

Changing Views of the Role of Superior Colliculus in the Control of Gaze

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Introduction

Located at the interface between sensory and motor processing, the superior colliculus (SC) serves as a useful model system for studying a number of important problems in integrative neuroscience. Based on traditional studies, the SC is known to contain maps of cells responsive to sensory stimuli as well as a motor map of neurons involved in generating commands for saccades, short-duration and high peak velocity eye movements that rapidly change fixation between meaningful stimuli.

Since the last detailed review of the control of saccades by SC (Sparks and Hartwich-Young 1989), our view of its participation in generating movements has changed significantly. Advances in understanding the role of the SC in the transformation of sensory signals into commands for orienting movements are reviewed here and by Wurtz & Sommer (Chapter 98). The first two parts of this chapter briefly review progress in our knowledge of the anatomical organization and coding mechanisms of the SC. Subsequent sections discuss selected contemporary issues about collicular participation in achieving accuracy of saccades and in controlling other oculomotor and skeletomotor movements.

Anatomical organization in the superior colliculus

The superior and inferior colliculi form the roof of the midbrain. In mammals the SC is composed of 7 alternating fibrous and cellular layers. On the basis of anatomical and behavioral data, these layers are grouped into two functional units: (1) superficial and (2) deep compartments. The superficial layers (*stratum zonale*, *stratum griseum superficiale* and *stratum opticum*) receive inputs devoted almost exclusively to vision. Cells in the superficial layers of each colliculus are activated by stimuli appearing in the contralateral visual field and are topographically organized according to receptive field location (Cynader and Berman 1972). Neurons with receptive fields near the center of the visual field are located anteriorly, those with receptive fields in the periphery are located posteriorly. Cells with receptive fields in the upper visual field are located medially; those with receptive fields in the lower visual field are located laterally. The perifoveal representation is enlarged with over one third of the collicular surface devoted to the central 10 deg of the visual field. The representation of the horizontal meridian runs from anteriolateral to posteromedial. The visual signals observed are in retinal coordinates; cells respond to visual stimuli if, and only if, particular regions of the retina are activated. The outputs of the superficial layers are primarily ascending and terminate, for the most part, in

various regions of the thalamus, including the pulvinar (see Sparks and Hartwich-Young (1989) for a review).

In contrast, the intermediate (*stratum griseum intermedium*, *stratum album intermedium*) and deeper (*stratum griseum profundum* and *stratum album profundum*) layers – collectively, the deep layers – receive sensory inputs of several modalities (for example, visual, auditory, and somatosensory) and contain neurons with motor properties. In their early description of SC neurons discharging before saccadic eye movements, Wurtz and Goldberg (1972) noted that the neurons have *movement fields*, i.e., each neuron discharges before or during saccades having a particular range of directions and amplitudes. The size of the movement field is a function of the amplitude of the optimal movement. Some neurons that discharge prior to saccades also have visual receptive fields, while other neurons have only movement fields. Neurons discharging in response to visual stimuli and prior to eye movements have overlapping, but not necessarily co-extensive movement and receptive fields (Wurtz and Goldberg 1972; Anderson et al. 1998).

Based on both neural recording and microstimulation experiments in head-restrained animals, it has been established that saccade direction and amplitude are topographically organized in the deep layers of the SC (Robinson 1972; Schiller and Stryker 1972). Neurons discharging prior to small saccades are located anteriorly and those firing before large saccades are found posteriorly. Cells near the midline discharge prior to movements with up components and those on the lateral side discharge maximally before movements with down components. Microstimulation of the deep layers produces a saccadic eye movement with an amplitude and a direction similar to the optimal vector encoded by the neurons near the tip of the electrode.

Despite the general correspondence between the motor and the overlying sensory maps, there is no essential functional linkage between retinotopically-coded visual activity in the superficial layers and saccade-related pre-motor activity in the deep layers of the SC. Vigorous activity may occur in the superficial layers and not be translated into saccade-related discharge in underlying cells in the deep layers. Conversely, saccade-related activity recorded from neurons in the intermediate and deeper layers may not be triggered by activity of the overlying visual neurons coding retinal error, i.e., the distance and direction of the target image from the fovea. Thus, the activity of visual neurons in the superficial layers is neither necessary nor sufficient to produce activation of saccade-related neurons in the deep layers of the underlying colliculus (Mays and Sparks 1980).

Yet, chemical inactivation in hamster SC (Mooney et al. 1992) and *in vitro* experiments in SC

slices using whole-cell patch-clamp methods (Lee et al. 1997; Isa et al. 1998) have demonstrated synaptic transmission from the superficial to intermediate layers. Excitatory postsynaptic potentials, evoked with mono- and polysynaptic latencies, were recorded from neurons in the intermediate layers when the overlying superficial layer was stimulated. In the presence of bicuculline, neurons in the intermediate layers even exhibited a burst upon stimulation of the superficial layers, suggesting that the signal transmission is suppressed by GABAergic inhibition. The burst property of intermediate layer neurons was also facilitated by activation of nicotinic acetylcholine receptors (Isa et al. 1998). Behaviorally, the occurrence of short-latency, express saccades increased after microinjections of the acetylcholinergic agonist nicotine in the SC of awake, behaving monkeys (see Kobayashi et al. (2001) for a review). Thus, this inter-laminar circuitry may play a critical role in reducing saccadic reaction time and triggering express saccades, which are absent following ablation of the SC (Schiller et al. 1987). A description of SC participation underlying saccadic initiation has been reviewed recently (Munoz et al. 2000; see Sparks et al. (2000) for a slightly different perspective).

Unlike the inter-laminar organization, the neurons within the deep layers likely use local excitation and distant inhibition mechanisms to shape the evolution of the population activity that leads to the generation of each saccade. The electrophysiological (McIlwain 1982; Munoz and Istvan 1998) and pharmacophysiological (Meredith and Ramoa 1998; Pettit et al. 1999) experiments that provide credence for such connectivity monitored extracellular activity while stimulation pulses were delivered to different parts of the collicular map. Thus, intracollicular connections likely shape the spatial and temporal profile of activity, although a potential confound may be introduced by stimulation of fibers of passage. Before and during each saccade, neurons in approximately 25-30% of the collicular map discharge, and the size of the active area remains relatively invariant across saccades of all amplitudes and directions (McIlwain 1975; Munoz and Wurtz 1995b; Anderson et al. 1998). The SC neurons project predominantly to brainstem structures that process the collicular commands to produce an appropriate movement.

Population coding

Each SC neuron in the deep layers discharging prior to a wide range of movement vectors translates into a large population of neurons active before and during any saccade. The large movement field characteristic of these cells led to population coding schemes for specifying the metrics of the desired

movement (McIlwain 1975, 1991; Sparks et al. 1976). Indeed, results of experiments in which a small subset of the population of neurons active before a saccade was reversibly inactivated support the hypothesis that each member of the active population participates in specifying the direction and amplitude of a saccade. The evidence indicates that saccadic accuracy results from the *averaging* of the movement tendencies produced by each unit in the active population (Lee et al. 1988; Sparks et al. 1990). Small changes in the direction or amplitude of saccades are produced by slight shifts in the location of the population of active cells within the motor map. Thus, the large movement fields of collicular neurons may contribute to, rather than detract from, the accuracy of saccadic eye movements (Baldi & Heiligenberg 1988). Because the contribution of each neuron to the direction and amplitude of the movement is relatively small, the effects of variability or 'noise' in the discharge frequency of a particular neuron are minimized.

Lesion data indicating that the SC is not essential for saccade generation (Schiller et al. 1987) does not necessarily indicate that it does not play a critical role in the initiation and execution of saccades in normal animals. Large deficits in saccade accuracy and latency are observed following reversible inactivation of SC (e.g., Hikosaka and Wurtz 1985, 1986; Lee et al. 1988; Aizawa and Wurtz 1998; Quaia et al. 1988). Metrics of eye movements evoked by stimulation of the frontal eye fields following inactivation of the SC also support the hypothesis that collicular neurons play an important role in controlling the direction and amplitude of saccades (Hanes and Wurtz 2001).

Neurons in the intermediate and deeper layers of SC also exhibit large receptive fields, and population coding schemes may also contribute to the accurate localization of sensory stimuli. Many neurons are responsive to auditory, somatosensory or visual stimuli and are organized in anatomical maps (see Stein and Meredith (1993) for a review). In anesthetized or paralyzed preparations, the visual, somatosensory, and auditory maps appear to be aligned, implying that the sensory signals have been translated into a common coordinate system. Before data from alert animals were available, it was commonly assumed that this alignment allowed a general, modality independent map of the external environment to be formed. In such a map, stimuli originating from a particular region of the external world, regardless of sensory modality, would activate a particular subset of multimodal neurons (neurons that respond to visual, auditory, or tactile stimuli). The activation of these sensory neurons, in turn, could initiate orienting responses by exciting adjacent cells with movement-related activity organized in a motor map aligned with the multimodal

map of sensory space. But, retinotopically organized visual signals, acoustic signals localized in head coordinates, and tactile signals organized in body coordinates will not be aligned when the eyes and limbs move with respect to the head.

A remapping is required to account for changes in the position of the relevant effector. For example, the spatial locations of the receptive fields of acoustically responsive cells shift with changes in eye position. This dynamic update of the site of acoustically driven activity encodes the direction and amplitude of the movement required to look to the auditory stimulus rather than the location of the target in space (Jay and Sparks 1987; Peck et al. 1995; Populin and Yin 1998). Groh and Sparks (1996) reported that the response of collicular neurons to tactile stimuli was significantly modulated by the position of the eyes in the orbits. Sensory signals in SC seem to be coding the direction and amplitude of the movement required to look to a stimulus rather than the location of that stimulus in space. This transformation of sensory signals into a motor frame of reference is necessary because the motor map in the superior colliculus is organized in relative coordinates - the signals specify the change in gaze position required to look to a target. Input signals that initiate a movement must also specify the location of the target with respect to the current gaze position, not the location of the target in body or head coordinates.

Incorporation of feedback signals in the SC

As the short-duration of saccades precludes visual feedback from contributing to their trajectory, these rapid eye movements once were considered ballistic. However, Robinson (1975) proposed a model in which a "local" feedback signal enables instantaneous control of saccades. While his original version has undergone various revisions, the skeleton of the models has remained the same: a corollary discharge signal is subtracted from the desired eye movement command to compute a dynamic motor error that specifies the metrics of the remaining eye movement; the ongoing eye movement continues until the feedback drives the motor error to zero.

According to some models (see Moschovakis et al. 1996 for a review), the command specifying the metrics of the desired eye movement originates in the SC, the feedback signal stems from the pontomedullary reticular formation in the brain stem, and the neural comparator performing the subtraction resides downstream of the SC. Therefore, the SC is in the feedforward pathway of the neural circuit controlling saccadic eye movements. This traditional view, however, has been challenged by two, non-exclusive hypotheses that place the SC inside the feedback loop. To maintain control of saccades, one theory employs

the temporal dynamics of SC neuron discharge while the other exploits the topographic organization of the SC. In this section, we describe the experiments used to support and dispute these hypotheses.

Temporal control scheme

Spikes were recorded as monkeys made saccades of the optimal amplitude coded by the movement field of the isolated neuron. The spike trains were converted into a continuous waveform representing spike rate by convolving each spike with a Gaussian kernel and then summing the individual signals as a function of time (Richmond et al. 1987). Superior colliculus neurons in the intermediate and deeper layers were classified into one of three categories based on the level of activity at the end of the saccadic eye movement (Waitzman et al. 1991). Neurons with saccade-related bursts that ended completely by saccade offset were termed *clipped* cells. Neurons with saccade-related bursts that declined significantly but maintained low level activity after the end of saccade were considered *partially clipped* cells. Neurons that failed to discharge a burst during the saccade but exhibited low-level activity before, during and after the movement were labeled *unclipped* cells. A quantitative index indicated that SC neurons, in actuality, spread into a continuum across the three categories.

The discharge rate of clipped and partially clipped neurons decreased monotonically during the saccade and, therefore, was linearly related to the motor error of the eye movement. This evidence led to the hypothesis that saccade dynamics are controlled by the discharge profiles of the SC neurons (Waitzman et al. 1991). In this model, the locus of activity on the SC encodes the desired eye movement and the level of activity represents the dynamic motor error. Thus, the subtraction of the feedback signal from the desired movement command occurs at the level of the SC, placing it in the feedback loop.

How robust is the correlation between neural activity and dynamic motor error when the dynamics of saccades are altered from their stereotypical short duration? Interrupted saccades can be produced by stimulation of the omnipause neurons (OPNs), which gate the brainstem neurons that deliver the drive to the extraocular motoneurons to produce the saccade (see Moschovakis et al. (1996) for an exhaustive review of brainstem physiology of the saccadic system). The stimulation, triggered on the onset of a saccade directed to a briefly flashed target, halted the ongoing movement in mid-flight, and shortly after the offset of the stimulation train, a resumed saccade was generated to bring the eyes to the location of the extinct target (see Keller et al. 1996). Since the dynamic motor error remains constant during the interruption duration

(because the eyes are not moving), the temporal control scheme predicts that SC neurons encoding dynamic motor error should exhibit a sustained discharge rate during the interruption. To test this hypothesis, Keller and colleagues (Keller and Edelman 1994; Keller et al. 2000) recorded activity of caudal SC neurons during saccades generated to the center of the movement field but interrupted by stimulation of the OPN region. As in the control condition, the cell exhibited a premotor burst prior to the onset of movement. Stimulation of the OPN region at the onset of the saccade attenuated SC activity, to various degrees in different cells, with the largest suppression observed in clipped and partially clipped neurons. During the interruption duration, the activity did not stabilize at a firing rate corresponding to the remaining motor error. At the onset of the resumed movement, the same neuron active for the initial saccade discharged again, provided that the interruption duration did not exceed approximately 100 msec; thus, for short interruption durations, the locus of collicular activity was not updated prior to the second eye movement. The peak activity associated with the second burst was significantly greater than the expected firing rate according to the temporal coding scheme. Also, the correlation between the firing rate and motor error of the resumed movement was weaker than for control saccades. These results suggest that clipped and partially clipped neurons do not quantitatively code dynamic motor error. However, it is possible that a stricter dynamic control may be exerted only towards the end of a saccade because the temporal relationship appears stronger for the later part of the movement, even in the case of interrupted saccades (compare the solid and dotted curves in Figure 11 in Keller and Edelman (1994)). For larger interruption durations, the initial and resumed movements appeared to be treated as two separate saccades, as the population of neurons activated for the resumed saccades was the same ensemble of cells that discharged for a control eye movement of the same amplitude. Thus, the desired eye movement signal may be updated during the longer duration interruption.

Another study delivered air puffs into the eye to perturb the saccadic trajectory and analyzed the corresponding activity in SC neurons (Goossens and Van Opstal 2000). The dynamics of the eye movements were grossly perturbed. The motor error and neural activity were not linearly correlated for many neurons, arguing against the temporal control mechanism.

The activity of SC neurons was also evaluated when the stereotyped trajectories of saccades were altered by injection of muscimol in the OPN region (Soetedjo et al. 2002a). The resulting saccades, although accurate, exhibited lower peak velocity and

longer duration. Corresponding activity of SC neurons consistently increased in duration, leading the authors to propose that the SC receives a feedback signal that regulates the duration of their discharge.

Soetedjo et al. (2002a) also analyzed the peak discharge rate of the SC neurons. The authors reasoned that the peak rate of SC neurons should remain the same for all saccades of the same metrics and, presumably, the same motor error. That less than half of the SC neurons in their sample of 11 cells showed a *decrease* in peak activity led them to conclude that the feedback signal does not result in collicular neurons coding dynamic motor error. Proponents of the temporal dynamic control scheme may argue with the expectation that collicular firing rate should be the same after inactivation of OPNs. As reviewed above, microstimulation of OPNs produces dramatic alterations in the spatiotemporal pattern of collicular activity and inactivation could similarly modify the discharge. A more direct test would have been to perform phase plane analyses of neural activity and dynamic motor error. A failure to demonstrate a linear relationship, particularly towards the end of the saccade, would be a more convincing argument against the temporal coding scheme

Spatial control scheme

Advocates of the spatial control hypothesis use a different nomenclature to classify SC cells (Munoz and Wurtz 1995a). Burst neurons reside dorsally within the deep layers of the SC, have a circumscribed movement field, and discharge a sharp burst for saccades made to locations within the movement field. Buildup neurons typically reside ventral to the burst neurons and generally have movement fields without a peripheral boundary (but see Freedman and Sparks 1997a). Fixation neurons constitute an extension of the buildup layer within the rostral pole of SC. They exhibit low-level activity during visual fixation and are silent during saccades (Munoz and Guitton, 1989; Peck 1989; Munoz and Wurtz 1993, 1995a). The region of the fixation neurons within the SC has been labeled the fixation zone and is hypothesized to inhibit the burst and buildup neurons in the saccade zone in the remainder of the SC.

According to the spatial encoding hypothesis (Munoz et al. 1991; Munoz and Wurtz 1995b), a population of burst and buildup neurons within the caudal SC is active around the onset of a large saccade. As the eye movement progresses, buildup neurons rostral to the initial site become activated *sequentially*. It has been hypothesized that the neural network in SC integrates the eye velocity feedback signal and shifts the population of active buildup neurons rostrally. According to this proposal, the locus of activity within

the buildup neuron layer of the SC map indicates dynamic motor error, while the site of activity of the burst neuron layer encodes desired movement. As the activity in the buildup layer reaches the rostral pole, fixation neurons are reactivated, which in turn inhibit the saccade zone of the SC as well as the premotor circuitry in the brain stem.

In reality, SC neurons fall along a continuum according to the presaccadic discharge parameter used to classify them into burst or buildup category (Anderson et al. 1988). Also, a closer examination of the discharge properties of the so-called fixation neurons (Munoz and Wurtz 1993) reveals that they only pause during ipsiversive saccades. Many fixation neurons typically discharge a presaccadic burst during small contraversive saccades generated to fixate parafoveal targets; some neurons increase their activity for movements as large as 15 deg in amplitude. Thus, the concept of the fixation zone and fixation neurons has been disputed (Gandhi and Keller 1999). Instead, it has been suggested that fixation neurons are the rostral extension of buildup neurons and that the rostral SC still constitutes a saccade zone (Krauzlis et al. 1997). Alternatively, Bergeron and Guitton (2000) proposed that each fixation neuron has a characteristic motor error, which when reached during a movement, will resume the cell's discharge. Consequently, some fixation neurons will not pause for saccades smaller than a particular amplitude, potentially explaining the lack of pause in fixation neurons during small contraversive saccades.

Support for the spatial encoding model was based on qualitative assessments of the population response of SC neurons in both cat (Munoz et al. 1991) and monkey (Munoz and Wurtz 1995b). However, another evaluation of the evidence (Sparks 1993) and other quantitative analyses have disputed the notion of a systematic and sequential shift from caudal to rostral SC. A basic requirement of this hypothesis is that a neuron must discharge for all saccades in the optimal direction and for all amplitudes larger than the one dictated by its location within the topographic map. Moreover, the closer the buildup neuron is to the rostral end of the SC, the later its activation must occur relative to saccade onset (and closer to saccade end).

Results of analyses that measured parameters of the neural discharge and correlated them with movement metrics have refuted the spatial encoding hypothesis (Anderson et al. 1998; Kang and Lee 2000; Soetedjo et al. 2002b). When activity of pairs of buildup neurons, separated on average by over 1 mm along the rostrocaudal axis of the SC, was recorded during large saccades (Port et al. 2000), a caudal to rostral activation was observed in approximately half of the pairs; several pairs exhibited the opposite, rostral to caudal, sequence of activation. This analysis,

however, was limited to the rostrocaudal dimension, as it could not determine the spread of activity along the mediolateral extent. Examination of the population activity in both dimensions, across the surface of the SC, depicts a more complicated picture (Anderson et al. 1998). Activity spread medially, laterally and rostrally during the saccade; no significant transition of activity was observed caudal to the initially active site. While the center of gravity of the activity in the buildup layer showed a small, rostrally directed shift by the end of the saccade, the shift was random, not sequential, on a msec-by-msec basis. Another study (Moschovakis et al. 2001) used [¹⁴C]-deoxyglucose autoradiography to visualize the two-dimensional activity in the intermediate layers of the SC during saccades and observed no indication of a rostrally directed spread of activity, although whether this method has the sensitivity required to detect the proposed rostral spread of collicular activity remains unclear.

The spatial encoding mechanism has also been tested by chemical inactivation experiments (Aizawa and Wurtz 1998; Quaia et al. 1998). It was reasoned that temporary inactivation by injections of muscimol to a local region of the SC would prevent or compromise the rostrally directed spread of activity during large saccades. Thus, the ongoing saccade was predicted to overshoot the target. The observed post-lesion saccades either undershot or landed near the target location. Thus, the notion of a rostrally directed spread of activity as a dynamic control mechanism for saccades has been refuted by many studies.

Static feedback

The two leading hypotheses of the role of SC in dynamic control of saccades have been tested extensively. Relevant experiments have raised various levels of doubt about each theory and, consequently, the controversy over a dynamic role of the SC in the control of saccades still exists. However, the notion of a *static* feedback, one that does not compute the instantaneous motor error, has been supported by almost every experiment that has examined the activity of SC neurons during perturbations of the eye trajectory. Referring to the interrupted saccade experiments described above (Keller and Edelman 1994; Keller et al. 2000), for example, the caudal region active at the onset of a large saccade discharges another burst at the onset of the resumed movement. If the SC does not receive feedback about the perturbation, i.e., the SC resides upstream of the feedback loop, a second burst would not be observed during the resumed movement. Of course, the *dynamics* of the movement need not be controlled by the temporal discharge pattern. Similar observations have been made when saccades were perturbed by

stimulation of cortical (frontal eye fields: Schlag-Rey et al. 1992) and other subcortical (SC: Sparks and Porter 1983; Munoz et al. 1996) structures.

Goossens and van Opstal (2000) proposed a conceptual model in which the SC plays a feedforward role in the control of saccades. They found that the number of spikes discharged by SC neurons during control and air-puff-induced perturbation trials was remarkably similar. Despite the altered burst dynamics, SC neurons executed the desired number of action potentials. Thus, these authors suggested that the role of the SC is to output an approximately fixed number of spikes to produce a desired change in the line of sight. But how does the SC know that its discharge has been altered? Either a non-metric based feedback signal must be transmitted to the SC to account for the change in burst properties (Keller and Edelman 1994; Soetedjo et al. 2002a) or intrinsic properties within the SC ensures that more than enough spikes are generated and transmitted to downstream structures (Goossens and Van Opstal 2000).

Contribution of the SC during other orienting responses

In the past, experiments that explored the neurophysiological substrate of oculomotor systems typically investigated each oculomotor subsystem (e.g., saccades, smooth pursuit, vergence) in isolation. In addition, the head was restrained as animals performed eye-movement tasks. In the natural environment, however, we often orient from one target to another by integrating several types of eye movements. For instance, head movements can often accompany the eye rotation, saccades and smooth pursuit are coordinated when tracking a moving object, and saccadic eye movements can have a vergence component.

As reviewed above and elsewhere (Sparks and Hartwich-Young 1989), the SC is considered a key structure in sensorimotor processes that control saccades. More recently, the role of the SC has been examined during saccades coordinated with head movements (head-unrestrained gaze shifts), eye movements other than saccades (smooth pursuit, vergence, accommodation), and reaching movements of the arm. In the remainder of this chapter, we will review recent studies suggesting that the SC is involved in the generation of eye movements other than saccades as well as commands for movements of the head and arm.

Coordinated eye-head movements

Gaze is defined as the direction of line of sight and is measured as eye position in space by computing the sum of eye-in-head and head-in-space positions. When the head is free to move but the trunk is

restrained in the straight-ahead position, coordinated movements of the eyes and head shift the direction of gaze. Gaze shifts are usually characterized by the *amplitudes* of the gaze, eye and head movements and the *contributions* of the eye and head to the change in gaze. The onset and offset of gaze, eye and head movements are typically determined by velocity criteria. Their amplitude values are computed by subtracting onset and offset positions, and eye and head contribution metrics are measured as the eye and head displacements, respectively, during the duration of the gaze shift (Freedman and Sparks 1997b). In general, the head continues to move for several hundred msec after the end of a gaze shift, and the eyes counter-rotate in the orbits during this period to maintain stability of gaze. Thus, the contribution component, particularly for the head movement, should be less than the amplitude measure.

The eye and head contributions for a desired change in gaze depend on the oculomotor range, which is species-dependent, as well as the initial eye-in-head and head-on-trunk positions. Because of their small oculomotor range (~25°), cats have a higher propensity to generate head movements and, therefore, have been excellent subjects for examining the role of SC in controlling head-unrestrained gaze shifts. Stimulation of the SC produced effects that were dependent on the stimulation site, stimulation parameters and initial position of eyes in the orbits (Guitton et al. 1980; Roucoux et al. 1980; Paré et al. 1994). Electrical pulses delivered to the anterior SC primarily produced saccades, even when the head was free to move. Head movements, when they occurred, were initiated around or after the end of saccades, thus minimizing their contribution to gaze shifts. Thus, the change in gaze evoked by stimulation of the anterior SC was similar in the head-restrained and head-unrestrained conditions. In contrast, gaze shifts evoked by stimulation of more caudal regions of the SC produced different effects in the head-restrained and head-unrestrained modes. When the head was prevented from moving, stimulation drove the eyes toward a specific orbital position. Thus, both contraversive and ipsiversive saccades were evoked when the initial eye position was ipsilateral or contralateral, respectively, to the desired orbital position. When the head was allowed to move, stimulation evoked relatively constant amplitude gaze shifts executed by a coordinated movement of the eyes and the head. The eye movement in the orbit, however, appeared similar to the movement observed in the head-restrained condition; that is, the eyes moved to specific orbital positions, independent of their initial positions (Roucoux et al. 1980; Paré et al. 1994).

To support the microstimulation studies, the movement fields of feline SC neurons were compared in the head-restrained and head-unrestrained conditions

(Munoz et al. 1991). The neural discharge was better modulated by gaze (eye-in-space) amplitude than either eye-in-head or head-in-space components.

Furthermore, the movement fields based on gaze parameters overlapped for the head-restrained and head-unrestrained conditions, suggesting that the phasic bursts of SC neurons encode gaze displacement. Collectively, the neural recording and microstimulation experiments have led to the hypothesis that SC encodes parameters of the gaze shift, as opposed to the eye-in-head or head-in-space components.

Unlike for the non-primate models, the SC in monkeys was traditionally considered to participate in the control of saccades only – the neural mechanism of the head component of coordinated eye and head movements was thought to be of extracollicular origin. This assumption was based on studies that examined the effects of stimulation of the anterior SC only (Stryker and Schiller 1975), which primarily evoked saccades, and was further supported by neural recording experiments that failed to find head movement signals in the SC (Robinson and Jarvis 1974). This topic was recently revisited (Seagraves and Goldberg 1992; Cowie and Robinson 1994; Freedman et al. 1996; Freedman and Sparks 1997a), and it is now assumed that the primate SC also controls coordinated eye-head movements.

Like the feline SC, the properties of stimulation-evoked gaze shifts in nonhuman primates were a function of the site and parameters of stimulation (Freedman et al. 1996). Gaze amplitude initially increased with stimulation duration and then reached a plateau level dictated by the site of stimulation (site-specific maximal amplitude). The peak velocity of the gaze shift increased and the variability in the onset decreased as the frequency of stimulation was raised. Increases in the stimulation intensity had modest effects on gaze peak velocity without changing the site-specific maximal amplitude, provided that the stimulation duration was extended to accomplish the entire movement. In general, the dynamics of stimulation-induced and visually-guided gaze shifts were similar. [Stimulation parameters have similar effects on saccades evoked in the head-restrained monkey (Van Opstal et al. 1990; Stanford et al. 1996).]

The head component of stimulation-evoked gaze shifts was also dependent on the stimulation parameters. For stimulation of middle and caudal sites, the head continued to move for the duration of the stimulation, and even after the end of the stimulation-evoked gaze shift (Freedman et al. 1996). Presumably, the head would have stopped moving once it reached the mechanical limits, although stimulation durations long enough to test this hypothesis were not applied. Head amplitude and duration were linearly related to

stimulation duration within the tested range. Similarly, average head velocity also increased linearly with stimulation frequency, although the effect was modest compared to that on gaze velocity. Thus, the head movement did not exhibit any site-specific maximal amplitude for the tested range of stimulation durations. Even though a significant proportion of the head movement continued after gaze offset, head contribution remained relatively independent of stimulation parameters (Freedman et al. 1996).

Changing the site of stimulation along the rostral-caudal dimension produced qualitatively similar effects in head-unrestrained monkey and cat. Stimulation of the anterior SC produced gaze shifts that were accomplished primarily by the eye (Freedman et al. 1996). Head movement, if observed, was usually initiated around gaze offset and, therefore, head contribution was negligible. In contrast, stimulation of middle and caudal regions produced coordinated movements of the eyes and head (Freedman et al. 1996). Across all sites, however, the eye movements observed in the head-restrained and head-unrestrained conditions were similar – fixed vector for anterior sites and goal directed for caudal regions. Thus, it appears that the movements observed during SC stimulation in the head-restrained animal were reduced by the amount the head would contribute if stimulation were applied to the same site in the head-unrestrained preparation. As a consequence, the amplitude axis of the (head-restrained) saccade motor map, particularly in the caudal end, is distorted by being more compressed than the map would be if it were constructed from head-unrestrained experiments (Freedman et al. 1996).

Analyses evaluating the effect of initial eye position in head (IEP_h) have decomposed the vector of the stimulation-evoked movement and IEP_h into horizontal and vertical components (Freedman et al., 1996). Alternatively, Klier et al. (2001) transformed the coordinate system to analyze the orthogonal component of the movement and initial gaze position (IGP). Gaze amplitude, particularly the horizontal component, evoked by stimulation remained relatively constant while eye and head contributions varied inversely as a function of IEP_h . [An assessment of Figure 13A-C in Freedman et al. (1996), however, suggests that the gaze amplitude as well as its horizontal component may depend on IGP.] When the IEP_h was deviated in the direction of the stimulation-evoked gaze shift, head contribution increased and eye amplitude decreased for a given change in gaze. Conversely, if the IEP_h was contralateral to the direction of the stimulation-evoked movement, head contribution decreased and eye amplitude increased for a given gaze shift. Furthermore, the head onset relative to gaze onset decreased (increased) as the IEP_h was ipsilateral (contralateral) to the direction of the ensuing

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gaze shift. Unlike the IEP_h , the effects of head position on stimulation-evoked gaze shifts and on eye and head contributions still remain to be examined systematically.

Unlike the horizontal component, the vertical and orthogonal components of the stimulation-induced gaze shift were linearly related to the vertical IEP_h and orthogonal IGP, respectively. Suppose stimulation of a specific SC site produced a gaze shift with an upward component when the eyes were initially centered in the orbits and the head was pointed straight-ahead. Stimulation of the same site with an upward IEP_h or IGP generated a smaller upward, and sometimes even downward, component of gaze compared to the corresponding component produced with a downward IEP_h or IGP. Thus, varying IEP_h while stimulating a caudal site and maintaining identical stimulation parameters does *not* produce gaze shifts of same amplitude and direction.

The slope of the linear regression, describing the relationship between the orthogonal gaze shift component and orthogonal IGP, changed with stimulation site (Klier et al. 2001). At rostral sites, the slope was near zero, indicating that the stimulation-evoked gaze shifts remained constant across all IGP and, presumably, IEP_h . As the stimulation electrode was positioned at increasingly caudal sites, the slope decreased gradually to negative one as the stimulation-evoked gaze shifts became goal-directed. The data obtained from stimulation of the rostral and caudal ends of the SC are consistent with the predictions of the constant gaze-displacement and desired gaze-position models, respectively. However, Klier et al. (2001) demonstrated that the distribution of the slopes are also consistent with another model that computes gaze displacement in *retinal* coordinates, as opposed to *spatial* coordinates (see Crawford and Guitton (1997) for a theoretical foundation). By accounting for the geometry of the eyeball, all gaze shifts evoked by microstimulation become constant vector across all initial gaze position, thereby avoiding the need to explain the transition from gaze-displacement to gaze-position. Hence, the updated view is that the SC controls coordinated movements of the eyes and head and, furthermore, the metrics of the gaze shifts are encoded in retinal coordinates.

These microstimulation experiments suggest that SC neurons issue a single signal to displace gaze by a desired displacement (“gaze displacement” hypothesis). Alternatively, one population of SC neurons can provide eye displacement signals and another group of neurons may submit head displacement commands (“separate channel” hypothesis). If these neurons are intermingled, stimulation could evoke gaze shifts similar to those expected from activation of neurons encoding gaze

displacement. If stimulation selectively activated eye or head movement neurons, the movement would be isolated to just one of the pathways. Cowie and Robinson (1994) presented evidence hinting that stimulation of certain sites within the deep layers of the SC may produce head movements without an accompanying gaze shift. Recently, Corneil and Munoz (Society for Neuroscience Abstract, 763.7, 1999) reported that stimulation of the SC with parameters sub-threshold to those required to produce gaze shifts can elicit head movements without changing the gaze position. While head-movements evoked by stimulation of the SC support the separate channel model, they are not inconsistent with the gaze displacement hypothesis. For example, the stimulation-induced output could be a gaze command that was gated by OPNs in the eye pathway, but not gated in the head pathway.

To differentiate between the gaze displacement and separate channel hypotheses, one might suggest correlating the neural activity with the metrics of gaze, eye and head components. However, this approach may not be definitive for two reasons. (1) Gaze, eye and head amplitudes and directions do not vary independently and typically are highly correlated. (2) Based on a scales of measurements argument (see Sparks and Gandhi (2002)), correlation analysis may not be an appropriate statistical test for neurons organized in a place code. Thus, conditions under which the three movement metrics can be dissociated, one held constant while the other two vary, are necessary to determine the representation of gaze in SC neurons (Freedman and Sparks 1997a).

One behavioral dissociation (Figure 1A) emphasizes that for large gaze shifts, the eye amplitude saturates at ~ 35 deg, even as the head and gaze components vary. The shaded regions in panel B show for three representative gaze shifts (a-c; vertical lines panel A and rows in panel B) how the encoding mechanism dictates the population of active SC neurons. The gaze-displacement hypothesis (gaze column, panel B) requires that, for gaze shifts of increasingly larger amplitudes, the active ensemble of neurons shifts to more caudal locations. Thus, in recording from a neuron with an optimal vector larger than the three representative gaze shifts (black dot, panel B), an increase in firing rate would be associated with larger gaze amplitude (gaze column, panel C). An increase in firing rate is also correlated with an increase in head amplitude (head column, panel C) because it covaries with gaze amplitude. In contrast, eye amplitude would remain relatively constant despite changes in the firing rate. According to the separate channel hypothesis, the same population of neurons encoding eye displacement would remain active for all three gaze shifts, holding the shaded region constant

(eye column, panel B). Hence, a neuron in the caudal SC would discharge at the same firing rate across a large range of gaze and head amplitude, as long as the eye movement remains relatively constant (eye column, panel C). Neurons encoding head displacement, on the other hand, will behave very much like SC neurons issuing gaze-displacement commands because head and gaze amplitude covary for large gaze shifts (compare head and gaze columns in panels B and C). Note that while this behavioral dissociation allows an evaluation of the eye encoding scheme, it does not distinguish between gaze and head displacements. Thus, an analysis of only this subset of movements may not be sufficient to distinguish between the gaze-displacement and separate-channel hypotheses.

In the second dissociation condition, SC activity is analyzed for the subset of movements for which the head metrics are held constant while eye and gaze amplitude and direction vary (panel D). In this case, the population of neurons encoding gaze or eye displacements will shift for different gaze shifts, but the active ensemble of neurons encoding head displacement will remain constant (panel E). Accordingly, the firing rate of a neuron encoding head displacement will not vary despite variations in gaze and eye directions (head column, panel F). Firing rates of neurons encoding gaze or eye displacements, on the other hand, will be related to gaze and eye directions, respectively, but not to head direction (gaze and eye columns, panel F). Thus, consideration of only this subset of movements allows a test of the head-displacement model but it does not dissociate between the gaze and eye displacement models.

In the final dissociation condition, gaze amplitude is held constant while eye and head contributions vary inversely as a function of IEP_h (panel G). In this situation, the same population of neurons encoding gaze displacement is activated for the three representative movements (gaze column, panel H). The neural activity remains constant for the same gaze amplitude, despite various combinations of eye and head components (gaze column, panel I). As the IEP_h is deviated in the direction of the ensuing gaze shift, the eye amplitude decreases and the head amplitude increases. Thus, for constant gaze amplitude, the population of neurons encoding eye displacement and head displacement shift their center of activity in opposite directions as a function of IEP_h (eye and head columns, panel H). Consequently, the firing rate of a representative neuron encoding either eye or head displacement, while not related to gaze amplitude, would be inversely related to eye and head amplitudes (eye and head columns, panel I).

Freedman and Sparks (1997a) performed these analyses on 36 SC neurons recorded during head-

unrestrained gaze shifts directed to visual targets. All neurons encoded gaze displacement; the relationship with gaze, eye and head amplitudes to firing rate obeyed the predictions of the gaze displacement hypothesis (gaze column, panels C, F and I). Thus, these authors concluded that SC neurons encode desired gaze displacement, and that the single gaze command is separated into eye and head pathways downstream of the SC.

While the experimental design of Freedman and Sparks (1997a) is the most thorough and quantitative to date, their conclusion depends critically on the assumption that the vestibulo-ocular reflex (VOR) is inactive during gaze shifts. If the VOR is significantly active, their interpretation may be contaminated by the neural uncertainty problem (Sparks 1999; Sparks and Gandhi 2002). For instance, the neurons considered to encode desired gaze displacement may actually issue a desired eye movement command only. Other neural pathways may generate an accompanying head movement and, because the VOR gain is near unity, submit an ocular counter-rotation signal of the amount that equals the head amplitude. Thus, the extraocular motoneurons incorporate the excitatory drive from the saccadic system and the inhibitory vestibular signal, resulting in a dissociation between the desired (encoded by SC neurons) and executed eye movement (see Sparks and Gandhi (2002) for details).

The results of Freedman and colleagues (Freedman and Sparks 1997a; Freedman et al. 1996) can be accounted for by yet other hypotheses of the role of SC in the control of gaze shifts. For example, the SC may contain separate populations of eye and head cells, but all neurons encode desired gaze displacement. Activation of either type of neuron sends signals to innervate muscles in the appropriate pathway. Downstream of SC, the eye and head pathways can interact (via mechanisms such as cross-coupling, vestibulo-ocular reflex, efference copy, proprioception), producing a dissociation between the desired movement command and executed movement amplitude (Sparks 1999). Thus, a thorough understanding of collicular participation in the control of gaze shifts is likely to remain elusive until interactions between the eye and head pathways are elucidated.

Smooth pursuit

Over the past decade the function of neurons in the rostral SC has come under considerable scrutiny. According to the traditional views, the cells in the rostral SC discharge prior to small saccades. A recent proposal that neurons in the rostral SC play a role in fixation was discussed in a previous section (**Incorporation of feedback signals in the SC: Spatial**

control scheme). In the next three sections, we consider the possibility that neurons in the rostral SC participate in the control of eye movements other than saccades (smooth pursuit, vergence and accommodation).

Behavioral experiments have demonstrated that small position errors (<3 deg) induced by stepping a moving target produce changes in the speed of ongoing pursuit (Morris and Lisberger 1987; Segraves and Goldberg 1994; Krauzlis and Miles 1996). Whether neurons in the rostral SC generate a general position error command that can be used to produce or modify smooth eye movements was the focus of a series of experiments by Krauzlis and colleagues (Krauzlis et al. 2000; Basso et al. 2000). They recorded the activity of neurons in the rostral SC during smooth pursuit eye movements and observed increases in discharge during contraversive pursuit movements, particularly when differences in target and eye speed created small position errors. Decreases in activity were observed during ipsiversive pursuit. Accordingly, one interpretation of the results is that neurons in the rostral SC issue commands used by the pursuit system. However, the same neurons also exhibited a burst of activity before small contraversive saccades. Thus, an alternative explanation is that the enhanced activity observed during pursuit eye movements could represent the *preparation* of catch-up saccades – small saccades made to the moving target – that were not executed. To address this possibility, the activity of cells on trials in which catch-up saccades were generated within 300 msec of the target motion ("early saccades") was compared with the activity of the same neuron during trials without early saccades (Krauzlis et al., 2000). If the neural activity on the trials without the early saccades reflects a saccade preparation signal, higher levels of activity should be present during the trials with early saccades because a rapid eye movement was actually produced. For most neurons, discharge rate during the early pursuit phase was not significantly different for the trials with and without the early saccades. Thus, the authors concluded that the enhanced activity was associated with smooth pursuit, not saccades.

Artificial activation (microstimulation) and inactivation experiments were also conducted in an attempt to establish a more direct role of the rostral SC in producing ocular smooth-pursuit (Basso et al. 2000). Microstimulation during fixation failed to elicit any smooth eye movements, at currents above or below the threshold for evoking saccadic eye movements. This is in contrast to the smooth eye movements produced by stimulation of a small portion of the arcuate fundus and neighboring posterior bank lying directly posterior to the principal sulcus in the frontal eye field area (MacAvoy et al. 1991; Gottlieb et al. 1993). Other

studies, however, have reported that prolonged duration, high frequency and large intensity stimulation of the SC evokes a staircase of saccades, often interspersed with smooth eye movements during the intersaccadic intervals (Breznen et al. 1996; Missal et al. 1996; Moschovakis et al. 1998), although there is no consensus whether these drift-like movements are actually smooth pursuit.

The failure to initiate pursuit movements with collicular microstimulation cannot be interpreted as evidence that the colliculus is not involved in pursuit eye movement. Behavioral experiments have shown that position errors introduced by jumping a moving target only affect ongoing pursuit movements (Morris and Lisberger 1987; Segraves and Goldberg 1994; Krauzlis and Miles 1996). Furthermore, position steps in the direction of motion modestly facilitate pursuit while steps in the opposite direction greatly suppress it. Thus, a stimulation-induced position error signal, which is the hypothesized output of the SC, should alter the kinematics of pursuit even if it does not initiate it. Ipsiversive pursuit should be suppressed by microstimulation, whereas contraversive pursuit should be facilitated. Basso et al. (2000) found that long duration (300-400 msec) microstimulation of the rostral SC applied near the onset of a moving target produced large suppressive effects on ipsiversive smooth-pursuit; these effects were significant and consistent with the predictions. The effect of microstimulation during contraversive smooth-pursuit was minimal and inconsistent.

In a complementary experiment, the activity of neurons in the rostral SC was reduced by application of muscimol, a GABA agonist, and pursuit performance was assessed as animals tracked a moving target. A step-ramp task was used to assess, independently, the effects of the direction of the pursuit and the location of the target in the visual field. Basso and colleagues (Basso et al. 2000) observed a muscimol-induced reduction in pursuit velocity for contraversive pursuit initiation and an increase in pursuit velocity during ipsiversive pursuit. However, deficits were more dependent upon which part of the visual field pursuit targets were presented than the direction of the pursuit movement. For example, with a right injection, pursuit velocities were reduced when the target was moving leftward in the left visual field, but not significantly reduced when the target was moving leftward in the right visual field. Also, for the example of a right injection, increased pursuit velocity was observed if targets were moving rightward in the right visual field.

Collectively, these results were interpreted as support for the hypothesis that neurons in the rostral SC issue a general position error command that is used by both pursuit and saccadic subsystems (Krauzlis et

al. 2000; Basso et al. 2000). According to this view, the rostral SC plays an important role in the control of pursuit eye movements. Although the data are suggestive, in our opinion, a convincing case that the superior colliculus has a causative role in the initiation or maintenance of pursuit eye movements does not yet exist. A brief evaluation of the recording, microstimulation, and inactivation experiments follows.

With respect to the recording experiments, critical details of the analyses used to reject the hypothesis that increases in activity were related to the preparation of catch-up saccades were not provided. For example, were the amplitudes of the movements in the early saccade trials within the center of the movement field of the neurons? Because neurons in the rostral SC have small movement fields, small changes in the saccade amplitude will result in a large change in the discharge characteristics. Furthermore, differences in firing rate in the two conditions would be easier to detect if the trials, in which saccades occurred, were aligned on saccade onset, not target motion. In the absence of information of these critical details, rejection of the hypothesis that changes in activity observed during pursuit movements are related to preparation of catch-up saccades seems premature.

In the microstimulation experiments, contrary to the predictions, stimulation of many sites, particularly those represented within 1-deg of the fovea, significantly reduced pursuit velocity. This was observed during initial and maintained smooth pursuit in both contraversive and ipsiversive directions. These findings are compatible with an alternative interpretation of the data in which stimulation-evoked perturbations in pursuit movements are an indirect effect of activating OPN neurons. Stimulation of the omnipause neurons (OPNs) in the pontine reticular formation is known to not only interrupt saccades but also attenuate ongoing pursuit (Missal and Keller, Society for Neuroscience Abstract, 363.13, 2000). Thus, stimulation of the rostral SC, which has dense, excitatory projections to the OPNs (Büttner-Ennever and Horn 1994; Paré and Guitton 1994; Gandhi and Keller 1997; Büttner-Ennever et al. 1999), may increase the OPN response and, in turn, reduce pursuit velocity. This suggestion is consistent with the observation that stimulation of increasingly caudal regions, which has weaker projections to the OPNs, did not suppress smooth-pursuit (Basso et al. 2000).

The results of the inactivation experiment are puzzling. The finding that pursuit velocity effects were more dependent upon the region of the visual field in which the pursuit targets were presented than upon the direction of the pursuit movement is not the result expected if the inactivated cells are generating a motor command for a movement in a particular direction.

This is the pattern of results that would be obtained if the inactivation were affecting visual motion processing in a particular region of the visual field or affecting the allocation of attention to particular parts of visual space.

Additional studies of role of rostral SC in the control of smooth pursuit are necessary. A convincing argument can be made if a pathway from the SC to neurons in the traditional pursuit system is identified. Anatomical and functional connectivity experiments that use a combination of orthodromic and antidromic stimulation techniques may be appropriate. Furthermore, the experiments must also show that the origin of the projections is limited to the rostral SC.

Saccade-vergence interactions

Eye movements to targets that are displaced in eccentricity and depth exhibit both version and vergence components, where version is the yoked, conjugate movement of both eyes and vergence refers to the non-conjugate movement of the eyes in opposite directions. In this section, we discuss the few studies exploring SC participation in these three-dimensional saccades (or saccade-vergence movements). It is reasonable to examine disparity coding and vergence movement signals in the SC since it receives projections from neurons in cortical areas that respond to spatial disparity or participate in producing vergence eye movements (e.g., Gnadt and Beyer 1998; Ferraina et al. 2000; Gamlin and Yoon 2000). In anesthetized cats, neurons in the superficial layers of SC exhibit coarse disparity sensitivity, unlike the sharply tuned cells in striate cortex (Dias et al. 1991; Bacon et al. 1998). Activity of visuomotor neurons in the deeper layers of awake, behaving monkeys exhibited no systematic vergence- or disparity-related signals (Mays 1996, Society for Neuroscience Abstract, 262.14, 1996), although there may be a concentration of disparity sensitive neurons located in the rostral SC (Berman et al. 1975; Jiang et al. 1996, Society for Neuroscience Abstract, 262.2, 1996).

Recently, Chaturvedi and Van Gisbergen (1999) used microstimulation to investigate the role of the SC in saccade-vergence movements. Figure 2 shows the vertical component of versional (left) and vergence (right) components of three-dimensional saccades when no stimulation was applied (V), when stimulation was delivered during fixation (E) and when stimulation was delivered during an ongoing movement (EV). Electrical stimulation (duration: 50 msec) delivered to the middle and caudal SC *during fixation* produced saccades (E; Figure 2, left) *without* a vergence component (E; Figure 2, right). However, effects on the vergence component were observed with stimulation of the same sites prior to or during target-directed three-dimensional saccades. As expected from

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previous studies (e.g., Schlag-Rey et al. 1989; Gandhi and Keller 1999), stimulation of a SC site *around the onset* of a visually-guided saccade produced a version component (EV; Figure 2, left) with a direction and amplitude that was an average of the saccades encoded by the stimulation (E) and target-activated (V) sites. Following a brief interval, the animal compensated for the stimulation-evoked perturbation of the visually directed saccade by executing another saccade to the visual target.

During the interval when the stimulation-evoked movement was being executed, the stimulation-evoked vergence component (EV; arrow 1; Figure 2, right) had a higher velocity than a control vergence movement without a version component (data not shown). When the stimulation-evoked version component ended (second vertical line), the vergence movement continued, albeit at a slower velocity (arrow 2), before reaccelerating during the saccadic movement made to compensate for the stimulation-induced perturbation (arrow 3).

When plotting amplitude as a function of *electrical latency*, defined as saccade onset minus stimulation onset, both initial saccade and intra-saccadic vergence components followed an averaging process that began when electrical latency was approximately -40 msec (stimulation led the visually guided saccade) and continued until roughly 40 msec after stimulation onset. The movement was primarily guided by the target-directed program for positive electrical latency, but dominated by the stimulation-evoked command for negative electrical latency; for electrical latency values around zero, the movement incorporated both target-directed and stimulation-evoked signals. The averaging process was highly correlated for the version and vergence components, both on a trial-by-trial basis and on average.

Because vergence movements could not be initiated without a saccadic component during the three-dimensional saccades, one conclusion that follows is that both types of movements are gated by the same mechanism. This conservative interpretation allows the commands for desired vergence movement to originate from an extracollicular source. But, could vergence commands also be represented in the SC? Chaturvedi and Van Gisbergen (1999) entertained the notion that the premotor neural discharge of SC specified both saccade and vergence metrics but that stimulation of the SC outputs a zero vergence command, not a lack of vergence signal. Accordingly, stimulation delivered during fixation produced no vergence component, and stimulation applied around saccade onset averaged the zero vergence command issued by the stimulation and the depth component programmed by the target-activated site. Focusing on the trials in which the visually guided three-

dimensional saccades were initiated *prior to* stimulation onset (Figure 2), Chaturvedi and Van Gisbergen (1999) assumed that the desired vergence signal must be fully encoded by the time of stimulation onset, as it presumably does for control conditions. If the vergence signal does not channel through the SC, then the intrasaccadic vergence components on stimulation and control trials should be similar. But the fact that averaging of the metric was observed led the authors to conclude that vergence signals are encoded in the SC output.

Stimulation of the rostral SC *after* the onset of three-dimensional saccades produced effects comparable to those observed for the middle and caudal SC (Chaturvedi and Van Gisbergen 2000). With longer stimulation duration (500 msec), the resumed version component was often truncated and the vergence component often reversed direction, sometimes diverging beyond the initial fixation plane. When the stimulation was delivered prior to the onset of saccade-vergence movements, the onset of version component was delayed until after stimulation offset. Unlike the middle and caudal SC, a small vergence component was observed during the microstimulation of the rostral SC. Thus, the onset of saccade and vergence movements could be separated when stimulation was delivered to the rostral SC. Further differences between the rostral and posterior regions of SC were uncovered when stimulation interacted with pure vergence movements without a saccade component. A vergence, but not version, component was initiated during stimulation of the rostral SC prior to the movement in depth (Chaturvedi and Van Gisbergen 2000). Ongoing vergence movements stopped and reversed direction, often diverging the eyes beyond the initial fixation plane.

Chaturvedi and Van Gisbergen (1999, 2000) concluded that stimulation of the SC outputs zero-vergence and desired saccade commands that interact with SC commands encoded for the three-dimensional saccade directed towards the visual target. The effect of the stimulation is to evoke a movement with version and vergence metrics reflecting an averaging process. While this concept makes a strong argument for participation of the SC in the control of vergence, additional experiments are required to support the hypothesis. A neural correlate of the vergence component within SC neurons has yet to be reported (Mays 1996, Society for Neuroscience Abstract, 262.14, 1996). Averaging effects observed during converging movements also need to be addressed during diverging movements with and without a saccade component.

Accommodation

As we converge or diverge our eyes, targets in the new depth plane become blurred. Accommodation is induced by contraction of the ciliary muscle, which changes the lens' radius of curvature. Thus, an important synkinesis exists between vergence and accommodation (Stark 1983).

Stimulation of the rostral SC for prolonged durations and at fairly low intensities can alter accommodation in both eyes (Sawa and Ohtsuka 1994). After a latency of approximately 200 msec, the dioptric power abruptly increased and then reached a plateau with prolonged microstimulation. The duration and maximum amplitude of the accommodative response was linearly correlated with stimulation duration and intensity, respectively. The low-threshold sites that produced accommodation were located within the superficial and intermediate layers of the SC. Since the SC region that evoked accommodation overlaps, at least partially, with the location of fixation neurons, some neurons within the rostral SC may participate in active fixation as well as accommodation. Ohtsuka and Nagasaka (1999) injected different dyes into regions involved in controlling fixation (OPN region) and accommodation (e.g., posterior pretectal nucleus) and identified the retrogradely labeled cells in the SC. While double-labeled neurons were found throughout the SC, the population was highest in the rostral SC.

Given the close integration between the vergence and accommodation systems, it is important to understand how vergence was perturbed by the stimulation; unfortunately, vergence eye movements were not recorded in these accommodation experiments. Further research is required to understand the role of SC in accommodation and vergence.

Arm-movement related neurons

So far, we have addressed SC participation during saccades, eye movements other than saccades and coordinated eye-head movements. Previous studies have also presented evidence that the SC participates in movements utilizing other skeletomotor systems. For example, stimulation of the cat SC evokes pinnae and vibrissae movements and prolonged stimulation of the rat SC can evoke circling behavior (see Freedman et al., 1996). More recently, neurophysiological studies have suggested that the deeper layers of the SC and the underlying mesencephalic reticular formation in monkey may also participate in the control of arm movements (Werner et al. 1997a, b; Stuphorn et al. 1999, 2000). These findings have important implications for our understanding of the neural control of integrated eye-hand movements.

Monkeys were trained to reach for targets in two conditions: one in which the subjects made a saccade to the target before touching it, and another in

which the animals maintained fixation at the central stimulus while reaching for a target presented in the visual periphery. Arm-movement related discharge in SC neurons and electromyographic (EMG) activity from muscles of the shoulder, arm, trunk and neck were recorded as the head-restrained animals performed the two tasks. The cross-correlations of discharge of many neurons and the EMG of several muscles, particularly those of the shoulder girdle, were highly significant. The discharge of most neurons and the EMG activity of many muscles led movement onset. For a small percentage of neurons, the average correlation coefficient between burst onset and movement onset was close to one. Thus, the authors speculated that the neural discharge may provide the initiation signal for the arm movement.

The majority of these "reach" neurons did not discharge during saccades. Those that resided deeper than 4 mm from the surface of the SC and, therefore, outside the SC and in the underlying mesencephalic reticular formation, were not modulated by gaze position. Hoffman and colleagues proposed that these gaze-position-independent reach neurons may encode information more specific to the recruitment of appropriate muscles, although this notion needs to be tested.

Some dorsal neurons were intermingled within the saccade-related neurons of the SC, and many of them also exhibited visual, somatosensory and/or saccade-related activity. Furthermore, the activity of reach neurons within the SC was often modified by gaze position. Since the gaze-position-sensitive reach neurons were insensitive to the temporal profile of the reach movement, Hoffman and colleagues (Werner et al. 1997a, b; Stuphorn et al. 1999, 2000) hypothesized that they might encode the amplitude and direction of the desired arm movement. It should be noted, however, that there is no existing evidence to support the hypothesis that either the location or firing rate of neurons with reach-related activity is related to either the amplitude or direction of an arm movement.

Although the extent of overlap in the saccade and reach movement fields still needs to be explored thoroughly, there appears to be a rough topography along the mediolateral extent – medial (lateral) regions encoding saccades and reach movements with upward (downward) movements. While saccades in the contralateral space were encoded by SC neurons, reach-related activity also included preferred movement directions into the ipsilateral hemifield. In this sense, the topography of the saccade and reach maps appears incongruent.

Summary

In this chapter we evaluated several new lines of research that have emerged since the last detailed

review of the role of SC in the control of orienting behavior (Sparks and Hartwich-Young 1989). Over the last decade, significant research efforts have been devoted to understanding the role of collicular neurons in controlling the dynamics of saccades, determining whether the SC is inside or outside the feedback loop controlling saccade duration, and studying the participation of the SC in accommodation, fixation behavior, smooth pursuit, vergence, coordinated movements of the eyes and head, and reaching movements of the arms. We described problems of interpreting results of experiments in which more than one movement system is active and issues that must be resolved before agreement can be reached on the expanded role of SC in various movements.

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Figure captions

Figure 1 – Strategy employed to determine whether the discharge of SC neurons obey gaze-displacement or separate-channel hypotheses. (*A*, *D*, and *G*) Replotted schematic diagrams illustrating the behavioral dissociations of movement metrics. Analyses focused on the neural data of movements in which one of the eye, head or gaze amplitudes remained constant while the other two signals varied, as noted by the vertical lines marked *a-c*. (*A*) Schematic of a behavioral dissociation in which eye amplitude is held constant while gaze and head amplitudes covary. (*B*) Hypothetical locations of the active population of cells in the SC map as predicted by the alternative hypotheses during movements indicated in (*A*: *a-c*); shaded region, active population; filled circle, location of hypothetical (test) cell used to illustrate the specific predictions of the alternatives. Column marked gaze outlines the locus of the active population according to the gaze displacement hypothesis during movements (*rows a, b, and c*). Similarly, the eye and head columns illustrate the loci of active populations according to the separate channel hypothesis. (*C*) Specific predictions of the hypotheses (columns) are outlined for the test cell in *B*. Gaze, eye, and head movement amplitudes (*rows*) are plotted as functions of hypothetical firing rate of test cell. (*D*) Schematic of a second behavioral dissociation, in which the head movement is constant while gaze and eye amplitudes covary. (*E*) Loci of active populations in SC map during three movements (*D*: *a-c*) according to the alternative hypotheses (columns: gaze, eye, and head). (*F*) Specific

predictions of gaze, eye, and head amplitude (*rows*) when plotted as a function of firing rate of test cell (filled circle in *E*). (*G*) Schematic of a third behavioral dissociation, in which gaze amplitude is held constant while eye and head contributions vary inversely as a function of horizontal initial eye position (IEP_h) in head; contra., contralateral IEP_h ; cent., IEP_h close to zero. (*H*) Loci of active populations in SC map during three movements (*G*: *a-c*) according to the alternative hypotheses (columns: gaze, eye, and head). (*I*) Specific predictions of gaze, eye, and head amplitude (*rows*) when plotted as a function of firing rate of test cell. [Figure and caption adapted from Freedman and Sparks (1997a).]

Figure 2 – An example of a perturbation induced by stimulation of SC during a three-dimensional saccade. Temporal traces of the vertical component of versional (*left*) and vergence (*right*) eye movements directed to a visual target (V), evoked by stimulation during fixation (E), or perturbed by microstimulation during a target-directed saccade (EV; thick, dotted trace). The fixation and saccade targets were identical in both V and EV conditions. The vertical, dashed lines mark stimulation onset and offset. Arrows (1-3) are referred to in the text. Averaging of the movements encoded by the neurons at the stimulation-evoked and target-activated sites is sufficient to explain the observed behavior: the stimulation-evoked output encodes a vergence movement of zero amplitude and a saccade component of nonzero amplitude. [Modified from Chaturvedi and Van Gisbergen (1999).]

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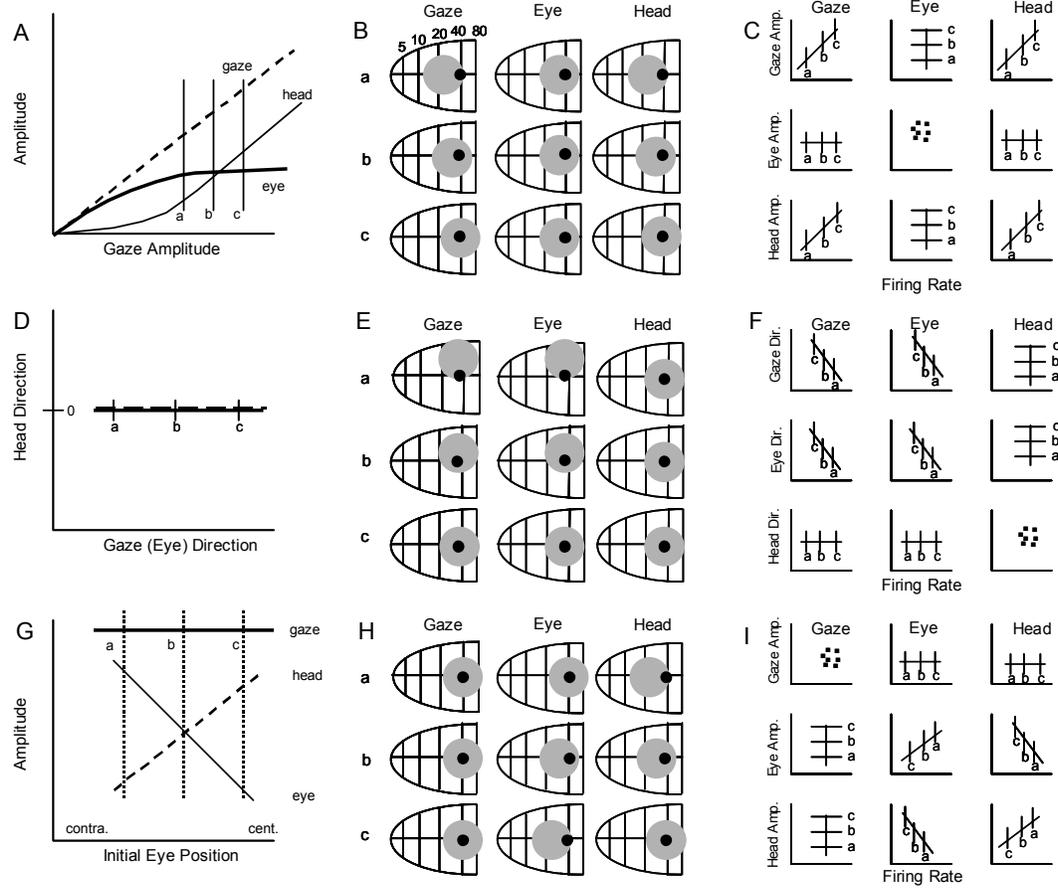


Figure 1

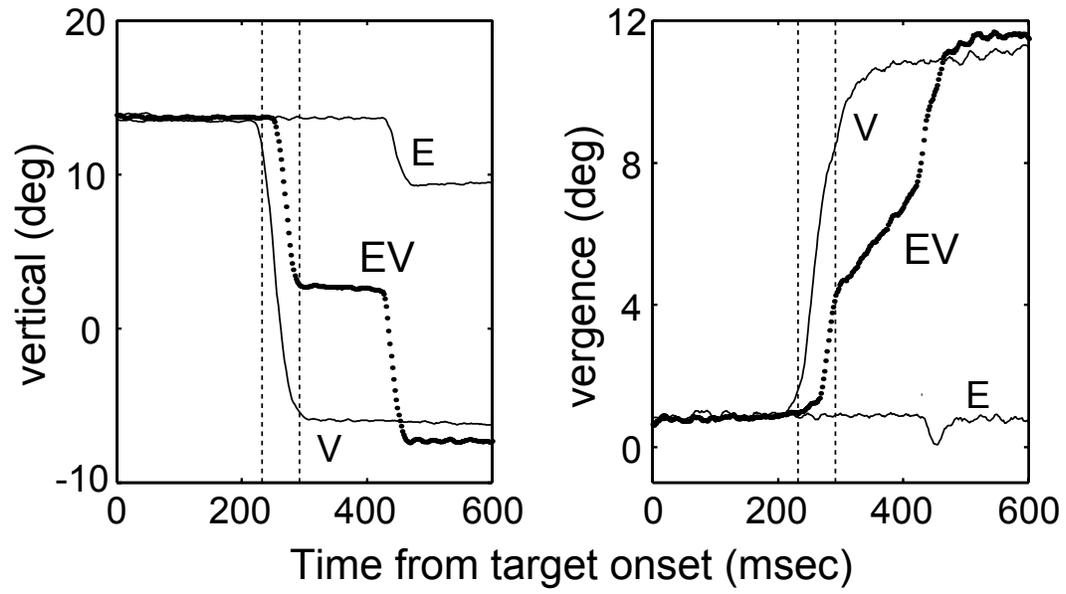


Figure 2