Spatial Distribution and Discharge Characteristics of Superior Colliculus Neurons Antidromically Activated From the Omnipause Region in Monkey

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Gandhi, Neeraj J. and Edward L. Keller. Spatial distribution and discharge characteristics of superior colliculus neurons antidromically activated from the omnipause region in monkey. *J. Neurophysiol.* 78: 2221–2225, 1997. One proposed role of the superior colliculus (SC) in oculomotor control is to suppress or excite the activity of brain stem omnipause neurons (OPNs) to initiate or terminate saccades, respectively. Although connections from the SC to the OPNs have been demonstrated, the spatial distribution and discharge characteristics of the projecting neurons from the SC remain unknown. We mapped the spatial distribution of the deeper-layer neurons of the SC by stimulating the region of the OPNs to identify antidromic projections and found that the density of direct projections from the SC to the OPNs was greatest in the most rostral region and decreased gradually for more caudal sites. On the basis of saccade-related discharge characteristics, the antidromically driven neurons were predominantly fixation and buildup neurons. The spatially distributed SC projections to the OPNs and the discharge characteristics of the SC neurons suggest that the direct projections from SC to OPNs are excitatory. Finally, we propose how excitation and disfacilitation from SC activity can contribute to modulation of OPN response and control saccades.

INTRODUCTION

The superior colliculus (SC) has long been considered an integral component of the saccadic system, although its exact contributions to control of rapid eye movements remain controversial. All proposed mechanisms of SC function require that it suppress or excite the activity of omnipause neurons (OPNs), located in the nucleus raphe interpositus on the midline of the brain stem, to initiate or terminate saccades, respectively. Fixation neurons, a specific subset of neurons found only in the rostral pole (equivalently, the most rostral 0.72 mm or up to the 2° amplitude meridian) of SC (Munoz and Wurtz 1995b), have been hypothesized to project to the OPNs and modulate the activity of the latter cells via excitatory connections because of similarities in their discharge characteristics; both types of neurons are tonically active during fixation but pause their discharge during saccades (Keller 1974; Luschei and Fuchs 1972; Munoz and Wurtz 1993a).

Anatomic and electrophysiological studies have demonstrated that the rostral SC, relative to caudal regions, projects more heavily to the OPN region (Büttner-Ennever and Horn 1994; Paré and Guitton 1994). However, neither study demonstrated the discharge characteristics of the output neurons. Studies that did characterize the output neurons of the SC (Istvan et al. 1994; Moschovakis et al. 1988) showed that the neurons project via the predorsal bundle but did not determine which axons terminated on the OPNs. On the other hand, an examination of the arborization onto the OPNs failed to stain the somata in the SC (Scudder et al. 1996). Other studies focused globally on connections between SC and OPNs (Langer and Kaneko 1984, 1990). Overall, a detailed spatial distribution of the density of SC projections to the OPNs and the discharge characteristics of these SC neurons have not been determined, except in a preliminary study (Gandhi and Keller 1996).

To address these issues, we used electrophysiological methods to antidromically activate and characterize SC neurons projecting to the OPNs. We found that the probability of antidromically activating SC neurons from the OPN region was indeed greatest in the rostral pole of the SC but decreased gradually for more caudal sites. On the basis of one classification scheme (Munoz and Wurtz 1995a), these cells were predominantly buildup and fixation neurons.

METHODS

Data presented in this report are pooled from three *Macaca mulatta* and two *Macaca fasicularis* male juvenile monkeys. All experimental protocols were approved by the Institute Animal Care and Use Committee at the California Pacific Medical Center and complied with the guidelines of the Public Health Service policy on Humane Care and Use of Laboratory Animals.

The surgical and experimental methods of the present investigation have been described recently (Keller and Edelman 1994). Briefly, two stainless steel chambers were placed stereotaxically on the skull, one slanted posteriorly at an angle of 38° in the sagittal plane and aligned on the SC and another slanted laterally at an angle of 25° in the frontal plane and aligned on the OPN region. A recording tungsten microelectrode (Frederick Haer) was lowered through the lateral chamber into the region of the OPNs. The microelectrode was positioned such that OPNs were isolated and interrupted horizontal saccades (Keller 1977; King and Fuchs 1977) were produced with minimal stimulation parameters (usually 15 μA, 15 ms, 400 pulses/s).

Another recording microelectrode was lowered through the posterior chamber until SC neurons with visuomotor discharge properties were recorded. Next, bipolar single-pulse stimulation (0.25 ms in duration) was applied to the OPN region while activity of the SC neuron was sampled at 20 kHz. Stimulation intensity was initially set to 50 μA and was raised or lowered until a threshold defined as antidromic activation on 50% of the trials was found. Intensity was increased up to a maximum of 150 μA. If an SC

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neuron was driven, we attempted to obtain a collision by triggering the stimulation when the discharge rate of the SC neuron reached a threshold (typically 50 spikes/s). Otherwise, the antidromic test was confirmed by a constant latency of neuron activation; a latency jitter ≤0.2 ms was considered tolerable in making the judgment of constant latency.

Discharge characteristics of isolated neurons before and during saccades were then determined by recording window-discriminated spikes at 1 kHz as the monkey made delayed saccades to several eccentricities in the preferred direction. Spike density traces were then produced by convolving the spike trains with a gaussian waveform ($\sigma = 10$ ms) (Richmond et al. 1987). Recording penetrations were made uniformly along the rostral-caudal dimension of the SC.

To map the spatial distribution of the antidromically activated SC neurons, their location within the SC needed to be determined. At the bottom of each track, ~2.5 mm from the SC surface, a brief stimulation train (range of parameters: 25–35 μA, 25–75 ms, 400 pulses/s) was applied during fixation to produce a fixed-vector or site-specific maximal amplitude saccade (Robinson 1972; Stanford et al. 1996). This vector was always similar to the optimal saccade associated with the most vigorous neural response in the delayed saccade task. The amplitude of the fixed vector saccade was used to compute the cell's location in the SC by the formulas provided by Ottes et al. (1986).

RESULTS

Irrespective of whether or not they were antidromically driven from the OPN region, only the SC neurons that exhibited visuomotor and motor responses and were typically found deeper than 1 mm from the surface were included in the analysis. On the basis of one classification scheme (Munoz and Wurtz 1995a), the cell types included in our study were burst neurons, buildup neurons, and fixation neurons. We often tested superficial layer neurons with only visual responses for antidromic activation from the OPNs and were unable to drive any.

Spatial distribution of SC neurons antidromically activated from the OPN region

We tested a total of 101 SC neurons for antidromic activation from the OPNs; of these, 47 were considered driven on the basis of either collision tests (25 of 47) or constant latency measures (22 of 47). The probability of antidromically activating SC neurons from the OPNs depended on the location of the cell along the rostral-caudal dimension. Figure 1 summarizes the spatial distribution of antidromically activated SC neurons. All neurons tested for antidromic activation were placed in one of five spatial bins on the basis of their location in the SC, and data in each bin were pooled from at least two monkeys. Binwidth was set to 0.72 mm, restricting fixation neurons to the first bin only (Munoz and Wurtz 1995b). The abscissa is the rostral-caudal spatial position in SC coordinates as well as the corresponding fixed vector saccade amplitude, and the ordinate shows the percentage of antidromically driven cells within each bin. A linear regression through the distribution indicates that ~70% of the most rostral neurons are antidromically activated from the OPNs; this value gradually decreases to ~10% for caudal cells. The trend in the density of projections to the OPNs is significantly different from a uniform distribution of antidromic activation at all SC sites ($P <$ 0.01). The analysis indicates that neurons outside the rostral pole of the SC also contribute directly to controlling OPN activity, although this influence diminishes for caudal regions.

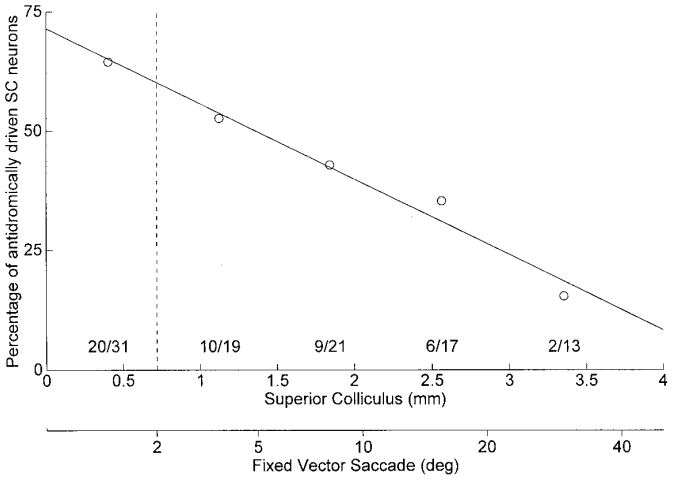

FIG. 1. Spatial distribution of superior colliculus (SC) neurons antidromically activated from the omnipause neurons (OPNs). Rostral-caudal extent of the SC, divided into 5 spatial bins (binwidth: 0.72 mm), and the corresponding fixed vector saccade scale are represented on the abscissa. Neurons were grouped in 1 of the 5 spatial bins depending on their location. Percentage of neurons antidromically driven within each bin is indicated on the ordinate, and the ratio (the number of neurons antidromically driven to the number of neurons) is stated. Solid line: linear regression fit through the data. Dashed vertical line is plotted at 0.72 mm from the rostral pole of the SC.

Discharge characteristics of tested SC neurons

Neural activity of the isolated SC neurons was recorded as the monkeys made delayed saccades in the preferred direction. We characterized a total of 63 neurons; of these, 30 were identified as antidromically activated from the OPN region. Figure 2 illustrates the antidromic activation and the saccade-related discharge characteristics of five driven neurons, one from each spatial bin of Fig. 1, for saccades of optimal and larger-than-optimal amplitude. The most striking observation of Fig. 2 is that many SC neurons antidromically activated from the OPN region displayed weak bursting or tonic activity, instead of suppression, during optimal saccades.

To classify the neurons antidromically activated from the OPN region and to compare their identity with those not projecting to the OPNs, we used the criterion established by Munoz and Wurtz (1995a). During an eye movement of optimal vector in the delayed saccade paradigm, cells with activity <30 spikes/s ≥100 ms before movement onset are burst neurons, and those with activity >30 spikes/s ≥100 ms before movement onset are buildup neurons. Fixation neurons are the subset of buildup neurons located in the rostral pole of the SC.

Accordingly, the maximum activity during the 100–150 ms (presaccadic period), averaged over 3–20 trials, before onset of optimal movements in the delayed saccade task was computed and used to separate all 63 neurons into burst or buildup types. Fixation neurons were the group of buildup neurons with optimal saccade amplitude <2° (equivalently,

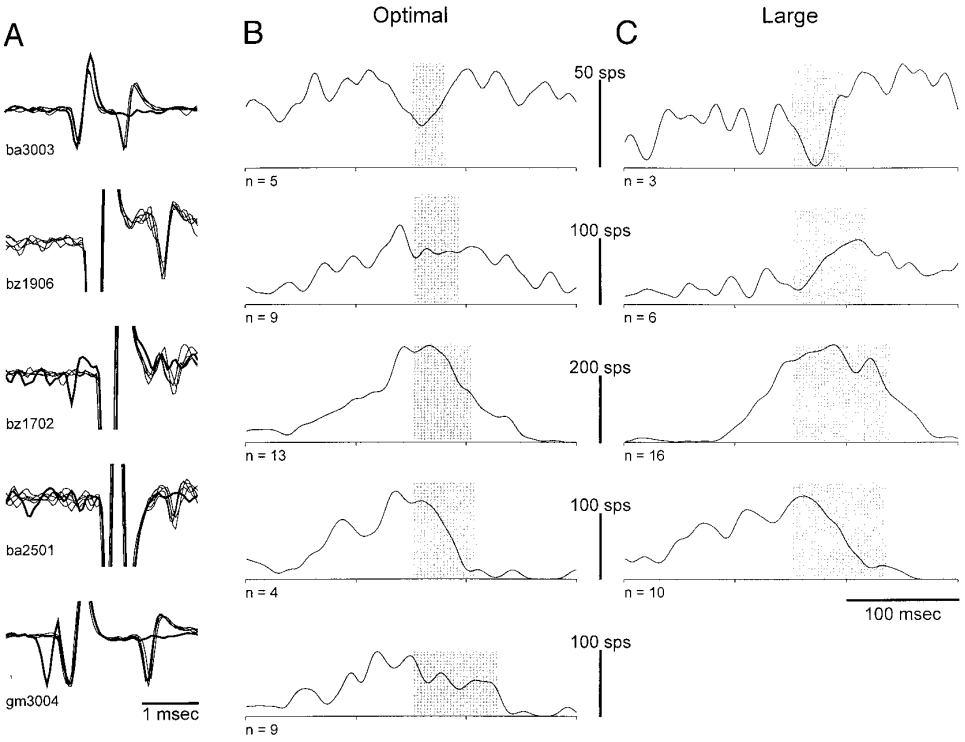

FIG. 2. Examples illustrating antidromic activation of SC neurons and their saccade-related discharge for optimal and larger-than-optimal delayed saccades in the preferred direction. Five neurons, 1 from each spatial bin of Fig. 1, are sorted from *top* to *bottom* and represent most rostral to most caudal location of the SC neurons, respectively. *A*: SC neurons activated from the OPNs discharged an action potential following each stimulus pulse (thin traces). Antidromic activation was confirmed either by collision (thick traces) or constant latency of activation (*2nd row*). Averaged spike density traces of the neurons for delayed saccades of (*B*) optimal and, where available, (*C*) larger-than-optimal saccades are also displayed. Number of trials averaged together is indicated at the *bottom left* of each plot. Spike density scale for each row is placed between *B* and *C*. All traces are aligned on saccade onset. Shaded region: average saccade duration over the trials.

located in the rostral pole). Figure 3 summarizes our sample of driven and nondriven neurons in each of the three classes. Only 1 burst neuron, 18 fixation neurons, and 11 buildup neurons constituted the 30 SC neurons antidromically activated from the OPN region. In contrast, 13 burst neurons, only 4 fixation neurons, and 16 buildup neurons formed the 33 non-antidromically driven SC neurons. The spatial distribution of the burst and buildup neurons not antidromically activated, although equally interesting for the cell classification analysis, was not determined because of the small sample size (n = 33 neurons).

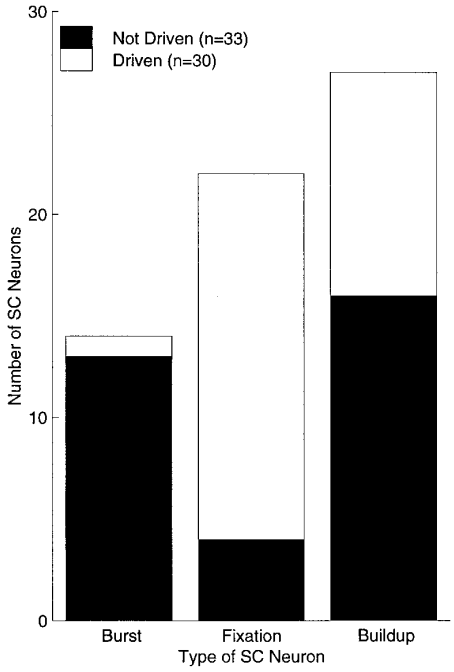

FIG. 3. Stacked bar graph of the number of burst, fixation, and buildup neurons antidromically activated (open region) and not antidromically activated (filled region) from the OPN region.

Latency and threshold of antidromic activation

The latency of the action potential generated in the SC neurons following a stimulus pulse to the OPNs ranged from 0.7 to 2.3 ms, with a mean ± SD of 1.13 ± 0.38 ms. The latency was not dependent on the location of the SC neuron. A threshold current at which the SC neuron was driven 50% of the time was determined for 30 of the 47 cells. The threshold values ranged from 10–120 μA with a mean ± SD of 65 ± 29 μA.

DISCUSSION

Uniform sampling of visuomotor and motor neurons along the rostral-caudal extent of the SC has demonstrated that the percentage of SC neurons antidromically driven from the OPNs is largest in the rostral pole of the SC and declines gradually for more caudal sites. Burst neurons, classified by the level of presaccadic discharge, were rarely observed to project to the OPNs. Thus fixation and buildup neurons constitute the majority of projections to the OPNs.

Although most fixation neurons were antidromically activated from the OPN region, a significant number of buildup neurons were not driven by the stimulation of the OPN region. The identification of buildup neurons (Munoz and Wurtz 1995a), requiring that the discharge rate be >30 spikes/s ≥100 ms before optimal saccade onset, is an arbitrary measure and may be an inadequate classification scheme taken alone. Perhaps multiple criteria (Munoz and

Wurtz 1995a) or other identification rules may possibly separate the driven and nondriven neurons into significantly different groups, but further investigation is needed to resolve the issue.

Similarity between fixation and buildup neurons

Fixation neurons are hypothesized to make excitatory projections to the OPNs, a claim supported by similarities in the discharge characteristics (Keller 1974; Luschei and Fuchs 1972; Munoz and Wurtz 1993a) and the production of interrupted saccades on stimulation of either group of neurons (Keller 1977; King and Fuchs 1977; Munoz and Wurtz 1993b). However, projections from SC cells other than fixation neurons, and therefore located outside the rostral pole, are not predicted by this hypothesis. Gandhi and Keller (1995) stimulated the deeper layers of SC during ongoing saccades and found that stimulation of SC sites within the rostral 2 mm (up to the 10° amplitude meridian) at saccade onset interrupted the ongoing eye movement, suggesting that the spatially distributed SC outputs to the OPNs shown in our present study are all excitatory and functionally similar. Of the continuum of projections, fixation neurons restricted to the rostral pole display clear suppression in activity during large saccades (Munoz and Wurtz 1993a). Buildup neurons found outside the rostral pole tend to show some suppression during large saccades as well, although the effect is not as dramatic (see Fig. 2*C, row 2*) (Gandhi et al. 1994). A pause in the activity of buildup neurons may perhaps become obvious for (head-free) gaze shifts larger than saccades restricted by the oculomotor limit. Therefore we suggest that buildup neurons are similar to fixation neurons and that separating them into discrete classes may be unjustified.

Modulation of OPN activity

Ideally, the excitatory connection hypothesis requires that SC neurons that project to the OPNs remain tonically active during fixation and suppress discharge during saccades. That many of these neurons also exhibit a burst of action potentials during saccades in their movement field, consequently, appears paradoxical. The confounding observations can be explained in terms of a net balance of excitatory and disfacilitatory influences from the population of SC neurons projecting to the OPNs. When the eyes are stationary, fixation neurons in the rostral pole are tonically active (Munoz and Wurtz 1993a), and their excitatory inputs to the OPNs maintain tonic discharge in the latter cells. For a saccade target presented close to the fovea, neurons in a broader rostral region of the SC are activated (Fig. 2*B, rows 1* and *2*), and, because a majority of them project to the OPNs, their activation results in an increased excitation of the OPNs. However, neurons that project to the OPNs but originate in the caudal, contralateral SC and in the entire ipsilateral SC decrease their discharge rate before saccade onset (Munoz and Wurtz 1993a, 1995a). The consequence of only local excitation from the rostral, contralateral SC but disfacilitation from a wide region of the caudal and the ipsilateral SC may result in a net disfacilitation of the OPNs and initiation of a saccade. Presentation of a target in the periphery produces activity in caudal buildup neurons. These then suppress activity of neurons in the rostral, contralateral SC and in the entire ipsilateral SC (Munoz and Wurtz 1995b), which could also lead to disfacilitation of the OPNs and generation of a saccade.

Despite the disfacilitation from the SC, an inhibition of the OPNs may be necessary to initiate saccades, and evidence of inhibitory inputs from long- and medium-lead burst neurons to the OPNs exists in the cat (Kamogawa et al. 1983, 1996). Kamogawa et al. (1983) specifically argued for two stages of excitability of the OPNs—an initial suppression of the OPNs, which occurs 40–50 ms before the onset of quick phase of vestibular nystagmus, followed by an intense and abrupt suppression of OPN activity at the beginning of the quick phase. Because OPN activity during the quick phase of vestibular nystagmus and saccades is similar (Keller 1974), the results of Kamogawa et al. (1983) may also apply for the saccadic system. The initial change in the excitability of the OPNs may be due to disfacilitation from the SC neurons, whereas the latter and rapid cessation of activity may be a result of an inhibition from the burst generator in the brain stem.

Saccade-related cells in the SC also project to the burst generator neurons in the brain stem (Chimoto et al. 1996a; Raybourn and Keller 1977). Thus disfacilitation of the OPNs and a simultaneous excitation of the burst generator by SC inputs, and a consequent inhibition of OPNs by the burst generator, are likely to initiate saccades. Certain features of the circuitry of the SC outputs to brain stem regions are likely. *1*) SC projections to the burst generator neurons may be greatest from the caudal SC and decrease gradually for more rostral sites (Chimoto et al. 1996b; Gandhi and Keller 1995), a trend opposite to that observed for SC projections to the OPNs. *2*) Some SC neurons may project to both brain stem burst neurons and OPNs (Scudder et al. 1996).

Evidence against current spread

The mean stimulation threshold current for antidromic activation of SC neurons from the OPNs was 65 μA, raising concern that the interpretations may be contaminated by current spread to neighboring regions or fibers passing near the stimulation region. Although we cannot completely rule out these possibilities, we believe that the effects of current spread are minimal for several reasons. *1*) The spatial distribution of the SC projections to the OPNs correlates well with the observation that stimulation of the rostral 2 mm, a region 3 times wider than the rostral pole of the SC, during large saccades interrupts the ongoing movement, whereas stimulation of the caudal region at saccade onset accelerates it (Gandhi and Keller 1995). *2*) The caudal SC appears to have ample projections to the burst generator region (Chimoto et al. 1996a,b; Raybourn and Keller 1977). Thus current spread laterally into this area should antidromically drive a greater proportion of neurons in the caudal SC. *3*) If the stimulation current were to spread and activate the predorsal bundle, which contains the axons of output neurons of the SC and lies immediately adjacent to the OPN region, all burst, buildup, and fixation neurons would have been antidromically driven (Istvan et al. 1994).

In conclusion, the observation that the projections from

the SC to the OPNs are greatest in the rostral SC and decrease gradually for caudal regions of the SC appears not to be an artifact of current spread from the stimulated OPN region. Instead, it is a conservative estimate of the spatial distribution of SC outputs to the OPNs.

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