

Correlation of Primate Superior Colliculus and Reticular Formation Discharge With Proximal Limb Muscle Activity

VEIT STUPHORN,¹ KLAUS-PETER HOFFMANN,¹ AND LEE E. MILLER²

¹*Department of Zoology and Neurobiology, ND 7/67, Ruhr-University of Bochum, D-44780 Bochum, Germany; and*

²*Department of Physiology, Northwestern University Medical School, Chicago, Illinois 60611*

Stuphorn, Veit, Klaus-Peter Hoffmann, and Lee E. Miller. Correlation of primate superior colliculus and reticular formation discharge with proximal limb muscle activity. *J. Neurophysiol.* 81: 1978–1982, 1999. We studied the discharge of neurons from both the superior colliculus (SC) and the underlying mesencephalic reticular formation (MRF) and its relation to the simultaneously recorded activity of 11 arm muscles. The 242 neurons tested with a center-out reach task yielded 2,586 pairs of neuron/muscle cross-correlations (normalized, such that perfect correlations are ± 1.0). Of these, 43% had peaks with magnitude as large as 0.15, a value that corresponds to the 5% level of significance, and 16% were as large as 0.25. The great majority of peaks in this latter group was positive. The median lag time within this group was 52 ms, indicating that the neuronal discharge tended to precede the correlated muscle activity. We found a small but significantly higher proportion of cells with these relatively strong correlations in the MRF than in the SC. For both areas, these occurred most frequently with muscles of the shoulder girdle and became less frequent for axial as well as for increasingly distal arm musculature. The results support a role for the SC and MRF in guiding the arm during reach movements via the control of proximal limb musculature.

INTRODUCTION

Recently, cells within the superior colliculus (SC) and underlying mesencephalic reticular formation (MRF) have been described which discharge in relation to limb movement (Werner 1993). Like eye-movement-related collicular neurons, the discharge of these “reach” cells varies with the direction of movement and has a duration corresponding to that of movement. The general shape and timing of the reach cell bursts bear considerable similarity to analogous measures of proximal muscle activity (Kutz et al. 1997; Werner et al. 1997a,b).

To make a more detailed and quantitative comparison between the reach cell discharge and muscle signals, we have adopted techniques that previously have been applied to recordings made from the magnocellular red nucleus (RNm) and the primary motor cortex (Miller and Houk 1995; Miller et al. 1993, 1996). Briefly, these techniques involve the calculation of long-time-span cross-correlation functions between single-unit discharge rate and signals obtained from chronically implanted electromyographic (EMG) electrodes. These cross-correlations reveal the similarity and timing between the neuronal signal and each of the muscle signals. A given reach

neuron would be expected to vary most consistently with the activity of a particular muscle or group of muscles to which it is functionally related.

METHODS

One male rhesus monkey was trained to attend to a circular array of touch detectors arranged in a vertical plane at arm’s length. The monkey reached toward and touched a central detector when it was illuminated, then held it for 1 s, pending the illumination of one of eight pseudorandomly selected outer lights. The monkey reached toward, pressed, and held this second detector for 1 s before returning its hand to a detector at its waist. The monkey received a liquid reward for correct performance. We recorded blocks of eight correctly performed trials, including at least three blocks for each cell if possible. In addition to this center-out task, we also trained the monkey to perform a visually guided saccade task.

After training, the monkey was anesthetized with ketamine hydrochloride (10 mg/kg im) followed by pentobarbital sodium (25 mg/kg iv). A stainless steel head holder and recording cylinder were implanted on the animal’s skull. A cylinder was placed on the midline over the occipital pole, tilted backward 45° from the vertical. Eye position was measured with a subconjunctival coil implanted on each eye (Judge et al. 1980). Intramuscular injections of analgesics and antibiotics were delivered postoperatively for 2 wk. All procedures were approved by a local ethical committee and followed the German Law on the Protection of Animals.

Recordings were made from cells within the SC and MRF using single tungsten microelectrodes and from muscles using chronically implanted bipolar “patch” electrodes. Unitary action potentials were detected with a level discriminator, and EMG signals were full-wave rectified, low-pass filtered, and sampled at 500 Hz. The following muscles were implanted: deltoideus anterior, biceps brachii, flexor digitorum superficialis (FDS), infraspinatus, latissimus dorsi, deltoideus medialis (MDI), pectoralis major, rhomboideus major, teres major, triceps brachii, and trapezius.

We could not collect data continuously across many trials, so instead we collected and concatenated individual trials. This had the effect of removing periods of inactivity and abortive movements. Interspike intervals were converted to instantaneous frequency and used to calculate analogue cross-correlations between the discharge rate and muscle activity signals. The cross-correlation equation is a function of the time shift τ , imposed between two signals. The basic relation is defined by the following equation

$$C_{xy}(\tau) = \frac{1}{T} \int_0^T n(t)m(t + \tau)dt$$

where T is the number of sampled data points of the time varying signals n and m . This expression actually yields the cross-covariance between signals. By subtracting the mean and dividing by the variance

The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

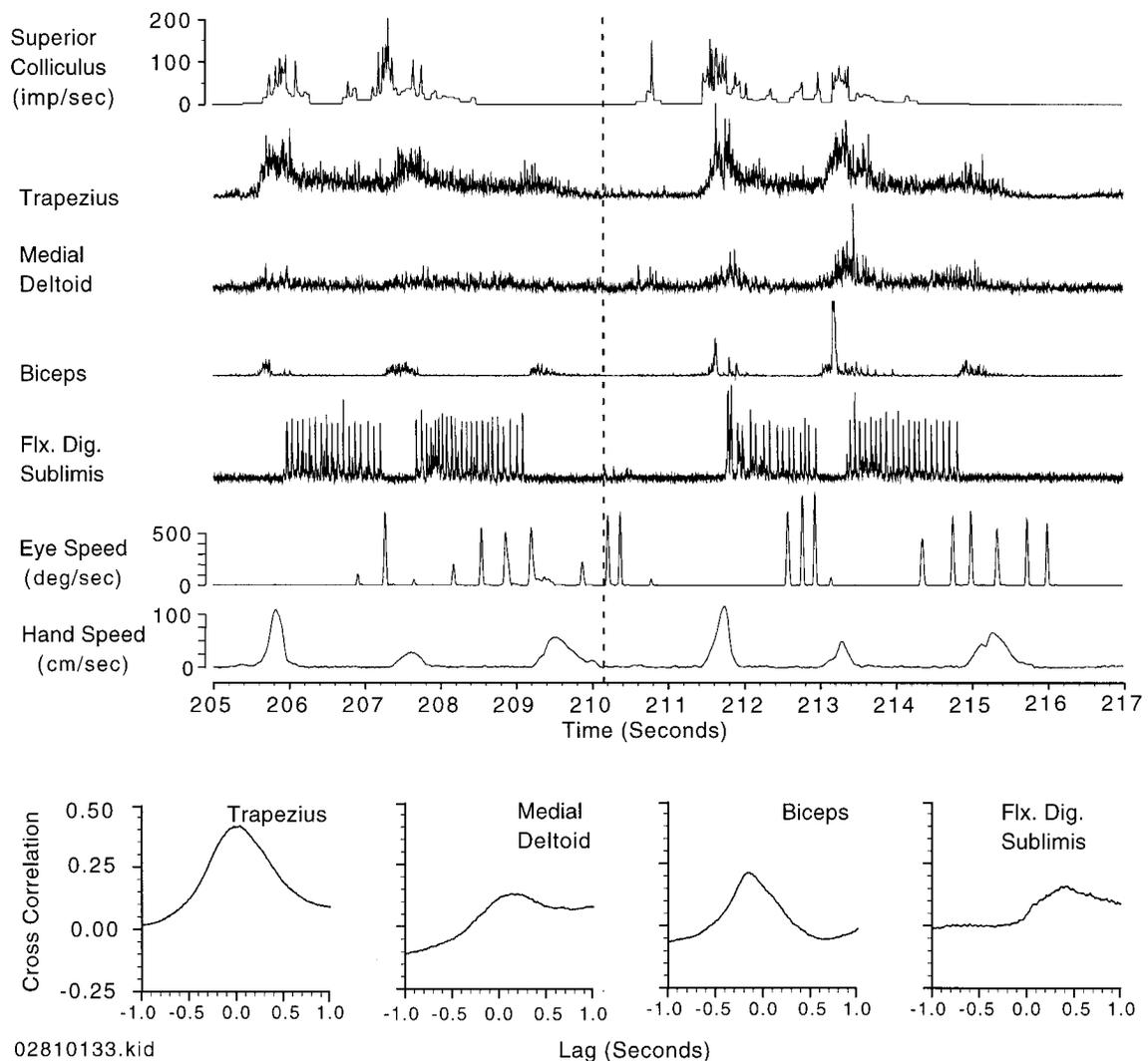


FIG. 1. *Top*: firing rate of superior colliculus (SC) neuron, activity of several muscles, and eye and hand movement. Cell was recorded 1.77 mm below the surface of the left SC. Trapezius electromyogram (EMG) was very similar to the neuronal discharge during these 2 successive trials. - - -, point at which data collection was interrupted. *Bottom*: cross-correlations between neuronal and muscle activity for entire file. Other muscles, although active in task, were less well correlated than trapezius.

of each signal (2nd equation), the equation is made analogous to the linear correlation coefficient such that it gives values of ± 1 for perfect correlations and a value of 0 for no correlation

$$\rho_{xy}(\tau) = \frac{C_{xy}(\tau) - \mu_x \mu_y}{\sigma_x \sigma_y}$$

For obvious reasons, this equation sometimes is referred to as the "correlation coefficient equation," but we will use the more common term, "cross correlation."

As shown in Fig. 1, we also obtained a simple measure of hand movement and calculated cross-correlations between neuronal discharge and a variety of movement-derived signals. A more detailed analysis of those results, and a comparison with these results, will be the topic of a later publication.

RESULTS

We recorded the discharge from 242 neurons with the center-out task. This included 161 cells within the SC proper and 81 cells within MRF, considering those cells recorded at a depth >4 mm below the surface of the colliculus to be within

the MRF. Typically, cells located within the more superficial layers of the superior colliculus had visual and or saccade related activity. Before testing the center-out behavior, we tested each cell during one or more saccade tasks. Those with obvious saccade related activity were not considered further. Figure 1 depicts the typical activity pattern of a reach cell for a sequence of two trials. The neuron reached peaks of discharge in excess of 100 imp/s during the first two movements but remained silent during the return to the touchpad. The separate, sequentially recorded trials were concatenated as indicated (- - -) to accommodate the cross-correlation analysis. As in this example, there was generally relatively little discontinuity between trials for any of the signals.

The figure also shows recordings from several muscles made simultaneously with the neural discharge. These muscles were selected from the larger group to show examples of muscles acting on the shoulder, arm, and wrist. The neural discharge clearly reflected bursts in the proximal muscles, in particular, that of trapezius. FDS was activated largely out of phase with the more proximal muscles, during the periods in which the

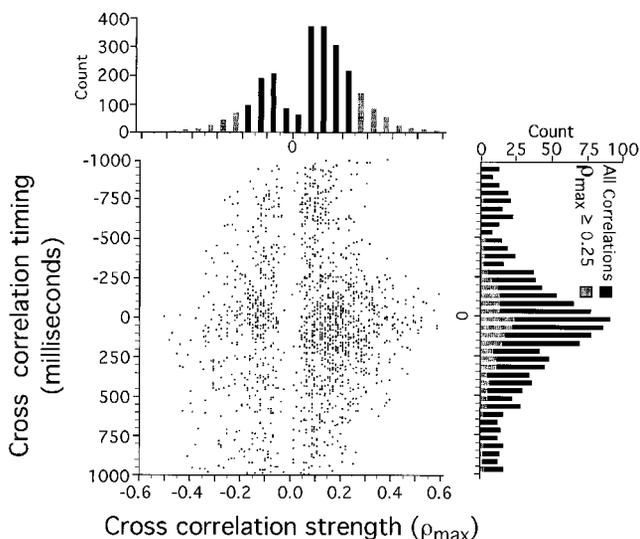


FIG. 2. Scatter diagram shows the time of the peak correlation plotted against its strength. Note that the vertical axis is reversed such that the corresponding histogram increases from left to right. *Top and right:* distribution of cross-correlation peak timing and lag, respectively. ■, cases having magnitude ≥ 0.25 . Positive correlations were more common than negative ones, and timing tended to be skewed toward positive lags, in which neuronal activity preceded muscle activity.

monkey was touching the sensors. There was no consistent relation between the bursts of discharge in this neuron and the monkey's eye movements.

In Fig. 1, *bottom*, are cross-correlations calculated between neural discharge and each of the muscle signals. The cross-correlations span ± 1.0 s and reflect the extent to which the modulation of each muscle signal resembled the rate modulations of the neuron. These correlations were calculated from a total of 24 trials. The large peak (0.41) that occurred for trapezius confirms the impression gained from these two trials that throughout the entire file the activity of this muscle closely resembled that of the neuron. The peak correlation occurred at ~ 40 ms, indicating that on average modulations in neuronal discharge preceded those of the muscle by 40 ms. Several other shoulder muscles that are not shown in this figure were also well correlated although not as strongly as trapezius. Biceps had a more prominent burst during the final movement to the touchpad than did either trapezius or the neuron. Perhaps for this reason, its peak reached only 0.19. MDI and FDS each were correlated weakly at a level slightly above that considered to be the 5% level of statistical significance (Miller et al. 1993).

Figure 2 summarizes the strength and timing of 2,586 pairs of correlations that we calculated for this monkey. Of these correlations, 1,738 were from SC neurons and 848 from the MRF. When occasionally more than one file was recorded from a given neuron, only the one containing the strongest correlations was included. A clustering of lag times can be seen near zero with long lags relatively rare for correlations > 0.25 . These relatively strong, short-lag correlations are more likely to be functionally "significant" and more reliably represent the properties of the collicular limb control system than those near the limit of statistical significance.

Figure 2, *top*, shows the distribution of cross-correlation strength. There were ~ 2.3 times as many positive as negative correlations in general, but if one considers only those correlations with magnitude > 0.25 , this ratio becomes even larger

(3.2 times more positive correlations). 43% of the correlations had magnitude ≥ 0.15 and 16% were as large as 0.25. A significant question is whether the cells recorded in the SC and MRF comprise a single functional group. The MRF cells were slightly, although significantly, more highly correlated than those of the SC (Mann-Whitney test; $P < 0.0001$; median magnitude of 0.16 for the MRF population and 0.13 for the SC population, respectively). Neurons located in the MRF yielded a correlation magnitude ≥ 0.25 in 21% of the cases whereas 16% of the SC correlations were at or above this level. A scatter plot constructed between correlation magnitude and depth had a small but significant positive slope, with $r = 0.14$ and $P < 0.0001$.

Figure 2, *right*, shows the distribution of cross-correlation peak timing. All the cases shown in the scatter plot are summarized by black bars, whereas the subset having magnitude = 0.25 is shown by gray bars. The mode of both distributions was within the 0–50 ms bin with the more strongly correlated distribution in particular skewed toward positive values. The median of the distribution of cases with $\rho_{max} \geq 0.25$ was 52 ms.

Within the distributions shown in Fig. 2 are included both muscles that were frequently well correlated and others that were only rarely correlated. Figure 3 indicates the likelihood that the correlations for any given muscle had a peak ≥ 0.25 and within 250 ms of zero. This has been expressed as a percentage of the observations for that muscle. The muscles have been arranged in an approximate proximal to distal sequence. As in the example shown in Fig. 1, trapezius was the most likely of all the muscles to be well correlated with a given neuron. Several other muscles of the shoulder girdle (e.g., rhomboid and infraspinatus) were well correlated nearly as often as was trapezius. Muscles of the back and chest wall were less frequent sources of correlation. The deltoids also were correlated somewhat less frequently than the shoulder girdle muscles and the elbow muscles, triceps, and biceps, along with FDS, even less so.

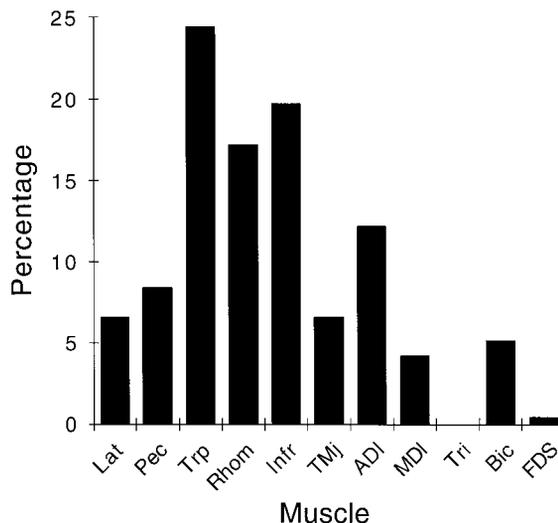


FIG. 3. Each bar indicates the proportion (percentage) of neurons having short-lag (less than ± 250 ms) correlations greater than or equal to ± 0.25 with the activity of a given muscle. The percentages are given relative to the total number of observations made for each muscle. Muscles of the shoulder girdle predominated with those of the axis and the arm and forearm less frequently well correlated.

DISCUSSION

The directional dependence of collicular and reticular reach cells and the timing of their initial and peak discharge have been compared with similar measures of proximal limb muscles (Werner et al. 1997a,b). These comparisons largely were limited to signals recorded at separate times, but they suggested that the discharge would be well correlated with muscle activity during reaching. We have now demonstrated directly that the discharge of many reach cells indeed is correlated strongly with the details of the modulation of muscle activity. There was a small difference between the correlation strength of neurons found in the SC and those of the MRF. Although the difference was slight, it was consistent with the possibility that the deepest neurons are linked most closely to muscle activity. However, there was nothing resembling a distinct anatomic border dividing the location of strongly and weakly correlated neurons. Further anatomic data related to the efferent and afferent connections of the SC and the MRF reach cells would be necessary to conclude that these neurons comprise two functional groups.

Considering that any given correlation took into account only one of the numerous neurons contributing to movement, the fact that the discharge could account for $\geq 6\%$ of the EMG variance (roughly equivalent to $\rho_{\max} = 0.25$) is remarkable. Comparison of the magnitude of these correlations with those of other motor areas is complicated by the dependence on the particular sets of muscles that were recorded and on differences among the criteria used to select neurons for recording during the separate experiments. In an effort to minimize the former factor, we have used the *single* muscle with which a given neuron was best correlated as a measure of overall strength of correlation. Using this measure, the average correlation magnitude across all SC and MRF neurons was 0.24. Similar measures for M1 and RNm were 0.22 and 0.28, respectively. It is likely that most of the neurons recorded in RNm would have been rubrospinal neurons, whereas the neurons recorded within M1 may well have included many corticofugal neurons, as well as neurons in layers other than V. These factors alone may account for much of the differences among these groups of neurons.

Beyond these comparisons of the absolute magnitude of correlation, the main strength of this method is its ability to quantify the relative correlation strength among a large group of muscles for a given neuron. Strong correlations were much more common among the muscles of the shoulder girdle and became less frequent for muscles of the axis or increasingly distal muscles. Because we had a limited number of recording channels available, we chose to emphasize the proximal musculature rather strongly. Even so, the decreasing trend of correlation strength from muscles of the shoulder girdle to those of the upper arm and forearm is clear.

This pattern contrasts with the analogous results reported for RNm neurons, which tended to be most strongly correlated with muscles of the distal limb (Miller and Houk 1995; Miller et al. 1993). Although the tasks used to study the two areas were different, red nucleus discharge was tested across a range of tasks with largely consistent results. Had the center-out task also been used to study RNm neurons, it is unlikely to have yielded significantly different results.

The center-out task was used previously to study motor

cortical neurons and yielded a great number of correlations with distal limb muscles (Glickstein 1998; Miller et al. 1996). The primary motor cortex also includes regions in which one would expect to find strong proximal muscle correlations, but these results indicate that this task exercises distal musculature adequately to yield a high correlation strength.

Even a highly significant correlation is not sufficient to establish a causal linkage between the two signals independent of other evidence. Some of this additional supportive evidence includes the work of Lawrence and Kuypers (1968), who divided the descending brain stem connections into dorsolateral (consisting principally of the rubrospinal tract) and ventromedial systems. The latter system included projections from the superior colliculus along with the reticular formation and vestibular nuclei. These combined projections terminated within regions of the spinal cord known to innervate trunk and proximal limb muscles. In addition, there is evidence that microstimulation within these regions of SC and MRF can evoke shoulder movement (Cowie and Robinson 1994).

These results strongly support the role of the superior colliculus and mesencephalic reticular formation in guiding the direction of reaching movements via the control of the proximal limb musculature. Although there is evidence that some RNm neurons project to proximal as well as distal muscles (Belhaj-Saïf et al. 1998; Sinkjaer et al. 1995), RNm neurons tested in a directional reach and grasp task were found to have relatively little directional component in their discharge, being predominately related to the grasp (McCurdy et al. 1997). The recognition of the superior colliculus and underlying reticular formation as brain stem areas controlling muscles of the shoulder and proximal limb is an important complement to the role of the RNm in controlling muscles of the forearm and hand.

This work was supported in part by a North American Treaty Organization Collaborative Research Grant to K.-P. Hoffman, and L. E. Miller. V. Stuphorn was supported by a fellowship from the German Science Foundation, Deutsche Forschungsgemeinschaft (Graduate Program KOGNET).

Present address of V. Stuphorn: Dept. of Psychology, Vanderbilt University, Nashville, TN 37240.

Address for reprint requests: K.-P. Hoffmann, Lehrstuhl für Allgemeine Zoologie und Neurobiologie, Ruhr-Universität Bochum, D-44780 Bochum, Germany.

Received 11 August 1998; accepted in final form 11 January 1999.

REFERENCES

- BELHAJ-SAIÏF, A., KARRER, J. H., AND CHENEY, P. D. Distribution and characteristics of poststimulus effects in proximal and distal forelimb muscles from red nucleus in the monkey. *J. Neurophysiol.* 79: 1777–1789, 1998.
- COWIE, R. J. AND ROBINSON, D. L. Subcortical contributions to head movement in macaques. I. Contrasting effects of electrical stimulation of a medial pontomedullary region and the superior colliculus. *J. Neurophysiol.* 72: 2648–2664, 1994.
- GLICKSTEIN, M. *Sensory Guidance of Movement. Novartis Foundation Symposium*, edited by J. A. Goode and G. R. Bock. Chichester: Wiley, 1998, p. 250.
- JUDGE, S. J., RICHMOND, B. J., AND CHU, F. C. Implantation of magnetic search coils for measurement of eye position: an improved method. *Vision Res.* 20: 535–538, 1980.
- KUTZ, D. F., DANNENBERG, S., WERNER, W., AND HOFFMANN, K. P. Population coding of arm-movement-related neurons in and below the superior colliculus of *Macaca mulatta*. *Biol. Cybern.* 76: 331–337, 1997.

- LAWRENCE, D. G. AND KUYPERS, H.G.J.M. The functional organization of the motor system in the monkey. II. The effects of lesions of the descending brain-stem pathways. *Brain* 91: 15–36, 1968.
- MCCURDY, M. L., BOYCE, C. J., KIRSCH, K. A., AND VAN KAN, P.L.E. Magnocellular red nucleus discharge in monkey during reaching to grasp in different directions. *Annu. Mtg. Soc. Neurosci.* 1997.
- MILLER, L. E. AND HOUK, J. C. Motor co-ordinates in primate red nucleus: preferential relation to muscle activation versus kinematic parameters. *J. Physiol. (Lond.)* 488: 533–548, 1995.
- MILLER, L. E., NOCHER, J. D., LEE, J. S., AND GARG, R. A. Muscle-space description of motor cortical discharge. *Annu. Mtg. Soc. Neurosci.* 1996.
- MILLER, L. E., VAN KAN, P.L.E., SINKJAER, T., ANDERSEN, T., HARRIS, G. D., AND HOUK, J. C. Correlation of primate red nucleus discharge with muscle activity during free-form arm movements. *J. Physiol. (Lond.)* 469: 213–243, 1993.
- SINKJAER, T., MILLER, L. E., ANDERSEN, T., AND HOUK, J. C. Synaptic linkages between red nucleus cells and limb muscles during a multi-joint motor task. *Exp. Brain Res.* 102: 546–550, 1995.
- WERNER, W. Neurons in the primate superior colliculus are active before and during arm movements to visual targets. *Eur. J. Neurosci.* 5: 335–340, 1993.
- WERNER, W., DANNENBERG, S., AND HOFFMAN, K. P. Arm-movement-related neurons in the primate superior colliculus and underlying reticular formation: comparison of neuronal activity with EMGs of muscles of the shoulder, arm and trunk during reaching. *Exp. Brain Res.* 115: 191–205, 1997a.
- WERNER, W., HOFFMAN, K. P., AND DANNENBERG, S. Anatomical distribution of arm-movement-related neurons in the primate superior colliculus and underlying reticular formation in comparison with visual and saccadic cells. *Exp. Brain Res.* 115: 206–216, 1997b.