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The fixation area of the cat superior colliculus: effects of electrical stimulation and direct connection with brainstem omnipause neurons

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Abstract The superior colliculus has long been recognized as an important structure in the generation of saccadic displacements of the visual axis. Neurons with presaccadic activity encoding saccade vectors are topographically organized and form a "motor map." Recently, neurons with fixation-related activity have been recorded at the collicular rostral pole, at the area centralis representation or fixation area. Another collicular function which deals with the maintenance of fixation behavior by means of active inhibition of orientation commands was then suggested. We tested that hypothesis as it relates to the suppression of gaze saccades (gaze = eye in space = eye in head + head in space) in the head-free cat by increasing the activity of the fixation cells at the rostral pole with electrical microstimulation. Long stimulation trains applied before gaze saccades delayed their initiation. Short stimuli, delivered during the gaze saccades, transiently interrupted both eye and head components. These results provide further support for a role in fixation behavior for collicular fixation neurons. Brainstem omnipause neurons also exhibit fixation-related activity and have been shown to receive a direct excitatory input from the superior colliculus. To determine whether the collicular projection to omnipause neurons arises from the fixation area, the deep layers of the superior colliculus were electrically stimulated either at the rostral pole including the fixation area or in more caudal regions where stimulation evokes orienting responses. Forty-nine neurons were examined in three cats. 61% of the neurons were found to be orthodromically excited by single-pulse stimulation of the rostral pole, whereas only 29% responded to caudal stimulation. In addition, stimuli delivered to the rostral pole activated, on average, omnipause neurons at shorter latencies and with lower currents than those applied in caudal regions. These results suggest that excitatory inputs to omnipause neurons from the superior colliculus are principally provided by the fixation area, via which the superior colliculus could play a role in suppression of gaze shifts.

Key words Omnipause neurons · Superior colliculus Fixation · Saccade · Gaze · Eye-head coordination · Cat

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Introduction

The oculomotor burst generator – a premotor circuit crucial for the generation of saccadic eye movements and composed of neurons exhibiting a high-frequency burst of activity during saccades – is thought to be reciprocally related to inhibitory neurons located in the raphe interpositus nucleus, the omnipause neurons (OPNs), which discharge tonically during fixation behavior (Fuchs et al. 1985; Hepp et al. 1989; Keller 1991). A complete cessation of OPN activity just prior to and during saccades releases the inhibition of the saccadic burst generator neurons. To make a saccade, it has been suggested that a motor error signal drives the burst generator while an inhibitory trigger signal turns off OPNs (Robinson 1975; Keller 1977; Fuchs et al. 1985). The superior colliculus (SC) has been proposed to provide the motor error signal (for review see Sparks 1986; Guitton 1991), since some collicular efferent neurons exhibit presaccadic burst activity and project to premotor areas. An anatomical projection from SC to OPNs has also been reported (Büttner-Ennever et al. 1988; Langer and Kaneko 1984, 1990), thereby suggesting that the SC may also provide the trigger signal.

The collicular projection to OPNs has been investigated electrophysiologically. Raybourn and Keller

(1977) were the first to establish, in the alert monkey, a direct excitatory connection between the SC and OPNs. Evidence for such a connection in the anesthetized cat was provided by King et al. (1980) and Kaneko and Fuchs (1982). An indirect inhibitory projection was also observed (Raybourn and Keller 1977; Kaneko and Fuchs 1982). Since the direct projection was found to be excitatory, the trigger signal that presumably silences OPNs was then considered to come from a structure other than the SC: either the rostral part of the pontine reticular formation or the mesencephalic reticular formation (Fuchs et al. 1985).

Recently, collicular neurons with fixation-related activity have been recorded in the area centralis representation in cat and in the foveal representation in the monkey (in cat: Munoz and Guitton 1989, 1991; Munoz et al. 1991; in monkey: Munoz and Wurtz 1992, 1993a). Their activity was found to be similar to that displayed by OPNs; they maximally discharge when the animal attentively fixates and cease firing during either saccadic eye movements or saccadic gaze shifts (gaze = eye in space = eye in head + head in space). In both cat (Guitton and Munoz 1991) and monkey (Istvan et al. 1994), these are collicular efferent neurons that send descending projections into the predorsal bundle. It was proposed for cat that they contact OPNs and that their activity during fixation contributes to the sustained activity observed in OPNs (Munoz and Guitton 1989, 1991; Munoz et al. 1991). The reduced firing of these collicular neurons during saccadic eye or gaze movements could contribute to the trigger signal that induces the cessation of discharge of OPNs. Given that microstimulation of the OPN area in the cat suppresses both eye and head motion (Paré and Guitton 1989), this hypothesis suggests that electrical microstimulation applied to the fixation area of the cat's SC should also prevent the occurrence of both eye and head movements that compose saccadic gaze shifts. The first objective of this paper was to verify this. The second objective was to investigate the direct connection between the SC and OPNs in the alert cat in order to test whether the SC fixation area projects more heavily to brainstem OPNs than other regions of the SC. A part of this study has been presented in abstract form (Paré and Guitton 1991).

Materials and methods

Three alert animals (referred to in the text as cats *G*, *V*, and *Y*) were used for the experiments involving OPN recording. Experiments involving SC fixation-area stimulation were conducted on the same three animals plus an additional one (cat *L*).

Surgical procedures

Surgery was performed under aseptic conditions. Each animal was initially given ketamine hydrochloride (10 mg/kg i.m.) and anesthesia was maintained using halothane inhaled through an endotracheal tube. A wire coil for the measurement of eye position with the magnetic search-coil technique was sutured to the sclera of one eye. Three holes were trephined through the skull to allow access to both superior colliculi and brainstem. One stainless steel cylinder, constructed to hold a micropositioner (Kopf), was positioned just rostral to the lambdoid crest, to provide access to the brainstem, and was tilted 25° back from the frontal plane. The second cylinder was positioned vertically, centered over both SC. The connector for the eye coil, an attachment for a coil monitoring head position, a head-holding device to immobilize the head of the animal during recording sessions, and the cylinders were secured in place by embedding them in a dental acrylic explant that was anchored to the skull with stainless steel bolts. At the end of the surgery, the animals received an intramuscular injection of gentamicin (15 mg/kg) or cefazolin (35 mg/kg) as a prophylactic measure against infection. These antibiotics were administered on a daily basis for 10 postoperative days. To alleviate any discomfort, animals were given analgesic medication (buprenorphine hydrochloride 0.01 mg/kg) as needed during the postsurgical period. All surgical and experimental protocols were approved by the McGill University Animal Care Committee and complied with the Canadian Council on Animal Care policy on use of laboratory animals.

In a second procedure, the animal was slightly anesthetized (ketamine hydrochloride 10 mg/kg i.m. supplemented by 2–5 mg/kg) for a period varying from 1 to 2 h. The movement vectors evoked at different sites in each SC were mapped out with stimulating electrodes (bipolar concentric electrodes Kopf NEX-25) placed in collicular layers for which electrical stimuli evoked eye movements with minimal threshold intensity. To do that, the animal's head was fixed to a platform to which a stereotaxic apparatus (Kopf) was attached and electrode carriers were employed to manipulate the stimulating electrodes. Stereotaxic coordinate references marked on the cat explant during the first surgery were used to aim the electrodes at the SC. This approach allowed us to determine the distance between the various positions of one stimulating electrode from one track to another, and between the different electrodes placed in each SC. The location of the stimulating electrodes used in the study of the SC-OPN projection is indicated in Fig. 1. In each cat, at least two stimulating electrodes were fixed in place, with dental acrylic, in the same SC: one in the fixation area (labeled 1 in Fig. 1) and the other in the caudal regions at a site where large gaze shifts could be evoked. The characteristics of the gaze shifts elicited at each caudal stimulation site were subsequently evaluated, with the animal fully alert, using parametric studies (see the accompanying paper, Paré et al. 1994). Briefly, stimulus current strength (from 10 to 80 μA) or pulse rate (from 100 to 600 pulses/s) were varied. The maximum amplitude of the gaze shift elicited at each site, along with the direction of the movement, indicated the location of an electrode on the collicular motor map. In cats *Y* and *V*, the caudal electrode (labeled 2) evoked gaze shifts of 60° and 45° amplitude, respectively (Fig. 1A,B). In cat *G*, two caudal electrodes labeled 2 and 3 evoked gaze shifts having 50° and 80° of amplitude, respectively (Fig. 1C). The minimal distance between the caudal electrode labeled 2 and the one in the fixation area was about 4 mm. The placement of the stimulating electrode in the SC fixation area was assessed by: (1) its position relative to other SC sites; (2) absence of electrically evoked saccades; and (3) by the inhibition of saccadic eye movements and vestibular quick phases following electrical current delivered through it. The fixation-area electrode was located in the left SC in cat *L* and in the right SC for cats *G*, *V*, and *Y* (Fig. 1). In cat *Y*, after the study of the collicular projection to OPNs, a second electrode was implanted in the fixation area of the left SC. Bilateral stimulation was then used to mimic natural fixation-related activity in the SC and yielded some of the data presented in the accompanying paper (Paré et al. 1994).

Experimental procedures

The positions of gaze and head relative to space were monitored by the search-coil-in-magnetic-field technique. Details of the coil

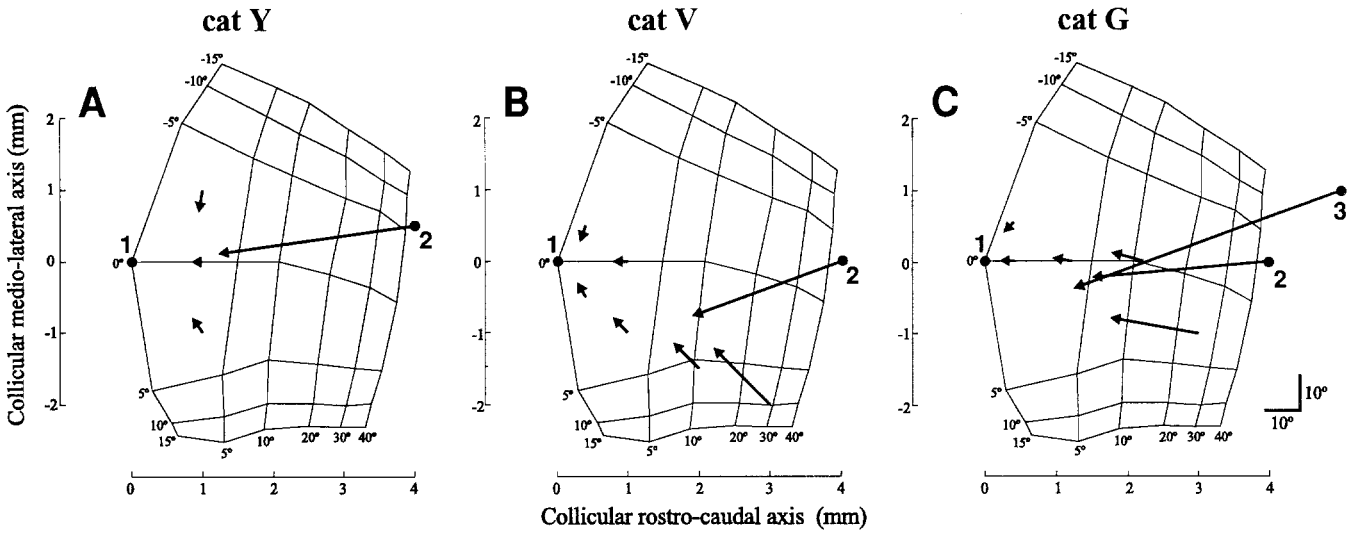

Fig. 1 Locations of collicular stimulating electrodes in cats *Y* (**A**), *V* (**B**), and *G* (**C**), and gaze vectors evoked by electrical stimulation of the deep layers of the right superior colliculus (SC) at the site of each electrode. A series of stimulation sites evoking gaze vectors (*arrows*) in each animal are also illustrated. Their spatial location (*origin of the arrows*) is superimposed on the map of the right SC obtained by McIlwain (1986). The *dots* (labeled with *numbers*) indicate the location of the stimulating electrodes used in the SC-omnipause neurons projection study

system and the calibration procedures have been reported elsewhere (Guitton et al. 1984). Briefly, the gain of the eye-coil and head-coil demodulators were set at the same value by rotating horizontally and vertically a reference coil at known angles with the help of a gimbal device placed at the center of the field-coil arrangement. The cat was placed on the recording table with its head at the center of the fields and held earth-fixed as the field coil was oscillated horizontally about it. A potentiometer measured the angular deviation of the field coil. Calibration of the eye- and head-coil signals was then made by comparing the potentiometer and coil signals, during saccade-free segments of data, so as to transform eye and head signals (volts) into corresponding angular deviations. In the head-fixed cat, the eye coil measured directly the eye position in the orbit. In the head-free animal, the eye position in the orbit was obtained by subtracting the head-coil signal from the signal of the eye coil, which then measured gaze position. The head-coil calibration obtained this way could be compared directly with that obtained with the gimbal. Gaze- and head-coil calibrations were also verified by having the alert head-free cat looking at food targets located at known positions.

During recording sessions, the alert cats were wrapped in a loosely fitting cloth bag and placed in a restraining box. The animals were previously trained to do simple visuomotor tasks (see below). Signals of gaze and head positions and neuronal activity were recorded on digital audio tape (TEAC RD-200T), the unit activity being sampled at 40 kHz and the movement at 10 kHz.

Stimulation of the collicular fixation area

A train of cathodal pulses generated by a stimulator (Grass S88) and constant-current stimulus isolation units (Grass PSIU6), was used to stimulate the collicular fixation area. The animal was trained to fixate and track a food target manually displaced from either side of a tangent opaque barrier positioned in front of it ("barrier paradigm"; Guitton et al. 1990; Munoz and Guitton 1991). The animal quickly learned that when the target disappeared from one side of the barrier it would reappear on the other side, and it readily made gaze shifts toward the new predicted location of the target, as soon as the target disappeared behind the barrier. The stimulus pulse train was applied either during ongoing eye-head gaze saccades or simultaneously with the disappearance of the target, i.e., before the onset of the gaze shifts. Experiments were conducted either with the laboratory light constantly dimmed or with an ambient stroboscopic light that was turned off for a period of 1–2 s at the onset of the gaze shift (Munoz and Guitton 1991). The stimulus pulse train was also applied during vestibular stimulation in the dark obtained by rotating en bloc the animal in a horizontal plane about an axis centered on the head at the level of the labyrinths. Different stimulus parameters were used. The range of stimulus current strength was 20–80 μA; pulse rate varied between 100 and 600 pulses/s and train duration, between 10 and 500 ms. Pulse duration was always 0.3 ms.

Collicular projection to OPNs

OPNs were recorded extracellularly using tungsten microelectrodes (3–4 MΩ; Frederick Haer). Protected by a cannula, recording electrodes were manually advanced through the dura and cerebellum to about 5 mm above the fourth ventricle. An hydraulic microdrive attached to the Kopf *x*-*y* micropositioner was subsequently used to advance electrodes into the brain. The reference electrode consisted either of a silver wire attached to a skull bolt or of the cannula itself. Conventional filtering, amplifying, and display techniques were employed. In these recording experiments, the animal's head was fixed. A region rostromedial and ventral to the abducens nuclei was examined. OPNs were identified by their tonic discharge during fixation and characteristic pause in activity in relation to saccadic eye movements, and their responses following collicular stimulation were tested. A diagram of the stimulation and recording setup is provided in Fig. 2A. Electrical stimulation involved a pulse of negative current of 0.2 ms duration followed by a brief positive current of 0.1 ms duration. Stimulus pulses were generated by a stimulator (Grass S88) connected to the stimulating electrode through constant-current photoelectric stimulus isolation units (Grass PSIU6). The level of stimulus current was determined from the voltage measured across a 10-kΩ resistor in series with the electrode and was monitored on an oscilloscope. Testing for activation was routinely done using stimulus currents of 500 μA. If no response was observed, the current was then increased gradually up to 1 mA. A cell was considered not driven by the electrical stimulation if no consistent responses were evoked with a stimulus current strength of 1 mA. Electrical stimuli never exceeded that current strength and the animal never displayed aversive reactions. Short stimulation trains of two or three pulses (pulse rate between 200 and 1000 pulses/s) were also used. Once an excitable OPN was found, its excitation level for each stimulating electrode was determined.

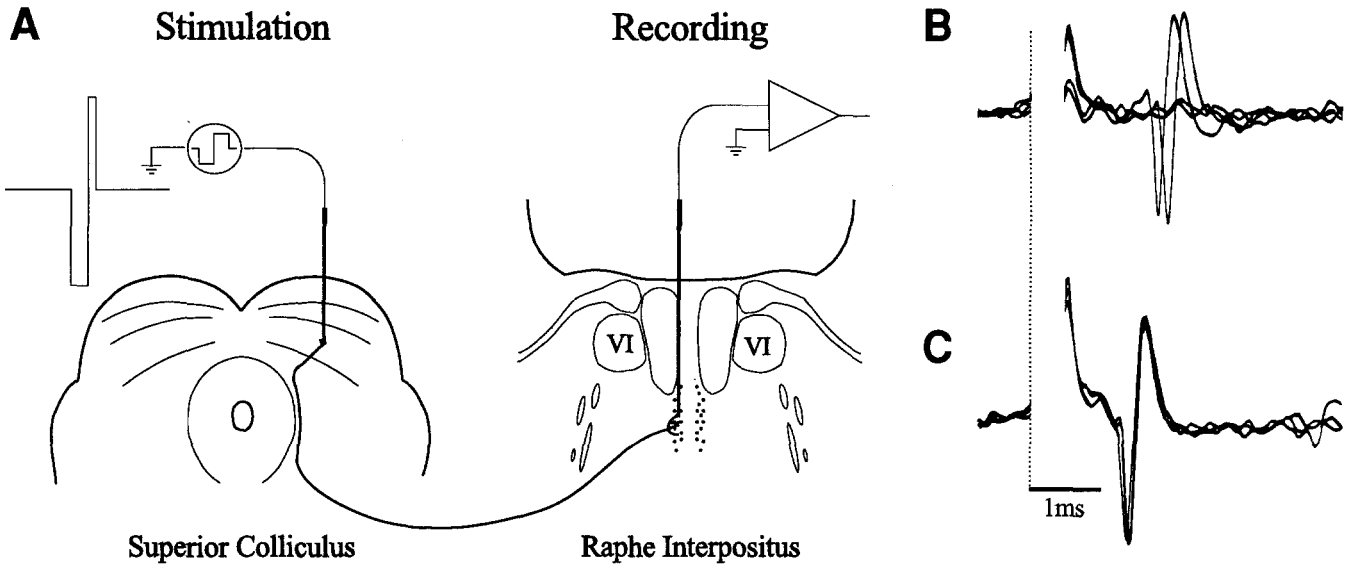

Fig. 2 **A** Stimulation and recording setup. Single omnipause neurons isolated by a microelectrode in the raphe interpositus were orthodromically excited by biphasic current pulses passed through a bipolar stimulating electrode within the deep layers of the superior colliculus. **B,C** Examples of excitatory responses of one neuron (cell *G*11) to single-pulse stimulation at just-threshold intensity, 100 μA (**B**) and at twice threshold, 200 μA (**C**). The *dotted line* marks the occurrence of stimulation pulses

The threshold intensity was defined as the current that yielded a response on 50% of stimulus presentations. For each neuron, the latency of the response (i.e., the mean time from stimulus onset to initiation of the orthodromic action potential) elicited by the electrical stimulus was taken as the latency observed for a current value 2 times greater than threshold (Fig. 2B,C). For some OPNs, we verified, using the collision test, whether they could be antidromically activated by SC stimulation. To perform such a test, a single-pulse SC stimulus was triggered by a spontaneous OPN action potential (Fuller and Schlag 1976). The maximum interval between the spontaneous spike and the electrical stimulus at which collision could occur corresponds to the response latency plus the refractory period of the axon; the latter can be functionally defined as the minimum delay between two electrical stimuli applied at the same site and such that the second stimulus does not elicit a response.

Data analysis

Blocks of records were played back and digitized by a PDP-11/73 computer for off-line analysis. A time-amplitude window discriminator (Bak Electronics) isolated single-unit activity and produced a logic pulse for each action potential that met amplitude and time constraints. Individual action potentials were stored with the position signals. The latter were low-pass filtered at 250 Hz were sampled at 1 kHz. Stimulation pulse and single-unit signals were displayed on a storage oscilloscope to measure response latencies.

The possible different positions of each stimulating electrode tip relative to collicular efferent neurons rendered difficult a direct comparison between the current threshold necessary for each electrode to elicit a response in OPNs. To remedy this problem, the current threshold (I) at which an OPN was responsive was weighted by the current threshold (I_o) needed at that site to evoke an eye movement with a train of pulses (0.2 ms pulse duration and pulse rate of 300 pulses/s). This yielded an intensity index (I/I_o) for each neuron activated by each stimulating electrode. For fixation-area electrodes, the threshold intensity was weighted by the current threshold needed to interrupt saccadic eye movements. To evaluate and compare the efficacy of each stimulating electrode in eliciting a response in a sample of OPNs, a coefficient of efficacy (CE) was calculated for each electrode and for each neuron using the following equation: $CE = [L/T_c \times (I/I_o)]^{-1}$, where L is the response latency, I/I_o is the response weighted intensity, and T_c is the mean conduction time (0.84 ms) needed for an action potential, in axons of tecto-reticular neurons, to reach the OPN area (see Guitton and Munoz 1991). The shorter the response latency and the lower the current threshold, the higher is the CE. A CE value of zero was attributed to undriven cells. The mean value of CE for all available cells was used to describe the efficacy of each SC stimulating electrode in exciting OPNs. Comparisons between the response characteristics (latency, current threshold, weighted intensity, CE) obtained for each stimulating electrode were performed using the distribution-free U-test of Wilcoxon-Mann-Whitney, because the assumption of normality of population distributions was considered not tenable. Results were considered significant only if they exceeded a one-tail level of $P<0.05$. Percentages were compared with the chi-square (χ^2) test.

To evaluate whether an OPN was monosynaptically driven by SC stimulation, we used the following reasoning. Guitton and Munoz (1991) measured the latencies of antidromic responses of tectoreticular neurons following stimulation near the OPN area. The shortest latency obtained was 0.4 ms. If we assume (1) 0.1 ms as the rise time for an action potential; and (2) 0.5 ms for synaptic delay, then the shortest disynaptic response should be $0.4+2(0.1+0.5)=1.6$ ms. Accordingly, OPNs showing response latencies less than 1.6 ms were probably monosynaptically activated.

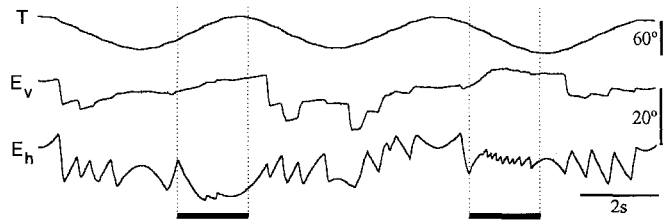

Fig. 3 Effects of electrical stimulation delivered at the right superior colliculus (SC) fixation area on vestibularly induced eye movements in the dark, obtained by subjecting the animal to horizontal whole body rotation. Data from cat *G* (right SC). *From top to bottom*: table position (T), vertical (E_v) and horizontal eye position (E_h), electrical stimulus (*thick horizontal line*). *Upward deflection on traces* indicates movements up and to the right, respectively. Stimulus current strength was 60 μA (2 × threshold); pulse rate was 300 pulses/s; train duration was 1800 ms

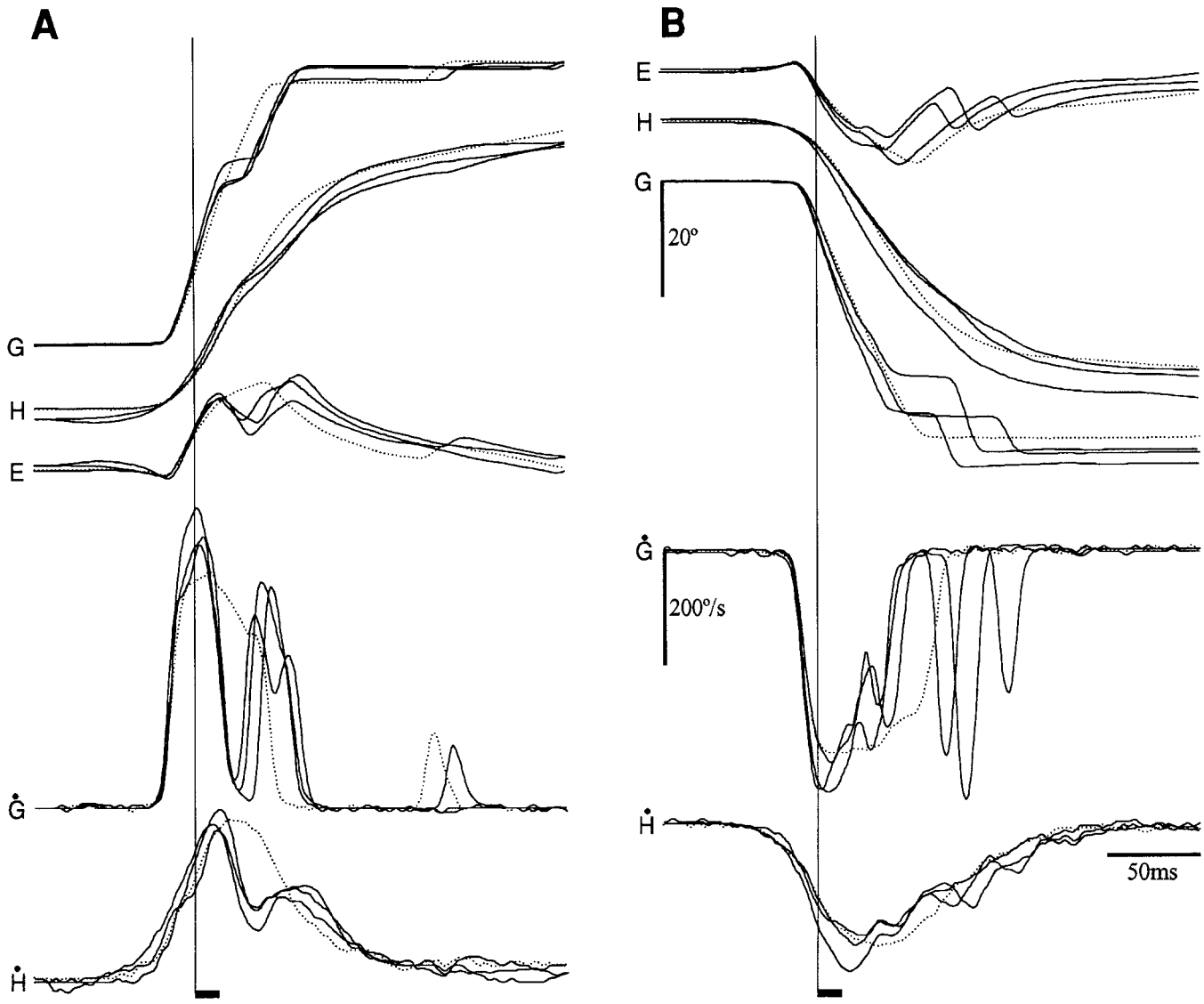

Fig. 4A,B Effects of electrical stimulation delivered at the superior colliculus (SC) fixation area during ongoing eye-head gaze saccades. Data from cat *G* (right SC). Rightward (**A**) and leftward (**B**) gaze saccades made to visual targets. A brief stimulus (50 μA, 300 pulses/s, 30 ms) during a gaze saccade interrupts momentarily the movement. Each panel shows a single, normal eye-head gaze saccade (*dotted traces*) and three stimulation trials (*solid traces*). *G*, *H*, *E* and $\dot{G}$, $\dot{H}$, are the position and velocity traces of gaze, head, and eye in the horizontal plane. *Thick horizontal line* under eye trace indicates the period of stimulus presentation

Results

Effects of stimulating the rostral pole of the superior colliculus

Electrical stimulation of the fixation area at the SC rostral pole elicited no saccades except sometimes very small and slow eye movements at high current strength. Figure 3 shows the effects on eye movements when the fixation area was unilaterally stimulated during horizontal sinusoidal whole body rotation in the dark. Vestibular quick phases were either greatly reduced in size or abolished. The inhibition of quick phases was more important when these were directed ipsilaterally to the SC being stimulated. In addition, the gain of the compensatory vestibulo-ocular reflex – slow-phase eye velocity/head velocity – was significantly reduced during stimulation. In cat *G*, the gain of the reflex, in the dark, had a mean value of 0.91 (SD 0.10, $n=21$) at 0.2 Hz. It dropped to 0.60 (SD 0.15, $n=32$) during the period when the fixation area was unilaterally stimulated.

The effects of stimulating the fixation area on natural gaze shifts was also investigated. In these experiments, the animal oriented to two targets situated on the horizontal plane. Examples of normal responses are shown in Fig. 4A,B (dotted traces). On random trials, the stimulation train, triggered by the gaze saccade, was delivered to the fixation area during the ongoing gaze shift. These stimuli transiently interrupted both the eye and

Table 1 Deceleration effect of superior colliculus (SC) fixation-area stimulation on gaze and head movements in four cats. Mean latency (and standard deviation) of the deceleration of gaze and head movements; ratio and percentage of movements decelerated by the stimulation.

Cat	SC	Gaze right			Gaze left			Gaze			Head right			Head left			Head		
		Latency (ms)	Ratio	%	Latency (ms)	Ratio	%	Latency (ms)	Ratio	%	Latency (ms)	Ratio	%	Latency (ms)	Ratio	%	Latency (ms)	Ratio	%
G	Right	11±3	52/54	96	11±3	28/54	52**	11±3	80/108	74	31±6	36/54	67	41±7*	6/54	11**	32±7	42/108	39**
L	Left	13±4	7/7		15±9	12/12		14±8	19/19		39±8	6/7	86	31±7	11/12	92	34±8	17/19	89
V	Right	16±7	14/14		16±4	16/24	67**	16±5	30/38	79	31±6	10/14	71	30±6	13/24	54	30±6	23/38	60
Y[a]	Both				12±3	69/69		12±3	69/69					31±6	33/69	48	31±6	33/69	48**

Latency means for rightward and leftward movements were not significantly different (Student *t*-test), except for head latencies of cat *G* (*asterisk*). Means of gaze and head latencies were significantly different ($P<0.01$).
** Percentage of leftward deceleration significantly different from rightward deceleration, or percentage of head deceleration significantly different from gaze deceleration (χ^2-test, $P<0.05$)
[a] The two fixation areas were stimulated; the stimulation effect was tested on gaze shifts electrically evoked from a site located in the right caudal SC (see Fig. 1)

head (and thus gaze) movements (Fig. 4A,B; solid traces). Similar to the inhibition of vestibular quick phases, the effect was stronger for gaze saccades directed ipsilaterally to the SC being stimulated (compare Fig. 4A and 4B). By analyzing velocity profiles, the percentage of gaze shifts and head movements decelerated by the stimulation was larger for ipsiversive than for contraversive ones (Table 1). Deceleration of the head movement was seen less frequently than gaze deceleration, perhaps due to the smoothing effects of head inertia. Mean latencies of the onset of deceleration of gaze and head movements following stimulation are shown in Table 1. On average, the latency of a movement's deceleration relative to the stimulus onset was about 13 ms for gaze and 32 ms for the head. In cat *G*, we used stimulus durations of 10, 20, 24, 30, and 50 ms (pulse rate of 300 pulses/s). The duration of the decelerating period, as measured on the gaze velocity trace, increased linearly with the stimulus duration. The head deceleration response was more variable. For short stimulus trains, perturbations were less noticeable in the head trace than in the gaze trace. As the stimulus duration increased the effect on the head trace was more prominent.

In two animals (cats *G* and *L*), a long stimulus train was delivered simultaneously with the target's disappearance in the barrier paradigm. Almost all gaze saccades directed ipsilaterally to the stimulated SC were canceled for the duration of the stimulation (Fig. 5A,D). The saccades were initiated only after the end of the stimulus train, after an interval estimated to be 94 ms (SD 45, $n=10$) and 104 ms (SD 29, $n=19$) in cats *G* and *L*, respectively. Saccades directed to the side contralateral to the stimulation site were initiated at a latency comparable with that of controls but were hypometric. Most displacements during the electrical stimulus were made by a succession of small gaze saccades (Fig. 5B), or were limited to a saccade of reduced amplitude (Fig. 5C). The dominance of one response type over another appeared to depend on stimulus pulse rate; the truncated saccades occurring during high-frequency stimulation. This phenomenon was not studied in detail because differences in response were also related to variations in the cat's behavioral "set", a characteristic difficult to control.

Responses of OPNs to collicular stimulation

Once we had studied the collicular fixation area we proceeded to evaluate its influence on OPNs. A total of 49 neurons were identified and characterized in three head-fixed animals (cats *G*, *V*, and *Y*). The firing behavior of this class of neuron is exemplified in Fig. 6. OPNs exhibited a more or less tonic rate during stationary eye position but ceased discharging prior to and for the whole duration of eye saccades made in all directions. The discharge characteristics of the neurons recorded in this study were similar to those described in our previous

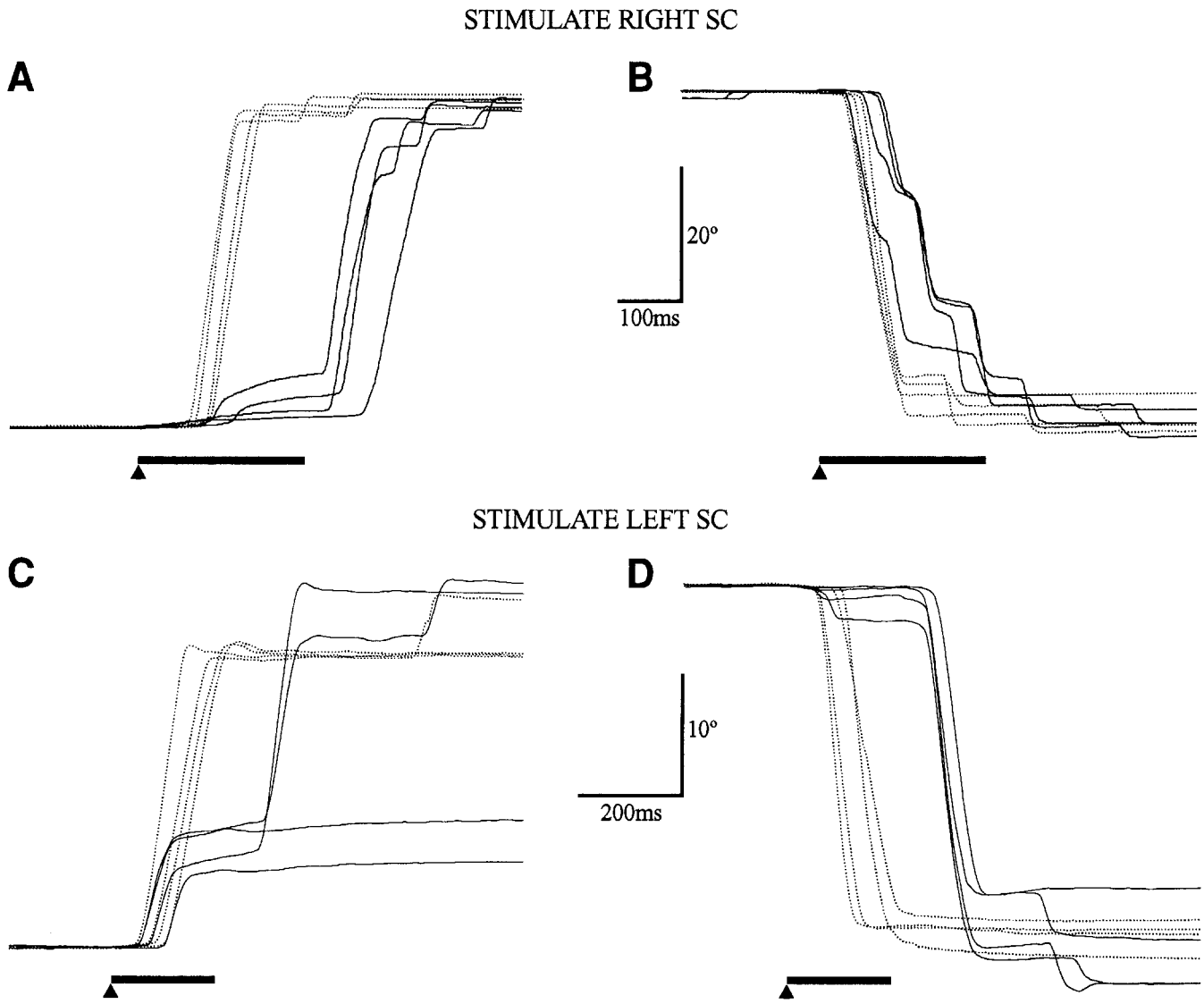

Fig. 5A–D Electrical stimulation delivered at the superior colliculus (SC) fixation area suppresses eye-head gaze saccade generation. **A,B** Data from cat *G* (right SC). **C,D** data from cat *L* (left SC). Rightward and leftward saccades made to visual targets (**A,B**) or to predictive targets in the dark (**C,D**). Long stimulus train delivered before the saccade suppresses ipsiversive gaze saccades (**A,D**) more than contraversive ones (**B,C**). *Dotted traces*, normal gaze saccades (controls); *solid traces*, stimulation trials. Stimulus parameters were 50 μA, 100 pulses/s, 500 ms in **A,B**; and 30 μA, 200 pulses/s, 200 ms in **C,D**. Movement traces are aligned on the same initial gaze position. *Arrowheads* mark the disappearance of the target from one side of the barrier, which is the cue for the animal to initiate the saccades. Light goes off at saccade onset in **C,D**. *Thick horizontal lines under movement traces* indicate stimulus presentation periods. Examples are horizontal gaze shifts

reports (Paré and Guitton 1990, 1992, 1994). Electrical stimulation of the SC was applied during fixation periods when OPNs discharged tonically. The excitability of these neurons has been shown to vary with the animal's level of arousal (Henn et al. 1984); their tonic activity decreases or completely vanishes when the animal becomes drowsy. Also, the latency of OPN responses to SC stimulation is known to increase when the stimulus is delivered during periods of reduced alertness (Raybourn and Keller 1977). For these reasons, the animals were kept fully alert during the administration of the electrical stimulus.

A large proportion of OPNs were activated by electrical microstimulation. Examples of responses for one cell are shown in Fig. 2B,C. Each neuron had a variable response latency, and its mean latency decreased with increasing stimulus intensity. In a few neurons, responses containing more than one spike were also observed. In addition, twin, closely spaced stimuli were more effective than single-pulse stimuli in eliciting action potentials. These observations strongly suggest that OPN responses to collicular stimulation were the result of transsynaptic mediation, i.e., of orthodromic invasion. Antidromic activation was ruled out by the collision test applied to ten OPNs. In all the neurons, the action potential response to the stimulus could not be made to collide with electrically evoked spikes.

In order to verify the hypothesis that SC fixation cells project predominantly to OPNs, the responses of OPNs to stimulation by electrodes located in the collicular fix-

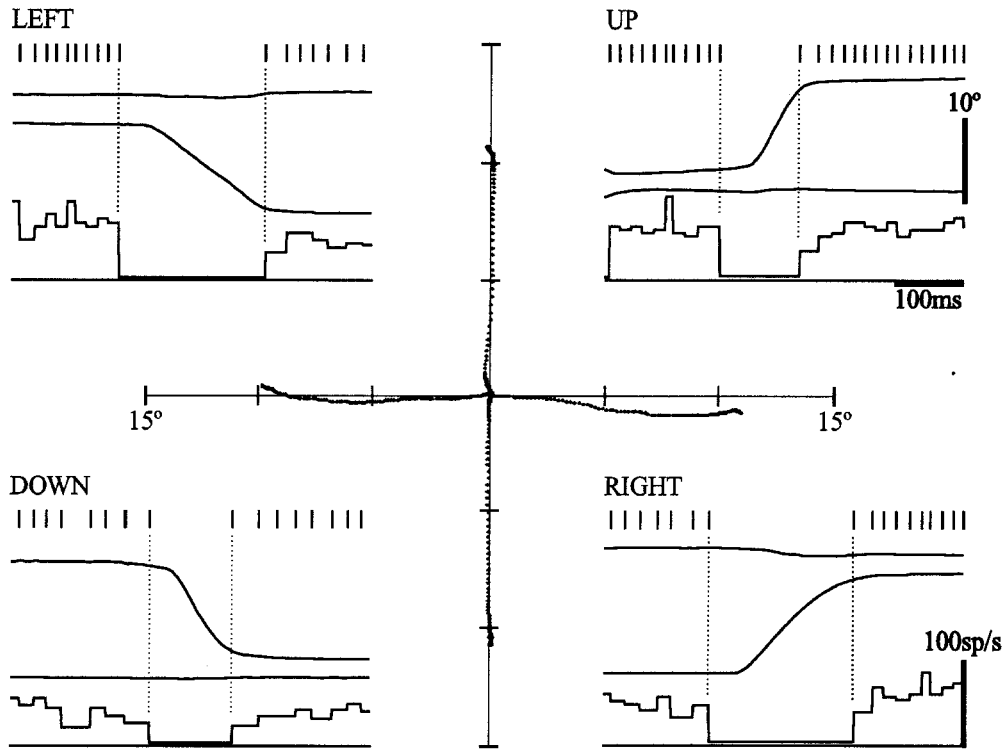

Fig. 6 Discharge pattern of one omnipause neuron (all *V12*) recorded in cat *V*. The *four panels* represent the unit response associated with each of the four orthogonal eye saccades shown in an *x-y* plot in the *center*. For each panel: *top*, spike activity, each *vertical bar* represents an action potential; *middle*, vertical and horizontal eye position traces; *bottom*, intantaneous firing rate. *Vertical dotted lines* indicate, respectively, the beginning and end of the pause in the neuron's activity

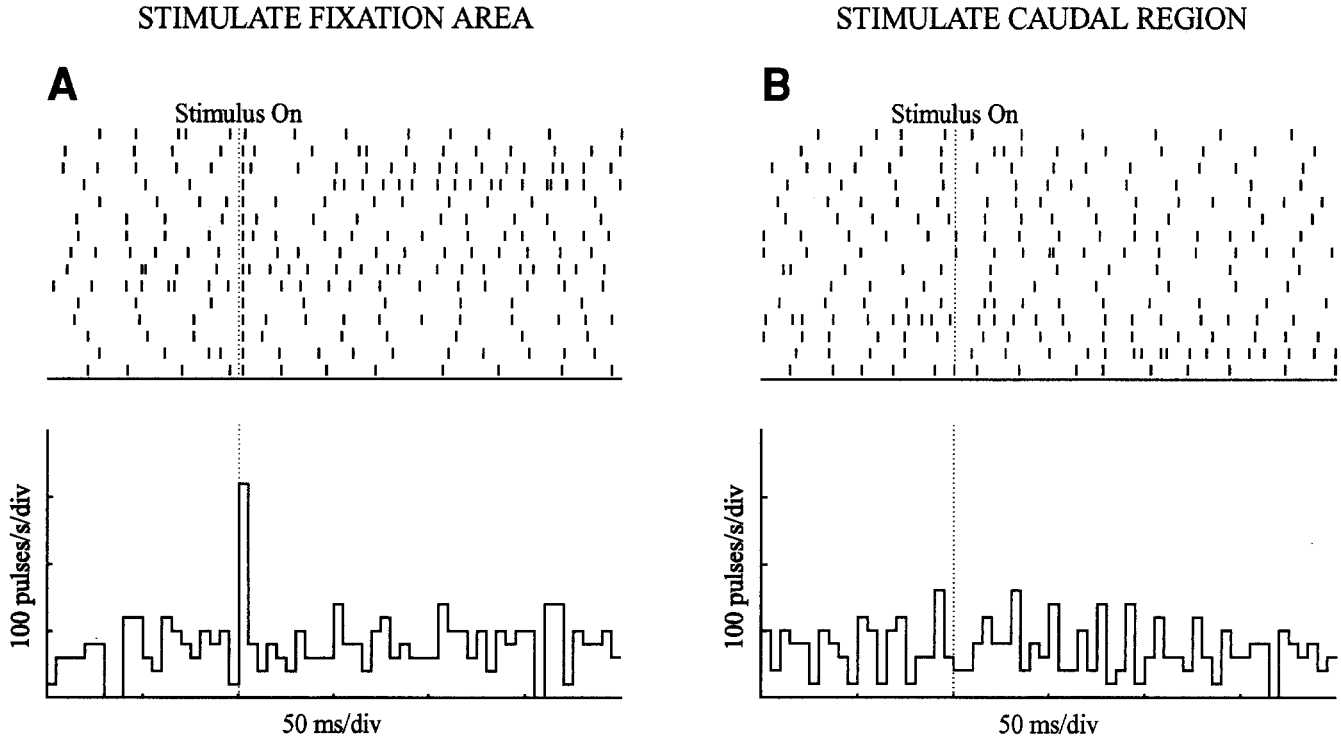

Fig. 7A,B Activity of one omnipause neuron (all *V12*) during single pulse stimulus applied in either the fixation area (**A**) or the caudal superior colliculus (SC) (**B**). *Top*, raster of 15 trials, each *vertical bar* represents an action potential; *bottom*, cumulative for the 15 trials (bin width: 5 ms). The rasters and histograms are aligned on the time of the stimulus (*vertical dotted line*). Stimulus current was 200 μA (2 × threshold) in **A** and 1 mA (maximum current) in **B**

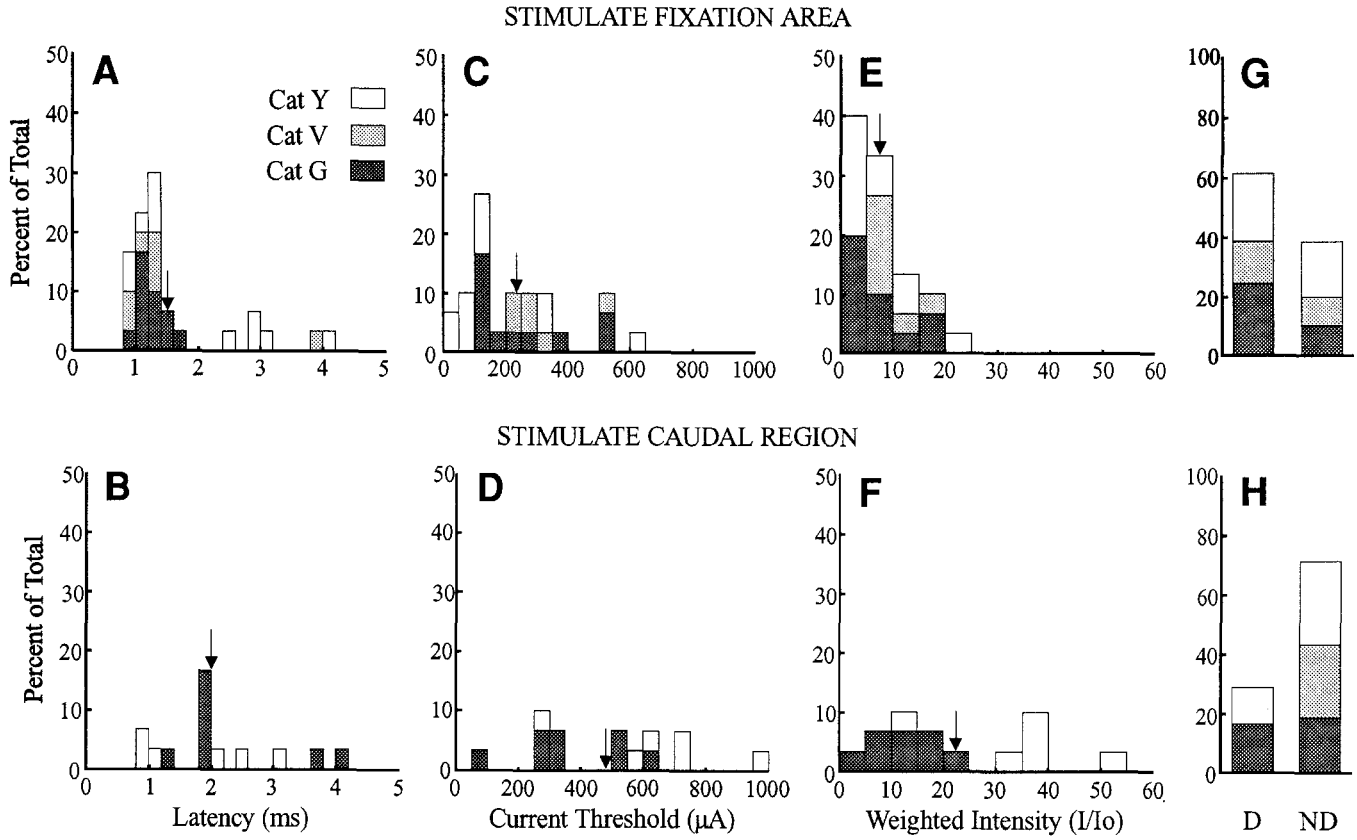

Fig. 8A–H Responses of 49 omnipause neurons, studied in three cats, to fixation-area stimulation and to caudal superior colliculus (SC) stimulation. Histograms are of response latencies (**A**,**B**), current thresholds (**C**,**D**), and weighted intensities (**E**,**F**) for orthodromic activation. *Vertical arrows* indicate the mean value of each distribution. For cat *G*, the mean of the effects of the two caudal electrodes on each neuron is depicted. **G**,**H** Percentage of neurons driven (*D*) and not driven (*ND*) by stimulation

ation area were compared with those elicited by electrodes located in caudal regions of the SC. Figure 7 illustrates typical effects of single-pulse stimuli applied at two different collicular sites on the firing activity of one OPN. When the fixation area was stimulated (Fig. 7A), this neuron was transiently activated. In each trial, the neuron responded with one or two spikes only; the neuron's firing rate dropped to its baseline immediately after the excitatory response. When the SC caudal region was stimulated, there was no change in this neuron's discharge (Fig. 7B).

The response characteristics of the OPNs recorded in each of the three cats are described in Fig. 8 and summarized in Table 2. In cat *Y*, stimulation of the fixation area and caudal electrodes activated 11 (55%) and 6 (30%) out of 20 OPNs, respectively. This difference in percentage was not statistically significant (χ^2, $P > 0.1$). For neurons driven by each of the fixation-area and caudal electrodes, differences between the latencies of responses elicited at the two sites were not statistically significant ($P = 0.31$, one-tail Mann-Whitney *U*-test). In contrast, important and significant differences were observed for the response current thresholds (fixation area 177 mA, caudal region 637 mA; $P < 0.005$) and weighted intensities (fixation area 6.6, caudal region 35.4; $P < 0.001$). Figure 9A illustrates the CE for each stimulating electrode and each neuron that was driven by stimulation. For all cells, the fixation-area electrode always had a higher CE than the caudal one. Furthermore, the CE values of the fixation-area electrode were significantly higher than those of the caudal electrode ($P < 0.001$, one-tail *U*-test).

In cat *V*, the fixation-area electrode elicited responses in 7 OPNs out of the 12 that were tested, whereas the caudal electrode did not activate any of these 12 neurons. The characteristics of OPN responses elicited in this animal also are described in Fig. 8 and summarized in Table 2. Figure 9B shows, for each neuron activated, the CE obtained from the stimulating electrode located in the fixation area. The CE obtained for each neuron from the caudal electrode was zero.

The results obtained in cat G were complementary to those of cats *Y* and *V* (Table 2 and Fig. 8). Of the 17 OPNs that were tested, stimulation of the fixation-area electrode elicited responses in 12 (71%). Stimulation of caudal electrodes 2 and 3 activated eight (47%) and seven (41%) OPNs, respectively. These latter percentages were not significantly different from that for the fixation-area electrode (χ^2, $P > 0.1$). For electrodes 1 and 2, the response latencies ($P < 0.0005$, one-tail *U*-test) and weighted intensities ($P < 0.02$) were significantly different, but not current thresholds ($P = 0.057$). Results were

Table 2 Characteristics of omnipause neuron responses to superior colliculus (SC) stimulation for each animal. (*D* neurons driven, *ND* neurons not driven by SC stimulation, *I* current threshold, I/I_o weighted intensity, *CE* coefficient of efficacy)

Cat	Electrodes	(*n*)	D		ND		Latency (ms)			*I* (μA)			I/I_o			CE $(ms \cdot \mu A)^{-1}$		
			n	%	*n*	%	Mean	SD	Range	Mean	SD	Range	Mean	SD	Range	Mean	SD	Range
Y	1[a]	20	11	55	9	45	1.9	1.1	0.8–4.0	177	183	45–640	6.6	6.8	1.7–23.7	0.21	0.23	0.02–0.62
	2	20	6	30	14	70	1.7	0.9	0.8–3.0	637*	230	250–950	35.4*	12.8	13.9–52.8	0.02*	0.01	0.01–0.03
V	1[a]	12	7	58	5	42	1.5	1.1	0.8–3.9	315	109	215–530	9.0	3.1	6.1–15.1	0.09	0.04	0.03–0.16
	2	12	0	0	12	100	–	–	–	–	–	–	–	–	–	–	–	–
G	1[a]	17	12	71	5	29	1.2	0.2	0.9–1.6	241	167	90–539	6.9	4.8	2.6–15.4	0.15	0.08	0.04–0.29
	2	17	8	47	9	53	2.5*	0.9	1.2–4.0	408	218	89–767	13.0*	6.5	2.5–21.3	0.06*	0.09	0.01–0.28
	3	17	7	41	10	59	1.7*	0.8	1.2–3.6	314	160	72–539	11.8*	7.0	3.6–24.3	0.07*	0.05	0.01–0.17

* Distributions significantly different from that found by stimulating the fixation area (one-tail *U*-test, $P<0.05$)

[a] Fixation area

similar for electrodes 1 and 3; the response latencies ($P<0.02$) and weighted intensities ($P<0.05$) were considered significantly different, but not current thresholds ($P=0.16$). The CE value for each neuron and for each stimulating electrode is shown in Fig. 9C. Comparison of this coefficient indicates that the electrode located in the fixation area was significantly more efficient in activating OPNs than those situated in the caudal regions ($P<0.05$, one-tail *U*-test). Only for cell **8** did the caudal electrodes have a higher CE than the fixation-area electrode.

The responses shown in Fig. 8 of all the OPNs tested in the three animals are summarized in Table 3. For cat *G*, the mean of the effects of the two caudal electrodes on each neuron was considered. Out of 49 OPNs that were tested for a response to stimulation of the SC fixation area, 30 (61%) were excited by the stimulus. By contrast, electrical stimulation delivered in the caudal SC activated only 14 neurons (29%). This difference in percentage was statistically significant by χ^2-test ($P<0.005$). The latency of the response obtained for rostral stimulation ranged from 0.8 to 4 ms, with a mean of 1.5 ± 0.9 ms. The latency of the response obtained for caudal stimulation ranged from 0.8 to 4 ms, with a mean of 2.0 ± 1.0 ms. The difference between the two latency distributions was significant ($P<0.05$, one-tail Mann-Whitney *U*-test). For fixation-area and caudal SC stimulation, respectively, 77% (23/30) and 64% (9/14) of the responsive OPNs could safely be considered monosynaptically driven, i.e., they had a response latency of less than 1.6 ms (see Materials and methods). This difference in percentage was not statistically significant (χ^2, $P>0.5$). Current threshold for orthodromic activation by stimulation of the fixation area and caudal region ranged from 45 to 640 μA and 80 to 950 μA, respectively. Mean current threshold was 235 ± 165 μA and 487 ± 237 μA, respectively. The difference between these two distributions was statistically significant ($P<0.0005$, one-tail *U*-test). The range of weighted intensity for stimulation of rostral and caudal SC was 1.7–23.7 and 3.0–52.8, respectively. The mean values were 7.3 ± 5.2 and 22.5 ± 14.8, respectively. The difference was highly significant ($P<0.0001$, one-tail *U*-test). The mean CE values for the fixation area and caudal stimulating electrodes were, respectively, 0.16 and 0.05. The difference between the CE values was also highly statistically significant ($P<0.0001$, one-tail *U*-test).

Discussion

In this paper, we have demonstrated that stimuli delivered within the rostral pole of the SC, where stimulation suppresses gaze shifts, are more efficient at exciting OPNs than stimuli applied to caudal regions. These observations suggest that the collicular excitatory input to OPNs is principally provided by the rostral pole, via which fixation cells found in this collicular area could exert their role in fixation behavior.

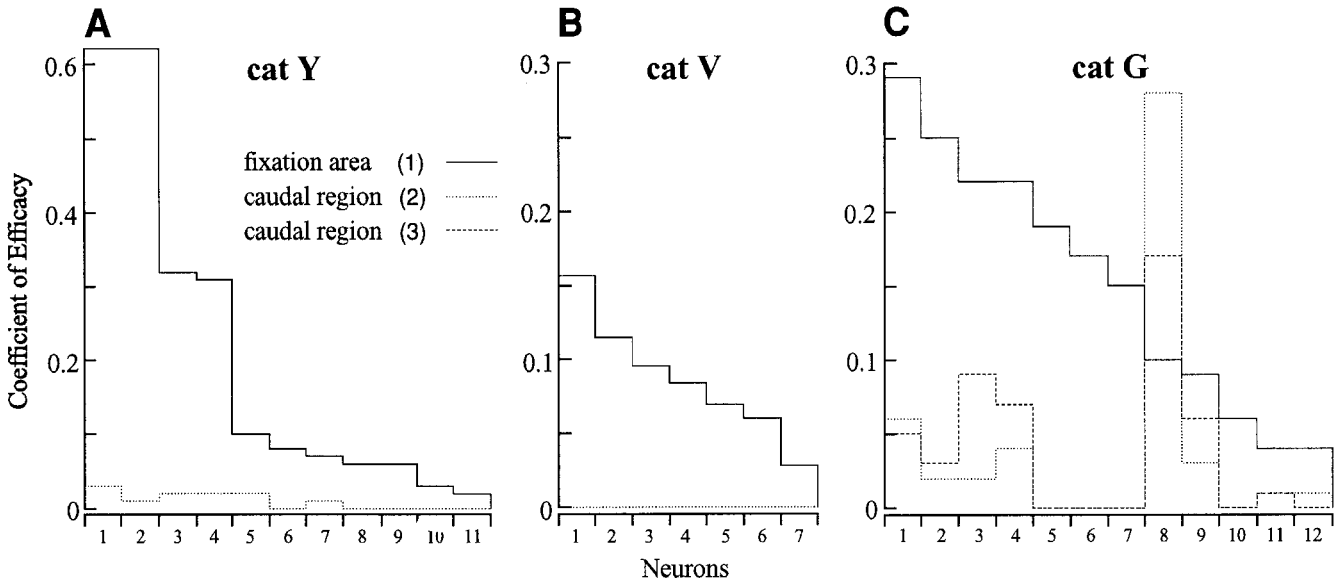

Fig. 9A–C Comparison of the efficacy in inducing a response following stimulation in superior colliculus (SC) fixation area and caudal regions. Values of the coefficient of efficacy for each stimulating electrode and each neuron in the three cats *Y* (**A**), *V* (**B**) and *G* (**C**). *Solid lines*, fixation-area electrodes; *dotted lines and dashed line*, caudal SC electrodes

Table 3 Characteristics of omnipause neuron responses to superior colliculus stimulation. (*SCf* superior colliculus fixation area, *SCc* superior colliculus caudal region, see Table 2, *Msyn* neurons monosynaptically driven by collicular stimulation)

	n	D		Msyn		ND		Latency (ms)			*I* (μA)			I/I_o			CE (ms · μA)$^{-1}$		
		n	%	*n*	%	*n*	%	Mean	SD	Range	Mean	SD	Range	Mean	SD	Range	Mean	SD	Range
SC*f*	49	30	61	23/30	77	19	39	1.5	0.9	0.8–4.0	235	165	45–640	7.3	5.2	1.7–23.7	0.16	0.15	0.02–0.62
SC*c*	49	14	29**	9/14	64	35	71	2.0*	1.0	0.8–4.0	487*	237	80–950	22.5*	14.8	3.0–52.8	0.04*	0.06	0.01–0.22

* Distributions significantly different from that found by stimulating the fixation area (one-tail *U*-test, $P<0.05$).
** A percentage significantly different from the fixation area (χ^2-test, $P<0.01$). In calculating these response characteristics we used for cat *G* the mean of the effects of the two caudal electrodes

Evidence for a fixation area at the rostral pole of the cat's SC

Recent recordings from cat collicular output neurons have revealed that those emanating from the area centralis representation at the rostral pole of the SC have discharge properties quite different from those elsewhere (Munoz and Guitton 1989, 1991; Munoz et al. 1991). They discharge tonically when the animal is fixating, but their firing ceases during gaze shifts. This discharge pattern is similar to that of brainstem OPNs (Keller 1974; Evinger et al. 1982; Paré and Guitton 1990, 1992, 1994). Cells with similar discharge properties also have been found in the rostral pole of the monkey SC (Munoz and Wurtz 1992, 1993a).

Since attentive fixation hyperpolarizes presaccadic SC efferent neurons located outside the fixation area (Guitton and Munoz 1991), Munoz et al. (1991) proposed that stimulating the collicular fixation area should suppress eye and gaze saccades or interrupt them if stimulation occurred during the movement. The authors speculated that this could be implemented via both a reduced drive from the collicular motor map and an excitatory projection of fixation neurons onto OPNs, which in turn inhibit a gaze saccade burst generator. Recently, it has been reported that activation of the monkey collicular fixation area suppresses ocular saccades (Munoz and Wurtz 1993b) and inhibits the activity of SC saccade-related cells (Munoz and Wurtz 1993c). The present results complement these two studies by supporting: (1) the inhibitory role of the SC fixation area on both eye and head motion in gaze saccade generation; and (2) the speculated projection from the SC fixation area onto OPNs which, themselves, have been shown to be implicated in gaze control (Paré and Guitton 1989, 1990).

Unilateral electrical stimulation of the SC fixation area decelerated ipsiversive saccades more than contraversive saccades. In other words, saccades generated by the SC whose own fixation area was being stimulated were less affected than those generated by the other SC, the one contralateral to the stimulated fixation area. Munoz and Wurtz (1993b) have reported the same effect in the monkey and have explained this asymmetrical

effect by intracollicular interactions. However, a brainstem mechanism cannot be rejected. According to the anatomy, the population of OPNs is segregated into two subpopulations lying on each side of the brainstem midline (Büttner-Ennever et al. 1988; Langer and Kaneko 1990). Efferent tectal axons that constitute the predorsal bundle cross the midline and thus may contact contralateral OPNs (Grantyn and Grantyn 1982; Ito et al. 1984; Olivier et al. 1993). Furthemore, OPNs appear to project predominantly to elements of the saccadic burst generator located on the contralateral side (Ohgaki et al. 1987). Thus activation of one fixation area, say of the right SC, may excite strongly the contralateral left OPN population, which in turn inhibits more specifically the right burst generator responsible for the generation of rightward saccades. Saccades directed ipsilaterally to the SC being stimulated will then be more affected.

OPN responses to SC stimulation

OPNs were excited at short latencies by electrical stimulation within the deep layers of the SC. Given the unstable latency of the responses and the negative results of the collision tests, we conclude that the responses of these cells were orthodromically evoked by SC stimulation. Indeed, there is no anatomical indication of a projection from OPNs to the SC (Langer and Kaneko 1983). Based on the calculations given in the Materials and methods section, the majority of the neurons that could be activated by SC stimulation were monosynaptically driven: 77% for fixation area stimulation and 64% for stimuli delivered to the caudal SC. Stimuli delivered within the fixation area were found to be significantly more efficient in activating OPNs than were those applied to caudal regions. First, stimulation of the fixation area excited more neurons than stimulation applied to caudal regions: 61% versus 29% for the three cats. Second, the values of the CE for the fixation-area electrode were significantly higher than those of the caudal electrodes. This was due primarily to differences in stimulus intensities and secondarily to response latencies. Thus our results support the hypothesis that the SC fixation area projects more heavily onto OPNs than other regions of the SC. These physiological results are corroborated by recent anatomical evidence (J.A. Büttner-Ennever, private communication).

The mean current threshold needed to evoked action potentials in OPNs by stimulating the rostral and caudal SC sites was 236 μA (range 45–640 μA) and 487 μA (range 80–950 μA), respectively. At these current strengths, it can be estimated that collicular tissue at distances of about 1 and 2 mm from the stimulation site, respectively, could have been excited by the stimulus (Ranck 1977; Yeomans 1990). The stimulating electrodes were located at least 4 mm apart. Thus, OPN responses elicited by stimulation of SC caudal regions with the mean current (487 μA) were not likely to be caused by direct fixation-area activation. However, it is possible that OPN activation by strong caudal SC stimulation (e.g., 950 μA) might have been caused by direct excitation of projecting cells in the fixation area, which is evaluated to be about 3 mm in diameter in the cat (Munoz and Guitton 1991) and 1.8 mm in monkey (D.P. Munoz, private communication).

Apart from current spread, there is no evidence suggesting that stimulation of a SC site activates fibers originating from areas distant from the one being directly activated by the electrical stimulus. The axons of SC efferent neurons that enter the predorsal bundle do not travel along the rostrocaudal axis within the SC (Grantyn and Grantyn 1982; Moschovakis and Karabelas 1985). They exit the SC deep layers at about the same anteroposterior level as the location of their cell bodies. Furthermore, activation of collaterals of distant efferent neurons can also be rejected. Some efferent neurons do possess collaterals (Grantyn and Grantyn 1982; Moschovakis and Karabelas 1985). However, the majority of these collaterals are connected to neurons located in the other SC through commisural projections. The others are recurrent collaterals projecting in the close vicinity of the parent cell body. Thus, there is no evidence suggesting that SC efferent neurons make contact with distant neurons within the same colliculus. Electrophysiology also supports this view. Stimulation of sites in caudal SC regions has been shown to orthodromically inhibit fixation neurons, and vice versa (Munoz and Wurtz 1993c). However, in either case, antidromic activation was not observed, suggesting that the inhibitory effect was mediated by local interneurons.

One explanation for the activation of OPNs by caudal SC stimulation is that this was caused by exciting collicular efferent neurons that, overall, have weak projections onto the OPN area (Olivier et al. 1993). These neurons control orienting eye saccades and gaze shifts and it is not clear why they project onto OPNs which, themselves, suppress orienting movements. Because this projection is weak, electrical stimuli applied in the caudal regions would necessarily need to excite a larger area of neural tissue to become as effective as stimuli delivered at the rostral pole in recruiting SC cells that project onto OPNs.

Comparison with previous studies

Without considering rostrocaudal variations in the SC-OPN projection, Raybourn and Keller (1977) reported that 85% (23/27) of primate OPNs are activated by electrical stimulation of the SC. Assuming a maximum conduction velocity of 50 m/s for SC output fibers, as found in the cat by Grantyn and Grantyn (1976), these authors estimated the percentage of responsive OPNs that were monosynaptically excited by SC stimulation to be 52% (12/23). Although monkey OPNs seemed to be activated by stimulation of any collicular site, there was some degree of variation in the SC-OPN projection similar to what we have found; stimulation of the rostral SC elicit-

ed a much higher percentage of monosynaptic responses than the rest of the SC.

In the cat, King et al. (1980) also studied the latency distribution of OPN responses to SC stimulation. Their results showed that OPNs had responses with latencies ranging from 1.0 to 4.0 ms (mean 2.6, SD 1.0). Based on the calculations that we have used in this paper, their results indicate that only 12% (2/17) of their responsive OPNs most probably received a monosynaptic projection from SC efferents. This very low percentage could be explained by the fact that their data were obtained in the anesthetized cat (ketamine) and that reduced alertness increases response latency and threshold intensity. Consistent with this explanation, these authors reported that SC stimulation failed to activate OPNs in many of their experiments; positive results were obtained in only three cats out of eight. With the same animal preparation, Kaneko and Fuchs (1982) reported that 66% (23/35) of OPNs were activated by SC stimulation. The remaining 34% (12/35) did not respond at stimulating currents of 1 mA or more. Unfortunately, no indication of the response latencies was provided by these authors.

Concluding remarks on the SC-OPN excitatory connection

It has been reported that some OPNs are phasically excited by visual stimuli (in cat: Evinger et al. 1982; Paré and Guitton 1992; in monkey: Fuchs et al. 1991) and that the pathway mediating that response appears to involve the SC (King et al. 1980). We suggest that this is mediated via an excitatory projection onto OPNs from fixation neurons, the efferent collicular neurons known to be active during fixation behavior. Indeed, the visual receptive field of cat OPNs are located in the central visual field (Evinger et al. 1982) and are therefore very similar to those exhibited by SC fixation neurons (Munoz and Guitton 1991). These observations further support the hypothesis of Munoz and colleagues (Munoz and Guitton 1989, 1991; Munoz et al. 1991) that the excitatory drive from the SC onto OPNs originates primarily from the area centralis representation by means of fixation neurons. In addition, activation of fixation neurons by either natural attentive fixation (see accompanying paper, Paré et al. 1994) or, as shown here, by electrical stimulation suppresses orienting behavior just like microstimulation of the OPN area does (Paré and Guitton 1989).

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