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Signal transformations from cerebral cortex to superior colliculus for the generation of saccades

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Abstract

The ability of primates to make rapid and accurate saccadic eye movements for exploring the natural world is based on a neuronal system in the brain that has been studied extensively and is known to include multiple brain regions extending throughout the neuraxis. We examined the characteristics of signal flow in this system by recording from identified output neurons of two cortical regions, the lateral intraparietal area (LIP) and the frontal eye field (FEF), and from neurons in a brainstem structure targeted by these output neurons, the superior colliculus (SC). We compared the activity of neurons in these three populations while monkeys performed a delayed saccade task that allowed us to quantify visual responses, motor activity, and intervening delay activity. We examined whether delay activity was related to visual stimulation by comparing the activity during interleaved trials when a target was either present or absent during the delay period. We examined whether delay activity was related to movement by using a Go/Nogo task and comparing the activity during interleaved trials in which a saccade was either made (Go) or not (Nogo). We found that LIP output neurons, FEF output neurons, and SC neurons can all have visual responses, delay activity, and presaccadic bursts; hence in this way they are all quite similar. However, the delay activity tended to be more related to visual stimulation in the cortical output neurons than in the SC neurons. Complementing this, the delay activity tended to be more related to movement in the SC neurons than in the cortical output neurons. We conclude, first, that the signal flow leaving the cortex represents activity at nearly every stage of visuomotor transformation, and second, that there is a gradual evolution of signal processing as one proceeds from cortex to colliculus. Published by Elsevier Science Ltd.

Keywords: Frontal cortex; Parietal cortex; Superior colliculus; Antidromic activation; Saccadic eye movements; Visual representation; Monkey

1. Introduction

The sophisticated control that primates have over their eye movements permits them to explore successive regions of their natural environment rapidly and accurately. The neuronal system that mediates these saccadic eye movements has been studied extensively and is known to include multiple brain regions extending throughout the neuraxis, from frontal and parietal regions of cerebral cortex to the midbrain and pons of the brainstem. Understanding how this system generates saccades, however, requires more than just analyzing the functional contribution of each individual brain region. Clearly it is also critical to determine how these areas interact. In this article we address this interaction by determining the sequence of activity between three saccade-related areas, the lateral intraparietal area (LIP), the frontal eye field (FEF), and the superior colliculus (SC).

The most straightforward approach to studying this interaction is to compare the activity related to saccade generation between areas, but there are limitations to this approach. Within the areas considered here we know that there is diverse activity, and neurons in the areas can project to a multitude of other areas. For example, an FEF neuron might have a strong presaccadic burst of activity, but one's interpretation of this burst will change substantially depending upon whether the neuron projects downstream to a motor area (suggesting the burst is a motor command) as opposed to

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upstream to a visual area (suggesting the burst provides information to sensory neurons that a movement is imminent). If we pool together many neurons from an area and compare their average properties to neurons in a downstream area, we may be misled as to the sequence of processing if a large fraction of the neurons in the first area actually do not project to the downstream area.

One approach to exploring the sequential processing is to explicitly identify the output neurons of the area under study by antidromically activating them using a pulse of electrical stimulation in a downstream area. By using such antidromic activation, output neurons of one region can be identified and the signals they convey can be directly compared to the activity of neurons in the next area. In a recent series of experiments, we applied this approach by recording from output neurons of the FEF and LIP that project to the SC as well as from SC neurons themselves (Paré & Wurtz, 1997; Sommer & Wurtz, 2000b; Paré & Wurtz, 2001; Sommer & Wurtz, 2001). In addition, we compared the signals conveyed from LIP to FEF with those conveyed from LIP to SC (Ferraina, Paré, & Wurtz, 2001). Because we used the same physiological and behavioral methods in studying the different populations of neurons, a direct comparison of the signal transformations that occur from the cerebral cortex to the SC and from one cortical area to another can be made. In the present article we make these direct comparisons based on this series of studies.

In the first set of studies, we identified the output neurons projecting from FEF or LIP to the SC by antidromically activating the cortical neurons with electrical stimulation of the intermediate layers of the SC. We then compared the activity of these output neurons to the activity of neurons in the SC intermediate layers. In the next study we compared the LIP output to SC with the LIP output to FEF. We always used a simple delayed saccade task to quantify the visual responses, the presaccadic discharges, and the delay activity that intervened between the visual and movement related activity. We analyzed the delay activity in detail, because this activity is highly likely to mediate the processes that link sensory representations to motor commands over time. To see the extent to which the delay activity was related to visual stimulation, we compared the delay activity that occurred when a target remained in the visual receptive field to the activity that occurred when a target was absent, while a monkey remembered the target location. To see whether the activity was related to movement, we used a Go/Nogo task in which visual stimulation was kept constant and only the requirement to make a saccade changed. We believe that the results of comparing output neurons of different parts of cortex to each other and to collicular neurons allow us to infer the nature of processing along steps in the circuit for the generation of saccades.

2. Methods

The physiological and behavioral procedures used in these experiments were reported previously (Sommer & Wurtz, 2000b; Paré & Wurtz, 2001) and only salient points will be summarized briefly here.

Neurons in FEF and LIP were antidromically activated from SC intermediate layers by passing current through microelectrode tips placed among neurons with saccade related activity, the signature of SC intermediate layer neurons. We located cortical areas using magnetic resonance imaging. Area LIP, within the lateral bank of the intraparietal sulcus, was further identified physiologically by the concentration of neurons with significant visual- and saccade-related activities. We identified the FEF as the area in the rostral bank of the arcuate sulcus containing saccade-related neurons where electrical stimulation reliably evoked saccades at currents of less than 50 μA. We studied only neurons that were antidromically activated from the SC (Fig. 1A). In subsequent experiments a stimulating electrode was placed in both the FEF and SC to compare the activity of LIP neurons identified as projecting to these two areas. The monopolar stimulation in all cases was a single biphasic pulse (~ 0.15 ms for each phase). We used the collision test (Fuller & Schlag, 1976; Lemon, 1984) which verifies the antidromic nature of the responses by determining whether a spontaneous action potential collides with one triggered by electrical stimulation thereby indicating that they both travel on the same axon.

Monkeys were trained on two tasks. The first was the delayed saccade task (Fig. 1B). After an initial period of fixation, a peripheral stimulus appeared, but the fixation point stayed on for an additional 500–1000 ms while the monkeys maintained fixation, creating a delay period before the saccade. Turning off the fixation point cued the monkey to make a saccade to the stimulus within 500 ms in order to receive a reward. In the visual version of this task, the peripheral stimulus remained on throughout the trial, while in the memory version, the stimulus appeared for only 100 ms and the monkey had to make a saccade to the remembered location of the target.

The second task was the delayed Go/Nogo task (Fig. 1C). This was essentially the same as the delayed saccade task except that the requirement to make a saccade to the visual stimulus varied form trial to trial. The monkey first looked at a blue fixation point. A peripheral stimulus then appeared, and after a 800–1200 ms delay, the fixation point changed color to instruct the monkey that a saccade would (green = Go instruction) or would not (red = Nogo instruction) be required on that trial. After another 800–1200 ms the fixation point turned back to its original blue color, providing the cue to respond. The monkey then had to

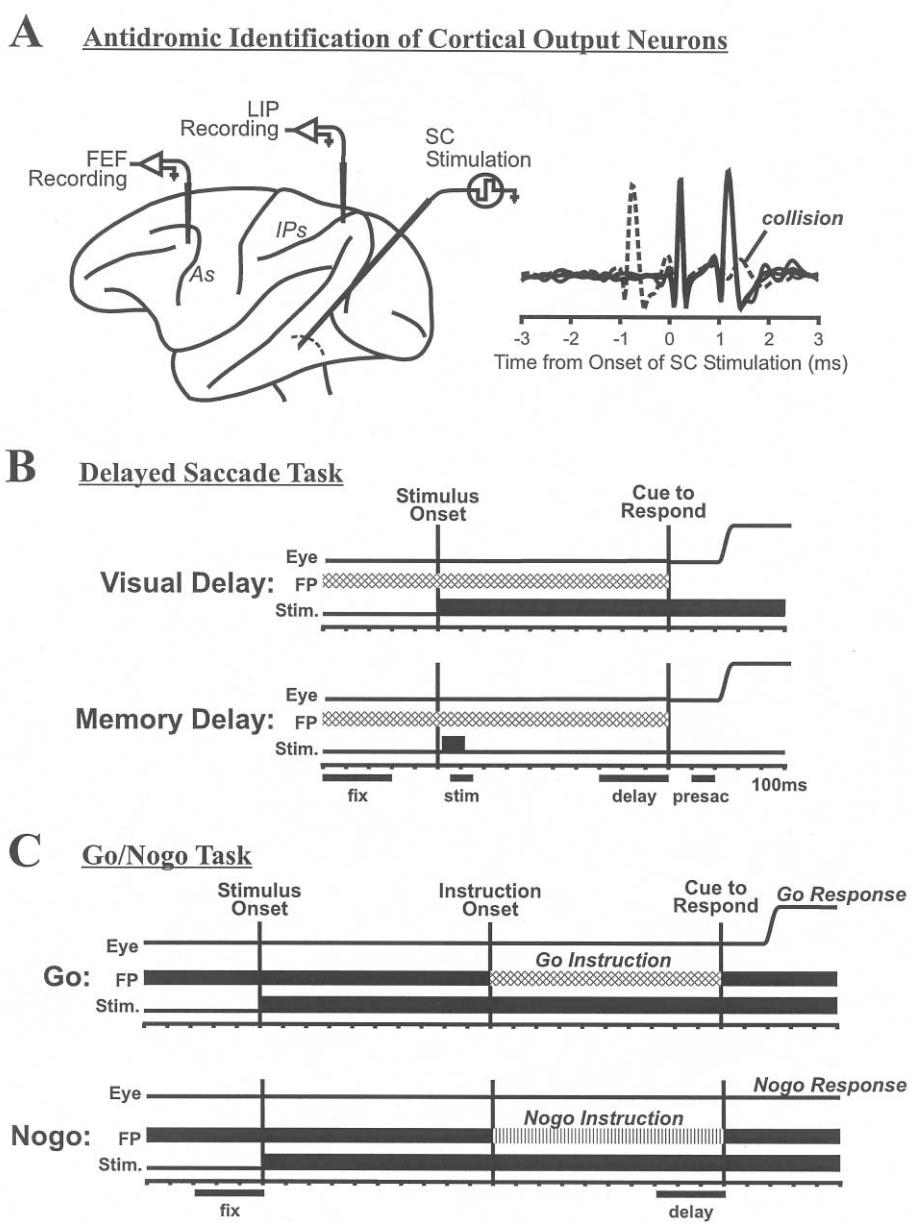

Fig. 1. Methods used for comparing the output of cortical areas. (A) Recording and antidromic stimulation techniques. At left is a lateral view of the monkey (*Macaca mulatta*) brain showing the recording locations, in LIP and FEF, and the stimulation location, in the SC (As, arcuate sulcus; IPs, intraparietal sulcus; dashed line, SC). At right are the action potentials of an LIP output neuron (solid traces). The stimulus artefact is at time 0 ms and the neuron's spikes all overlap at time 1 ms. The waveform from one trial (broken trace) demonstrates the result of the collision test; when a spontaneous spike of the neuron occurred just prior to the stimulation (in this case at time −1 ms), stimulation failed to evoke a spike from the neuron (collision), because the spontaneous and stimulation-evoked action potentials collided along the neuron's axon. (B) The delayed saccade task, used to reveal the fundamental visual responses, delay activity, and saccade-related discharges of the neurons: in visual delay trials (top) the visual stimulus remained on during the delay period, and in memory delay trials (bottom) the stimulus disappeared after 100 ms. The mean firing rate was measured in four time periods: the fixation period occurred during steady fixation, from 500 to 200 ms before target presentation (fix); the visual period occurred 50–150 ms after visual stimulus onset (stim); the delay period occurred during the last 300 ms interval of the delay interval, ending at the fixation point disappearance (delay); the presaccadic period occurred during the last 100 ms before saccade onset (presac). (C) The Go/Nogo task was used to test whether a neuron's delay activity was related to movement. Go trials are shown at top and Nogo trials at bottom. The trial type shown is a visual, post-stimulus instruction trial; the visual stimulus remained on during the trial and the instruction occurred after the visual stimulus. For analysis, we defined a fixation period occurring during the final 300 ms before stimulus onset (fix) and a delay period occurring during the final 300 ms before the cue to respond (delay), and a neuron had significant delay activity if its mean firing rate during the delay period was significantly greater than that during the fixation period. In B and C the eye position (Eye) and the presentation of the visual stimuli (central fixation point, FP; peripheral stimulus, stim) are shown as a function of time (ticks are placed every 100 ms along the time axis as indicated in panel B).

make a saccade to the stimulus location within 500 ms (Go trials) or else maintain fixation for 1000 ms (Nogo trials) in order to receive a reward. The delayed Go/Nogo task included several types of trials that were randomly interleaved. Half of the trials were visual trials as shown in Fig. 1C, and half were memory trials in which the target disappeared after 200 ms and its location had to be remembered during the delay period. The order of target and instruction presentation also was varied so that in half the trials the instruction occurred after the stimulus as shown in Fig. 1C (post-stimulus instruction trials) and in half the trials the instruction occurred before the stimulus (pre-stimulus instruction trials).

A major goal of our study was to determine the extent to which delay activity in the various neuronal populations was related to visual stimulation (revealed by comparing the activity in visual vs. memory trials of the delayed saccade task) and the extent to which the delay activity was related to movement instruction (revealed by comparing the activity in Go versus Nogo trials of the delayed Go/Nogo task). To make these comparisons of delay activity during the different trial types, we used a method analogous to the ordinal dominance (OD) graphic technique (Darlington, 1973) and the well-established receiver operating characteristic (ROC) analysis (Green & Swets, 1966). Our analysis is described in detail in a previous paper (Paré & Wurtz, 2001). Briefly, the technique measured the probability for each neuron that an ideal observer could inspect one trial of its delay activity and determine whether the activity occurred during task condition X or task condition Y (where X and Y are the visual and memory trials of the delayed saccade task or the Go and Nogo trials of the delayed Go/Nogo task). With this method, chance probability was 0.5, indicating that the distribution of delay activity in conditions X and Y overlapped completely, whereas probabilities near 0 or near 1 indicated that the delay activity was much stronger during one of the conditions, X or Y. We used the probability values as an index for each neuron to describe how its delay activity was related to visual stimulation or to movement instruction.

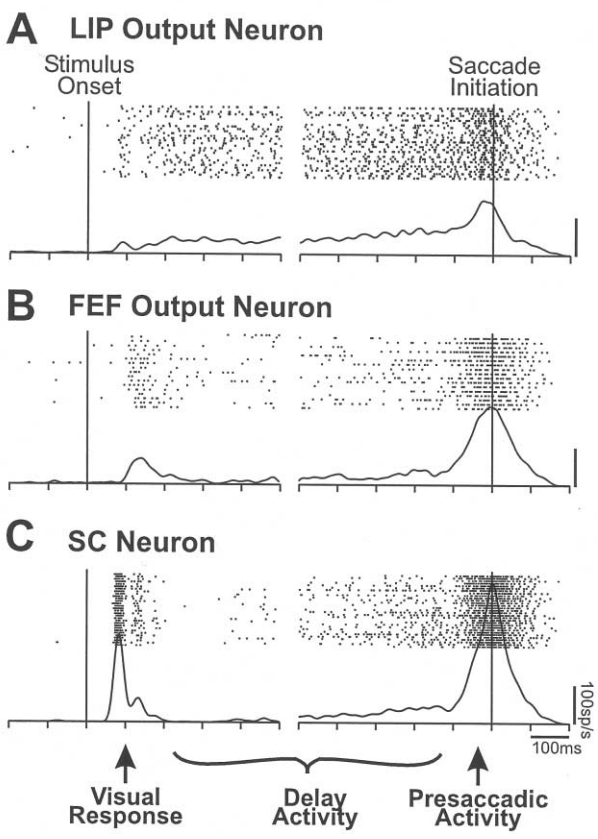

Fig. 2. Examples of an (A) LIP output neuron, (B) FEF output neuron, and (C) SC neuron, showing activity in the visual delayed saccade task. Rasters and spike density functions show the activity aligned to the onset of the visual stimulus, at left, or to the saccade initiation, at right. The three periods of neuronal activity are indicated qualitatively: the visual, the delay, and the presaccadic (examples in A and C are from Paré and Wurtz (2001)).

3. Results

3.1. Comparison of visual, delay, and saccadic activity of cortical output and SC neurons

We first analyzed the basic visual, delay, and presaccadic activity of the neurons. Fig. 2 shows the activity of an example LIP output neuron (Fig. 2A), FEF output neuron (Fig. 2B), and SC neuron (Fig. 2C) during the visual delayed saccade task. Each of these example neurons had a visual response, delay activity, and a presaccadic increase of activity. Fig. 3 shows the frequencies of occurrence of visual, delay, and presaccadic activity across the three neuronal samples. The responses were objectively determined by using an ANOVA ($P < 0.01$) and multiple comparison tests ($P < 0.05$); we considered a neuron to have a visual response if its firing rate in the visual period exceeded that during the fixation period (see Fig. 1B for analysis periods), delay activity if its firing rate in the delay period exceeded that during the fixation period, and presaccadic activity if its firing rate in the presaccadic period exceeded that during both the delay period and the fixation period. During the visual delayed saccade task about 3/4 of the LIP output neurons had a visual response, about 2/3 had delay activity, and about half had presaccadic activity (Fig. 3A). Of the FEF output neurons, about half had a visual response, about half had delay activity, and about half had presaccadic activity. Within the SC, half of the neurons had a visual response, about 2/3 had delay activity, and 90% had presaccadic activity. Even though the sample sizes were relatively small, one critical point can be made: visual,

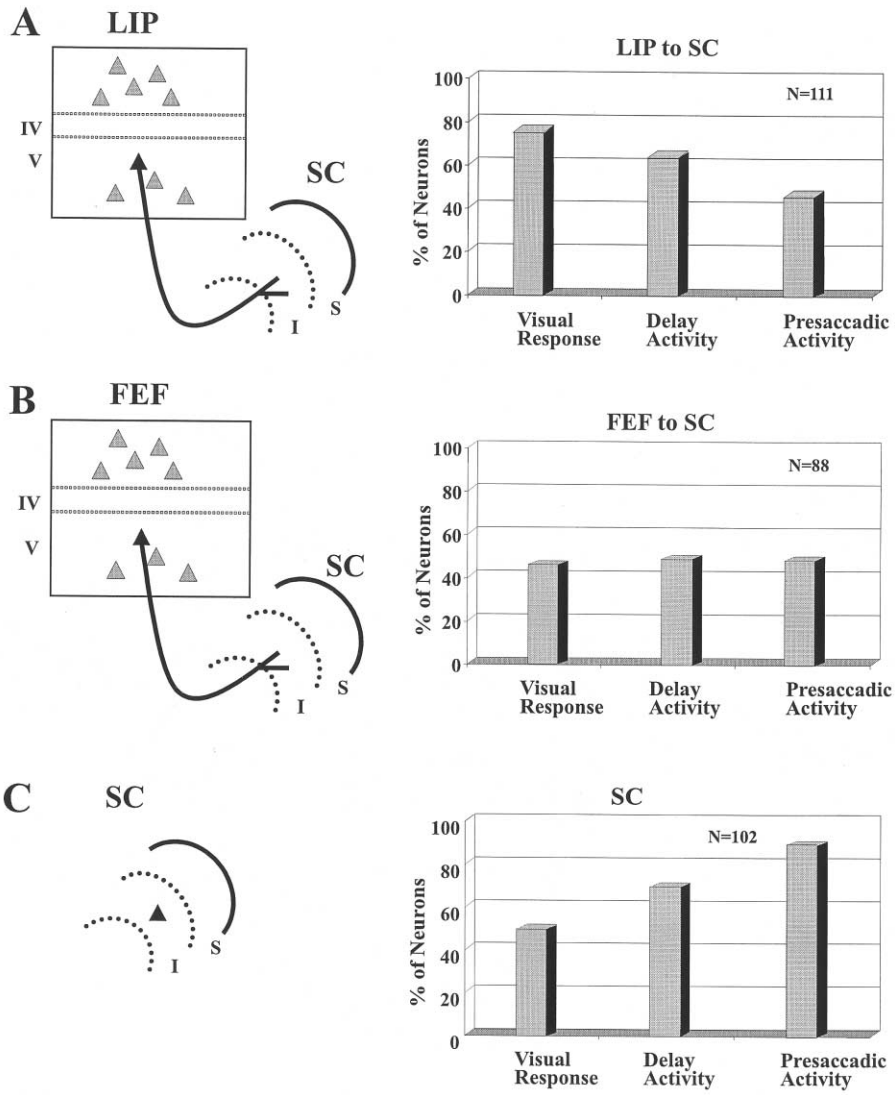

Fig. 3. Frequencies of occurrences of visual, delay, and presaccadic activity in the (A) LIP output neurons, (B) FEF output neurons, and (C) SC neurons. At the left of each panel is a diagram indicating the neurons under study. In the SC picture, I indicates intermediate layer and S the superficial layer. At the right of each panel is a graph of the percent of neurons in each sample having each type of response (values for LIP were derived from Paré and Wurtz (1997); for FEF from Sommer and Wurtz, (2000b); and for SC from Paré and Wurtz (2001)).

delay, and saccadic signals were carried by substantial fractions of the efferent neurons of both cortical areas as well as by neurons within the SC intermediate layers. Visual, delay, and saccadic signals were combined in a variety of ways in individual LIP, FEF, and SC neurons. In these aspects, all three neuronal populations were similar.

In light of the overlap in the types of activity in the three neuronal populations, we next compared the relative strengths of the various discharges in the populations. Fig. 4A plots the magnitude of the visual activity against the magnitude of the delay activity (both measured in the intervals shown in Fig. 1) for each individual LIP output neuron (yellow circles), FEF output neuron (red triangles) and SC intermediate layer neuron (white squares); data from visual and memory delayed saccade tasks are in the left and right graphs, respectively. In all three neuronal populations in both tasks, the delay and visual activity were directly correlated ($P < 0.001$, Spearman rank correlation for all analyses because many of the distributions in Fig. 4 were highly skewed). That is, in all three populations, the stronger the visual response, the stronger the subsequent delay activity.

Fig. 4B compares the same delay activity to the presaccadic activity. Here for the presaccadic activity we use the peak rate found within ± 20 ms from saccade initiation (measured using spike density functions) (MacPherson & Aldridge, 1979). We found three substantial differences between the neuronal populations. First, in both the visual task and the memory task, the LIP neurons fell closer to the unity line (Fig.

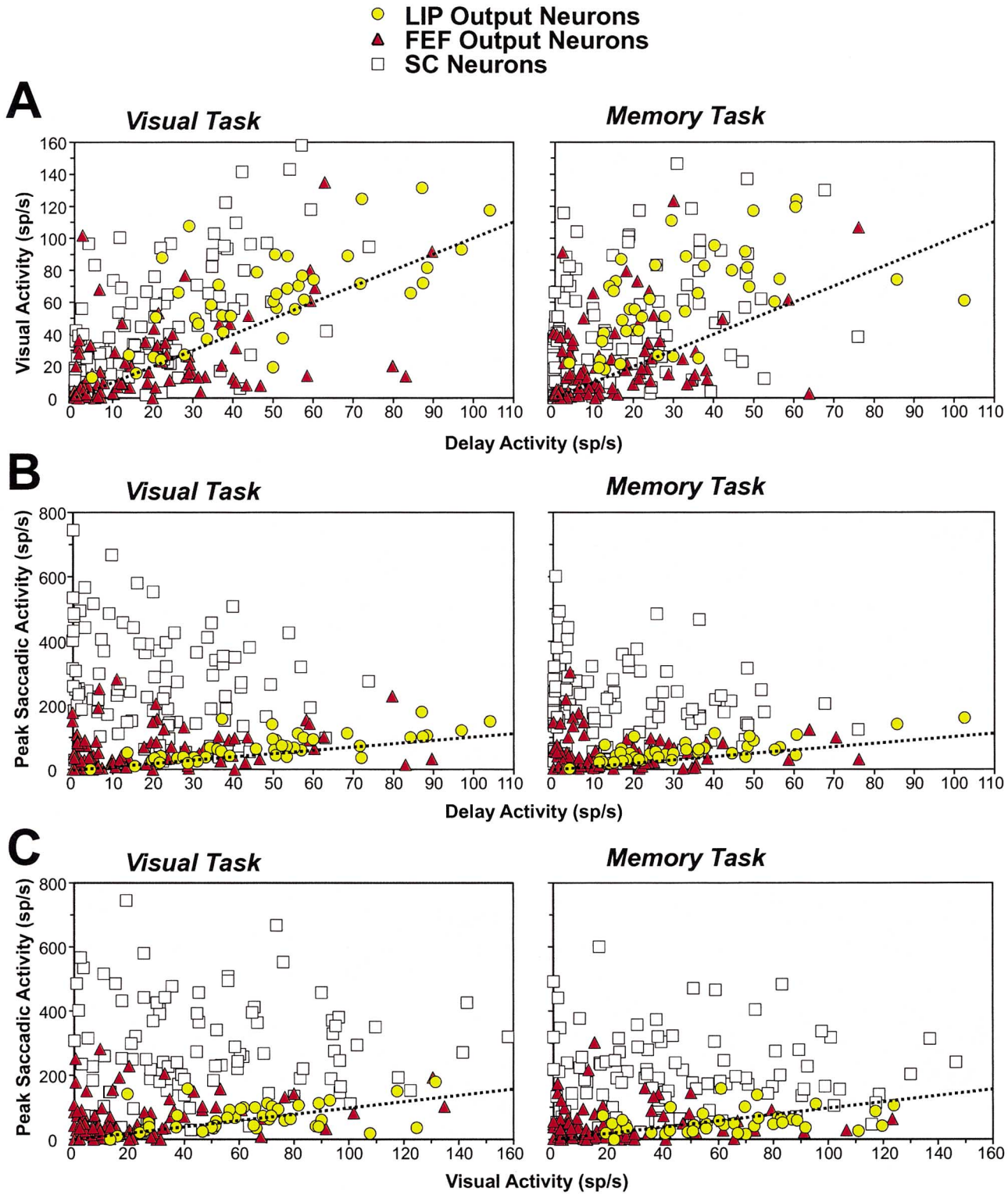

Fig. 4. Discharge properties of the samples of LIP output neurons, FEF output neurons, and SC neurons during the delayed saccade task. In each panel, graphs on the left show results from the visual version of the task and those on the right show results from the memory version of the task. In each graph, the dotted line is a unity line showing equivalent firing rates on the ordinate and abscissa. We plot absolute firing rates in all the graphs, i.e. we did not subtract baseline fixation firing rates from the data or normalize the data in any other way. Note that the ordinates and abscissas are at different scales. Sp/s, spikes per second. (A) Visual activity (ordinate) plotted against delay activity (abscissa). (B) Peak saccadic activity (ordinate) plotted against delay activity (abscissa). (C) Peak saccadic activity (ordinate) plotted against visual activity (abscissa) (LIP and SC data are from Paré and Wurtz (2001); FEF data were derived from Sommer and Wurtz (2000b)).

4B, dotted line) than did the FEF and SC neurons; the delay activity and presaccadic activity levels were directly correlated for LIP neurons ($P < 0.001$ in both tasks) but not for the FEF or SC neurons. For LIP output neurons, therefore, the stronger the delay activity, the stronger the presaccadic activity. The second difference was that there was a large group of FEF neurons having very little delay activity (< 10 sp/s) but appreciable presaccadic activity (up to 300 sp/s) in both tasks (Fig. 4B, left and right), whereas we found no such LIP output neurons. The third main difference was that, overall, the SC neurons had more intense presaccadic activity (200–600 sp/s) than did the FEF and LIP output neurons (few above 200 sp/s).

Finally, in Fig. 4C we compared the levels of the visual response and the saccadic activity in the three neuronal populations, which revealed two further differences between the neurons. For LIP neurons the saccadic and visual activities were directly correlated ($P = 0.014$ for both tasks), whereas significant correlations were found for neither the FEF nor the SC neurons. Again, there was a large group of FEF neurons strikingly different from the LIP neurons; these FEF neurons had small visual responses (< 20 sp/s) but large presaccadic bursts (up to 300 sp/s).

Another way in which the LIP output neuron and FEF output neuron populations seem to have differed was with respect to topographies of cell locations and projections. Nearly all neurons in both areas discharged only if targets appeared in a restricted range of the visual field or if a restricted range of movements was made; that is, the neurons had restricted visual receptive fields and movement fields. For the FEF, it was very clear that the eccentricities of visual and movement fields, i.e. the distances from the fovea to the centers of the fields, were strongly correlated with cell location in the cortex (see Fig. 11 of Sommer and Wurtz (2000b)). Also, the projections of FEF neurons from different regions of the FEF map appeared to terminate on the logically appropriate region of the well-known SC map. In contrast, a topography of visual receptive fields or movement fields was not as evident in LIP, although the optimal movement vectors of LIP neurons tended to overlap those of the neurons in the area of the SC to which they projected (Paré & Wurtz, 1997) suggesting some topographic order in the LIP projections to SC.

In summary, using the delayed saccade task, we found substantial overlap between the LIP and FEF output neurons and the SC target neurons in that they all had visual, delay, and presaccadic activity. There were two major differences between LIP and FEF output neurons during the delayed saccade task. First, the LIP output neurons were somewhat homogeneous, tending to exhibit a canonical visual-delay–saccadic activity profile that was simply modulated in its overall intensity in different neurons (i.e. the strengths of the visual, delay, and presaccadic activities all were correlated). In contrast, FEF output neurons and SC neurons were much more varied. Second, no LIP output neurons had only a presaccadic burst of activity, whereas many FEF output neurons did. Finally, a major difference between the cortical output neurons and the SC neurons was that the SC presaccadic bursts were much more intense than the bursts of the FEF or LIP output neurons.

3.2. Relation of delay activity to the visual stimulus and to the impending movement

We have already found that the strength of the delay activity is correlated with the strength of the preceding visual response (Fig. 4A). We next determined the extent to which this delay activity was actually dependent upon the presence of the visual stimulus by comparing the delay activity when the stimulus was continuously present (visual trials) vs. when the stimulus disappeared (memory trials). We quantified the relative strength of delay activity in these two trial types using ROC analysis (see Section 2), which yielded a value ranging from 0 to 1 that we called the visual/memory separation index. An index value near 0 indicated that a neuron's delay activity signaled target absence. Conversely, a value near 1 meant that a neuron's delay activity signaled target presence. An index value near 0.5 meant that a neuron's delay activity provided no information about whether the target was present or absent. Fig. 5 shows the outcome of this analysis for all three neuronal populations. For both the LIP and the FEF output neurons (top two histograms), the median visual/memory separation index was around 0.8 (significantly greater than 0.5, $P < 0.001$), showing that in general the neurons had delay activity that was strongly related to visual stimulation. In other words, for many of these neurons the delay activity was increased by tonic visual input. In contrast, the median Index for SC neurons did not significantly differ from 0.5 ($P = 0.10$), indicating that the delay activity tended to be independent of the sustained visual stimulation.

We next compared the extent to which delay activity in the three areas was related to the impending movement by looking at changes between trials when the monkey did or did not make a saccade, using the Go/Nogo task (Fig. 1C). Fig. 6 illustrates the activity patterns of example LIP, FEF, and SC neurons during the Go/Nogo task as the visual stimulus appeared (left), a Go or Nogo instruction was presented (middle), and a cue to respond was given (right). For all three neurons, delay activity (in the shaded boxes) was much stronger after the Go instruction than after the Nogo instruction.

Fig. 7 illustrates the results for all the neurons during the Go/Nogo task, during visual trials of the task (Fig. 7, left) or memory trials of the task (Fig. 7, right). We used the same ROC analysis method described above, except that for these data we derived a Go/Nogo separation index. An Index value near 0 meant that the neuron's delay activity after the Nogo instruction was greater than its activity following the Go instruction; in other words, the activity seemed related to withholding a saccade to the visual stimulus. Conversely, a value near 1 meant that the neuron's delay activity was greater after the Go instruction than after the Nogo instruction, and thus seemed related to preparing a saccade. Index values near 0.5 indicated that the delay activity did not differentiate between Go and Nogo instructions, i.e. it was unrelated to the impending movement. When we consider the cortical output neurons, the Go/Nogo separation indices for LIP significantly exceeded 0.5 during both the memory and visual versions of the task. In contrast, for FEF the index was significantly greater than 0.5 only for the memory condition. This indicated that the delay activity of LIP output neurons tended to be related to making saccades in general, regardless of whether a target was present or absent, while the delay activity of FEF output neurons seemed specifically related to making saccades toward remembered target locations. The SC, however, showed the strongest dependence of delay activity on the planning for the saccade; the median Go/Nogo separation index for the SC neurons far exceeded that for the LIP and FEF output neurons.

We therefore conclude that the influence of sensory stimulation and movement planning on delay activity is different at the output of cerebral cortex as compared to within the SC. For the cortical output neurons, the delay activity was multiply determined, being affected

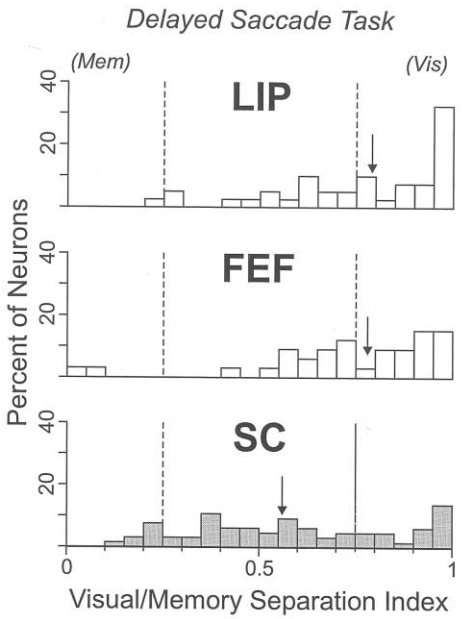

Fig. 5. Distribution of the visual/memory separation index for LIP output neurons, FEF output neurons, and SC neurons. As indicated at top, values near 0 meant that a neuron had stronger delay activity during memory delayed saccade trials (Mem), whereas values near 1 meant that a neuron had stronger delay activity during visual delayed saccade trials (Vis). Values near 0.5 meant that a neuron had identical delay activity during memory and visual delayed saccade trials. The vertical broken lines at the 0.25 and 0.75 index levels mark the thresholds of statistical significance. Arrows indicate the median index value of each distribution. Bin width is 0.05 (LIP and SC results are from Paré and Wurtz (2001); FEF results were calculated from data presented in Sommer and Wurtz (2000b)).

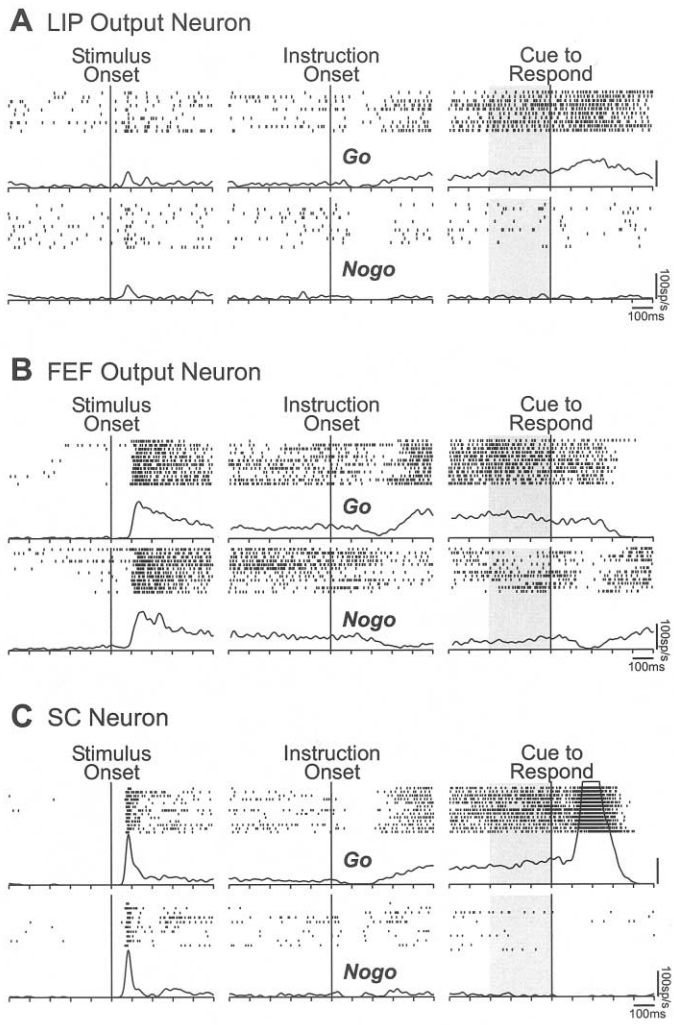

Fig. 6. Example data during the Go/Nogo task from an (A) LIP output neuron, (B) FEF output neuron, and (C) SC neuron. In each panel, data from Go (top) and Nogo (bottom) trials are aligned to stimulus onset (left), to instruction onset (middle), and to the cue to respond (right). Delay activity was measured during the time periods shown with the shaded boxes. All of these examples are from visual, post-stimulus instruction trials of the Go/Nogo task. Note that for each neuron, delay activity during Go trials is greater than that during Nogo trials, demonstrating that the delay activity is related to movement instructions (examples are from Paré and Wurtz (2001) and Sommer and Wurtz (2001)).

both by the presence of the visual stimulus and by the requirement to move. Delay activity in LIP output neurons frequently increased in the presence of the visual stimulus and the activity also frequently increased when a saccade was being planned. Delay activity in FEF output neurons also was dependent upon the presence of the visual stimulus, but it tended to be related to saccade planning only for saccades made to a remembered target. For the SC the results were simpler: delay activity was largely independent of visual stimulation but was highly dependent upon generation of a saccade.

3.3. Temporal sequence during Go/Nogo trials

Fig. 8 shows the average spike density functions of all the LIP output neurons, FEF output neurons, and SC neurons during memory trials of the Go/Nogo task. By examining the post-stimulus instruction trials (Fig. 8A), in which the target was presented (left) and then the instruction was given (middle), we could estimate when the instruction began to influence the neuronal activity (arrows). In general the activity began to differentiate between Go and Nogo instructions at about the same time in all three populations of neurons, although it appeared that the divergence in activity occurred slightly sooner in LIP (top, latency of about 190 ms) than in FEF or in SC (middle and bottom respectively, latencies of about 240 ms). It is also quite evident that the absolute magnitude of the Go/Nogo difference in delay activity is much larger in SC neurons than in LIP and FEF output neurons, as was indicated in Section 3.2 using ROC analysis.

By examining the pre-stimulus instruction trials (Fig. 8B), in which the instruction was given and then the target appeared, we could determine whether the instruction alone was sufficient to cause a difference in neuronal activity. In short, the instruction alone had very little effect. For the LIP and SC neurons, there was only a slight difference in activity in Go versus Nogo trials prior to stimulus presentation, and for the FEF neurons a divergence of activity in Go vs. Nogo trials only occurred after stimulus presentation (Fig. 8B, arrows).

3.4. Comparison of a cortical–cortical projection to a cortical–SC projection

In addition to the projections from LIP and FEF to the SC, these two cortical areas are interconnected (Andersen, Asanuma, Essick, & Siegel, 1990Schall, Morel, King, & Bullier, 1995; Stanton, Bruce, & Goldberg, 1995). This organization offers the unusual opportunity to compare the information conveyed across the cortex to that transmitted subcortically. We compared the signals flowing from LIP to FEF to those flowing from LIP to SC, using the same monkeys performing the same tasks (Ferraina et al., 2001).

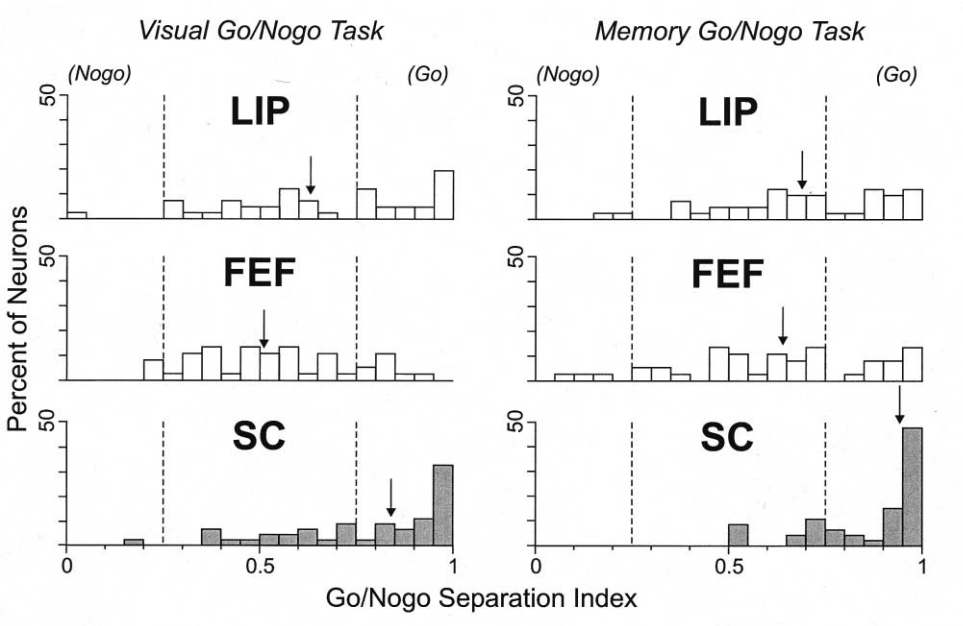

Fig. 7. Distribution of the Go/Nogo Separation Index for LIP output neurons, FEF output neurons, and SC neurons. Data from visual trials (left) and memory trials (right) of the Go/Nogo task are shown separately; all data are from post-stimulus instruction trials. As indicated at top, values near 0 meant that a neuron had stronger delay activity during Nogo trials, whereas values near 1 meant that a neuron had stronger delay activity during Go trials. Values near 0.5 meant that a neuron had identical delay activity during Go and Nogo trials. The vertical broken lines at the 0.25 and 0.75 Index levels mark the thresholds of statistical significance. Arrows indicate the median Index value of each distribution. Bin width is 0.05 (LIP and SC results are from Paré and Wurtz (2001); FEF results were calculated from data presented in Sommer and Wurtz, (2001)).

We first determined whether the same neurons projected to both the cortical and subcortical targets. In a series of penetrations through LIP, we found that the neurons projecting to FEF were always different from those projecting to SC. In addition, the neurons projecting to FEF were usually shallower in the penetration through the cortex. Both observations are consistent with the anatomical evidence that layer II-III neurons project to other cortical areas while layer V neurons project to the SC.

But does LIP send qualitatively different information to the FEF as opposed to SC? The answer was no. As Fig. 9 indicates, during the delayed saccade task output neurons from LIP to FEF conveyed visual responses, delay activity, and presaccadic activity just as did the LIP to SC neurons (cf. Fig. 3A). There were two important differences. First, only 44% of the LIP neurons projecting to the FEF had task-related activity, i.e. that was modulated during the delayed saccade task, as compared to 69% of the LIP neurons projecting to SC. Second, of the task-related LIP neurons projecting to FEF only 17% showed increased activity before saccade initiation, which was a significantly smaller proportion than the 42% of LIP neurons projecting to SC in the same study that had presaccadic activity. In the sample of neurons from this study (Ferraina et al., 2001), the task-related LIP neurons projecting to FEF or SC were similar in that over 90% of both types of output neurons responded to the visual stimulus, over 80% of both types of output neurons had delay activity, and neither type of output neuron ever had a presaccadic burst as its only signal.

In sum, once again the information conveyed from one area to the other was qualitatively the same, although we could discern clear quantitative shifts in the relative types of information conveyed.

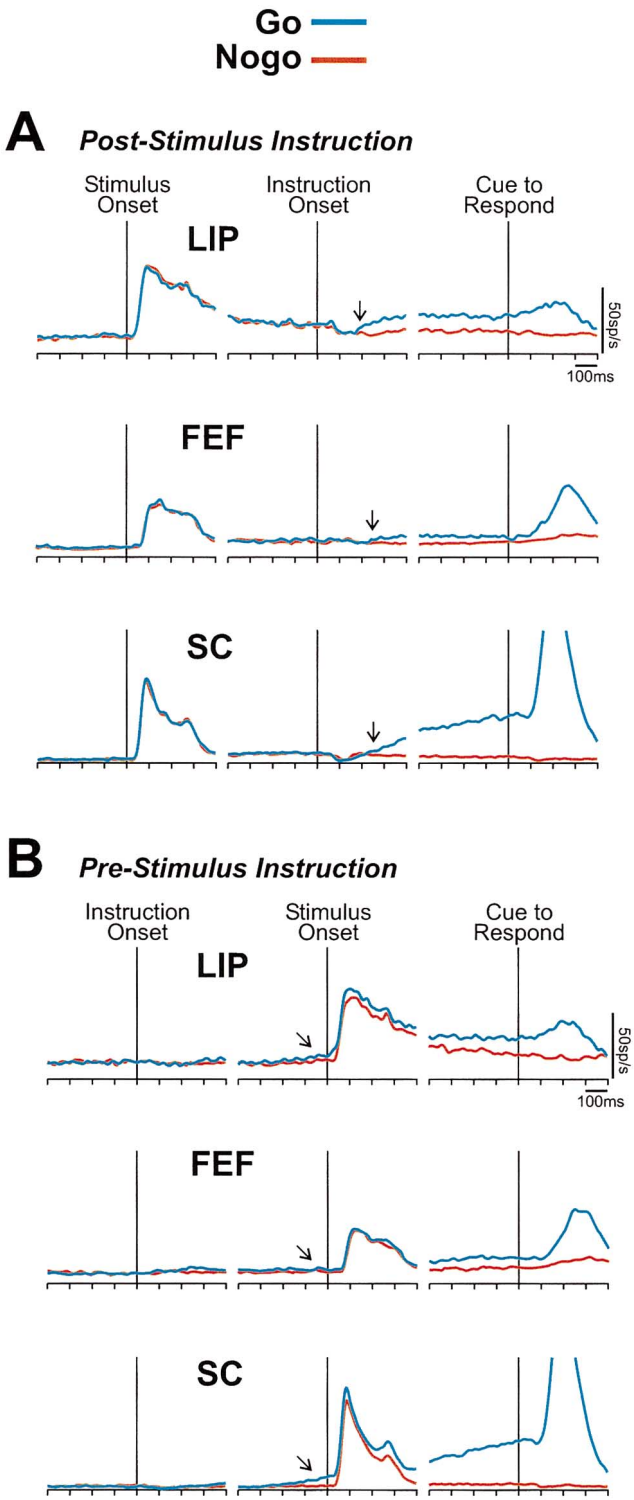

Fig. 8.

4. Discussion

4.1. Signal transformations from cortex to colliculus

The overlap in activity between the LIP output neurons, FEF output neurons, and SC neurons was substantial, with neurons in all three populations having visual responses, delay activity, and presaccadic discharges. This finding is consistent with a number of ways in which processing might evolve from cortex to

Fig. 8. Average time course of neuronal activity during the Go/Nogo task for the population of LIP output neurons, FEF output neurons, and SC neurons. Legend at top. Data from (A) post-stimulus instruction trials and (B) pre-stimulus instruction trials are shown separately. All data were from the memory trials of the task, i.e. the version of the task in which all three populations of neurons were moderately to strongly selective for movement instructions (see Fig. 7). Arrows in panel A show approximate time when the delay activity during Go trials diverged from that during Nogo trials. Arrows in panel B point out the effects of Go vs. Nogo instructions presented alone, i.e. prior to peripheral stimulus onset. Spike density functions were calculated using 10 ms wide Gaussians (LIP and SC data are from Paré and Wurtz (2001); FEF results were calculated from data presented in Sommer and Wurtz (2001)).

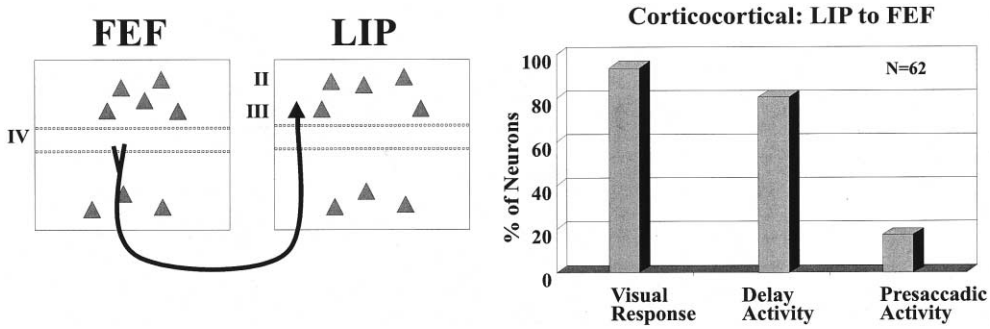

Fig. 9. Frequencies of occurrence of visual responses, delay activity, and presaccadic activity in LIP neurons that project to FEF. Visual responses occurred in 93% of the task-related neurons, delay activity in 80%, and presaccadic bursts in 17%. For comparison, see data collected from the LIP neurons that project to SC (Fig. 3A) (data are from Ferraina et al. (2001)).

colliculus. Fig. 10A shows two possible models of the signal transformation. The first model posits that there is a sequence of processing within an area, which in our experiment is from visual input to saccade related output, and it is the final signal (saccade related activity) that is the output from the area (discrete multistage, Fig. 10A). In the second model, the same local sequence of visuomotor processing occurs within an area, but there is output from each processing stage (continuous multistage, Fig. 10A). Looking only at the activity of neurons in an area, it would be impossible to choose between these alternative models. Identifying the output neurons makes it possible to do so, and our results unequivocally support the continuous multistage model, because we found that the output neurons of LIP and FEF carry visual, delay, and presaccadic signals that seem to represent nearly every stage of visuomotor transformation. Although it is possible that a specific task might reveal a subtle shift in the strength of an output at one of the stages within an area, our results simply show that all stages of visuomotor transformation are available in the output from both FEF and LIP. Any neuronal model of sequential processing would have to take into account this conclusion that cortical output represents multiple successive stages in the visuomotor transformation.

A second conclusion that can be drawn from our results is that there is a gradual, quantitative change in the signals moving from cortical output to colliculus (Fig. 10B). During the delay period, the activity of LIP and FEF output neurons is strongly influenced by visual stimulation, whereas the activity of the SC neurons depends little on visual stimulation (Fig. 5). That the SC delay activity is generally independent of visual stimulation complements our finding using the delayed Go/Nogo task that SC delay activity is very strongly related to the impending movement (Fig. 7). In contrast, the delay activity of LIP and FEF output neurons is relatively less related to the impending movement. Therefore a shift in information content takes place in the delay activity from cortical output neurons to SC neurons; the delay activity becomes less visual-related and more saccade-related.

What causes this signal transformation? We do not know, but we suggest two hypotheses (not mutually exclusive). First, the SC might combine the delay activity it receives from FEF and LIP with more motor-related delay activity that it receives from elsewhere. The other sources of delay activity could include, for example, the substantia nigra (Hikosaka & Wurtz, 1983a,b; Handel & Glimcher, 1999) or the mesencephalic reticular formation (Waitzman, Silakov, & Cohen, 1996; Chen & May, 2000). Second, it may be that processing within the SC itself contributes to the change in information content of the delay activity. It is known, for example, that neurons throughout the SC have functional interconnections with each other that could mediate signal processing within this structure (Munoz & Istvan, 1998).

The third point to be made about the sequence in processing is that it may make more sense to regard LIP, FEF, and SC as part of a functional unit rather than as a unidirectional processing stream (Fig. 10C). The physiological evidence for this is that there is great overlap in the signals exhibited by the cortical and collicular neurons, and also that the signals leaving cortex seem very similar to the signals generally found within cortex (continuous multistage model). Anatomical evidence also has shown that there is a clear pathway back primarily from the intermediate layers of the SC to the FEF (Lynch, Hoover, & Strick, 1994) and primarily from the superficial layers of SC to LIP (West, Lynch, & Strick, 1998). Consequently, what is seen in cortex might be influenced by activity carried up from the colliculus. Further work is needed to understand the impact of the ascending pathways on cortical activity and the implications of viewing these structures as being distributed nodes in a single, highly interconnected processing system.

4.2. Limitations in interpreting the data

Our goal was to identify the output neurons of two cortical areas and compare their activity to that found within the brainstem structure targeted by these output neurons. Our general conclusions relied on techniques

having limitations that should be explicitly considered. First, the possibility remains that while all signals are contained in the stream of output signals from an area, some signals may actually predominate. The small samples studied in our experiments make evaluation of this point impossible. Second, we have been comparing the output neurons of an area to the general population of neurons in the next, but we do not know that the output neurons impinge on a uniform distribution of neurons in the downstream structure. One possibility is that there are separate streams from one area to another, and that each output neuron goes only to one of its own (akin to the labeled line organization of the magno- and parvocellular pathways of the retinogeniculostriate system). While there is very little evidence on this point, and none from the current experiments, we have tested this in the LIP to SC projection using orthodromic stimulation techniques (Paré & Wurtz, 1998). Because LIP output neurons were found to have pronounced delay activity (Fig. 3A), we asked whether LIP neurons project selectively onto the neurons in the SC that have pronounced delay activity as opposed to those having no delay activity. We reversed the procedure described in the present report (cf. Fig. 1A) and stimulated LIP while recording from SC neurons. We found that both types of SC neurons, those with or without delay activity, could be orthodromically activated from LIP at about the same latencies. Helminski

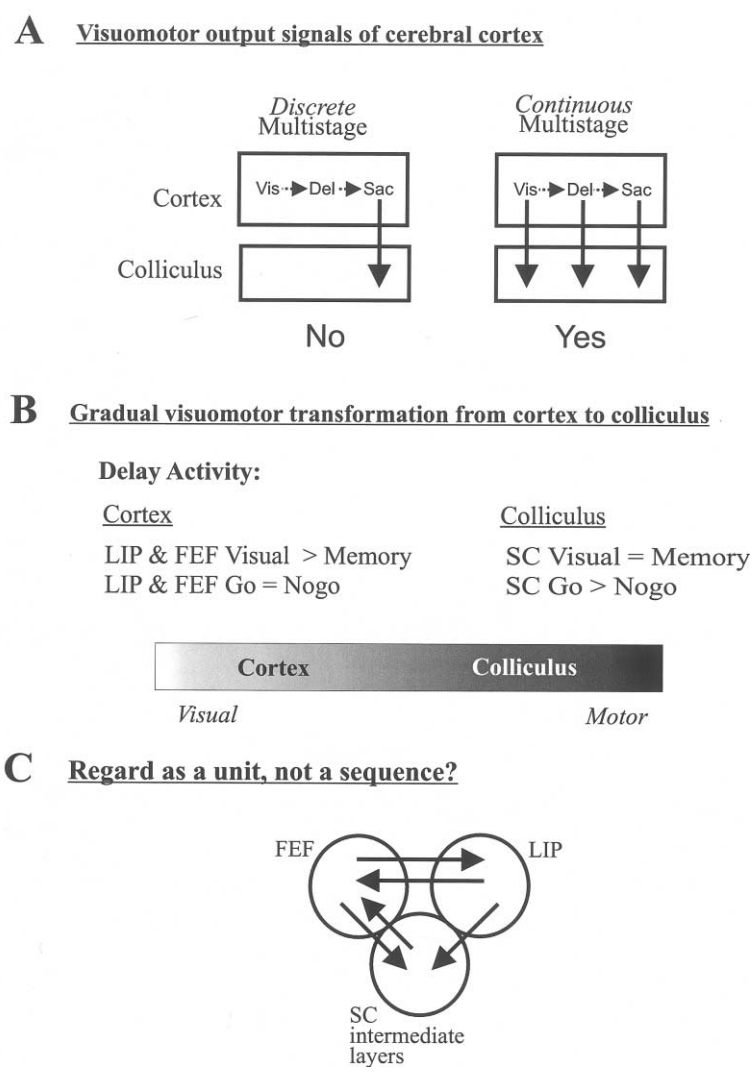

Fig. 10. Evolution of signal processing for saccade generation from the LIP and FEF regions of cerebral cortex to the colliculus. (A) Visuomotor output signals of the cerebral cortex are extremely diverse: signals flowing out of LIP and FEF did not conform to a simple, discrete multistage model (left) but instead to a continuous multistage model (right). Vis, visual responses; Del, delay activity; Sac, saccadic bursts. Dotted arrows within 'cortex' boxes indicate a presumed visuomotor transformation occurring within the cortical areas. (B) The visuomotor transformation from cerebral cortex to colliculus is a gradual one. We found that delay activity at the output of cortex was strongly related to vision (visual > memory) and only moderately related to movement (Go = Nogo). In contrast, delay activity expressed by SC neurons was generally unrelated to vision (Visual = Memory) but was very strongly related to movement (Go > Nogo). (C) LIP, FEF, and the SC intermediate layers may be most appropriately viewed as forming a functional unit rather than a series of processing stages. For details see Section 4.

and Segraves (1996) reported similar results for SC neurons orthodromically activated by FEF stimulation. Hence we doubt that LIP and FEF neurons impinge selectively on a subset of neurons in the SC intermediate layers. This argues that cortical neurons tend to target SC neurons uniformly, but again we cannot rule out a quantitative preference that we cannot see in our small samples.

A third more technical issue concerns whether our cortical output neurons actually terminated in the SC. We have implicitly assumed that our electrical stimulation activates fibers that terminate within the SC, but we could also be stimulating fibers of passage. However, built into the orderly map seen in the projection from FEF to SC (Sommer & Wurtz, 2000b) is an argument against the likelihood of a substantial contribution from stimulation of fibers of passage. Since most of the fibers from cortex enter the rostral SC, pass caudally (Stanton, Bruce, & Goldberg, 1988), and terminate as they go along, it should have been easier to get antidromic activation of FEF from rostral SC than from caudal SC and the projection map should have been skewed rostrally. However, the FEF output neurons were equally likely to be activated from rostral as from caudal SC, and there was little skewing of the projection map (Sommer & Wurtz, 2000b). These results are consistent with the stimulation acting primarily near axon terminals in SC.

4.3. Similarities and differences between the outputs of LIP and FEF

In our comparison of LIP and FEF we found both similarities and differences in the activity leaving the two areas. Both LIP and FEF had output neurons responding to the visual target stimuli, they both had neurons showing an increase of activity before saccades, and they both had delay activity between the visual and saccadic activity. In both areas the delay activity could be related to visual stimulation, to impending movement, or to both. There were some quantitative differences in the percentages of visual responses, delay activity, and presaccadic activity in the two populations. However, were there any large, qualitative differences between LIP and FEF output?

We found a number of substantial differences between the outputs of LIP and FEF. The first was that LIP output neurons that were active during the delayed saccade tasks tended to be 'cut from the same cloth'; they were relatively homogeneous with a typical visuo-delay-saccadic activity profile. In comparison, FEF output neurons were much more heterogeneous in their activity profiles. The second difference was related to the first: many FEF output neurons, but no LIP output neurons, had a presaccadic burst of activity as their sole signal. A third main difference was that the activity of the FEF neurons was altered by the intention to make a saccade primarily when the saccade was to a remembered target whereas the activity of LIP neurons was altered regardless of whether the saccades were to visual or to remembered targets. Finally there seemed to be a clearer topographic map reflected in the FEF output than in the LIP output.

In three of the ways described above, i.e. in terms of functional heterogeneity, presence of presaccadic burst neurons, and topographical organization, FEF output neurons had a tendency to resemble neurons of the SC more than the LIP output neurons did. Possible interpretations of this are that FEF has a stronger influence on the SC than does the LIP, or that FEF is perhaps closer than LIP to the output of cortical visuomotor processing. While we cannot reject these possibilities, we doubt them. We think another interpretation, which acknowledges the pathway from SC back to the cortex, seems more likely. Evidence gathered in the course of the antidromic stimulation experiments on FEF and SC revealed that there was a functionally active pathway that returns to the FEF from the SC intermediate layers (Sommer & Wurtz, 1998), probably via the well known projection from SC to the mediodorsal nucleus of the thalamus and from there to the FEF (Lynch et al., 1994; Sommer & Wurtz, 2000a). No such pathway from the intermediate layers of the SC projects to LIP, although a pathway primarily from the superficial visual layers of the SC does project via the pulvinar to cortex, including to parietal cortex (Diamond & Hall, 1969; Marrocco, McClurkin, & Young, 1981; West et al., 1998). Our hypothesis is that the ascending pathway from SC to FEF might be a critical factor in causing several of the major differences between FEF and LIP that we found. The heterogeneity of cell types in the output of FEF might be caused in part by the signals coming from similarly heterogeneous SC neurons. More specifically, the FEF output neurons having presaccadic bursts of activity as their only signal might inherit this activity from ascending projections of saccade-related burst neurons that are common throughout the intermediate layers of the SC. In support of this idea, we recently found that some SC burst neurons do indeed project to the vicinity of thalamic relay neurons that in turn project to the FEF (Wurtz & Sommer, 2000). Finally, having a well-organized topographic map in the FEF might facilitate the relay of activity in one region of the SC map to corresponding neurons within the FEF. In may be, therefore, that in the absence of the ascending pathway from SC, neuronal activity of FEF output neurons might become much more similar to that of LIP output neurons.

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