

# A Neural Correlate of Oculomotor Sequences in Supplementary Eye Field

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## Summary

Complex learned motor sequences can be composed of a combination of a small number of elementary actions. To investigate how the brain represents such sequences, we devised an oculomotor sequence task in which the monkey had to choose the target solely by the sequential context, not by the current stimulus combination. We found that many neurons in the supplementary eye field (SEF) became active with a specific target direction (D neuron) or a specific target/distractor combination (C neuron). Furthermore, such activity was often selective for one among several sequences that included the combination (S neuron). These results suggest that the SEF contributes to the generation of saccades in many learned sequences.

## Introduction

A learned action is often composed of sequential movements. Many experimental and theoretical studies have been done to elucidate how such motor sequences are represented and produced by the brain (see Hikosaka et al., 1999, for a review). These studies have largely been focused on sequential hand movements. Such learned hand movements are usually associated with eye movements, suggesting that sequences of eye movements can also be learned and would be represented in the brain. However, there have been few studies on the learning of sequential eye movements. Epelboim et al. (1995) asked human subjects to make saccades sequentially over many visual stimuli, but found little evidence for learning. During an object manipulation task in an unfamiliar environment, eye movements tend to be triggered by visual stimuli rather than guided by working memory (Ballard et al., 1992). These observations may suggest that eye movement remains stimulus bound, while hand movement can be learned.

However, other lines of evidence would argue against this idea. Hikosaka et al. (1995) trained monkeys to perform sequential button presses correctly and quickly. After long-term practice, the monkeys became ex-

tremely skillful (accurate and quick) in performing learned sequences, not new sequences. Miyashita et al. (1996) found that learned hand movements were led by, and possibly guided by, saccadic eye movements that brought the gaze to the target in an anticipatory manner. That eye movement may guide hand movement was also suggested by human studies. Johansson et al. (2001) asked human subjects to grasp an object and move it toward a target. Interestingly, a saccadic eye movement was often directed to a point in midair where the object would travel by the subject's next action. These findings suggest that a learned action is acquired as a sequence of eye movements, as well as a sequence of hand movements.

If there is a learning mechanism for eye movements, it must be capable of overpowering the stimulus-bound nature of eye movement. An effective way to test this capability would be to ask subjects to make different eye movements under the identical environment, depending on the learned context. For this purpose, we trained two monkeys on an oculomotor sequence task (Figure 1) in which different sequences ("hypersets") could be learned, each consisting of five saccades. Each saccade was a two-alternative forced choice response ("set"): while the monkey was fixating on a central spot, two identical spots appeared simultaneously out of four positions. After the fixation point went off, the monkey had to make a saccade to one of the two spots that was designated to be the target (the other distractor) (Figure 1A). A unique feature of this task was that the target was determined solely by the context of a given sequence. Since monkeys M and L mastered 12 and 7 hypersets, respectively, and there are only 12 ( $4P_2$ ) target/distractor combinations, a given combination appeared five and three times on the average, respectively, among the learned hypersets (see Figure 1C).

## Results

The SEF was identified by its location (dorso-medial frontal cortex, 1–4 mm from midline, slightly anterior to the level of the frontal eye field) and the results of intracortical microstimulation (saccades, not body movements, evoked with currents less than 50  $\mu$ A) (Schlag and Schlag-Rey, 1987; Figure 1D). Among 279 neurons recorded in the SEF, 158 were related to the sequence task. The neuronal activity was classified into three types depending on the grade of specificity for sequence: direction-dependent (D activity), combination-dependent (C activity), and sequence-dependent (S activity). Examples of these types are shown in Figures 2–5.

Figure 2 shows a sample neuron with D activity. The neuron became active at some sets during the posttarget period (while the target/distractor pair was presented). The activity was selective for the direction of the target (hence, saccade) (ANOVA,  $p < 0.001$ ): leftward (hyperset M4–16, set two and hyperset M4–10, sets three and five) and weakly downward (hyperset M4–16, set four and hyperset M4–10, set four) directions. A

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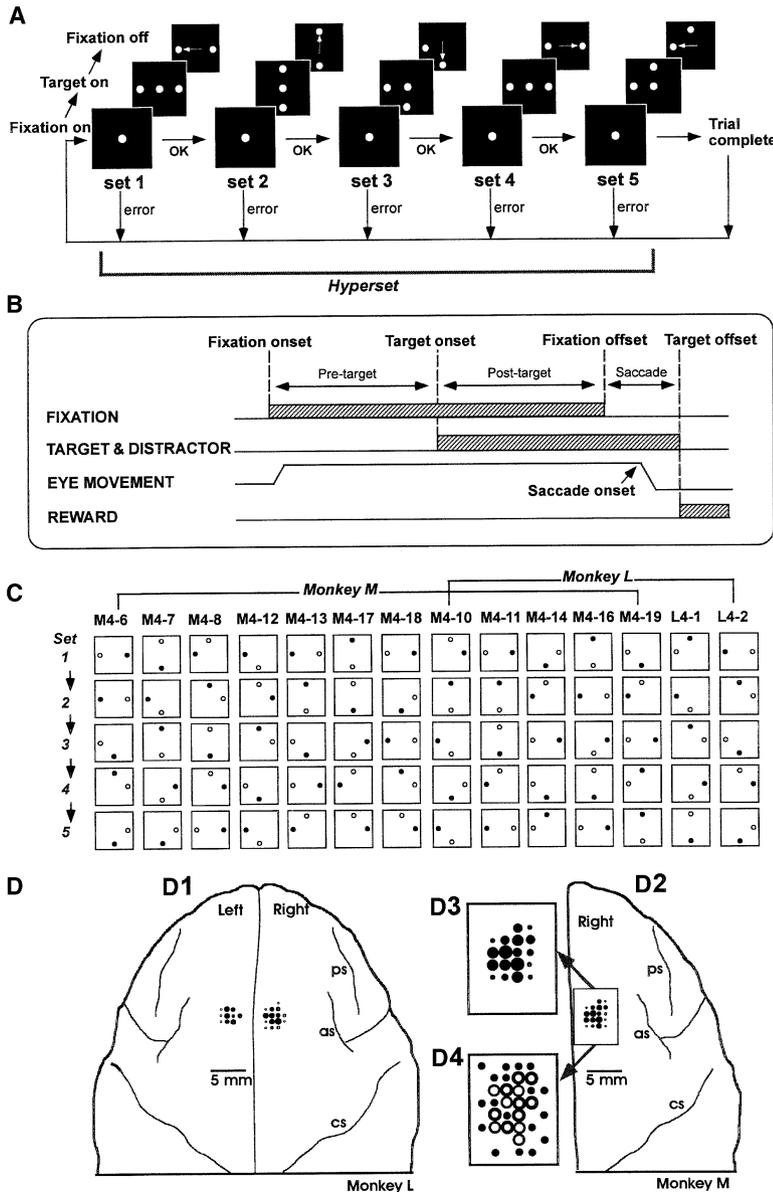


Figure 1. Experimental Design

(A) An example of oculomotor sequence ("hyperset"). The hyperset was composed of a fixed sequence of five sets in each of which the monkey had to make a saccade by choosing a correct target, not a distractor.

(B) The temporal sequence of events in each set of a hyperset. The pre-target and post-target periods were both 800 ms in duration.

(C) The whole sets of hypersets for monkey M and monkey L. The target and distractor are indicated by closed and open circles, respectively. Since the same combinations of visual stimuli or target/distractor appear in different hypersets or even within a single hyperset, the monkey could not rely only on the visual stimuli to perform the task.

(D1–D4) Recording sites of SEF neurons for monkey L (D1) and monkey M (D2). Each dot indicates an electrode track in which task-related neurons were recorded. The area of each dot is proportional to the number of task-related neurons, with the largest and smallest dots representing five neurons and one neuron, respectively. (D3) Enlarged view of the recording sites for monkey M. (D4) Sites of microstimulation for evoking saccades: thick circles indicate short latency sites (threshold < 50  $\mu$ A and latency < 50 ms), thin circles indicate long latency sites (threshold < 50  $\mu$ A and latency > 50 ms), and dots indicate no saccades evoked at 50  $\mu$ A. The following abbreviations are used in (D1) and (D2): as, arcuate sulcus; cs, central sulcus; ps, principal sulcus.

similar direction selectivity was observed in the control task (Figure 2, right), in which only a single target was presented. The selectivity in the sequence task was striking if we compare the cases in which target and distractor were reversed. For example, at sets two and five of hyperset M4–16, two identical stimuli were presented at both left and right positions and, yet, the neuron was active only in set two, depending on the monkey's intention to make a leftward saccade. However, the neuron was not selective for the target/distractor combination; there was no statistical difference in the neuron's activity between hyperset M4–16, set two and hyperset M4–10, sets 3 or 5 in which the target was the same, but the distractor was different.

Some neurons, on the other hand, showed selectivity for target/distractor combination (C activity), as illustrated in Figure 3. The neuron preferred the up-target/left-distractor (UL) combination. The UL combination appeared once for each of the two hypersets shown in Figure 3, and the neuron exhibited similar patterns of

activity (M4–14, set five and L4–1, set one). Again, there was little activity for the reversed combination, LU (M4–14, set two). A critical feature of C activity was that the neuron's activity was dependent on the distractor as well (or combination). Thus, the neuron in Figure 3 was significantly less active for UR combination (L4–1, set three).

A higher selectivity for individual sequences was found as sequence-dependent activity (S activity), as illustrated in Figure 4. The neuron was highly active at hyperset M4–18, set five with RU combination. The same RU combination appeared in M4–8 and M4–12, but the neuron was significantly less active (ANOVA,  $p < 0.001$ ). We repeated hyperset M4–18 and found that the neuron was again active at set five in a similar manner (Figure 4, right), confirming the reproducibility of the data. The selectivity of this neuron was not absolute, however. It combined weak D activity (preference for R direction) and C activity (preference for RU combination).

Since the same RU combination appeared as the fifth,

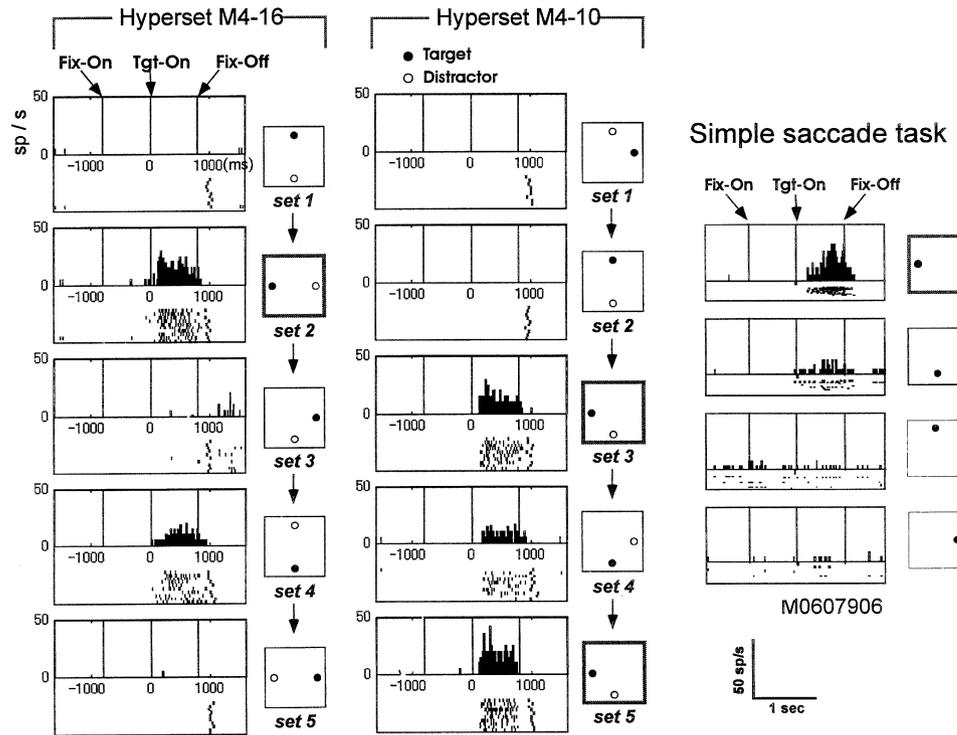


Figure 2. Direction-Dependent Activity (D Activity) of a Neuron in the Right SEF during Performance of Two Hypersets (Left) and a Control Task (Right)

Spike activity, shown by rasters and histograms, are aligned on fixation onset (Fix-On), target onset (Tgt-On), and fixation offset (Fix-Off) for each set. Beside the raster/histogram, the combination of target (closed circle) and the distractor (open circle) for the set is shown. Dots in each raster indicate saccade onsets. The neuron was consistently active before leftward saccades and less strongly before downward saccades in both the sequence task and the control task.

fourth, and second sets in hypersets M4-18, M4-8, and M4-12, respectively, the selectivity of the neuron in Figure 4 could be related to the numerical order in a sequence (Clower and Alexander, 1998; Shima and Tanji, 2000). However, the numerical order could not always account for the selectivity of S activity. For example, LU combination appeared in hyperset M4-14 and hyperset M4-19 at the same numerical order (set two) (Figure 5). Yet, the neuron shown in Figure 5 was active in hyperset M4-14, but not in hyperset M4-19 (ANOVA,  $p < 0.001$ ).

Among 158 task-related neurons, 85 (54%) showed D activity, 82 (52%) showed C activity, and 114 (72%) showed S activity at more than one of the three task periods (Figure 1). Some neurons showed more than one type of activity. Particularly interesting among the three types was S activity because it could be used to differentiate between different hypersets, even though they may have contained identical target/distractor combinations. Figure 6A shows the best and worst activity of five neurons with S activity. Neuron L0823904 showed differential activity after the onset of stimuli (posttarget period). The activity of the other neurons became differential before the onset of stimuli (pretarget period), even before the onset of the fixation point (neurons L0809902 and L0823902). On the other hand, differential activity was absent after the offset of the fixation point when a saccade was made (saccade period), except for neuron L0809902.

These results suggest that a neuron with S activity might contribute to the neural representation of a spe-

cific element (set) in a specific sequence (hyperset). This further suggests that a sequence of saccades could be represented by a set of SEF neurons with S activity. However, this hypothesis requires that neurons with S activity (hereafter called S neurons) altogether prefer all elements in all sequences. Support for this hypothesis is found in Figure 6B, which shows that most sets among the learned hypersets were preferred by at least one neuron. There was no tendency that SEF neurons overall preferred earlier or later sets.

## Discussion

### Supplementary Eye Field Is Related to Eye Movement Sequences

We have shown that many SEF neurons exhibited activity related to oculomotor sequences with different levels of specificity. The results suggest that oculomotor sequences are represented in the SEF or neural networks involving the SEF. Previous studies have shown that neurons in the monkey SEF change their behavior flexibly, depending on many kinds of task-specific demands: object-centered coding of saccades (Olson and Gettner, 1995), arbitrary visuo-oculomotor association (Chen and Wise, 1995), antisaccades (Schlag-Rey et al., 1997), performance monitoring (Stuphorn et al., 2000), and reward-prediction and detection (Amador et al., 2000). Given such diverse capabilities of SEF neurons, their relation to sequential eye movements may not be surprising.

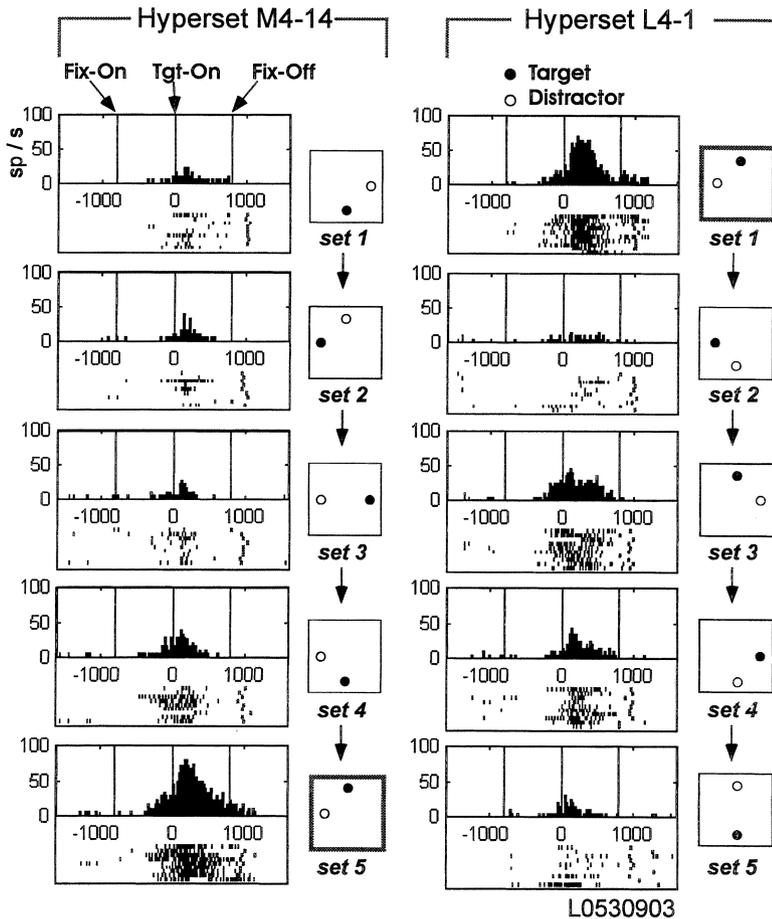


Figure 3. Combination-Dependent Activity (C Activity) of a Neuron in the Right SEF during Performance of Two Hypersets

The same format as in Figure 2. The neuron was most active for up-target/left distractor (UL) combination. It was only weakly active for up-target/right distractor (UR) combination, even though it required the same rightward saccade.

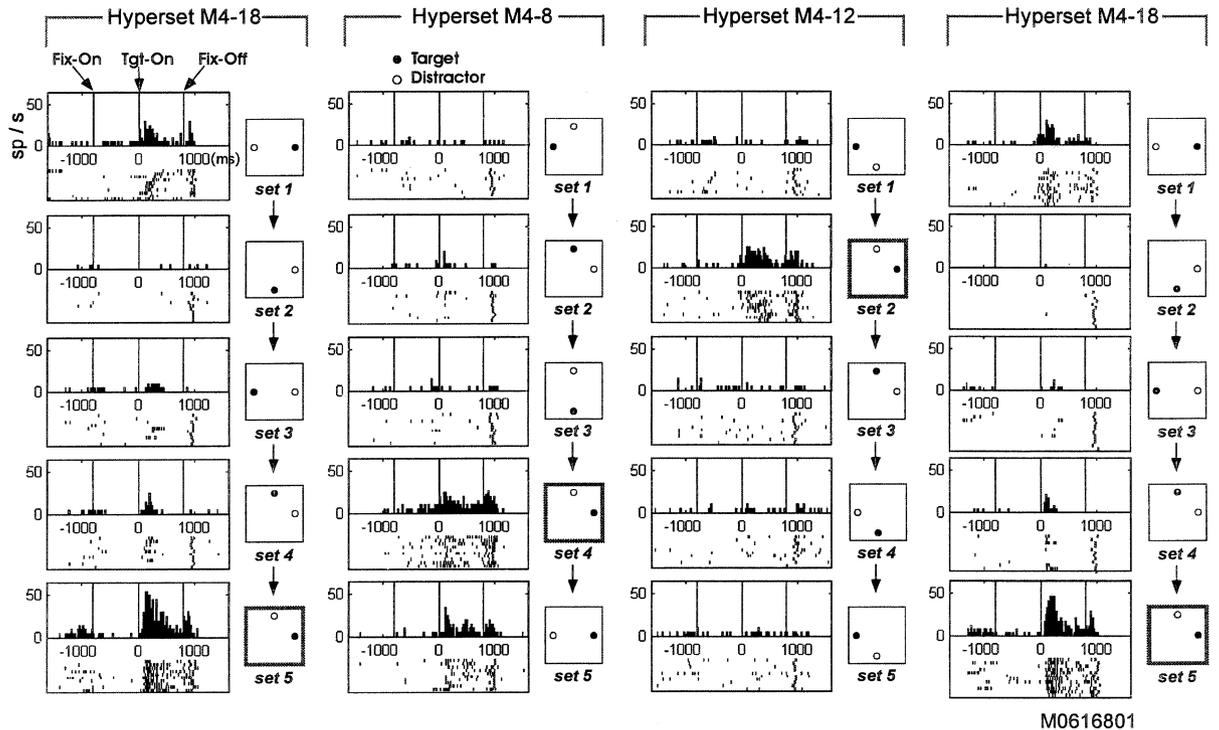
However, there has been no study, to our knowledge, that examined sequential saccades in animal subjects.

Our finding may be more relevant to some studies on human subjects. Patients with lesions in the supplementary motor area (SMA) were impaired in executing sequential memory-guided saccades, not a single saccade (Gaymard et al., 1990). Transcranial magnetic stimulation over the SMA disrupts execution of sequential memory-guided saccades (Müri et al., 1995, 1994). Petit et al. (1996) and Kawashima et al. (1998) found that the execution and learning of sequential saccades were associated with activation several brain areas, including midline frontal areas. It has been argued that, in humans, the SEF is located in the medial wall of the frontal cortex, just anterior to the SMA (Petit et al., 1996). If so, deficits in sequential saccades by transcranial magnetic stimulation (described above) could be due to functional blockade of the SEF, rather than the SMA. Likewise, functional activation associated with sequential saccades could have included the SEF.

Interestingly, different areas in the medial frontal cortex are known to be related to learning and memory of hand motor sequences in different ways (Picard and Strick, 1996). Different types of sequence-specific activity have been found in many neurons in the SMA and the preSMA (Tanji and Shima, 1994; Clower and Alexander, 1998; Shima and Tanji, 2000). These data were obtained after the monkeys had learned the hand movement sequences extensively. Nakamura et al. (1998) showed

that activity of SMA and preSMA neurons changed during learning of hand movement sequences. Their task is a prototype of the task used in the present study and, therefore, had the same design principle. They showed that many neurons in the preSMA, rather than the SMA, were active during the initial learning. This conclusion was confirmed by a human functional MRI study (Sakai et al., 1998).

These data on sequential hand movements and together with our data on sequential eye movements may suggest that the medial frontal cortex constitutes a neural conglomerate for sequential eye-hand movements. This architecture might reflect tight, but dissociable, relationships between eye and hand movements in purposeful behavior (Prablanc et al., 1986; Carnahan and Marteniuk, 1991; Van Donkelaar and Staub, 2000). The relationship is particularly interesting in realistic situations in which different movements are performed sequentially. If the environment is unfamiliar, eye movements may occur frequently to scan the environment, independently of hand movements (Ballard et al., 1992). As a subject becomes skillful in sequential action with extensive practice, eye and hand movements tend to occur simultaneously and in an anticipatory manner (Miyashita et al., 1996). Immediately after hand contact with an object, the eyes may start moving away from the object toward the next (Johansson et al., 2001). These findings are consistent with the hypothesis that there exists separate neural mechanisms, one for sequential



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Figure 4. Sequence-Dependent Activity (S Activity) of a Neuron in the Right SEF during Performance of Three Hypersets

The same format as in Figure 2. The neuron was active for right-target/up distractor (RU) combination, but only when the combination appeared in hyperset M4-18.

eye movements (corresponding to the SEF) and the other for sequential hand movements (corresponding to the SMA). They further suggest that the relationship between the eye and hand mechanisms is flexible, either independent or well-coordinated, depending on the context or the level of practice.

#### Functional Organization in Supplementary Eye Field

A remarkable finding in our study was that different groups of SEF neurons showed different levels of specificity for oculomotor sequences. We now discuss the functional significance of individual neuron types in the SEF.

At the least specific level, neurons were active whenever a saccade was to be made in a particular direction (D activity). This activity would reflect the readiness to make a particular saccade in a given context. Quite often, however, D activity appeared visually driven as its onset was time locked with the onset of the stimuli (target and distractor). The selectivity of D activity might then reflect visual spatial attention. In a traditional experiment studying spatial attention, two stimuli are presented simultaneously, one inside and the other outside the neuron's receptive field, and the subject is instructed to use one of them and ignore the other (Wurtz et al., 1980). It has been shown that neuronal visual responses were larger when the receptive field stimulus is attended than when ignored (Colby and Goldberg, 1999; Treue, 2001). However, the response to the ignored stimulus rarely disappeared, suggesting that attention operates

as a modulator, not a gate (Treue, 2001). In contrast, D activity found in our study was usually very selective in an all-or-none manner (see Figure 2). An obvious difference was that in our study, the target was determined in a sequential context in which the subject had been trained extensively, while in the conventional attention studies the target was determined for each experiment. To summarize, although D activity is determined only by the current stimulus environment, its selectivity seems to be aided by the sequential context acquired with long-term practice.

The second level of context dependency (C activity) indicates a clear departure from attentional modulation. C activity was selective not only for the target position, but also for the distractor position. If spatial attention acts to select one position at the expense of the others (Bashinski and Bacharach, 1980), C activity would be unsuitable for attention because the preferred position may or may not be coded by the neuron, depending on the position of the distractor. Instead, C activity may be more tightly related to memory. Some SEF neurons may have been shaped up by extensive practice, so as to respond specifically to particular combinations of visual stimuli and a particular intention of saccade, which we characterized as C activity. However, neurons of this activity alone could not represent the oculomotor sequences used in our study because a given target/distractor combination appeared many times in different sequences.

S activity showed the highest specificity. It was preferential for a particular target/distractor combination that

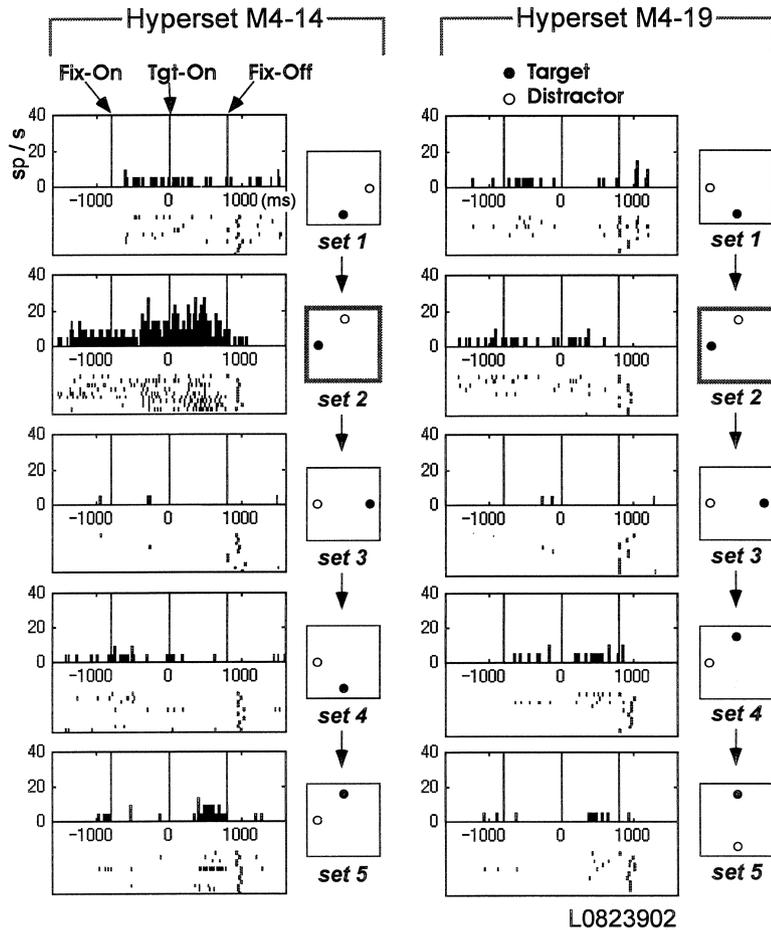


Figure 5. Another Example of S Activity of a Neuron in the Right SEF

The same combination (left-target/up-distractor [LU]) appeared as the second set in both hypersets (M4-14 and M4-19) and, yet, the neuron was active only in M4-14.

appeared in a particular sequence. Unlike the three kinds of activity, S activity could differentiate multiple sequences that share the same elements. Different elements in different sequences would be encoded differentially within SEF neurons exhibiting S activity, even though they are physically identical. In other words, different sequences would be encoded by separate groups of S neurons. If so, the preference of S activity should be distributed among all sets in all sequences. Our data (Figure 6B) suggest that this is probably true.

What might the mechanism underlying S activity be? Neurons with both C activity and S activity were preferentially active for a particular target/distractor combination. However, in S activity, but not C activity, the activity for the preferred combination was different, depending on which sequence the combination appeared. Since a given target/distractor combination usually appeared in different numerical orders and in different sequences (as in Figure 4), the selectivity of S activity could depend on the numerical order. In fact, many neurons in the SMA and the preSMA were active in particular numerical or rank orders in any learned manual sequences (Clower and Alexander, 1998; Shima and Tanji, 2000). We did not find such numerical order selective activity in the SEF. Nonetheless, S activity could be generated if C activity is conditioned by the numerical order selective activity. Note, however, that this mechanism may still be insufficient in some cases (see Figure 5).

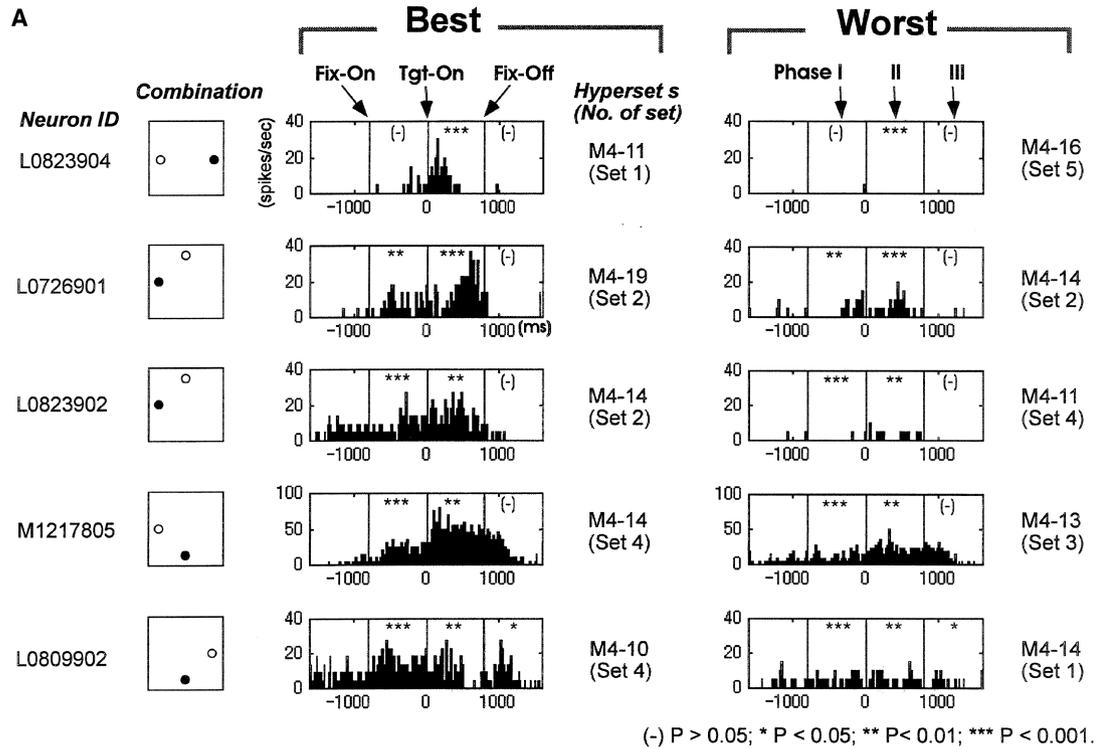
## Conclusion

We have shown that the oculomotor sequence task revealed different levels of context dependency in SEF neurons: D activity, C activity, and S activity. S activity corresponded to an element in a particular sequence. C activity corresponded to an element in sequences. D activity corresponded to a selected sensorimotor signal. The various levels of context dependency would be useful for generating saccades accurately according to learned sequences.

## Experimental Procedures

### Animal Preparation

We used two male Japanese monkeys (*Macaca fuscata*): monkey M (9.8 kg) and monkey L (10.5 kg). The monkeys were kept in individual primate cages in an air-conditioned room where food was always available. At the beginning of each experimental session, they were carried to the experimental room in a primate chair. The monkeys were given a restricted amount of fluid during training and recording periods. Their health condition, including factors such as body weight and appetite, was checked daily. Supplementary water and fruit were provided daily. The experiments were carried out while the monkey's head was fixed and his eye movements were recorded. For this purpose, a head holder and an eye coil were implanted under surgical procedures (Lu et al., 1998). The recording sites were determined using MRI (Hitachi, AIRIS, 0.3 T). All surgical and experimental protocols were approved by the Juntendo University Animal Care and Use Committee and are in accordance with the National Institutes of Health Guide for the Care and Use of Animals.



**B** The distribution of the preferred sets of the sequence-dependent activities (M=94; L=103)

Monkey M						Monkey L					
Sequence ID	Set 1	Set 2	Set 3	Set 4	Set 5	Sequence ID	Set 1	Set 2	Set 3	Set 4	Set 5
M4-6	2	4	3	1	3	M4-10	3	4	2	10	2
M4-7	3	2	2	2	2	M4-11	3	3	2	3	4
M4-8	1	0	3	2	2	M4-14	4	3	3	3	1
M4-12	3	1	2	1	2	M4-16	2	2	4	1	2
M4-13	2	3	1	2	1	M4-19	2	4	2	4	2
M4-17	1	1	2	1	2	L4-1	3	2	3	3	1
M4-18	2	2	1	3	1	L4-2	2	3	2	2	7
M4-10	2	1	1	2	1						
M4-11	1	1	1	1	0						
M4-14	1	0	2	2	1						
M4-16	1	2	1	1	1						
M4-19	1	1	1	1	1						

**Figure 6. S Activity of Five SEF Neurons**

(A) For each neuron, the strongest (best) and weakest (worst) activity for its preferred target/distractor combination (shown on the left) in different hypersets (indicated on the right of each histogram) are shown. The statistical difference is indicated for each of three periods (\*, p < 0.05; \*\*, p < 0.01; \*\*\*, p < 0.001): pretarget (FixOn-TgtOn), posttarget (TgtOn-FixOff), and saccade (Fix-Off). As shown at the top, for example, the activity of neuron L0823904, for a combination of right-target and left-distractor, was clear when the combination was included in hyperset M4-11 (set one) and was absent when it was included in hyperset M4-16 (set five).

(B) Distribution of the best sets for neurons with S activity.

**Task Procedures**

The monkeys were trained to make learned sequences of saccades. Each sequence (hyperset) consisted of five saccades (Figure 1A). For each saccade (set) (Figure 1B), a spot of light (fixation point) appeared in which the monkeys had to fixate (pretarget period). After 800 ms, two identical spots of light appeared at two out of four directions (up, down, right, and left) (posttarget period). One of them was designated to be the target and the other, the distractor. After another 800 ms, the fixation point turned off and the monkeys had to make a saccade to the target. If the saccade was correctly made to the target (saccade period), the monkeys obtained a small amount of liquid reward and proceeded to the next set; otherwise, the trial was aborted, and the monkeys had to start from the first set. The trial was regarded successful only when the monkey made saccades correctly for the whole hyperset, at which time the monkey

obtained an extra amount of reward (i.e., bonus). The same hyperset was repeated as a block until the monkey completed ten trials.

Since the target and the distractor were physically identical, the monkeys initially had to find the target by a trial-and-error process. However, the number of errors decreased after long-term practice for a particular hyperset, as the target/distractor locations were fixed for the consecutive sets in the hyperset. After 5-6 months of training, monkeys M and L became able to perform 12 and 7 hypersets, respectively (Figure 1C).

**Experimental Procedures**

All recordings were done after the monkeys mastered a repertoire of 12 or 7 hypersets. We aimed at the SEF, a medio-dorsal portion of the frontal cortex where visual-saccadic cells are clustered (Schlag and Schlag-Rey, 1987). To confirm the localization of the

SEF, we applied intracortical microstimulation (ICMS) (50 negative pulses of 0.2 ms duration at 330 Hz, with currents of 10–50  $\mu$ A). For each neuron recorded, we had the monkey perform two to three hypersets. If the neuron was active in any of the hypersets (e.g., the first hyperset), we performed the recording experiment in the following steps. (1) We first recorded the neuronal activity while the monkey performed the first hyperset as a block of ten successful trials. (2) We chose other hypersets (e.g., second, third, etc.) that included the same set for which the neuron was active in the first hyperset and recorded the neural activity. (3) We examined simple saccades as a control task in which a single target was presented randomly out of the four directions. (4) We repeated the process used in (1) to confirm the stability of recording.

#### Data Analysis

Task-related activity was classified into three types depending on the grade of specificity for sequence: either direction-dependent, combination-dependent, or sequence-dependent. For the direction-dependent type, we examined whether the neuron's discharge rates were different among the four target directions (ANOVA,  $p < 0.05$ ). If the activity for one target direction was significantly higher than for the others (post-hoc Fisher's LSD test,  $p < 0.05$ ), the neuron was defined as direction-dependent. For the combination-dependent type, we examined whether the neuron's discharge rates were different among the target/distractor combinations tested (ANOVA,  $p < 0.05$ ). If the activity for one target/distractor combination was significantly higher than for the others (post-hoc Fisher's LSD test,  $p < 0.05$ ), the neuron was defined as combination-dependent. For the sequence-dependent type, each combination was included in 3–5 hypersets (Figure 1C), since there were only 12 target/distractor combinations. We examined whether the discharge rates for the neuron's preferred target/distractor combination were different across different hypersets that included the combination (ANOVA,  $p < 0.05$ ). If the neuron's activity for the target/distractor combination in one hyperset was significantly higher than that in the other hypersets (post-hoc Fisher's LSD test,  $p < 0.05$ ), the neuron was defined as sequence-dependent. This analysis was done for three task periods (see Figure 1B): the pretarget period, the posttarget period, and the postsaccade period.

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