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Persistent LIP Activity in Memory Antisaccades: Working Memory For a Sensorimotor Transformation

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Zhang, Mingsha and Shabtai Barash. Persistent LIP Activity in Memory Antisaccades: Working Memory For a Sensorimotor Transformation *J Neurophysiol* 91: 1424–1441, 2004. First published October 1, 2003; 10.1152/jn.00504.2003. The lateral intraparietal area (LIP) contains neurons that are active during the memory interval of memory saccades. We call these "persistent neurons." Here we study the activity of the persistent neurons in memory antisaccades, "motor" (the saccade is made toward the response field, although the response field is not stimulated visually) and "visual" (the response field is stimulated visually, but the movement is away from the field). Most persistent neurons are active during parts of the memory intervals of both visual and motor memory-antisaccades. Typically, these parts significantly overlap each other and together span the entire memory interval. The amplitude of the activity changes systematically during the memory intervals of visual and motor memory antisaccades. These changes are reflected in an antisaccade differential activity, which turns first to the visual direction and then crosses over to the motor direction. Some persistent neurons appear to show the paradoxical activity previously characterized in visual neurons; paradoxical activity accelerates the transition of the neuron's activity from visual to motor. These observations suggest that the persistent neurons reflect working memory for the computation of the antisaccade sensorimotor transformation. Ensembles of persistent neurons with different response fields may make up modules of working memory.

INTRODUCTION

In memory saccades, a subject must withhold a saccadic eye movement to a previously specified location for the duration of a "memory interval." Some neurons, in several brain regions, discharge during the memory interval until the movement is made. One prominent region with persistent activity is the lateral intraparietal area (LIP) (Barash et al. 1991a,b; Bracewell et al. 1996; Chafee and Goldman-Rakic 1998; Colby et al. 1996; Gnadt and Andersen 1988; Mazzoni et al. 1996; Pare and Wurtz 2001; Powell and Goldberg 2000; Thier and Andersen 1998). This area is part of the dorsal stream of visual cortex. Activity in LIP has been associated with intention to make saccades, with both reflection and control of attention (Bisley and Goldberg 2003), and with additional cognitive processes, such as perceptual decisions (Roitman and Shadlen 2002; Shadlen and Newsome 2001), predicted motion (Eskandar and Assad 2002), and assessment of hedonic utility (Platt and Glimcher 1999). Responses to memory saccades naturally segregate into three types, according to the timing of the activity during the trial. These three types of activity are visual, or light sensitive; persistent, or sustained, memory interval; and perisaccadic, or motor.

The present manuscript pertains to three problems, which relate to area LIP's neuronal activity during the memory interval of memory saccades (Barash et al. 1991a,b; Bracewell et al. 1996; Colby et al. 1996; Gnadt and Andersen 1988; Mazzoni et al. 1996; Pare and Wurtz 2001; Platt and Glimcher 1997; Thier and Andersen 1998). The first problem is whether the memory, which is conveyed by this activity, is visual or motor. This question is relevant to the two main theories of posterior parietal cortex function: one, the motor-intention theory, suggests that based on sensory input to this region, intentions are formed (Andersen 1987; Mountcastle et al. 1975); the other, the sensory-attentional theory, suggests that all activity in posterior parietal cortex reflects sensory and attentional processing (Bisley and Goldberg 2003; Bushnell et al. 1981; Colby et al. 1996; Colby and Goldberg 1999; Gottlieb and Goldberg 1999; Gottlieb et al. 1998; Powell and Goldberg 2000) or is used to control attention (Bisley and Goldberg 2003). Most previous studies, which tried to dissociate whether the memory-interval activity is visual or motor, had in common a conclusion that a neuron's memory activity is either visual or motor but not both (Barash et al. 1991b; Colby et al. 1996; Mazzoni et al. 1996; Powell and Goldberg 2000). We will relate to these contentions, as applied to memory antisaccades, as the visual and motor hypotheses, respectively.

The second problem to which this work pertains is how does the brain compute the sensorimotor transformation specific for antisaccades? What areas, what neurons, are involved in this computation? Antisaccades are saccadic eye movements directed away from rather than toward a visual target (Everling and Fischer 1998; Hallett 1978; Hallett and Adams 1980). The geometric transformation necessary for this computation was analyzed by Schlag-Rey et al. and is called the "inversion problem" (Schlag-Rey et al. 1997).

The third problem is this: does persistent activity reflect working memory? Persistent activity is widely perceived as a mechanism for preserving memory contents for short durations (seconds). But short-term memory is only one aspect of working memory. The notion of working memory was introduced by analogy to the computer metaphor (Miller et al. 1960; see also Dudai 2002); in a computer, the CPU changes memory contents according to the needs of the computation. It therefore appears to us that to qualify as a mechanism of working memory, it must be shown that computations can modify the persistent activity on the fly. This would hold for all neurons with persistent activity not only those in LIP. However, one difficulty must first be resolved. During memory, when the alleged computation occurs, subjects are instructed not to be-

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have. How can the computation be tapped in the absence of behavior?

This manuscript is concerned with the response properties of single LIP neurons. Neurons are units of information processing, but the response properties of single neurons are meaningful in the context of neuronal networks. Neurons are components of large networks; the function of single neurons is reflected in their effect on the network. Newsome and colleagues (Newsome et al. 1989) came up with a simple, compelling method for thinking about the effect of a neuron on a network. They defined for each neuron, an "antineuron," a hypothetical neuron defined as having the same response properties as the recorded neuron except for the position of the response field, which is opposite the recorded neuron's position. The notion of antineuron is particularly suitable for antisaccades (see RESULTS); the logic of antineurons underlies much of our analysis of the activity of individual neurons. We intentionally avoid detailed discussion of the entire network (Shadlen et al. 1996); such considerations go beyond the scope of the present article, which focuses on the properties of single neurons. Nevertheless, the analysis leads to the provisional conclusion that a neuron and its antineuron would make up a module of working memory for memory antisaccades in which targets are placed along the axis defined by the response fields of the neuron and the antineuron. Thus more generally, a set of persistent neurons with distributed response fields could serve as a working memory module for computing plans of where to look.

METHODS

The experimental procedures conform to the National Institutes of Health guidelines and Israeli law and were approved by the Animal Care and Use Committee of the Weizmann Institute. All techniques are, in essence, standard. We mention here mainly the variations from the standard which we used.

Preparation of monkeys

We used two adult *Macaca fascicularis* monkeys. The monkeys were born in a colony in Israel (BFC). After an habituation period, the monkeys were implanted with chronic-recording chambers placed over their posterior parietal lobules, with head holders, and with scleral search-coils for eye-position measurements. Monkeys were operated under general anesthesia in sterile, aseptic conditions. The recording chambers had 3-cm ID. The head holder was a 2-cm-wide hollow cylinder. Both head holders and chambers were made of tough plastic reinforced with removable stainless steel frames, internal (head holder) or external (chamber). Both head holder and chamber were produced by the local workshop. We used sterile orthopedic white bone cement (CMW 1, CMW Laboratories, Devon, UK) and never had problems of bone infection. The bone cement holding the head holder and the chamber was fixed to the skull with surgical titanium mini-screws (Aesculap, Tuttlingen, Germany).

Experimental setup

The recording setup was based on a Unix workstation running IEEE real-time extensions that communicated via a sockets protocol with computers running initially DOS, later Windows, that held data-acquisition equipment. The stimuli were produced by a GL-compatible board with refresh rate of 67 Hz. The real-time loop was locked on the vertical refresh signal and was closed within <1 ms. Spikes were collected with a temporal resolution of 0.1 ms. The computers were connected via a dedicated Ethernet loop. Two amplifiers were used for data collection, one of A-M, the other of Alpha-Omega. The signals generated by the two amplifiers were very similar. Eye position was recorded using the Robinson search coil technique (Fuchs and Robinson 1966) (Remmel Laboratories, MA), with surgery performed according to the procedure of Judge (Judge et al. 1980). Spikes of up to three different neurons were classified in real-time by Alpha-Omega shape discriminator from the same electrode (MSD, Alpha-Omega). We used a hydraulic microdrive (Trent-Wells) with its own *x–y* table for fixing the electrode location. The Trent-Wells *x–y* table has a 0.1-mm resolution but small range. A special adaptor was used to place the *x–y* table in 1 of 12 positions over the 3-cm-diam chamber so that the entire area of the chamber could be covered. The electrodes we used were of glass-covered tungsten, typically of 0.3- to 1-MΩ impedance at 1 kHz. Initially we scraped the dura of the monkeys, but subsequently we adopted a technique in which a guide tube is used to just penetrate the upper layer of the dura. When the electrode is lowered, a phase of high-noise high-impedance typical for crossing dura is faced before neuronal recordings are obtained.

Localization of LIP

The location of area LIP was determined according to standard physiological criteria (Barash et al. 1991a,b) and with the help of MRI images relative to chamber coordinates in one monkey. According to these criteria, the neurons reported here are from area LIP. Nevertheless, a minority of the neurons may have come from area MP/7m (Cavada and Goldman-Rakic 1989; Thier and Andersen 1998) or other neighboring regions (Andersen 1987; Colby et al. 1988).

Training and recording

Monkeys were first trained to perform memory prosaccades with >1 s of memory, only then to make memory antisaccades. The task is illustrated in Fig. 1. The red and green stimuli are isoluminant discs of the same size. The monkeys were also trained and tested in other oculomotor tasks. Some blocks contained the task of the present paper together with other conditions. We verified that these do not interact with the conditions described here by testing 12 cells with and without the additional conditions; the discharge characteristics remained unchanged. All recordings were conducted with the monkey in a completely darkened, sound-attenuated, and electrically shielded room. Following the isolation of a cell, we first mapped its preferred direction by testing the activity in memory prosaccades made toward a target in 1 of 12 equally spaced locations typically on a 15° circle around central fixation spot. Typical LIP neurons have a clear preferred direction, and in visuomotor neurons, this direction is common to the visual, memory, and motor discharges (Barash et al. 1991a). All the cells in the present study had clear preferred directions and were much less activated, if at all, in memory prosaccades made in the opposite directions.

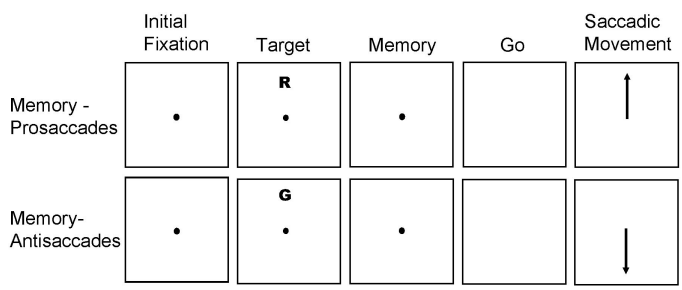

FIG. 1. Task details and trial stages. The only differences between memory prosaccades and memory antisaccades are in target color and required movement. **R**, a red target, **G**, a green target. Targets were always uniformly filled circles of the relevant color. The targets are not drawn to scale.

RESULTS

Database

We collected neurons from areas LIP of two monkeys. Having isolated a neuron, we first mapped the neuron's response field by running a block of memory saccades to 12 targets placed 30° apart from each other on a circle usually of 15° diam. Response fields in LIP tend to be arranged primarily by direction (Barash et al. 1991a). Neurons were admitted to the present study if they had, first, stable, healthy, sufficiently long recordings and, second, a clear directional selectivity in at least one response phase of memory saccades. Directional selectivity implies a significant difference between the activities in two opposite directions during at least one stage of memory-saccade trials (see next section for a specification of the trial stages or intervals). Third, we used the following test to determine whether the response of a neuron during the memory interval of memory prosaccades is persistent. We divided the 1-s memory interval into three disjoint consecutive subintervals and tested each subinterval whether the activity in memory-prosaccades made toward the response field is significantly greater than that in memory-saccades made in the opposite direction, using a *t*-test and 0.05-level threshold. A neuron is considered "persistent" only if its activity in the three subintervals is significantly higher than baseline (see next section for definition of trial classes).

Task

Figure 1 shows the mixed memory prosaccade, memory antisaccade task—for short, the "mixed task" (see METHODS for details). The two types of trials, memory prosaccades and memory antisaccades, differ from each other exactly in two parameters. First, they differ by the target's color; second, they differ by the corresponding required saccade: the red target indicates "saccade to the location in which the target had appeared;" the green, "saccade to the opposite location." Neurons of LIP, which is part of the dorsal visual stream, are generally insensitive to color. Differences in activity between the two types of trials are likely to reflect differently prepared saccades, not target colors (see DISCUSSION). All trials are made up of a sequence of four stages, or intervals, with the same timing: a 0.5-s initial fixation, 0.25-s cue, 1-s memory, and saccadic movement. The fixation spot's offset serves as the "go" signal. The identical durations of the different trials make it possible to directly compare how the responses evolve in different types of trials. These fixed durations may have effected certain details of our results (see section on antisaccade differential activity) but probably not their essence (see *Dispersion of the inversion times of individual neurons*).

Two active locations are assigned to each block of the mixed task. With respect to the central fixation spot, the two active locations are always opposite to each other. In each trial, a target is positioned in one of the block's active locations. The active locations are chosen for each neuron so that one location falls in the neuron's response field, the other in the location opposite the response field. This design, of two target locations × two tasks, yields four trial types. These trial types are illustrated in Fig. 2 for a schematic neuron with response field directed upward. The arrangement of the panels in Fig. 2 will be used repeatedly in all subsequent figures depicting examples of single neurons.

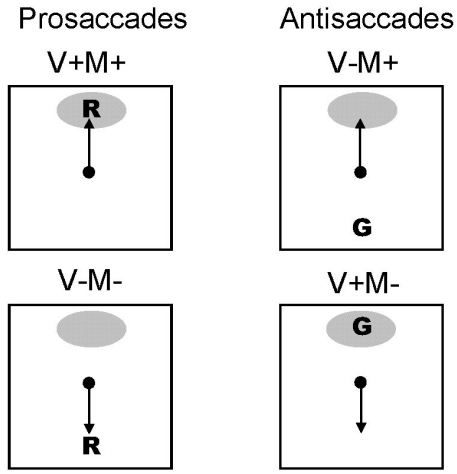

FIG. 2. The 4 types of trials mixed in each block. + and −, directions toward and away from the response field of the neuron being recorded. Here a schematic response field is drawn as a grey patch. Small black circles at the centers denote the fixation spot. Filled circle, **R**, a red target; **G**, a green target. Targets were always uniformly filled circles of the relevant color. The fixation spot and targets are not drawn to scale.

We will mark trials by V+ or V− according to whether the visual stimulus falls either in the response field or in the opposite direction and by M+ or M− according to whether the movement is made toward the response field or opposite to it. The visual and motor response fields are well aligned for the great majority of neurons (Barash et al. 1991a). Thus memory prosaccades are V+M+ or V−M−; either both visual stimulus and movement are toward the response field or both are in the opposite direction. V−M− is the baseline condition because activity in this condition is nonspecific, reflecting factors such as anticipation, in the absence of specific activation of the response field (Barash et al. 1991b; Colby et al. 1996). Memory-antisaccades are either V−M+ or V+M−. In V−M+, the saccade is made toward the response field although the response field is not stimulated visually. Therefore we call this condition "motor memory-antisaccades." Similarly, V+M− trials are "visual memory-antisaccades" because the response field is stimulated only visually but the required movement is away from the field.

Together, the two classes of memory antisaccades dissociate whether persistent memory-interval activity in V+M+ is related to the visual or the motor stimulation of the response field. This is the rationale we will use: if memory prosaccades show that a neuron has persistent activity, then persistent activity in visual memory antisaccades indicates that the activity is visual, because visually stimulating the response field evokes the activity in the absence of movement to the field; similarly, activity in motor memory antisaccades suggests that the activity is involved with motor intentions for making saccades toward the response field. This rationale is similar to that used in a previous study of mixed prosaccades and antisaccades in LIP (Gottlieb and Goldberg 1999) and also in other dissociation studies (Barash et al. 1991a; Bracewell et al. 1996; Mazzoni et al. 1996).

Note that a memory-antisaccade trial is not "visual" or "motor" on its own; a memory-antisaccade trial can be visual or motor only with respect to the response field of an individual neuron. Moreover, for two neurons with response fields opposite to each other, if a given memory-antisaccade trial is visual

for one neuron, it is motor for the other and vice versa: if a memory-antisaccade trial is motor for one neuron, it is visual for the other. This observation has an important consequence. We assign to each neuron an "antineuron" (Newsome et al. 1989), defined as a hypothetical neuron having the same response properties as the recorded neuron except for the position of the response field. The position of the antineuron's response field is defined to be the one opposite to the recorded neuron's response field. The activity recorded during memory-antisaccade trials visual and motor with respect to the recorded neuron are taken to reflect the antineuron's activity during motor and visual memory-antisaccade trials, respectively. We interpret the quantitative relationship between the activity in visual memory antisaccades and in motor memory antisaccades as reflecting the collective activity of the neuron and its antineuron in simultaneously recorded memory-antisaccade trials in which the target falls with equal frequency in the two active locations.

The mixed task is based on the presumption that neuronal responses to color in LIP are weak or absent. We did control recordings to support that contention, but recently Toth and Assad (2002) reported that in a specific condition they observe color-dependent differences in response. In the DISCUSSION, we show that the special condition of Toth and Assad does not apply to our task, so that in fact Toth and Assad's data provide more orderly support for the contention of color independence than available previously.

Neuron that might reflect pure visual memory

Using the mixed task, we now seek to find out whether the memory-interval activity of persistent neurons might reflect visual memory or intention.

The activity of the neuron illustrated in Fig. 3 may represent visual memory but not intention to make a saccade. The neuron has persistent activity in memory prosaccades: a target falling in the neuron's response field triggers a discharge that outlasts the target's offset and persists throughout the memory interval (Fig. 3*A*, V+M+). This persistent activity is directional: a target in the opposite location elicits no response (Fig. 3*B*, V−M−). Is the persistent activity of this neuron visual or motor intentional? Memory antisaccades suggest that the memory conveyed by this neuron is probably visual. In motor memory antisaccades (V−M+, Fig. 3*D*), the neuron is hardly activated. In visual memory-antisaccades (V+M−, Fig. 3*E*), the neuron briskly responds to the appearance of the target. The response persists throughout the 1-s memory interval until the movement. Thus this neuron's memory-interval activity appears to be, first, related to the visual memory of a target falling in the response field and, second, unrelated to the intention to make a saccade toward the response field. This response pattern is consistent with the visual-memory hypothesis. Nevertheless, this response pattern is not common in LIP (see following text).

Figure 3, *C* and *F*, illustrates the neuron's prosaccade and antisaccade differential activities, which are defined and discussed in the following text.

Neuron that might reflect pure motor intention

Figure 4 shows the activity of another LIP neuron that is consistent with the alternative hypothesis, ie, that the memory-interval activity represents the intention to make the requested saccade at the end of the trial.

In memory prosaccades toward the neuron's response field (V+M+, Fig. 4*A*), the neuron responds with a build-up that follows the target and persists throughout the memory interval. Memory-prosaccades in the opposite direction evoke no response (V−M−, Fig. 4*B*). Thus this neuron, too, has persistent memory-interval activity. Is the memory conveyed by this activity likely to be visual or motor intentional?

Memory antisaccades show that the memory conveyed by this neuron probably reflects the intention to make the saccade. The neuron is inactive in visual memory antisaccades (Fig. 4*E*). The activity in motor memory antisaccades shows a build-up similar to that in memory prosaccades; the activity is higher in motor memory antisaccades than in visual memory antisaccades from the beginning of the memory interval continuously until after the saccade. This pattern is consistent with the intention hypothesis. Nevertheless, this response pattern is also uncommon in LIP, as we describe in the following text.

Differential activity (DA)

Running the mixed task while recording the activity of a neuron, we measure the neuron's response in trials of four types (Fig. 2). We can therefore compute an array of mean activity for each of these trial types: $A_{V+M+}(t)$ and $A_{V-M-}(t)$ for prosaccades, $A_{V+M-}(t)$ and $A_{V-M+}(t)$ for antisaccades. Here t signifies time in the trial, and $A_X(t)$ the mean rate at time t of the trials of group X.

We compare two activity arrays by examining their differential activity. Differential activity can be a most useful tool; we will use it in two contexts.

First, a neuron's activity in a typical memory-saccade trial reflects stimulation of its response field, by a target falling in the response field, or by the planning of a saccade toward a position inside the response field or by both. However, not all the unit's activity reflect is response-field dependent; for example, activity during the initial fixation interval is nonspecific. How can we segregate specific activation from nonspecific?

One possibility is to subtract from the total response a baseline estimating all nonspecific activations, such as caused by anticipation (Colby et al. 1996). Because in V−M− trials the response field is not stimulated, the mean activity in these trials gives the nonspecific activation. Net responses of the other trial types are defined as the differential activity with respect to A_{V-M-}. For example, a neuron's net response in memory prosaccades made toward its response field is defined as *net* $A_{V+M+}(t) = A_{V+M+}(t) - A_{V-M-}(t)$.

Net activity filters out nonspecific factors that affect all trial types equally. Yet in principle, the fixed trial durations that we use may differentially affect response-field-dependent activity (Leon and Shadlen 2003). Consider the example of visual memory antisaccades. Had we used a very short memory interval instead of 1 s, perhaps after target offset the activity would have returned to baseline more quickly. Nevertheless, it appears to us that the main results reported in this paper do not depend on the fixed trial duration because we are interested not in the dynamics of one element but in the way all elements work together (see DISCUSSION, section on dispersion of the time of inversion of individual neurons).

Differential activity is particularly useful also to characterize

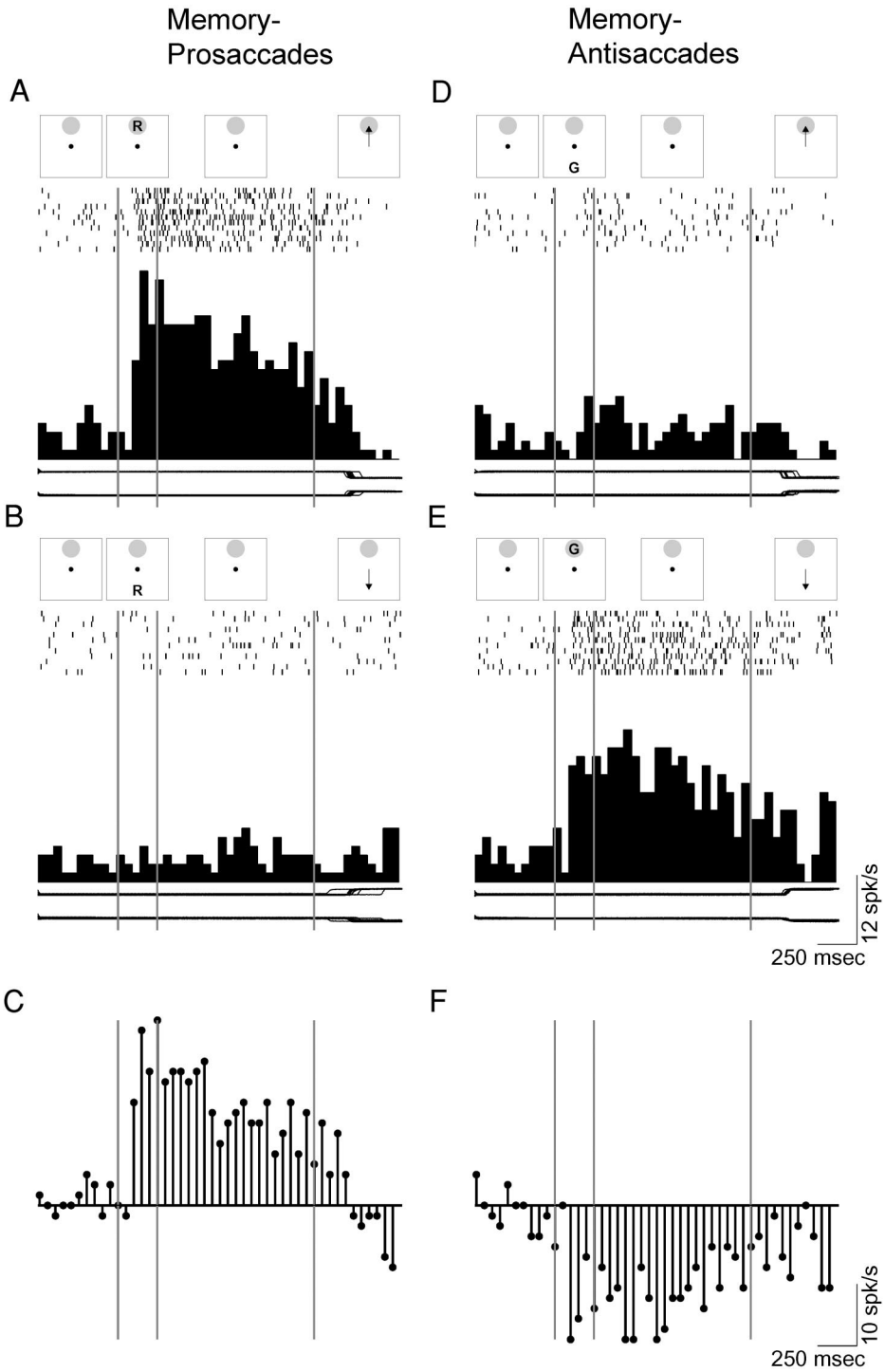

FIG. 3. A persistent neuron that might reflect purely visual memory. The panels are organized as in Fig. 2. *A, B, D,* and *E*: from top, a scheme of the task in the format of Figs. 1 and 2, raster and spike histograms, and vertical and horizontal components of eye position. The records of each trial are drawn as separate lines in the raster but are superimposed in the eye position records. *C* and *E*: the differential activities (for prosaccades and antisaccades, respectively). Trials are aligned with respect to the stimuli. The records begin when the monkey saccades to a fixation spot that had just come on. The vertical gray lines denote, from left, the onset and offset of the target, followed by the memory interval, and then offset of the fixation spot, followed by the saccade.

task-specific activity. We define an antisaccade differential activity as the time-dependent difference of the activities in motor and in visual antisaccades, $DA_{Anti}(t) = A_{V-M+}(t) - A_{V+M-}(t)$ and, similarly, a prosaccade differential activity as $DA_{Pro}(t) = A_{V+M+}(t) - A_{V-M-}(t)$. The prosaccade differential activity is identical to the net prosaccade response, *net* A_{V+M+}; we use either name according to context.

The antisaccade differential activity establishes a visual-motor dimension for each neuron. A negative value of the differential activity at a given time in the trial reflects a higher activity at that time in visual memory antisaccades than in motor memory antisaccades. Thus, negative values of DA_{Anti} correspond to predominantly visual activity. Similarly, positive values of DA_{Anti} correspond to activity that may reflect motor intention.

The antisaccade differential activity is readily interpreted in terms of antineurons as the difference in activity between the recorded neuron and its antineuron during the same trial (see *Task* above. Formally, the differential activity can be defined as a weighted sum of the activity of the two neurons with the weight of each neuron being -1 or $+1$ according to whether the target falls in or out of the neuron's response field). Thus the difference between the activity in separate trials—of visual

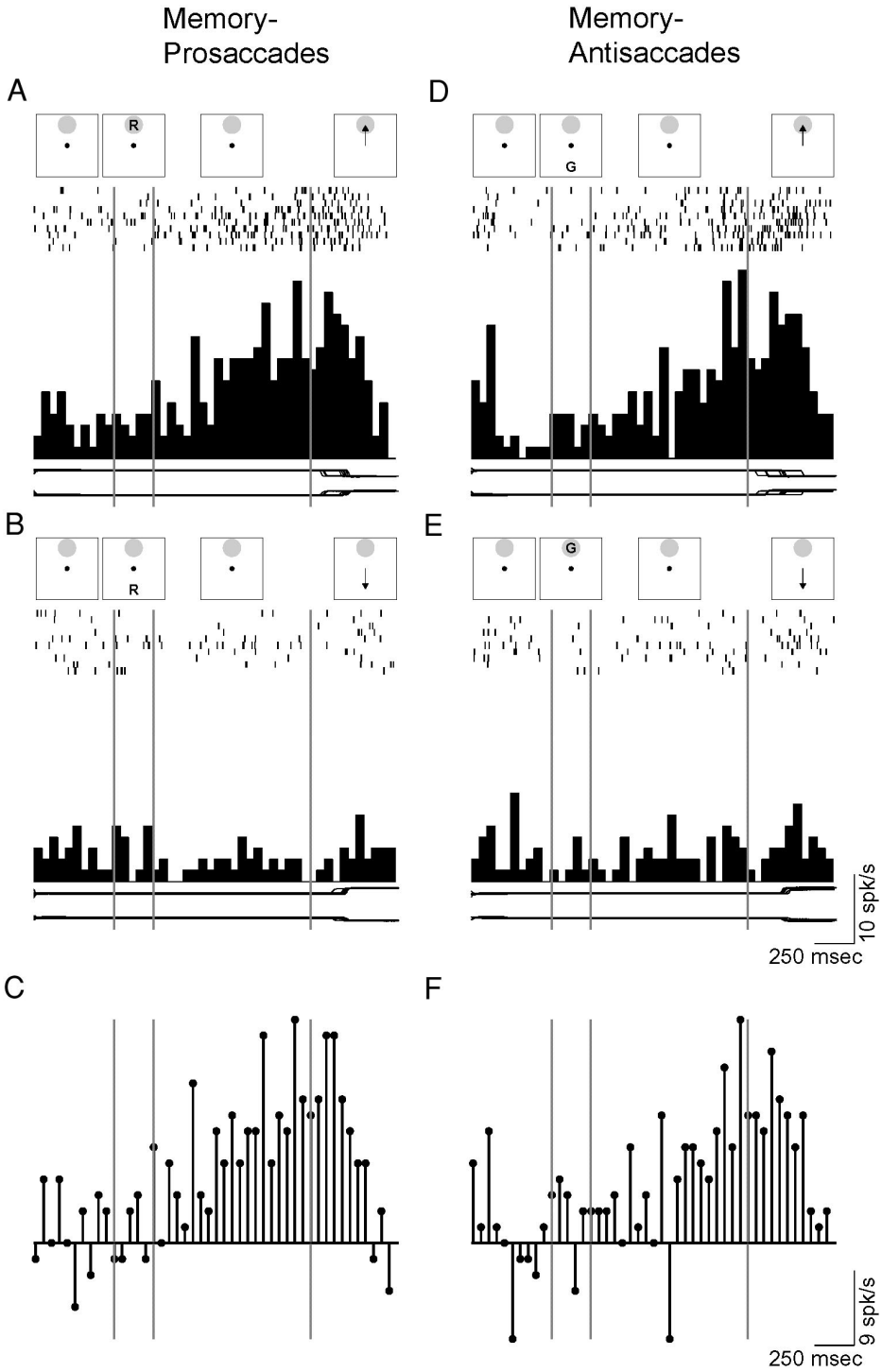

FIG. 4. A persistent neuron that might reflect the intention to make a saccade. Same format as Fig. 3.

memory antisaccades and of motor memory antisaccades—is interpreted as a difference in simultaneous activity of two neurons. This interpretation is pertinent to the analysis of the responses of single neurons presented in the rest of RESULTS even when not explicitly referenced.

For the neurons illustrated in the preceding text, the putative visual memory neuron's DA_{Anti} is negative throughout the memory interval (Fig. 3*F*) and the putative motor intention's neuron's DA_{Anti} is positive (Fig. 4*F*). The differential activities of both neurons during the memory interval reflect mostly a single memory-antisaccade condition (V+M− in Fig. 3, V−M+ in 4) because the activity in the other memory-antisaccade condition is close to zero. An example of a neuron for which the antisaccade differential activity is shaped by both types of memory-antisaccades now follows.

Neuron active during the memory interval of both visual and motor memory antisaccades

Figure 5 illustrates the response of a persistent LIP neuron, whose response pattern is more common in LIP than the

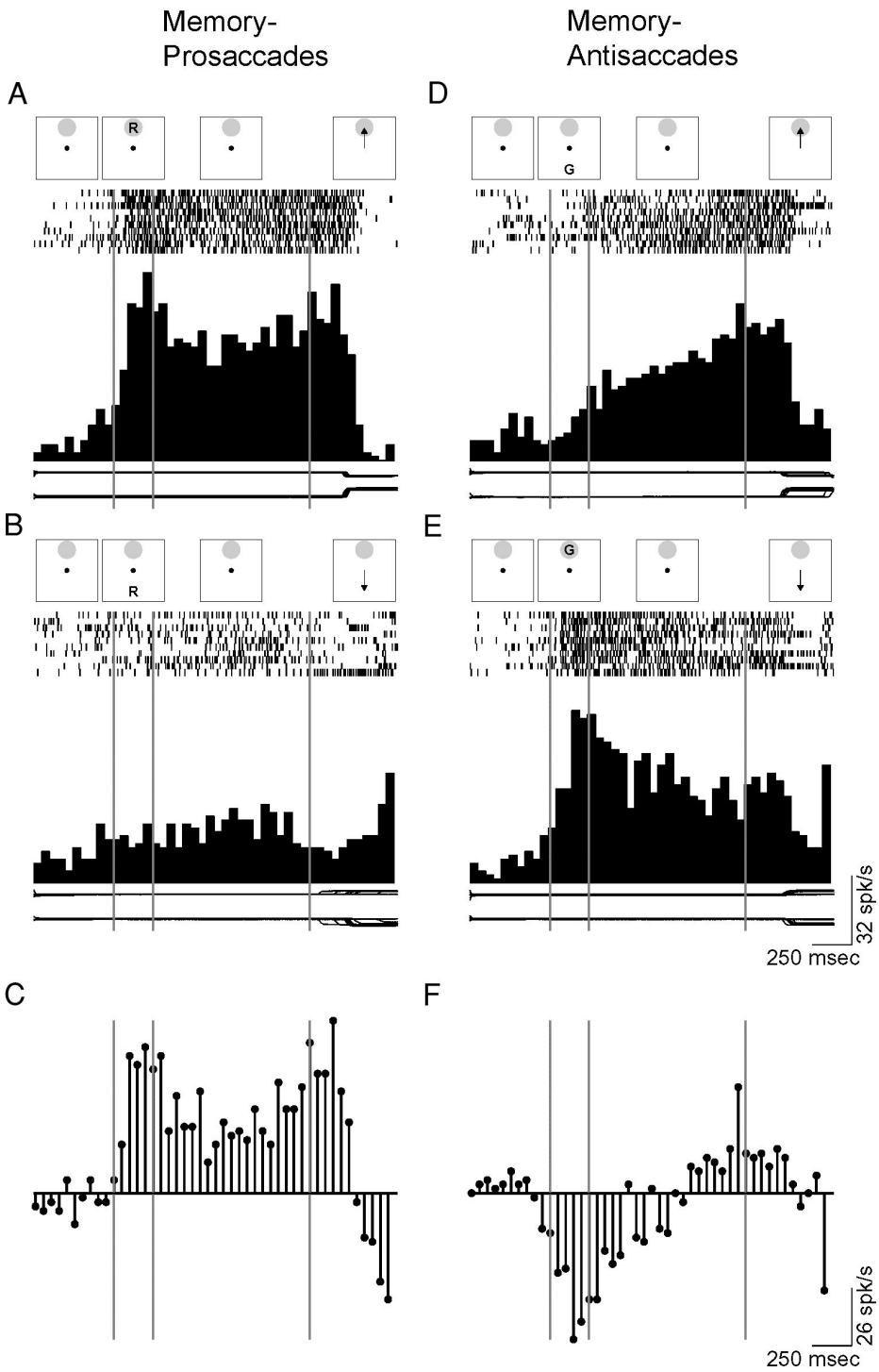

FIG. 5. A persistent neuron with memory-interval activity in both visual and motor memory antisaccades. Same format as Fig. 3.

response patterns of the neurons of Figs. 3 and 4. The response in memory prosaccades (Fig. 5, *A*, V+M+ compared to *B*, V−M−; hence DA_{Pro} in *C*) confirms that this neuron's response persists throughout the memory interval of memory prosaccades until the movement. In memory antisaccades, this neuron is active in both visual and motor memory antisaccades. The neuron's responses during the memory intervals, of both visual and motor memory antisaccades, are persistent (Figs. 5, *D* and *E*)!

The activity of the neuron of Fig. 3 is consistent with the visual memory hypothesis because that neuron is active during the memory interval only in visual not in motor memory antisaccades. Given a recording of that neuron's activity in a memory-antisaccade trial, we can reliably assess whether the trial is a visual or a motor memory antisaccade according to whether the given trial has or does not have significant memory-interval activity. Similarly, we can reliably state for the neuron of Fig. 4 that it is a motor not visual memory antisaccade if the given trial has significant memory-interval activity. Thus for each of these neurons, knowing whether the neuron

was or was not active during the memory interval of a given trial allows us to predict the direction of the planned saccade.

No such prediction can be made from the observation of memory-interval activity in a trial of the neuron of Fig. 5 simply because memory-interval activity is present in both visual and motor memory antisaccades. Thus the neuron of Fig. 5 is not strictly consistent with either the visual hypothesis or the motor hypothesis: the response of this neuron in motor memory antisaccades, by itself, could seem to suggest that the build-up activity encodes the evolving motor intention (Fig. 5*D*). The sharp onset of the response in visual memory antisaccades, by itself, could seem as a visual response persistent into memory (Fig. 5*E*).

Although the presence of activity does not distinguish between visual and motor memory antisaccades, quantitatively the two responses differ from each other. The changes in the activity during the memory interval of visual and motor memory antisaccades, correspondingly, are reflected in the antisaccade differential activity (Fig. 5*F*). Nearly zero before target onset, the differential activity sharply turns to the visual direction shortly after target onset. But it points to the visual direction only transiently: the differential activity crosses over to the motor direction and remains so directed until the movement is made. Thus the antisaccade differential activity reflects the transition from visual to motor.

We previously showed that the differential activity of a sample from the entire population of area LIP reflects the inversion (Zhang and Barash 2000). However, the inversion of the mean differential activity of the population could result from contrasting contributions of separate subpopulations of visual and of motor-intention neurons. Here we show that this does not happen. Instead, inversion is observed on the level of LIP's single neurons.

Impact of the paradoxical activity

We previously described a "paradoxical activity" in LIP. It is a discharge that occurs in about one-third of the neurons that are classified as visual by the timing of their response in memory prosaccades. As expected of all visual neurons, these neurons have a visual response in visual memory antisaccades. Unlike truly visual neurons, neurons with paradoxical activity discharge also in motor memory antisaccades. Even though the response field is not visually stimulated, paradoxically, these neurons fire with nearly the timing of visual activity. The latency of the mean paradoxical response is only slightly higher than that of the mean visual response. The paradoxical activity differs from the well-described build-up of persistent activity that might reflect the motor intention to make the saccade as illustrated in Figs. 4*D* and 5*D*. In the case of visual neurons with paradoxical activity, the paradoxical activity returns to baseline long before the saccadic movement begins (Zhang and Barash 2000).

Some neurons with persistent activity appear to also involve paradoxical activity. Figure 6 illustrates the response of one such neuron. Memory prosaccades show that this neuron's activity is indeed persistent (Fig. 6, *A–C*). Visual memory antisaccades show a vigorous visual response (Fig. 6*E*). Initially, this visual response is similar to the neuron's visual response in memory prosaccades (Fig. 6*A*). Several hundred milliseconds into the memory interval, the response in visual memory antisaccades decreases—though not quite to baseline, persisting throughout the memory interval (compare Fig. 6, *E* to *B*). The main difference of the response of this neuron (Fig. 6), as compared with that of Fig. 5, is in motor memory antisaccades (Fig. 6*D*). The slow, monotonic build-up of Fig. 5*D* is replaced with a response that appears to be the sum of two components: one is a slowly increasing build-up, similar to that of Fig. 5*D;* the other component, unique to Fig. 6*D*, is a discharge with a sharp onset with a latency slightly longer than the neuron's visual latency (the difference in latencies is ~50 ms). This second component continues for less than half a second and is then shut off. This second component resembles a visual response with a slightly increased latency. However, this activity component can not be visual because the target falls in the direction opposite the neuron's response field (see task diagram above the raster in Fig. 6*D*). The second component of the activity illustrated in Fig. 6*D* thus has the defining characteristics of paradoxical activity.

We thus suggest that paradoxical activity occurs in persistent neurons like in visual neurons. A quantitative study of the paradoxical activity in persistent neurons is, however, not possible because of the confounding presence of the simultaneous motor build-up.

The paradoxical activity profoundly influences the neuron's antisaccade differential activity. The transition from visual to motor occurs much earlier during the trial in persistent neurons with paradoxical activity than in persistent neurons without (compare DA_{Anti} in Figs. 5 and 6). Although the speed with which the transition from visual to motor is computed is not functionally significant in the laboratory conditions of our task, in nature, the speed of the transition from visual to motor can be very significant. Therefore the paradoxical activity might be a mechanism for speeding up the computation of the specific sensorimotor transformation in which these monkeys are experts.

Duration of responses in memory antisaccades

This paper focuses on neurons that have persistent activity in memory prosaccades. Is the activity of these neurons in memory antisaccades also persistent? We first have to define more precisely the sense in which a memory-antisaccade response would be considered persistent. Do these neurons behave like memory cells of contemporary digital computers in which contents are maintained until a new value is written into the cell (Miller et al. 1960)? We suggest the following analogy: the memory represented by a neuron can have two values, visual or motor, according to the classes of memory antisaccades in which the neuron is active. The question is whether our neurons maintain at least one of these values, visual or motor, throughout the trial. In other words, whether at each point during the memory interval there is activity in either visual or motor memory antisaccades. Neurons for which the answer to this question is positive would thus be considered "persistent" also in memory antisaccades. Although memory content is computed here from the activity of the recorded neuron in separate trials, the simultaneous activity of a neuron-antineuron pair would reflect memory content in the same way.

Figure 7 shows that, with the preceding definition, most neurons classified as persistent in memory prosaccades are also persistent in memory antisaccades. We divide the memory

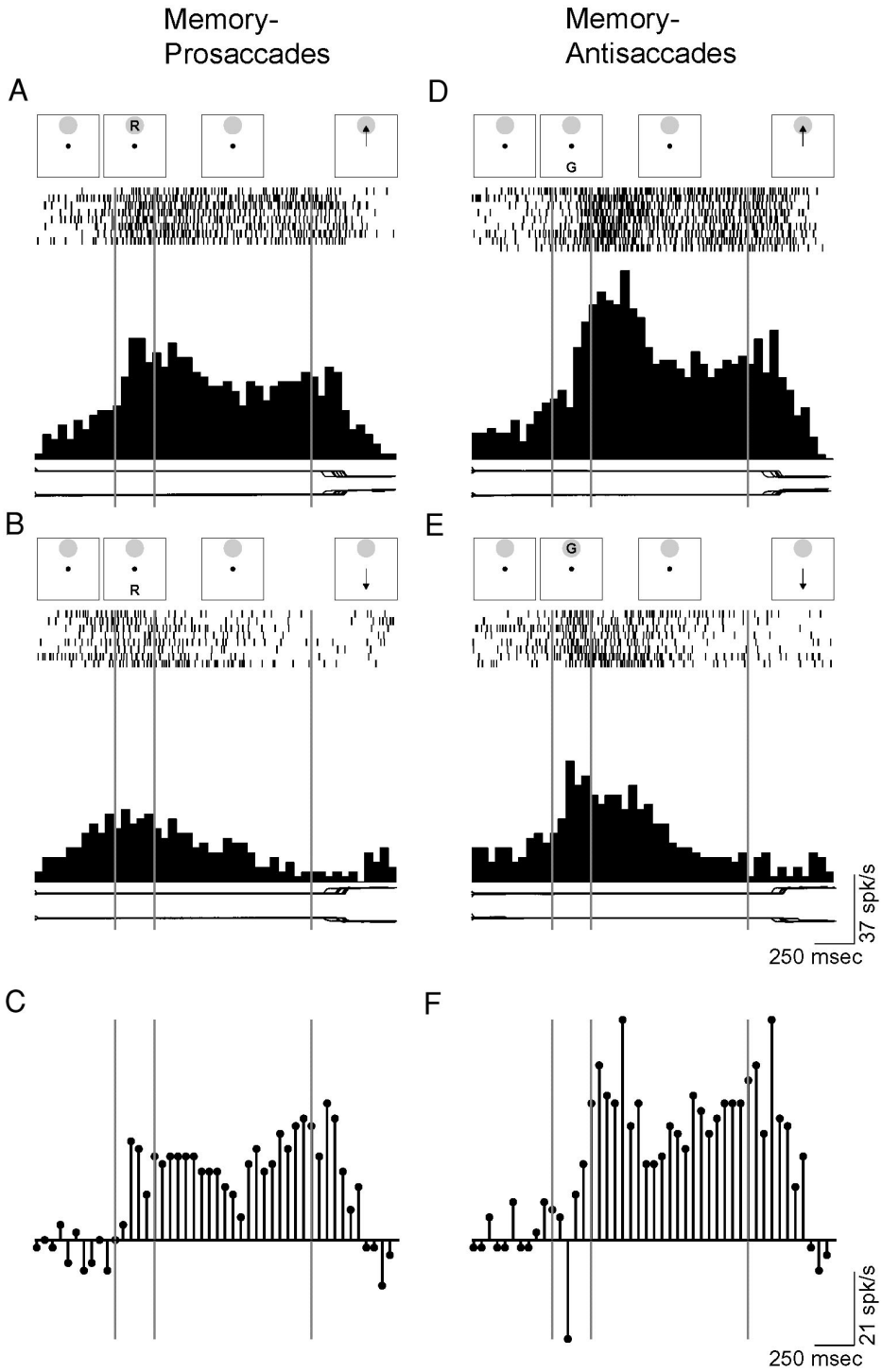

FIG. 6. A persistent neuron with memory-interval activity in both visual and motor memory-antisaccades *and* with paradoxical activity. Same format as Fig. 3.

interval into 10 100-ms bins; for each neuron, and each trial type, we count the number of bins in which the respective net activities are positive. The median duration of the activity in memory prosaccades is 1 s, the full duration of the memory interval—not a surprise because persistent activity in memory prosaccades is the defining criterion of our sample of neurons. In both memory-antisaccade classes, the duration is commonly less than the full memory interval—with both medians at 900 ms, for V+M− and V−M+. Thus most neurons are active for most of the duration of both memory-antisaccade trials. To evaluate the total extent of the activity in the two directions, we define a combined antisaccade activity as the activity in the direction with greater activity of each bin, that is, $\max_t[\text{net } A_{V+M-}(t)\ \text{net}A_{V-M+}(t)]$ where t goes over all memory-interval bins. The duration of the combined activity is usually the full duration of memory (median: 1 s). In sum, the combined activity is persistent in memory antisaccades. This results can be interpreted as stating that either the neuron or its antineuron are active at any given instance of the memory interval. These results are relevant for the involvement of LIP in working memory (see DISCUSSION).

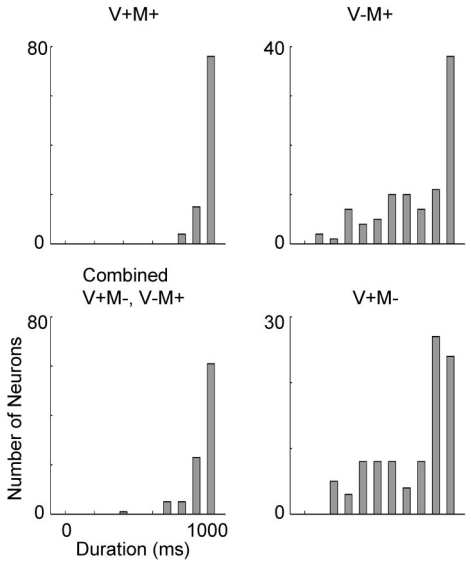

FIG. 7. Duration of the combined memory-interval activity during the memory interval of memory antisaccades: most persistent neurons are active in at least one direction for the entire duration of the memory.

Mean responses of all persistent neurons

The neurons of Figs. 5 and 6 are active during the memory intervals of both visual and motor memory antisaccades. These responses overlap in time; it is impossible to point to a time in the trial such that before that time most of the activity is visual and after that time most of the activity is motor.

Figures 8*A* and 9*A* show the mean net responses of all 102 persistent neurons in visual memory antisaccades (thin black traces), motor memory antisaccades (thick black traces), and, for comparison, also memory prosaccades (gray traces). For brevity, we will subsequently refer to these as "mean net responses," or just "mean responses" if no confusion is likely to occur. In Fig. 8*A*, the mean net responses are aligned on the stimuli; in Fig. 9*A*, they are aligned on the beginning of the saccadic movements. Both mean net responses are persistent throughout the memory interval (Fig. 8*A*), indeed, until the saccade begins (Fig. 9*A*).

The mean net response in motor memory antisaccades (thick black traces) begins with a phase that appears to reflect mostly neurons with paradoxical activity such as that of Fig. 6. Indeed, the latency of the mean paradoxical response in visual neurons is slightly longer than that of their visual response (Zhang and Barash 2000). In correspondence, we observe that the latency of the mean net response in motor memory antisaccades is slightly (by ~100 ms) longer than the latencies of the mean net responses in both visual memory antisaccades and memory prosaccades (thin black and gray traces); the mean net responses in the last two conditions reflect visual responses. When the mean net response in motor memory antisaccades eventually begins, it increases sharply, almost as sharply as the mean net visual responses, and subsequently, toward the middle of the memory interval, it decreases. Thus this initial phase of the mean net response is reminiscent of the activity component thought to reflect paradoxical activity in Fig. 6*D;* the initial phase of the mean net response in motor memory antisaccades probably represents paradoxical activity in persistent neurons. After this phase, the activity builds up again toward the time of the saccade.

The mean net response in visual memory antisaccades begins with a vigorous initial peak that reflects the visual responses. After the target's offset, the mean net response gradually decreases. Nevertheless, the mean net response remains elevated above baseline throughout memory (Fig. 8*A*), and this elevation continues even after the saccade is made (Fig. 9*A*).

Thus on the level of the population, the mean net responses in visual and motor memory antisaccades are both persistent and overlap each other throughout the 1-s memory interval.

Mean antisaccade differential activity

The mean net responses in both visual and motor memory antisaccades persist throughout the memory interval. Nevertheless, the amplitudes of these persistent activities change. These changes are reflected in the mean antisaccade differential activity, which can be defined either as the mean of the differential activities of the individual neurons—or, equiva-

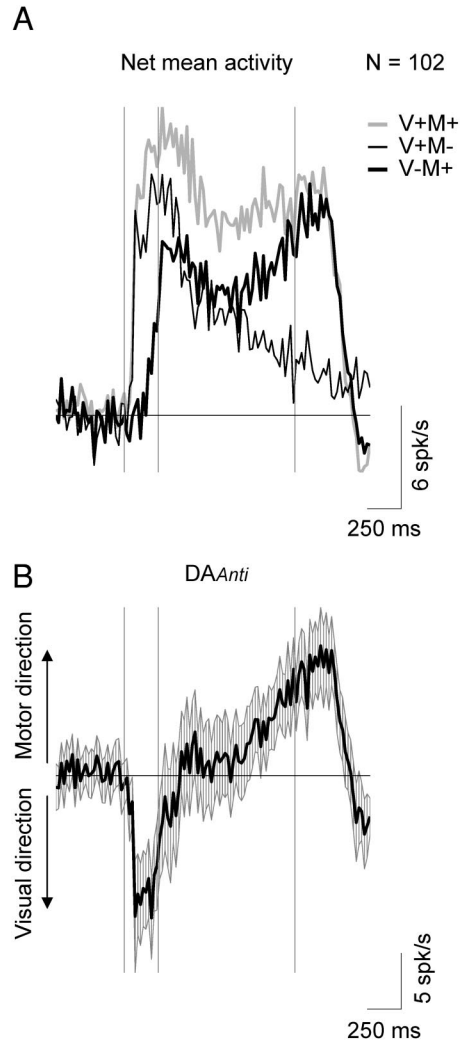

FIG. 8. Mean responses and differential activity computed from the 102 persistent neurons. *A*: mean net responses. Gray, response in memory-prosaccades; thin black and thick black, responses in visual and motor memory antisaccades, respectively. Responses are aligned on stimuli. Vertical gray lines denote, from left, target onset, target offset, and fixation spot offset. *B*: antisaccade differential activity. Vertical bars show pointwise 95% confidence interval.

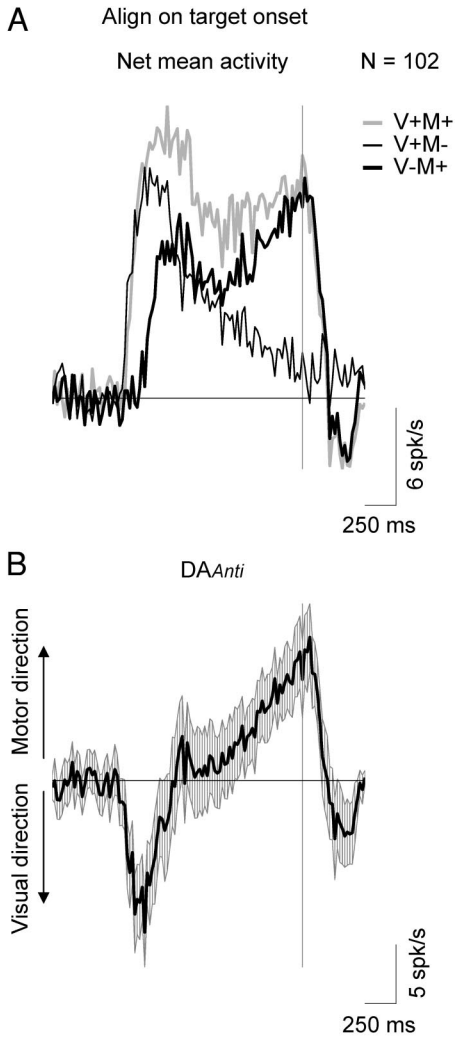

FIG. 9. Same as Fig. 8 but aligned on the beginning of the saccadic movement (marked by gray vertical line).

lently, as the difference between the mean responses. The mean antisaccade differential activity is illustrated in Figs. 8*B* and 9*B*, aligned, correspondingly, on the stimuli and on the beginning of the saccade. The gray regions in the two figures show the pointwise 95% confidence intervals for the antisaccade differential activity; that is, it is the 95% confidence interval calculated separately for each time bin.

Nearly zero until shortly after stimulus onset, the mean antisaccade differential activity rapidly increases in the visual direction but then reverses direction and crosses over to the motor direction at the beginning of the memory interval (Fig. 8*B*). After turning to the motor direction, the mean differential activity is initially low, and the 95% confidence intervals are not entirely positive (Fig. 8*B*). Thus the null hypothesis that the antisaccade differential activity is zero or even negative at each of these time bins cannot be rejected. However, this appears to reflect mainly a limitation on the amount of data because, taken together over this interval, the mean differential activity is significantly positive (not shown). At about the middle of the memory interval, the mean differential activity begins to increase, becomes significantly positive, and peaks at the time of the saccade (Fig. 9*B*).

Overlap on the level of single neurons

Although Figs. 8*A* and 9*A* show that the mean net responses in visual and motor memory antisaccades overlap throughout the memory interval, it does not specify how the activity is distributed at any given time over the neuronal population. Thus the thin and thick black curves of Figs. 8*A* and 9*A* could in principle reflect contributions of disjoint sets of neurons—thin black curves, neurons active during the memory interval of visual memory antisaccades but not during the memory interval of motor memory antisaccades as illustrated in Fig. 3; the thick black curves, neurons active during the memory interval of motor memory antisaccades but not during the memory interval of visual memory antisaccades as in Fig. 4. Alternatively, the overlap of visual memory and motor intention could truly be on the level of single neurons as in Figs. 5 and 6. Figures 3–6 show that each of these two possibilities holds for some neurons. Which one is typical for LIP's persistent neurons?

We used two approaches to answer this question, and both gave similar answers. The first approach was to use a statistical test for assessing whether activity of individual neurons during subintervals of the memory interval is significant. We adapted the test used to determine whether a neuron is persistent based on its activity in memory prosaccades. We divided the 1-s memory interval into three disjoint consecutive subintervals and tested for each subinterval whether the activity in either type of memory antisaccades is significantly greater than that in V−M− using a *t*-test and 0.05-level threshold. Fourteen of the 102 neurons had significant activity only in subintervals of the memory interval of visual memory antisaccades. Twelve had significant activity only in subintervals of motor memory antisaccades. Four neurons did not reach significance in either type of memory antisaccades. The other 72 neurons had significant activity in subintervals of both visual and motor memory antisaccades.

In the second approach to the question of overlap on the level of single neurons, we compare each neuron's normalized activity during the core of the memory intervals of visual and motor memory antisaccades. We define visual and motor indices for each persistent neuron in the following manner. The net numbers of spikes generated during the middle halves of the memory intervals, in visual memory antisaccades and in motor memory antisaccades, are normalized by the net number of spikes during the same time window of memory prosaccades: $(N_{V+M-} - N_{V-M-})/(N_{V+M+} - N_{V-M-})$ and $(N_{V-M+} - N_{V-M-})/(N_{V+M+} - N_{V-M-})$ respectively. Here N_X is the number of spikes in the middle half of the memory interval in trial class X; the "middle half" of the memory interval spans the 0.5 s starting at 0.25 s and ending at 0.75 s into the 1-s memory interval. Figure 10*A* shows the scatter of these indices; each dot represents a persistent neuron.

The visual and motor indices are useful for testing the visual and motor hypotheses (see INTRODUCTION). The visual hypothesis leads to the prediction that the motor index of most neurons would be close to zero, whereas the visual index would be significantly greater than zero. Thus if the visual hypothesis holds, most neurons would fall in the visual sector of Fig. 10*A*. Similarly, if the motor hypothesis holds, most neurons would fall in the motor sector of Fig. 10*A*. Thus each

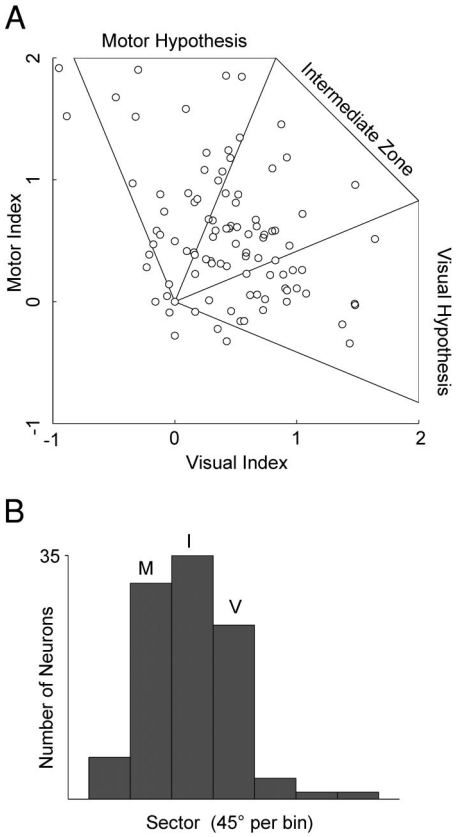

FIG. 10. Activity indices during the middle 0.5 s of the memory in the visual and motor directions. *A*: scatter diagram of the visual and motor indices of each neuron. ○, a neuron. There are 3 sectors, 2 representing regions that are consistent with either of the 2 hypotheses described in the introduction. *B*: a histogram of the numbers of neurons in each sector of *A* shows that neither hypothesis is supported by the data. Each bin in the histogram reflects the similarly colored sector of *A*.

hypothesis predicts that most of the neurons would fall in a single sector.

A quick glance at Fig. 10*A* suffices to show that neither of these predictions is valid. Figure 10*B* shows the number of the neurons in the different sectors. The results show that the neurons are not concentrated in either the visual sector or the motor sector. Furthermore, a compromise prediction, stating that neurons are either visual or motor but not both, also fails: the distribution is not bimodal with one mode in the visual sector and a second mode in the motor sector. In fact, the distribution is unimodal, the single mode falling in the zone of neurons with combined visual and motor activity. Thus there is a continuum of neurons on the dimension of visual to motor.

Incidentally, Fig. 10*A* shows that neurons with very high visual and motor indices, that is, neurons placed far from the origin in Fig. 10*A*, tend to fall in the motor sector. This tendency is on the border of statistical significance.

In summary, the responses of most persistent neurons in visual and motor memory antisaccades significantly overlap in time. The neurons of Figs. 5 and 6 are more typical of LIP than those of Figs. 3 and 4.

Distribution of the time of inversion of individual neurons

Now that we know that most neurons are active during the memory intervals both of visual and of motor memory antisaccades, another question comes up. Is the inversion of the mean antisaccade differential activity, plotted in Figs. 8*B* and 9*B*, typical for single neurons or is it a construct of the population? There are two more specific questions. First, how typical is it for single neurons that their antisaccade differential activity inverts from the visual to the motor direction? The antisaccade differential activities of the neurons of Figs. 5 and 6 do invert, but those of Figs. 3 and 4 do not. The second question may have interesting general implications for the role of single neurons in coding by populations. It relates to those neurons whose antisaccade differential activities do invert from visual direction to motor. The question is: what is the distribution of the times of inversion of the antisaccade differential activities of these neurons? Although the neurons illustrated in Figs. 5 and 6 both invert from visual to motor, they do so at very different times. Which one of the two neurons is typical? Are the two neurons functionally equivalent?

Of the 72 neurons that had significant activity in both visual and motor memory antisaccades, the antisaccade differential activity of 61 neurons (85%) inverted from visual direction to motor. Figure 11 shows the distribution of the times of inversion. There are five consecutive 0.25-s bins, the first spanning the time the visual target is on, the others spanning together the 1-s memory interval.

Many neurons invert early in the trial. The antisaccade differential activity of nine neurons (15%) turns to the motor direction while the target is still on. This fraction is remarkable because at this time the monkey's attention is probably powerfully drawn to the single, very salient visual stimulus present. The early inversion times of these neurons probably reflect the presence paradoxical activity in their responses in motor memory antisaccades.

Of the neurons that invert during the memory interval, those

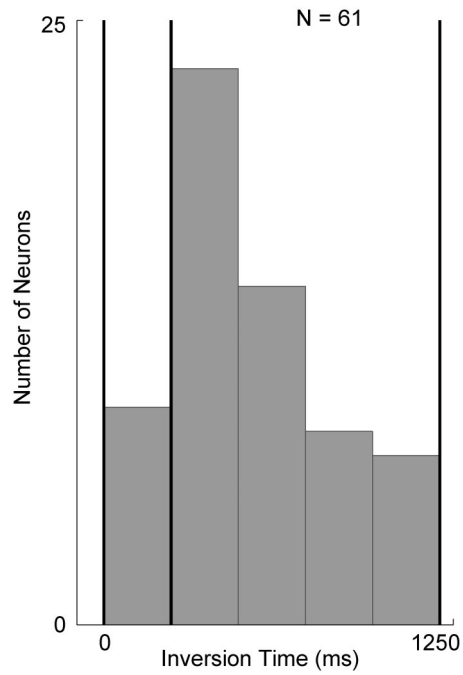

FIG. 11. Distribution of the times during the trial in which the differential activity of individual neurons inverted from the visual direction to the motor. Vertical lines show target onset and offset and fixation spot offset, as in the figures above.

that invert *early* during the interval predominate. More neurons invert during the first 0.25 s subinterval of the memory than during the other subintervals. Afterward, fewer and fewer neurons invert with every additional bin. The mean inversion time is 285 ms into the memory interval, the median is 219 ms.

Nevertheless, not all neurons invert early. Fifteen neurons (25%) invert during the second half of the memory interval. Overall, inversion times vary significantly between neurons; the standard deviation is 311 ms, the inter-quartile range is 480 ms.

Comparison with activity in memory prosaccades

The mean net response in visual memory antisaccades is lower than the mean net response in memory prosaccades throughout the trial (Fig. 8*A*, thin black trace compared with gray trace). The same holds for the mean net response in motor memory antisaccades (Fig. 8*A*, thick black trace compared with gray trace), except, perhaps, for a brief period just before the saccade begins, when the activity in motor memory antisaccades is almost the same as that in memory prosaccades (Fig. 9*A*, thick black trace compared with gray trace). Thus mean net activity in a memory antisaccade is typically less than the mean net activity in a memory prosaccade. What does this difference reflect? Is the overall activity in memory prosaccades greater than that in memory antisaccades?

Figure 12 compares the overall activity in memory prosaccades and in memory antisaccades. More specifically, the gray curve shows the mean summed activity in memory prosaccades; the mean, over all neurons, of $A_{V+M+}(t) + A_{V-M-}(t)$. The black curve shows the mean summed activity in memory antisaccades; the mean, over all neurons, of $A_{V+M-}(t) + A_{V-M+}(t)$.

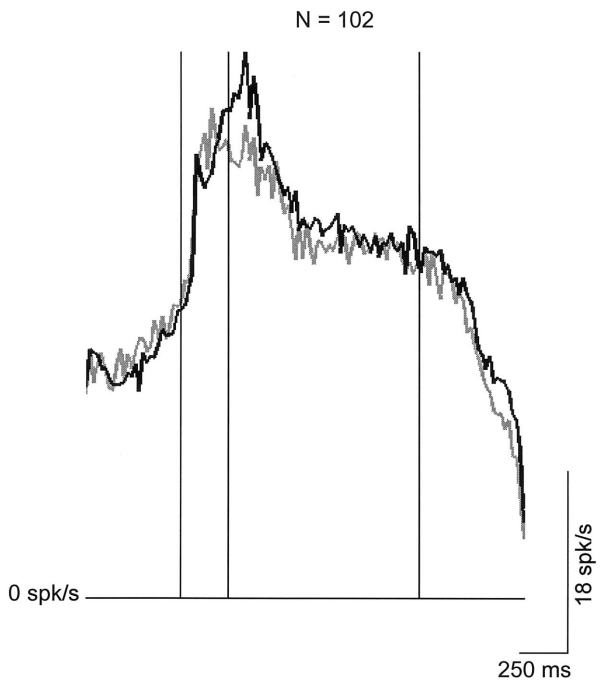

FIG. 12. Total activity in memory-prosaccades (gray trace) and memory-antisaccades (black trace). The traces show the sum of activity toward the response field and away from it for all persistent neuron. Vertical lines mark target onset, offset and fixation spot offset.

Thus in contrast to all previous figures in which the activity was aligned on the neurons' response fields, Fig. 12 approximates the total activity, independent of the specific response fields of individual neurons.

The black and gray curves are very similar to each other. The black curve is just slightly higher than the gray curve almost throughout the trial, the only exceptions being: first an interval of paradoxical activity, an interval of ~0.25 s duration beginning just before target offset and continuing into the beginning of the memory interval. At that time, the black curve is more significantly higher than the gray. The second exception is another subinterval of ~0.2 s close to the end of the memory interval when the two responses are almost equal. Thus the overall activity of the persistent neurons in memory prosaccades and the overall activity of the persistent neurons in memory antisaccades are very similar to each other.

Figure 12 suggests that the main difference between memory prosaccades and memory antisaccades appears to be not in the total amount of activity evoked in LIP but in the *distribution* of the activity among the various neurons in LIP's population.

DISCUSSION

We will discuss the pertinence of our results to the three problems presented in the introduction and then allude to two issues that concern our experimental design.

Functional properties of neuronal activity that give rise to the differential activity

The visual and motor response fields of most LIP neurons, including all neurons studied here, are in the same direction. Thus on antisaccade trials in which the visual stimulus is in the response field of the neuron, movement-related activity cannot be observed because the direction of the saccade is 180° away from the direction of saccades associated with vigorous motor-related activity. Conversely, on those trials in which the direction of the saccade is in the response field of the neuron, the visual target appears in the position opposite to the visual response field of the neuron. Accordingly, activity on individual antisaccade trials is visual or motor, never both. This property of the activity is what allows the antisaccade differential activity to tease apart the visual and motor components of the memory-interval activity. The antisaccade differential activity is obtained by plotting the difference in activity observed in two different trial types: one, of visual memory antisaccades, V+M−, in which the visual stimulus is in the response field of the neuron but the movement is not; the second, of motor memory antisaccades, V−M+, in which the visual stimulus does not activate the neuron, but the movement is made in the direction of the neuron's response field. The sign of the differential activity is negative when the activity observed on V+M− trials exceeds the activity observed on V−M+ trials. Thus the amplitude of the visual and motor segments of the plot of differential activity and the timing of the inversion, the crossover from visual to motor, depends upon the relative levels of visual and motor discharges of the neuron. For example, the differential activity plot for a neuron displaying a strong and sustained visual response on V+M− trials and relatively weak and delayed activity on V−M+ trials would have a large-amplitude visual component and a small-

amplitude motor component, and the crossover from visual to motor would occur late. Similarly, the differential activity plot for a neuron displaying a weaker, phasic visual response on V+M− trials and early, vigorous activity on V−M+ trials would display a small-amplitude visual component and a large-amplitude motor component, and the crossover from visual to motor would occur early.

Although the activity of any individual neuron on antisaccade trials is visual or motor, but not both, on the population level, a memory-antisaccade trial activates two groups of neurons with oppositely positioned response fields. The activity of the neurons in one of these groups is visual because the target stimulus falls in the visual response fields of the neurons in this group; the activity of the neurons in the other group is motor because the saccade falls in the movement fields of those neurons. The plots in Figs. 8 and 9 estimate the relative amplitude and duration of activity in these two groups of neurons. The simultaneous activity of the two groups determines the mean antisaccade differential activity. The mean antisaccade differential activity can, in principle, be assessed from a single memory-antisaccade trial. In contrast, the antisaccade differential activity of an individual neuron in principle cannot be recorded in a single trial because it is computed from different sets of trials, of visual and motor memory antisaccades. Yet for individual neurons too, the antisaccade differential activity captures the net effect that the individual neuron has on the computation by the population. A gedanken experiment useful for comprehending the contribution of a single neuron is that of an "antineuron" (Newsome et al. 1989). Indeed, the antisaccade differential activity reflects the net contribution of two neurons with identical response properties except the position of the response field, which is opposite each other.

Significance of the inversion of the differential activity

How would the sensorimotor transformation of an antisaccade be reflected in extracellular single-unit activity? Antisaccades are a laboratory model for movements that shift the line of gaze not toward the target ("canonical sensorimotor transformation") but to other locations. How would any such noncanonical sensorimotor transformation be reflected in single-neuron activity? The answer might be, for antisaccades, in the inversion of the antisaccade differential activity; for other noncanonical transformations, in an analogous relationship. Let us consider why that might be the case.

For simplicity, the following discussion does not account for the paradoxical activity (Zhang and Barash 2000); the paradoxical activity can, however, be readily integrated into the deliberation without affecting its implications (Barash 2003).

Let us make the following simplistic but useful assumptions. Suppose that *1*) we are recording from the brain region that computes the sensorimotor transformation. Suppose further that *2*) this region has only visual and motor neurons, *3*) the visual neurons connect to the motor neurons, and *4*) these connections can be modified. Then conceivably, by changing the connections the visual neurons make on the motor neurons, this region can compute any given noncanonical sensorimotor transformation. The core of the transformation would be combinatorial: it would be the *coupling* of activity in a given set of sensory neurons with activation of the *appropriate* set of motor neurons.

In memory antisaccades, the coupling of visual and motor neurons is such that the target activates one set of neurons, whose response fields cover the target location—and the eventual motor plan activates a second set of neurons, whose response fields cover inverse the target location. This pattern of activation, the transition of the activity during the trial from predominantly in visual memory antisaccades to predominantly in motor, is reflected in an inversion of the antisaccade differential activity (see *Differential activity*). Therefore in the region that computes the sensorimotor transformation, the inversion of the antisaccade differential activity would directly reflect the computation of the antisaccade sensorimotor transformation.

Inversion transformation and LIP

Should we expect to observe a visual to motor inversion of the antisaccade differential activity only in the brain region in which the sensorimotor transformation is computed? What does the observation of an inversion in a given region tell us about this region's involvement?

We think that the observation of an inversion in memory antisaccades is a *necessary condition* for a region to be directly involved in the computation of the sensorimotor transformation. The reasons are alluded to in the previous section. Note that inversion would be necessary only for memory antisaccades with a sufficiently long memory not for immediate antisaccades (see *Significance of memory*).

Is the observation of inversion in memory antisaccades also a *sufficient condition* for a region to be directly involved in the computation of the sensorimotor transformation? We are less clear about this question. In principle, the answer might be not necessarily; there is no a priori reason to reject the possibility that regions with visual and motor neurons, which may not compute the inversion transformation, would nevertheless show inversion. This might specifically be the case for regions with motor neurons that are gated by the area that does compute the inversion. Nevertheless to the best of our knowledge, this question has not been tested experimentally, and it is possible that we are in for surprises. In dorsolateral prefrontal cortex, inversion may not occur (Barash 2003; Funahashi et al. 1993).

We previously showed that the mean antisaccade differential activity of an entire sample of neurons from LIP inverts from visual to motor. Hence, the entire population of LIP satisfies the necessary condition for being directly involved in the antisaccade sensorimotor transformation. Here we show that this necessary condition is satisfied not only by the entire LIP but also by a specific subpopulation, which is likely to be directly involved in working memory for sensorimotor transformation (see following text).

Thus this paper provides further evidence in support of the possibility that LIP neurons with persistent activity are involved in the computation of the antisaccade sensorimotor transformation. The mean antisaccade differential activity of the persistent neurons inverts from visual to motor. Furthermore, the paradoxical activity, which might be related to the transformation, appears to be present in visuomotor neurons;

the paradoxical activity accelerates the inversion of the differential activities of these neurons.

Because we have recorded only from neurons in LIP, on the basis only of our results we cannot tell whether involvement in the computation of the sensorimotor transformation is *specific* to LIP. Nevertheless, several other studies suggest that such specificity is present. Schlag-Rey and collaborators, who put forward the inversion problem, did not report analogous findings in either supplementary or frontal eye fields (Schlag-Rey et al. 1997). Some human-evoked potential recordings did report inversions that appear to support our findings (Everling et al. 1998). Recently, Gottlieb reported preliminary results of transient inactivations of small sites in LIP (Gottlieb 2001). Gottlieb inactivated spots of cortex in which neurons had similar response fields. Gottlieb reported most severe dysmetria to occur on antisaccade trials in which the target fell in the response field common to the neurons in the inactivated region. In this condition, it appears that the monkey tends to look more toward the target than toward the opposite direction. One possible interpretation for this result is that the inactivation impaired the computation of the antisaccade sensorimotor transformation; by default, the antisaccade sensorimotor transformation was replaced with the sensorimotor transformation of prosaccades.

Visual memory or intention

Previous studies of responses of LIP neurons in memory prosaccades and related tasks reported that the persistent activity conveys mostly either the plan for the next saccade (Barash et al. 1991a; Mazzoni et al. 1996) or visual memory (Colby et al. 1996). To our surprise, we found that during the memory interval of memory antisaccades, most neurons are active during the memory intervals of both visual and motor memory antisaccades. Thus most neurons appear to combine activity consistent with reflecting both visual memory and motor intention. Given the evidence reviewed in the previous section, the combination of visual and motor memory and the change from mostly visual to mostly motor memory suggest that these neurons might be involved in computing the sensorimotor transformation for antisaccades. This observation is consistent with the suggestion that the posterior parietal cortex implements sensorimotor transformations (Andersen 1987).

Recently, Goldberg and colleagues suggested that LIP holds a saliency map (Gottlieb et al. 1998) and that activity in this map reflects attentional priorities: at each instance, visual attention is allocated to the location of maximal LIP activity (Bisley and Goldberg 2003). Coupled together with our data, particularly with that of our Fig. 8, Bisley and Goldberg's suggestion leads to the prediction that in memory antisaccades, the monkey's visual attention is allocated according to the sign of the differential activity. According to this argument, attention would be directed to the target's location starting shortly after target onset and continuing till ~100 ms into the memory interval; then, quite rapidly, attention would shift to the motor direction. It would remain allocated at the expected saccade's end point till the saccade is made. Thus attention would reflect the sign of the differential activity. This prediction is testable. It is also reasonable because visual attention probably accompanies the sensorimotor transformation and the plans to make saccades that emerge out of these transformations.

Nevertheless, in our eyes, attention is highly unlikely to *cause* all of LIP's activity. Consider, for example, the onset of the activity in motor memory antisaccades (thick black trace in Fig. 8*A*). This rather abrupt rise occurs while the target is still on. It is a bright stimulus on dark background. Except for the small fixation spot, it is the only visual stimulus present. It is a suddenly appearing stimulus that stays on for only a quarter of a second. Therefore, attention is probably allocated to the target's location at the time that neurons with the opposite response field suddenly burst on. Thus the rise of activity in the motor direction does not appear to reflect attention.

Note that the previous two paragraphs are consistent with each other. Bisley and Goldberg (2003) distinguish between two questions. One question is what does the activity reflect? Does it always reflect attention? Not necessarily, they answer, and we agree (see previous paragraph). The second question is what is LIP's activity used for? Their answer is: for controlling attention. This suggestion is consistent with the hypothesis outline in the preceding text.

In sum, we speculate that LIP reflects and is likely to contribute to planning of both of saccades and of covert attention. Both overt and covert shifts together comprise the process of looking.

Dynamics of working memory

Short-term memory and working memory are not identical concepts (Baddeley 1986, 2001, 2003; Miyake and Sakata 1999). Persistent activity can reflect short-term memory (Fuster and Alexander 1971), but it may actually reflect working memory (Goldman-Rakic 1995). Miller, Galanter, and Pribram introduced working memory in 1960 by analogy to memory of digital computers and, more specifically, to the use of memory in program execution (Miller et al. 1960). The contents of a computer's memory (or of the tape of a Turing machine) is maintained until the central processor writes new values into it. Thus computer memory stores contents all the time, and these contents change to suit the computation. Thus it appears to us that to qualify as part of working memory, neurons need to fulfill four conditions: *1*) in one, "static" condition, the activity of these neurons should be persistent. *2*) in another, "dynamic" condition, the activity of the neurons should change during memory in a manner consistent with reflecting a change of memory content; *3*) in the dynamic condition, the combined activity of most neurons has to be persistent, suggesting that memorization continues throughout content change. ("Combined activity" means here the maximal level of activity in all possible memory values. In the case of memory antisaccades, it is the maximal activity in visual and in motor antisaccades, at any given moment, as in Fig. 7). And *4*) the alleged change of contents must be recorded independently, preferably directly from behavior; the neuronal dynamics must be consistent with the independent assessment of content change.

In the case of LIP, memory-prosaccades satisfy *criterion 1*, indeed this criterion defines the sample of neurons studied in the present paper. Memory antisaccades satisfy *criterion 2*. Note that this is by no means the only paradigm which satisfies *criterion 2*. Changes of persistent activity have been, explicitly or implicitly, described in several studies (Constantinidis et al. 2001; Platt and Glimcher 1999; Sabes et al. 2002). To the best of our knowledge, *criteria 3, 4* were not explicitly tested in

previous studies. Here we show that, for memory antisaccades, LIP's persistent neurons satisfy *criterion 3*. We do not explore *condition 4* in the present paper, but this criterion is also satisfied. These observations show that the short-term memory associated with the persistent activity is indeed working memory.

Effect of color on neuronal responses in LIP

Area LIP is part of the dorsal visual stream, and its neurons have been thought to be color insensitive for many years. A recent paper reported color-dependent response differences in a specific condition (Toth and Assad 2002). Because the mixed task uses targets of different colors, at a first look Toth and Assad's results may seem to confound the interpretation of our results. A closer look shows, however, that there is no confound. In fact, Toth and Assad provide more systematic, careful evidence for the color independence of normal LIP responses than had previously been available.

Toth and Assad studied LIP neuronal activity in two tasks: a location-relevant task, in which monkeys had to make memory saccades toward red or green targets, regardless of their color; and a color-relevant task, in which the cue colors became instructions (e.g., red target might mean saccade to the left, green to the right, regardless of target location; these couplings were changed every block of trials). Toth and Assad made the following observations. First, in the location-relevant task, the activity was overwhelmingly independent of the target's color. Again, this is perhaps the most carefully derived evidence that parietal neurons are indeed usually color independent. However, in the color-relevant task, some neurons were sensitive to the target's color. This effect is limited in magnitude: even in the color-relevant task, the area under the color-sensitive mean differential activity is less than one-third of the area under the location-sensitive mean differential activity (compare the areas between the black and gray curves in Toth and Assad's Fig. 3 *A* and *B*). Though not very large, this effect is interesting and surprising. Nevertheless, it has little relevance in the context of explaining our results.

Toth and Assad analyze their data in terms of each neuron's color selectivity not in terms of red and green. Implicitly this means that neurons selective for red and neurons selective for green are present in about equal numbers. This point, by itself, suffices to show that Toth and Assad's observations cannot explain our data. Even in their color-relevant task, the mean responses to red and green target are, presumably, the same. This is very different from our data (Figs. 8 and 9).

Although the preceding point already shows that our data cannot be explained by the visual sensitivity to color, it is worth noting that the role of color in our task is very different from that in Toth and Assad's task. In their case, color is a direct, indeed nonspatial instruction (such as red instructs look left, green instructs look right). In our case, color is used to select the task, select the sensorimotor mapping; but the actual determination of the required movement relies primarily on the target's location. There is no a priori reason to assume that Toth and Assad's observation would generalize to the very different use of color in our task. Furthermore, the movements made in Toth and Assad's color-relevant task are not antisaccades in the standard sense because the heart of an antisaccade is the inversion sensorimotor transformation; but in Toth and Assad's study, this transformation is replaced by a look-up table (with entries such as "red means left movement"). Finally, the dynamics of the color-dependent differential activity in Toth and Assad's color-relevant memory-saccades is very different from our antisaccade differential activity (the 1st is nearly 0 at the time of the saccade, the 2nd is maximal at this time).

In sum, Toth and Assad made a surprising, interesting discovery. However, it does not explain our data. The activity patterns we observe are not likely to reflect target color differences; rather, they reflect the different tasks.

Significance of memory

Our results are based exclusively on memory saccades. We used this experimental design because memory has a record of being useful for segregating the motor activity from visual (Barash et al. 1991a,b; Gnadt and Andersen 1988). Indeed, a study comparing responses to prosaccades and antisaccades in LIP but without memory reached somewhat different conclusions (Gottlieb and Goldberg 1999). In our experience, LIP's visual responses are often stronger but less spatially selective than motor responses (not shown): strong visual responses to targets in the response fields may be accompanied by weak responses to targets in the opposite direction, whereas weaker responses for saccades toward the response fields may go with no response or even inhibition for saccades in the opposite directions. Therefore in the absence of memory, the stronger visual response can hide the motor response, which is present, functional, and part of the output of LIP (Ferraina et al. 2002; Pare and Wurtz 2001).

But do experimental paradigms based on memory reflect conditions particularly remote from nature? In our mind, this is not the case. Any experimental paradigm such as that of antisaccades is not perfectly natural. The additional requirement of memory does not appear to significantly change this situation because memory is integral into many of our actions (Miyake and Sakata 1999). Indeed, orienting to memorized (and to predicted) object locations is sometimes critically important, as in the case of a hidden predator or prey. This is even true for humans: consider the realistic situation of troops lying in an ambush, up on a hill, with a limited field of view. A narrow pavement curls up the hill. Based on the area's topography, the troops may know that sounds of steps coming from one direction indicate that, after some time, a hostile figure would visually emerge in another direction, where the pavement ends. Usually such an appearance would require immediate action. Thus memory-guided orienting occurs in nature and in human life. In addition, memory may also play a part in normal control of looking. This is illustrated by new studies of parietal neuropsychology. Some studies suggest that impairments in memorizing the eyes' trajectories contribute to neglect after parietal lesions (Husain et al. 2001; Vuilleumier et al. 2002; Wojciulik et al. 2001).

Dispersion of the inversion time of individual neurons

Inversion of the activity from visual direction to motor is evident on the level of the single neurons: the antisaccade differential activity of 85% of the neurons active in both visual and motor memory antisaccades turn first to the visual direc-

tion, then cross over to the motor direction and remain directed toward the motor direction until the saccade was made. Nevertheless, the times in which individual neurons invert (that is, the time their antisaccade differential activity crosses 0 on the way from the visual direction to the motor) are highly variable: the antisaccade differential activity of the neuron illustrated in Fig. 6 turns to the visual direction sharply but only for 50 ms; the antisaccade differential activity of the neuron in Fig. 5 remains pointing to the visual direction for >700 ms. This large variability brings up two questions. First, what causes the variability? Second, does it have functional implications? Could the inversion times of individual neurons bear on whether they might play a different role in the dynamics of the sensorimotor transformation?

In discussing the source of the variability of the inversion times, the question comes up could the fixed trial durations that we have used contribute to the variability of inversion times of the individual neurons? We over-trained the monkeys using 0.25-s target and 1-s memory intervals. The sensorimotor transformation can occur at any time during this 1.25-s interval. Could these loosely constrained timings be reflected in large variability of the neuronal dynamics? We think that the answer is probably not. It appears to us that the shape of the distribution of the inversion times (Fig. 11) would not have changed much had we used a different memory interval. Because most of the distribution is concentrated early in the trial, before the middle of memory (0.75 s in Fig. 11), we do not think that using a longer memory—say, 3 s—would have made much difference. The tail on the right of the distribution would probably extend beyond 1 s, but the basic shape would be the same. Because the peak of the distribution is already in the first bin of the memory, we also do not think that using a short memory would have made much difference either. The tail of the distribution would be clipped, and some of the inversion times of some of the neurons would perhaps shift to slightly earlier values preceding target offset; but, again, the basic shape of the distribution would probably be the same. How would the distribution have looked had we used no memory interval at all? It is an interesting question to ask but a difficult one to answer because activity in the motor direction may be masked out (see previous section).

It thus appears to us that the variability of the inversion times is not primarily caused by our use of the fixed 1-s memory interval. What, then, causes this variability? Could the distribution of inversion times have a physiological function? Could the neurons of Figs. 5 and 6 have somewhat different function?

We end the discussion by suggesting two hypotheses. We already alluded to them previously. First, we suggest that neurons with late inversion times, such as the neuron illustrated in Fig. 5, are part of a general mechanism for computing arbitrary sensorimotor transformations. Neurons with early inversion times are part of a specialized mechanism for computing a specific transformation. The specialized mechanism emerges during a long training in that specific transformation. The neurons that reflect the expertise in that single sensorimotor transformation probably do not make a similar contribution to other sensorimotor transformations. By default, the specialized mechanism takes effect early in the trial.

After expertise is gained and the specialized mechanism has emerged, as far as the transformation subject for the expertise goes, does the general mechanism become redundant? More specifically, for memory antisaccades, do neurons with late inversion times become nonfunctional, redundant? We suggest that the answer is negative because this is a distributed system. The neurons of Figs. 5 and 6 reflect processes that take place in parallel. If the shortcut route works, fine. If it does not, the slower but more general background route is still there to take over.

Conclusion

Studying LIP's persistent activity with memory antisaccades reveals that neurons with persistent activity appear to reflect both visual memory and motor plans for making saccades. The combined activity in the two types of memory antisaccades is also persistent. These neurons appear to reflect working memory for the computation of the inversion from visual to motor directions, the core of the sensorimotor transformation for antisaccades. A set of persistent neurons with distributed response fields might serve as a module of working memory for computing plans of where to look.

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