was also followed by a second “delay” period of 1.5 s, after which the fixation point was extinguished and the monkey was rewarded for maintaining fixation. The location of the second stimulus was either identical to the first, or diametric to it. We refer to the identical stimulus as a “match”, and the diametric as a “nonmatch”, in analogy to stimuli employed in delayed-match-to-sample tasks (e.g., in Constantinidis and Steinmetz 2001), however, the location and identity of stimuli in our experiment had no behavioral significance for the monkeys. A few neurons were tested with a stimulus presentation schedule that randomized the time interval of stimulus presentation. In this paradigm, the fixation interval prior to stimulus appearance varied randomly between 1, 2, or 3 s. The stimulus presentation and delay period lasted 0.5 and 1.5 s, respectively, as above. A second stimulus appeared in 75% of the trials and was followed by a second delay period of either 0.5 or 1.5 s. The trial ended without a second stimulus presentation for the rest 25% of the trials.

The feature set of stimuli consisted of 8 white, geometric shapes (Fig. 2B). The stimuli were calibrated for size and luminance (they consisted of a number of pixels within 1% of each other, and could fit in a 2° outline). Blocks of trials with the feature stimuli were typically delivered at the same spatial location, but the feature of each stimulus varied randomly from trial to trial. The timing and duration of stimulus presentations were identical to those used for the spatial set, and a second stimulus presentation could either be the same (match) or

different than the first (nonmatch). The feature set was typically presented after the spatial set, and stimuli were positioned at the spatial location that evoked the best response in the spatial set. If no significant response was observed for any spatial location, the feature stimuli were presented at the fovea, over the fixation point. Typically, 20 repetitions of each stimulus presentation were collected during the neurophysiological recordings.

Animals were trained to perform these passive fixation tasks in the following manner. They were initially rewarded for moving their eyes to the fixation point, which disappeared shortly after they shifted their gaze to it. The duration of fixation was progressively increased, so that the monkeys were required to maintain fixation for longer and longer intervals in order to receive the reward, and the trial was terminated if they broke fixation. Once the monkeys were able to fixate for up to 5 s, peripheral stimuli were progressively introduced. The stimuli originally had very low luminance so that they were barely perceptible. The luminance of the stimuli was progressively increased over several weeks while the monkey continued to be rewarded for simply maintaining fixation. In this way, we trained the animals not to attribute any behavioral significance to the visual stimuli. The monkeys were exposed to the full set of our stimuli prior to beginning neurophysiological recordings.

Surgery and Neurophysiology

Once the animals were proficient in the task, recordings commenced. A 20-mm-diameter craniotomy was performed over the lateral prefrontal cortex and a recording cylinder was implanted over it. The location of the recording cylinder was visualized with anatomical MRI imaging. Extracellular recordings were performed with either single or multiple microelectrodes. We used glass-coated, tungsten electrodes of $250 \mu\text{m}$ diameter, with an impedance of $1 \text{ M}\Omega$ at 1 kHz (Alpha-Omega Engineering, Nazareth, Israel). Arrays of up to 4-microelectrodes spaced 0.5–0.9 mm apart were advanced into the cortex through the dura with a microdrive system (EPS drive, Alpha-Omega Engineering). The electrical signal from each electrode was amplified, band-pass filtered between 500 and 8 kHz, and recorded with a modular data acquisition system (APM system, FHC, Bowdoin, ME). Waveforms that exceeded a user-defined threshold were sampled at $25\text{-}\mu\text{s}$ resolution, digitized, and stored for off-line analysis.

Data Analysis

Recorded waveforms were sorted into separate units by an automated cluster analysis method using the KlustaKwik algorithm (Harris et al. 2000). The method relied on principal component analysis of the waveforms and was implemented in the Matlab software platform. Responses from each unit were subsequently analyzed. We first sought to test whether neuronal responses were significantly elevated in the 500-ms interval of stimulus presentation, compared with the preceding 1-s interval of fixation. A neuron was identified as visually responsive if its discharge rate during presentation of any stimulus was significantly above the baseline period (paired *t*-test; $P < 0.05$). The spatial tuning of visually responsive neurons was assessed by comparing the discharge rates during the presentation of single stimuli at the 9 grid locations. Neurons with significantly different responses to the 9 conditions (analysis of variance [ANOVA]; $P < 0.05$) were included in further analysis. The best (most responsive) and worst (least responsive) locations were identified for each neuron. Feature selectivity was determined by comparing responses to the 8 different feature stimuli. Neurons with significantly different responses to the 8 shapes (ANOVA; $P < 0.05$) were judged to be feature selective.

We tested whether a neuron exhibited persistent activity in the delay period following a stimulus by comparing its discharge rate in the delay period with its rate in the baseline, fixation period. To avoid the effect of stimulus-off or long latency visual responses that carried over into the delay interval, we only analyzed discharge rate in the last 1 s of the 1.5-s delay period. Neurons were deemed to be exhibiting persistent responses if they displayed significantly different responses between fixation and delay period as judged by a paired *t*-test, ($P < 0.05$). The Bonferroni correction was used to account for multiple comparisons; the correction was applied separately in tests involving the spatial task (9 locations) and the feature task (8 features). We further analyzed the

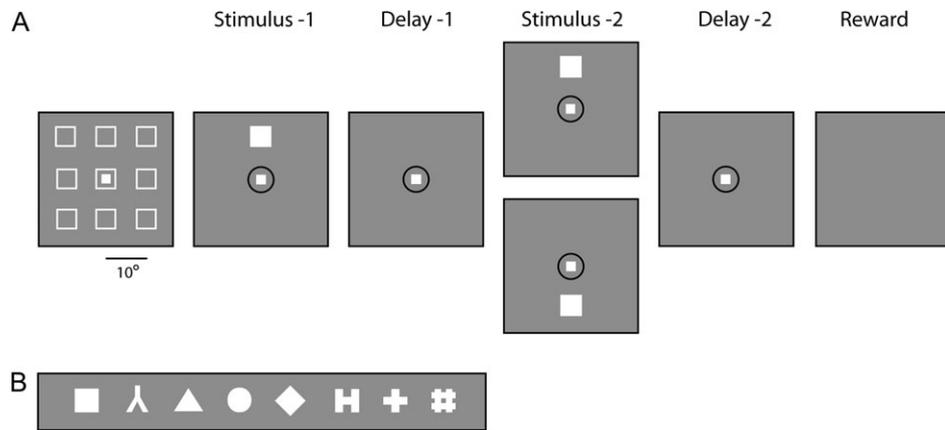


Figure 2. (A) Sequence of events in the spatial set of the passive viewing task. Successive frames represent stimulus presentations on a computer screen. The monkeys were required to fixate on a target while a stimulus appeared at one of 9 spatial locations arranged on a 3×3 grid of 10° dimensions. Circle indicates the (invisible) fixation window. A stimulus could be followed by a second stimulus at the same or diametric spatial location. At the last frame, the fixation point was turned off and the monkeys were rewarded simply for maintaining fixation up to that point. (B) The 8 stimuli used in the feature task.

spatial and feature selectivity of delay-period activity by comparing the discharge rate recorded after each of the stimuli in our spatial and feature sets (ANOVA; $P < 0.05$).

Population responses were evaluated by averaging discharges from multiple neurons and constructing population Peri-Stimulus Time Histograms (PSTH). PSTHs were constructed using the best and worst stimulus responses of each neuron.

Results

Neuronal activity was monitored from the lateral prefrontal cortex (areas 8, 46, 12, and 45) of 2 monkeys (Fig. 1). These animals were never trained in any kind of memory task and were only passively viewing visual stimuli (Fig. 2). Eight hundred ninety-three neurons were recorded in total. Of those, 254 neurons exhibited significantly elevated activity during the presentation of a stimulus compared with baseline fixation (paired t -test; $P < 0.05$). The median response latency among these neurons was 90 ms (estimated as the time of half-rise to maximum discharge rate). Ninety-one neurons exhibited significant suppression of firing rate below the baseline for one or more stimuli, without any significant elevation for the rest of the stimuli tested. Of the neurons with elevated stimulus discharges, 52 (20%) continued to discharge in the last second of the delay period following the first visual stimulus, with a significant elevation in discharge rate over the baseline fixation (paired t -test; $P < 0.05$, corrected for multiple comparisons). An example of activity persisting after a stimulus presentation is shown in Figures 3 and 4. This prefrontal neuron responded to a visual stimulus with a phasic increase of firing rate and maintained an elevated discharge rate even after the offset of the stimulus, throughout the delay period.

Spatial and Feature Selectivity

We used 2 different sets of stimuli to evaluate neuronal responses (Fig. 2). A spatial set involved presentation of the same square stimulus at any of 9 locations on a 3×3 grid, spaced 10° apart from each other. A feature set was also used, involving presentation of 8 different geometric shapes, always presented at the same location, inside the neuron's receptive field. A total of 29 neurons displayed significant elevation of their firing rate during the last second of the delay period in the spatial set and another 29 neurons displayed elevated delay-period firing in the

feature set. Six neurons exhibited delay-period activity in both sets.

In principle, persistent activity could be a phenomenon not specifically linked to the mnemonic encoding of information but could instead be associated with factors unrelated to the stimulus, such as reward anticipation. To distinguish between these possibilities, we examined whether delay-period activity was dependent on the preceding stimulus. Among neurons with delay-period activity in the spatial task, 18 (62%) exhibited a mean firing rate in the delay period that varied significantly depending on the location of the previous stimulus (ANOVA; $P < 0.05$). An example is shown in Figure 3. Similarly, 14 (48%) of the neurons with delay-period activity in the feature set had significant selectivity for the feature of the preceding stimulus. These neuron populations could provide a memory trace encoding the properties of the preceding stimulus. To further ensure that delay-period activity was not somehow tied to the timing of events relative to the beginning of the trial or the delivery of reward, we used an alternative stimulus presentation schedule that randomized the time interval of stimulus presentation. Ten neurons with delay-period activity were tested in this fashion. No significant difference in the delay-period discharge rate was observed depending on the timing of stimulus presentation for any of these neurons (ANOVA, $P > 0.2$ in each case).

We next examined the time course of delay-period activity following appearance of a stimulus inside or out of the receptive field by constructing population PSTHs. Averaged responses from the 29 neurons that had significantly elevated responses in the delay period of the spatial set are shown in Figure 5. Stimulus presentation in the most responsive location within the receptive field caused a sharp phasic response, followed by a tonic response that was sustained over the delay period (Fig. 5A, red line). No such activation was seen following a stimulus that appeared at the diametric location (Fig. 5A, green line).

Successive Stimuli

The results presented so far were based on the analysis of responses following the initial presentation of a stimulus. However, delay-period activity was observed after the second stimulus, as well. Among the 52 neurons with significant

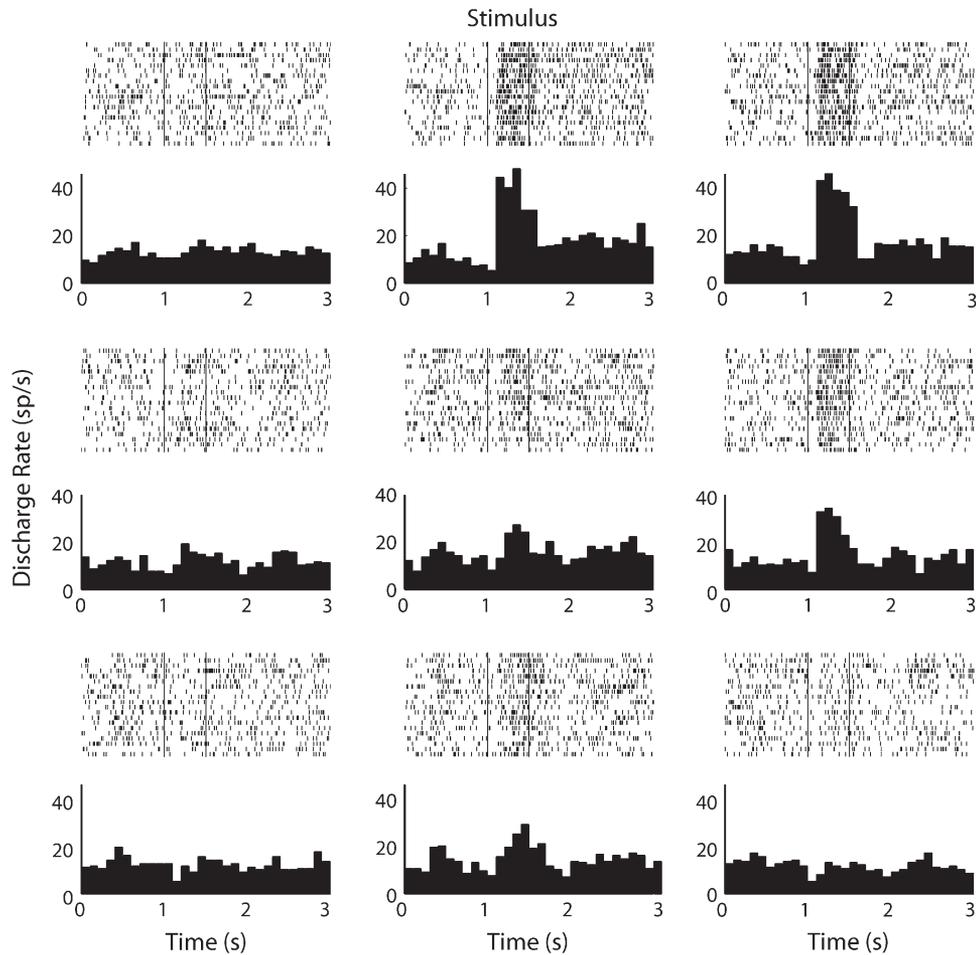


Figure 3. Rasters and histograms of a representative prefrontal cortical neuron that exhibited spatial selective visual responses and persistent discharges after a passive stimulus presentation. Responses to 9 spatial stimuli are shown; the position of each histogram in the figure indicates the location of the stimulus on the 3×3 grid used.

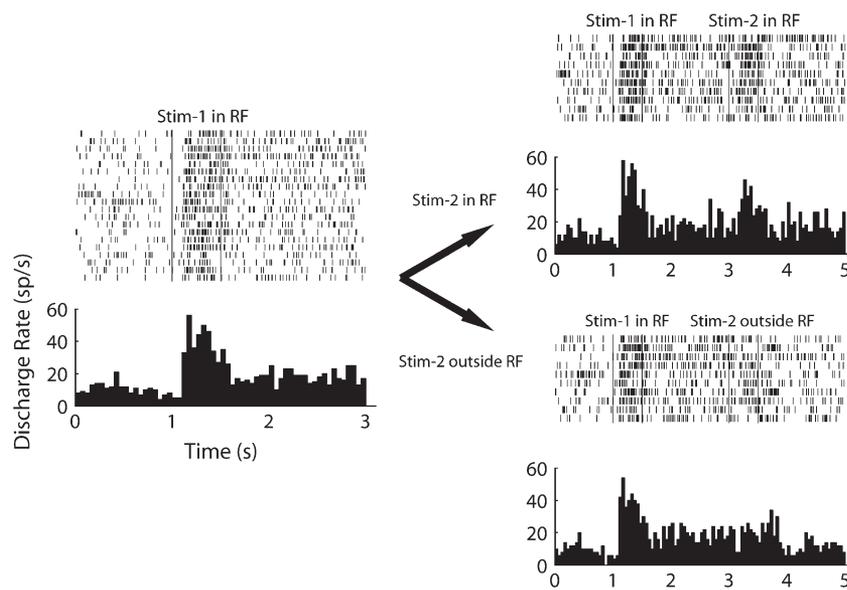


Figure 4. Delay-period responses following the initial and second stimulus. Responses of the same neuron as in Figure 3 are shown. Initial stimulus presentation (left) produced a phasic elevation of the firing rate. This remained significantly elevated in the delay period after the offset of the stimulus. Presentation of a second stimulus in the receptive field produced a second, transient activation (top right). However, when a second stimulus appeared out of the receptive field, the elevated discharge rate was terminated (bottom right).

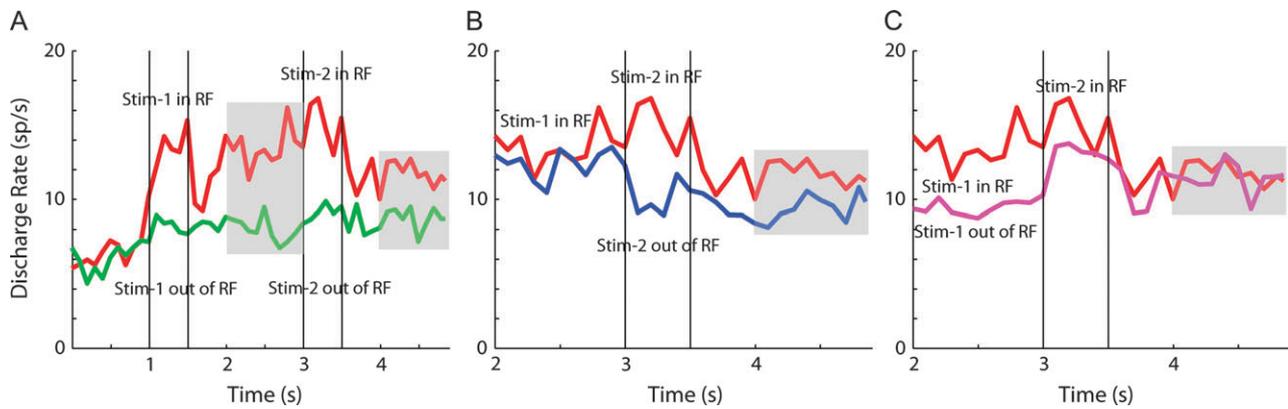


Figure 5. Population PSTH representing responses from 29 neurons with significantly elevated delay-period activity in the spatial set. (A) Neuronal responses to presentation of a stimulus in the receptive field (red line) and out of the receptive field (green line), followed by an identical stimulus. Vertical lines represent times of stimulus presentation. Shaded area represents the time period that was used for the analysis of delay-period responses. (B) Red line represents a detail of the same trace shown in A. Blue line additionally indicates responses of the same neurons to a second stimulus out of the receptive field. Firing rate was significantly higher during the delay period following the second stimulus presentation in the receptive field, compared with a stimulus out of the receptive field (paired t -test, $P < 0.005$). (C) The purple line represents population responses to a second stimulus in the receptive field, following an initial stimulus out of the receptive field. Red line same as in A and B. No significant difference was observed between the 2 response rates in the delay period (paired t -test, $P > 0.8$).

delay-period activity following a stimulus, 45 (87%) also had significantly elevated activity in the delay period following a second stimulus, compared with baseline fixation (paired t -test; $P < 0.05$). This result suggested that persistent activity is not necessarily tied to the first stimulus appearing on the screen.

Previous studies have suggested that prefrontal neuronal activity is unique in its ability to resist distracting stimulation once a stimulus is held in working memory (reviewed by Constantinidis and Procyk 2004). We were therefore interested to know how delay-period activity could convey information about multiple stimuli presented in sequence, in passively viewing monkeys. To address whether a second stimulus appearance could disrupt persistent delay-period activity, we examined how delay-period activity differed depending on whether the stimulus appeared in or out of the receptive field. We first identified trials that started with a stimulus in the receptive field and we compared discharge rates recorded when the second stimulus also appeared in the receptive field and when it appeared at a diametric location. Of the neurons with delay activity following the first spatial stimulus, 15/29 (52%) had significant delay activity after a second stimulus at the same location and only 3/29 (10%) had significant delay activity after a second stimulus at the diametric location. The effect can be observed in the population PSTH. Activity following the second stimulus in the receptive field was significantly higher than activity following a second stimulus out of the receptive field (paired t -test, $P < 0.005$), even though the first stimulus appeared in the receptive field in both cases (Fig. 5B).

We also wished to test whether the location of an initial stimulus affected the delay-period activity following a second stimulus. We observed no significant difference (paired t -test, $P > 0.1$) in the population responses following a second stimulus in the receptive field, when this was preceded by either a stimulus in the receptive field or out of the receptive field (Fig. 5C). Similarly, delay activity following a second stimulus outside the receptive field did not differ significantly (paired t -test, $P > 0.1$) depending on the location of the original stimulus (green and blue lines in Fig. 5). Both of these comparisons suggest that the position of the initial stimulus did not influence neuronal activity significantly once another

stimulus had appeared, and that prefrontal neurons in naïve monkeys represented in a persistent fashion the most recent stimulus appearing on the screen.

Discussion

Our results indicate that a population of prefrontal cortical neurons was active in a persistent fashion after the offset of sensory stimuli. This was evident even though the subjects were not required to remember the stimuli, which had no behavioral relevance for them. In fact, the subjects had never been trained in any cognitive or working memory task. Furthermore, the rate of persistent discharges in a population of neurons depended on the properties of the stimuli, namely their spatial and feature attributes. When we examined neuronal activity during successive stimulus presentations we determined that information about the identity of a stimulus generally did not survive a second stimulus presentation, but that successive presentations were followed by persistent activity related to the most recent stimulus. Our results suggest that persistent activity is not entirely dependent on training or effortful execution of a behavioral task. On the contrary, it appears that task-irrelevant stimuli presented in a passive manner generate neuronal responses that outlast the physical stimulation and could provide a buffer for working memory available for a number of possible functions.

Characteristics of Persistent Activity

The mean firing rate of a population of prefrontal neurons continued to be significantly elevated after the offset of a stimulus, compared with the baseline fixation interval. Responses to visual stimuli recorded during the stimulus presentation have been previously described in the prefrontal cortex of passively fixating monkeys, naïve to working memory training (Suzuki and Azuma 1983) and even anesthetized monkeys (Schmolecky et al. 1998). Anecdotal evidence of persistent discharges in a monkey that was only trained to fixate has been previously reported in the ventrolateral prefrontal cortex, for face-selective neurons (Scalaidhe et al. 1999). Our current results confirm and extend these findings to the entire lateral prefrontal cortex, and suggest that persistent

discharges can be selective for stimulus properties such as spatial locations and stimulus features. Persistent discharges in animals passively viewing stimuli may not be an exclusive property of the prefrontal cortex; we have observed persistent discharges (albeit tested with a much shorter delay interval) in the posterior parietal cortex of behaviorally naïve animals (Joelving et al. 2007).

The discharges of neurons in our sample resembled in many ways the responses recorded in monkeys trained to perform working memory tasks. Discharges were maintained for up to 1.5 s after the offset of the stimulus (the maximum interval that we tested). Two general temporal profiles were observed, either slightly decreasing during the delay period (as in Fig. 4), or slightly increasing (as can be seen in Fig. 5), similar to the profiles that have been reported during the execution of working memory (Quintana and Fuster 1992; Constantinidis et al. 2001). The rate of persistent discharges differed depending on the spatial location and feature of the preceding stimulus, suggesting that neurons could selectively encode these properties. Such activity could not be related to nonspecific factors such as the anticipation of the end of the trial or the expectation of reward.

Approximately 20% of neurons that responded to visual stimuli exhibited sustained responses during the delay period. Of those neurons, 48–62% displayed spatial or feature selectivity for our stimulus set. These percentages are generally lower than those reported in previous studies in monkeys trained to perform working memory tasks. For example, delay-period activity was reported in 51%, 65%, and 63% of task-responsive prefrontal neurons in 3 previous studies of working memory (Fuster and Alexander 1971; Funahashi et al. 1989; Rao et al. 1997). However, it is difficult to directly compare our results with these previous studies due to methodological differences in neuron selection and analysis, and differences in the sets of stimuli used. In the present study, we collected data from all neurons encountered by our multiple-electrode array, with no attempt to select them in terms of their response properties, and we relied on a limited set of visual stimuli. Our results therefore cannot establish at this point that training in a memory task increases the number of neurons exhibiting persistent activity, or their selectivity for stimulus properties.

Stimuli in Sequence

Our experimental design involved presentation of stimuli in sequence, in analogy to tasks that engage working memory such as the delayed-match-to-sample task. Prior studies have suggested that prefrontal cortical neurons can encode information about an initial stimulus presentation that survives stimulation from nonrelevant distractors (Miller et al. 1996). Furthermore, this appears to be a property of the prefrontal cortex, which is not observed in its cortical afferents, the posterior parietal and inferior temporal cortex (Miller et al. 1993; Constantinidis and Steinmetz 1996). Our current study indicated that prefrontal neurons do not automatically track the first stimulus of a sequence, but that their discharges reflect the most recent stimulus of a sequence. In that sense, resistance to interference is unlikely to be a passive property of the prefrontal cortex, but it is likely to emerge as a result of execution of a memory task.

Implications for Memory

Since the realization that long-term and short-term memory are mediated by distinct neural systems, several types of short-term

memory have been described. These include *iconic*, *immediate*, and *working* memory; however, these distinctions more accurately reflect the changing perceptions and models of short-term memory, rather than distinct brain structures and neural correlates mediating different types of memory (Fuster 1999). The definition of working memory widely used today emphasizes its dynamic nature and its role in the integration and manipulation of information for the guidance of behavior, as opposed to a passive storage (Baddeley 2003; Funahashi 2006; Smith and Kosslyn 2007). Our current results, however, suggest that the neural systems implicated in working memory may also be active during passive stimulus presentation. These findings do not exclude the possibility that training in a memory task can alter the magnitude, prevalence, or other characteristics of persistent discharges, and we do not wish to equate these discharges with memory. Our results unequivocally indicate, however, that neither training, nor effortful execution of a memory task is required for the generation of persistent activity.

Notes

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References

- Baddeley A. 1992. Working memory. *Science*. 255:556–559.
- Baddeley A. 2003. Working memory: looking back and looking forward. *Nat Rev Neurosci*. 4:829–839.
- Constantinidis C, Franowicz MN, Goldman-Rakic PS. 2001. The sensory nature of mnemonic representation in the primate prefrontal cortex. *Nat Neurosci*. 4:311–316.
- Constantinidis C, Procyk E. 2004. The primate working memory networks. *Cogn Affect Behav Neurosci*. 4:444–465.
- Constantinidis C, Steinmetz MA. 1996. Neuronal activity in posterior parietal area 7a during the delay periods of a spatial memory task. *J Neurophysiol*. 76:1352–1355.
- Frith C, Dolan R. 1996. The role of the prefrontal cortex in higher cognitive functions. *Brain Res Cogn Brain Res*. 5:175–181.
- Funahashi S. 2006. Prefrontal cortex and working memory processes. *Neuroscience*. 139:251–261.
- Funahashi S, Bruce CJ, Goldman-Rakic PS. 1989. Mnemonic coding of visual space in the monkey's dorsolateral prefrontal cortex. *J Neurophysiol*. 61:331–349.
- Fuster J. 1999. *Memory in the cerebral cortex*. Cambridge (MA): MIT Press.
- Fuster JM, Alexander GE. 1971. Neuron activity related to short-term memory. *Science*. 173:652–654.
- Goldman-Rakic PS. 1988. Topography of cognition: parallel distributed networks in primate association cortex. *Annu Rev Neurosci*. 11:137–156.
- Harris KD, Henze DA, Csicsvari J, Hirase H, Buzsaki G. 2000. Accuracy of tetrode spike separation as determined by simultaneous intracellular and extracellular measurements. *J Neurophysiol*. 84:401–414.
- Joelving FC, Compte A, Constantinidis C. 2007. Temporal properties of posterior parietal neuron discharges during working memory and passive viewing. *J Neurophysiol*. 97:2254–2266.
- Miller EK. 2000. The prefrontal cortex: no simple matter. *NeuroImage*. 11:447–450.
- Miller EK, Erickson CA, Desimone R. 1996. Neural mechanisms of visual working memory in prefrontal cortex of the macaque. *J Neurosci*. 16:5154–5167.

- Miller EK, Li L, Desimone R. 1993. Activity of neurons in anterior inferior temporal cortex during a short-term memory task. *J Neurosci.* 13:1460-1478.
- O Scalaidhe S, Wilson FA, Goldman-Rakic PS. 1997. Areal segregation of face-processing neurons in prefrontal cortex. *Science.* 278: 1135-1138.
- Postle BR. 2006. Working memory as an emergent property of the mind and brain. *Neuroscience.* 139:23-38.
- Quintana J, Fuster JM. 1992. Mnemonic and predictive functions of cortical neurons in a memory task. *NeuroReport.* 3:721-724.
- Rainer G, Asaad WF, Miller EK. 1998. Memory fields of neurons in the primate prefrontal cortex. *Proc Natl Acad Sci USA.* 95: 15008-15013.
- Rao SC, Rainer G, Miller EK. 1997. Integration of what and where in the primate prefrontal cortex. *Science* 276:821-824.
- Scalaidhe SP, Wilson FA, Goldman-Rakic PS. 1999. Face-selective neurons during passive viewing and working memory performance of rhesus monkeys: evidence for intrinsic specialization of neuronal coding. *Cereb Cortex.* 9:459-475.
- Schmolsky MT, Wang Y, Hanes DP, Thompson KG, Leutgeb S, Schall JD, Leventhal AG. 1998. Signal timing across the macaque visual system. *J Neurophysiol.* 79:3272-3278.
- Smith EE, Kosslyn SM. 2007. *Cognitive psychology: mind and brain.* Upper Saddle River, NJ: Pearson Education.
- Suzuki H, Azuma M. 1983. Topographic studies on visual neurons in the dorsolateral prefrontal cortex of the monkey. *Exp Brain Res.* 53:47-58.
- Wilson FA, Scalaidhe SP, Goldman-Rakic PS. 1993. Dissociation of object and spatial processing domains in primate prefrontal cortex. *Science.* 260:1955-1958.