

Identifying corollary discharges for movement in the primate brain

Robert H. Wurtz* and Marc A. Sommer

Laboratory of Sensorimotor Research, National Eye Institute, National Institutes of Health, Bethesda, MD 20892-4435, USA

Abstract: The brain keeps track of the movements it makes so as to process sensory input accurately and coordinate complex movements gracefully. In this chapter we review the brain's strategies for keeping track of fast, *saccadic* eye movements. One way it does this is by monitoring copies of saccadic motor commands, or *corollary discharges*. It has been difficult to identify corollary discharge signals in the primate brain, although in some studies the influence of corollary discharge, for example on visual processing, has been found. We propose four criteria for identifying corollary discharge signals in primate brain based on our experiences studying a pathway from superior colliculus, in the brainstem, through mediodorsal thalamus to frontal eye field, in the prefrontal cortex. First, the signals must originate from a brain structure involved in generating movements. Second, they must begin just prior to movements and represent spatial attributes of the movements. Third, eliminating the signals should not impair movements in simple tasks not requiring corollary discharge. Fourth, eliminating the signals should, however, disrupt movements in tasks that require corollary discharge, such as a double-step task in which the monkey must keep track of one saccade in order to correctly generate another. Applying these criteria to the pathway from superior colliculus to frontal eye field, we concluded that it does indeed convey corollary discharge signals. The extent to which cerebral cortex actually uses these signals, particularly in the realm of sensory perception, remains unknown pending further studies. Moreover, many other ascending pathways from brainstem to cortex remain to be explored in behaving monkeys, and some of these, too, may carry corollary discharge signals.

Introduction

Generating movements is a key to survival for animals. Food gathering, escape from predators, and reproduction all involve coordinated movements. Generating movements, however, presents two major challenges to the nervous system. The first is in the sensory domain. Many movements cause sensory input identical to that elicited by external events, and consequently animals must be able to distinguish whether they, or another entity, caused the sensory input. A valuable aid in making this distinction is

to keep track of movements as they are generated and predict the sensations that will result from them. The second challenge is in the motor domain. As behaviors become more elaborate, the need for internal information about movements becomes more critical. During quick, complex motor sequences such as those produced while fighting a competitor, information about prior actions helps to generate appropriate future ones.

For both sensory perception and motor production, therefore, nervous systems need to keep track of the movements they generate. In this chapter, we consider how the brain might monitor movement information in the primate visual-oculomotor system. We review studies exploring how visual input from the world is distinguished from visual input caused by eye movements, and how primates keep track of

*Corresponding author. Building 49, Room 2A50, MSC 4435, NEI, NIH, 9000 Rockville Pike, Bethesda, MD 20892-4435, USA. Tel.: +1-301-496-7170; Fax: +1-301-402-0511; E-mail: bob@lsr.nei.nih.gov

their eye movements while they look around rapidly. Based on experience from our own laboratory we also propose criteria for identifying internal records of movement within the primate brain.

Sources of knowledge about self-movement

Among the most common movements made by primates are eye movements, and how these movements are internally monitored has been the focus of speculation for centuries and quantitative study for decades (Bridgeman, 1995a; Grüsser, 1995; Colby and Goldberg, 1999). As a primate makes rapid or *saccadic* eye movements to explore the visual scene, the apparent motion of objects in the scene is an artefact of the saccadic eye movement and is not due to actual object movements. How does the brain distinguish this self-induced, illusory object motion from real motion? As might be expected from a biological system that undoubtedly resulted from eons of evolution, there are multiple mechanisms for making this potentially life and death distinction.

One useful clue is contained in the visual signal from the retinas: when the eyes move the whole visual field moves, whereas when a visual object moves it moves alone. Full-field motion, often referred to as optic flow (Fig. 1A), is a reasonable indicator of eye movement as long as the head and body remain stationary. Optic flow so frequently indicates self-motion that it provides critical information about the heading taken by an animal as it proceeds through its environment (Warren and Hannon, 1990; Wurtz and Duffy, 1997; Duffy, 2000). This clue to self-motion, however, requires a lighted, contoured environment that of course is not always present.

A second clue comes from proprioceptors in the eye muscles (Fig. 1A). As the eyes move, proprioceptive input may report eye-muscle contraction to the brain, providing information that apparent visual motion is due to eye movements. The role of the proprioceptors has been investigated for many years (Ruskell, 1999; Donaldson, 2000) and yet their exact contribution remains to be determined. There is growing evidence, however, that the major contribution of proprioception is in long-term calibration of the eye-movement system rather than in monitoring

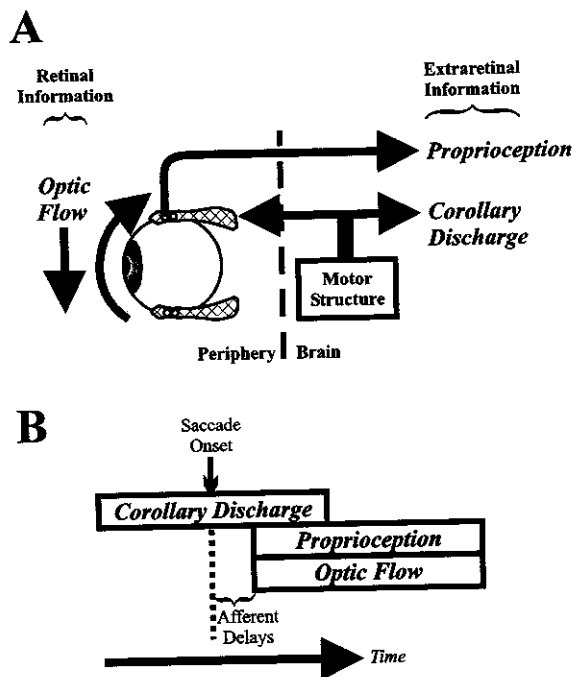


Fig. 1. The three major sources of information about one's own eye movements. (A) At left, a source of retinal information is indicated: *optic flow*, or full-field visual motion caused by a saccade. At right, two sources of extraretinal information are diagrammed. *Proprioception*, or input to the brain from receptors in the eye muscles, and *corollary discharge*, a signal within the brain representing the movement command, both accompany a saccade. (B) Time course of the three sources of information. Corollary discharge signals can occur before, during, and after a saccade. Proprioception and optic-flow signals, however, are available only after a saccade, following afferent delays from periphery to the brain.

movements on a saccade-by-saccade basis (Keller and Robinson, 1971; Guthrie et al., 1983; Lewis et al., 2001).

These two sources of information are sensory in nature, arising peripherally in either the retinas or the proprioceptors. They provide clues about eye movements through afferent inputs to the brain. A third source of information is from within the brain itself (Fig. 1A), and we refer to it as a corollary discharge. This is also known as an efference copy; for a discussion of the nomenclature, see Bell (1984). A corollary discharge for movement is just that: it is a corollary signal sent to other regions of the brain at the same time that the signal is sent on the pathway

to activate the muscles to generate the movement. The corollary logically could be from any level of the circuit within the brain generating the movement, including the final common path to the eye muscles. The advantages of corollary discharges are that they are generated within the brain itself, making them impervious to disruptions of the peripheral receptors, and that they are available even before the movement begins, whereas sensory information is available only afterward (Fig. 1B).

The specific idea of a corollary discharge evolved from the 18th century onward (McCloskey, 1981; Bridgeman, 1995b; Grüsser, 1995), culminating in Hermann von Helmholtz's 19th century reference to an 'effort of will' as the mechanism compensating for the spurious visual motion caused by one's own eye movements. The most influential papers of the 20th century were published by Sperry (1950) and by von Holst and Mittelstaedt (1950), who examined the behaviors of fish and flies, respectively, after ocular rotation/inversion. In both preparations the animals' abnormal behaviors could be explained most easily by postulating that internal copies of motor commands were monitored by the nervous system. Since then the concept of corollary discharge has been invoked to help explain a wide range of animal behaviors, such as electrolocation in fish (Bell, 1984), song learning in birds (Troyer and Doupe, 2000), and chirping in crickets (Poulet and Hedwig, 2002). In all these behaviors the animals must distinguish the sensory consequences of their own actions from environmentally produced sensations. Psychophysical and lesion studies have demonstrated that corollary discharge signals exist in humans (McCloskey, 1981; Skavenski, 1990; Haarmeier et al., 1997; Thier et al., 2001; Pierrot-Deseilligny et al., 2002). Much current work on human motor control is focusing on how the generation of limb movements, especially during motor learning, relies on corollary discharge signals (or 'forward internal models'; Jordan and Rumelhart, 1992; Frith et al., 2000; Wolpert and Ghahramani, 2000).

In principle, neurophysiologists can take at least two approaches to demonstrating the existence of corollary discharge signals in neurons of any sensorimotor system (Fig. 2). The first approach is to identify the *effect* of the corollary discharge on a neuron's sensory responses. The second is to identify

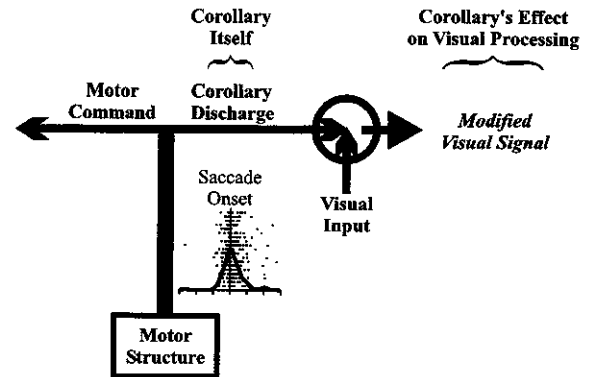


Fig. 2. Two ways of detecting corollary discharge in the visual-oculomotor system. Experimenters usually detect corollary discharges indirectly by demonstrating otherwise inexplicable changes in sensory processing (right). For example, a modified visual signal, such as a visual response that changes just prior to saccade initiation, may suggest that a corollary discharge is present. The more direct approach is to identify the corollary discharge itself (left). To do this, one must establish criteria for determining whether movement-related neuronal activity (as in the example shown with rasters and a spike density function) is a corollary discharge or a movement command. The corollary discharge would interact at a later stage with visual input to produce a modified visual signal. Many types of interactions are possible (MacKay, 1966; Bell, 1984).

the corollary *itself*, but this raises the question of how to distinguish a corollary discharge signal from a movement command. We consider both of these approaches in turn as they have been applied in the monkey visual-oculomotor system.

Searching for the influence of corollary discharge on visual processing

The classical approach to studying corollary discharge in the primate visual-oculomotor system has been to search not for the corollary itself but instead for the impact of the corollary on visual processing. The logical first place to look for the effect of a corollary discharge was in primary visual cortex, which receives input from the retinas via the lateral geniculate nuclei. The principle was to compare neuronal activity evoked by motion of an object (with the eyes still) with activity evoked by movement of the eyes (with the object still). If the neuron responded differently to the nearly identical object

motion on the retina in the two conditions, then the neuron had to be receiving information that an eye movement was occurring. This meant the neuron's activity was influenced by corollary discharge signals. This experiment was performed in the awake, trained monkey (Wurtz, 1968), and in fact was the very first recording of visual neurons achieved in an awake, trained monkey. No clear difference was detected in the two conditions, indicating that corollary discharge signals probably have little influence on processing in primary visual cortex. There was, however, evidence that the presence or absence of a visual background influenced the neuronal responses, emphasizing that other lines of information such as optic flow (Fig. 1A) can provide clues as to the cause of visual motion. A corollary discharge associated with pursuit movements also has been sought in primary visual cortex, but none has been found (Ilg and Thier, 1996). Subsequent studies on saccades have reported slight effects of corollary discharge on primary visual-cortex neurons (Bridgeman, 1973; Galletti et al., 1984). These latter results might indicate true corollary discharge influences, but they also may be due instead to significant differences in the motion produced by the saccade versus the stimulus movement generated by the experimenter.

Primary visual cortex is not the only recipient of visual signals from the retina in primates; the retina also projects directly to the superficial layers of the superior colliculus (SC), a structure on the roof of the midbrain. Neurons in the SC superficial layers respond to visual stimuli and do not increase their activity before eye movements (in contrast to neurons just below them in the SC intermediate layers that discharge in tight correlation with saccades; Schiller and Koerner, 1971; Wurtz and Goldberg, 1971; Sparks and Hartwich-Young, 1989). The same test for the presence of a corollary discharge was done on these SC superficial-layer neurons as on the primary visual-cortical neurons, but the outcome was substantially different. In contrast to the results in primary visual cortex, many SC superficial-layer neurons showed strong differences in their responses to moving visual stimuli (Robinson and Wurtz, 1976a) depending upon whether the motion was caused by visual stimulus motion with the eyes stationary (Fig. 3A, left) or by a saccade with the visual stimulus stationary (Fig. 3A,

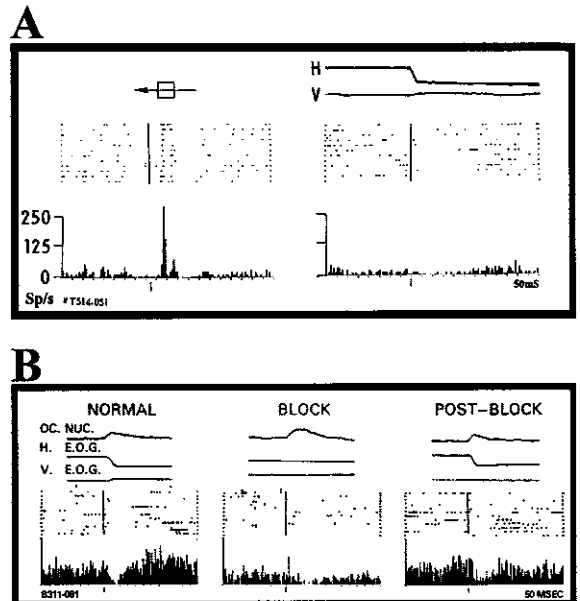


Fig. 3. Identifying the effects of corollary discharge on visual neurons of the SC superficial layers. (A) Example of an SC neuron that may have been influenced by corollary discharge signals. The neuron showed a clear visual response when a spot of light moved across its receptive field while the eye was stationary (see the rasters and histogram of neuronal activity, left panel), but it did not respond when a saccade moved the receptive field across a stationary stimulus at about equal speed (right panel). In fact, background activity was actually suppressed when the eye moved. This was evidence that there was an extraretinal input (corollary discharge or proprioception) to these neurons. H, V, horizontal and vertical components of the eye position; Sp/s, spikes per second. From Robinson and Wurtz (1976b). (B) Demonstration that the effect is due to corollary discharge. The saccade-related suppression of background activity of an SC superficial-layer neuron (left panel) continued when the monkey attempted to move its eyes even though a retrobulbar block prevented movement (middle panel). Because the eye muscles did not contract, there were no proprioceptive signals. The attempted eye movement was indicated by an increase in activity from integrated multiple neuron activity recorded from the oculomotor nucleus (Oc. Nuc.). Activity after the block recovered is shown in the right panel. E.O.G., electrooculogram. From Richmond and Wurtz (1980). Only a few of the rasters contributing to the histograms are shown. The rasters were retouched to compensate for faint dots resulting from digitization.

right). The motion resulting from saccades frequently did not produce the usual increase of activity at all, but instead produced suppression in the background activity.

This difference in visual responses to eye- versus stimulus-generated motion was necessary, but not sufficient, to demonstrate the influence of corollary discharges. There was still the possibility that the effects were due entirely to proprioceptive input. Therefore, a further test was done to determine whether the suppression of activity accompanying the saccade persisted in the absence of proprioception (Richmond and Wurtz, 1980). Proprioception was eliminated by stopping the movement of the eye by numbing eye muscles with xylocaine. During the block the monkey attempted in vain to move its eyes, as indicated by bursts of activity recorded from the oculomotor nucleus, and corollary discharge signals still should have been generated accordingly. The suppression persisted (Fig. 3B, middle), so it must have been dependent upon corollary discharge. This experiment probably provides the best evidence in the primate visual-oculomotor system for the action of a corollary discharge on early visual processing. The inverse experiment was not done (eliminate the corollary discharge and keep the proprioception), so the possibility remains that proprioception may contribute to some extent; however, corollary discharge alone was sufficient to explain the effect.

We noted above that corollary discharge has little, if any, influence on activity in primary visual cortex. However, it does seem to exert an effect later in the visual stream. For example, visual receptive fields of many cerebral cortical neurons suddenly shift to new locations just prior to a saccade; the new locations are those where the receptive field would be just after the saccade (Duhamel et al., 1992a; Colby and Goldberg, 1999). This predictive remapping must use corollary discharge information because it occurs before the eye actually moves. This effect has been seen in the frontal eye field (FEF) of prefrontal cortex (Umeno and Goldberg, 1997) and seems to diminish gradually in extrastriate cortex as one approaches primary visual cortex (Nakamura and Colby, 2002). Recently, a difference between stimulus- and eye-produced motion was found for neurons in extrastriate cortical area MT of the monkey (Thiele et al., 2002). This demonstrates the presence of an extra-retinal input that may be a corollary discharge, although influences of proprioception were not explicitly ruled out.

Identifying the corollary discharge itself

Demonstration of an *effect* of corollary discharge has been accomplished many times, not only in the monkey with respect to the modification of visual processing, but also in a large number of vertebrate and invertebrate species. In contrast, the identification of the corollary discharge signal *itself* has been attempted in only a few studies, among them investigations of the corollary discharge of weak electric signals (the generation of which involve a muscle-like organ) in mormyrid fish (Bell, 1984) and of the corollary discharge of leg movements in cockroach and cricket (Delcomyn, 1977; Poulet and Hedwig, 2002). A critical issue in such experiments is to differentiate the signal that is the corollary from that which is the movement command (Fig. 2, left). For example, in monkeys the saccade-related discharges of SC intermediate-layer neurons could logically be either movement commands or corollaries of the commands. Certainly many are movement commands because low-threshold electrical stimulation or reversible inactivation of the SC intermediate layers elicits or impairs saccade generation, respectively (Robinson, 1972; Hikosaka and Wurtz, 1985). Whether some of the saccade-related discharges in SC are actually corollary discharge signals, however, has been unknown.

In our own attempts to investigate corollary discharge signals we developed a list of criteria for identifying them within the complex circuits of the primate brain (Table 1). First, putative corollary discharges should originate from a brain structure known to be involved in the generation of the movement as indicated by changes in activity preceding the movement and alterations in the movement resulting from activating or inactivating the structure. Second, the signals should occur just prior to the movement and represent spatial

Table 1. Criteria for identifying corollary discharges

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1. The signals originate in a motor area
 2. The signals precede and spatially represent the movement
 3. Eliminating the signals *does not* impair movements in tasks not requiring corollary discharge
 4. Eliminating the signals *does* impair movements in tasks requiring corollary discharge
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parameters of the movement. Third, eliminating the signals should not impair movements in simple tasks not requiring corollary discharge. Fourth, eliminating the signals should, however, disrupt the performance of tasks that require corollary discharge. While we think these criteria should apply to the identification of corollary discharge in systems other than the visual oculomotor and in animals other than the monkey, we make no pretense that these are the only criteria that could be used. Using these criteria, we considered whether neurons in a pathway from SC up to frontal cortex could be regarded as conveying corollary discharges for saccades, as will be discussed next.

Criterion 1: The signals originate from a motor area

We investigated a pathway suspected on anatomical grounds to run from a clearly established brainstem-oculomotor region up to the cerebral cortex. It was thought to originate from SC intermediate-layer neurons that project to relay neurons in the mediodorsal nucleus of the thalamus (MD) that in turn project to the FEF (Fig. 4A). Evidence for the existence of this pathway came from retrograde-labeling and anterograde-degeneration studies (Benevento and Fallon, 1975; Goldman-Rakic and Porrino, 1985) taken together with a transynaptic retrograde-labeling study using herpes simplex virus (Lynch et al., 1994).

To confirm that this pathway existed and was functional, we first attempted to identify and record from MD relay neurons. The activity of thalamic neurons in and around MD during visuosaccadic behavior had been studied only once before in the monkey (Schlag and Schlag-Rey, 1984; Schlag-Rey and Schlag, 1984). While finding MD neurons in the awake monkey is itself an experimental challenge, identifying the small subset of MD neurons that relay signals from SC to FEF would seem even harder. There are, however, electrophysiological methods for identifying MD neurons that project to FEF and receive SC input, namely, antidromic and orthodromic stimulation techniques (Fig. 4B) that we described in detail previously (Sommer and Wurtz, 1998, 2002). Using these techniques, we identified 51 neurons in two monkeys that were clearly MD relay

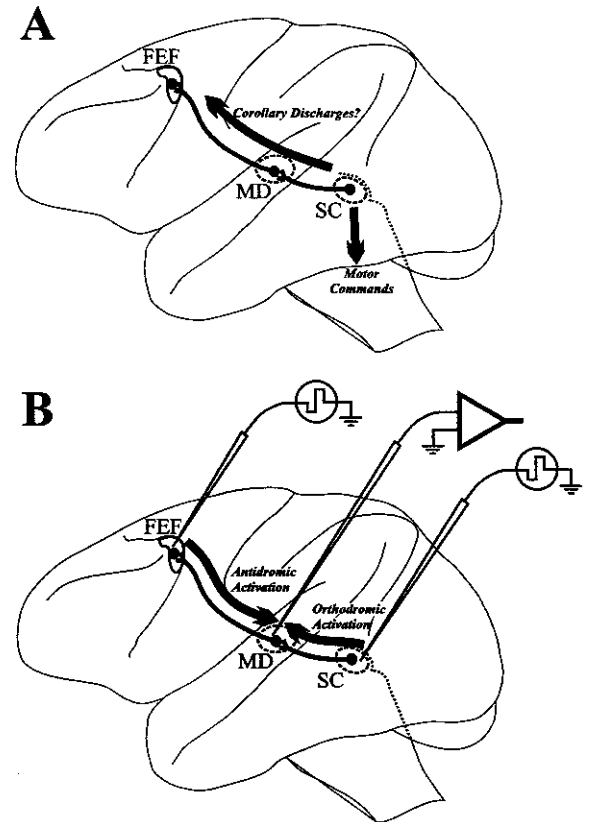


Fig. 4. Technique for satisfying Criterion 1, ensuring that the signals under study originate in a motor area. (A) Anatomical studies indicated that some neurons in the SC intermediate layers project to mediodorsal thalamus (MD), onto relay neurons that in turn project to the frontal eye field (FEF). The SC intermediate layers also send commands that ultimately cause saccade generation down to the brainstem saccade-generating circuits. Arrows indicate direction of signal flow. (B) Method used to identify the neurons in MD that both receive input from SC and project to FEF. Every MD relay neuron was double-identified: it was both antidromically activated from the FEF (showing that it projected to FEF) and orthodromically activated from the SC (showing that it received input from the SC). Arrows show direction of action potential propagation from the stimulating electrodes.

neurons, in that each one was both antidromically activated from the FEF and orthodromically activated from the SC (Sommer and Wurtz, 2002). They may project additionally to frontal cortical areas other than FEF and they may receive other inputs besides that from the SC, but all of them

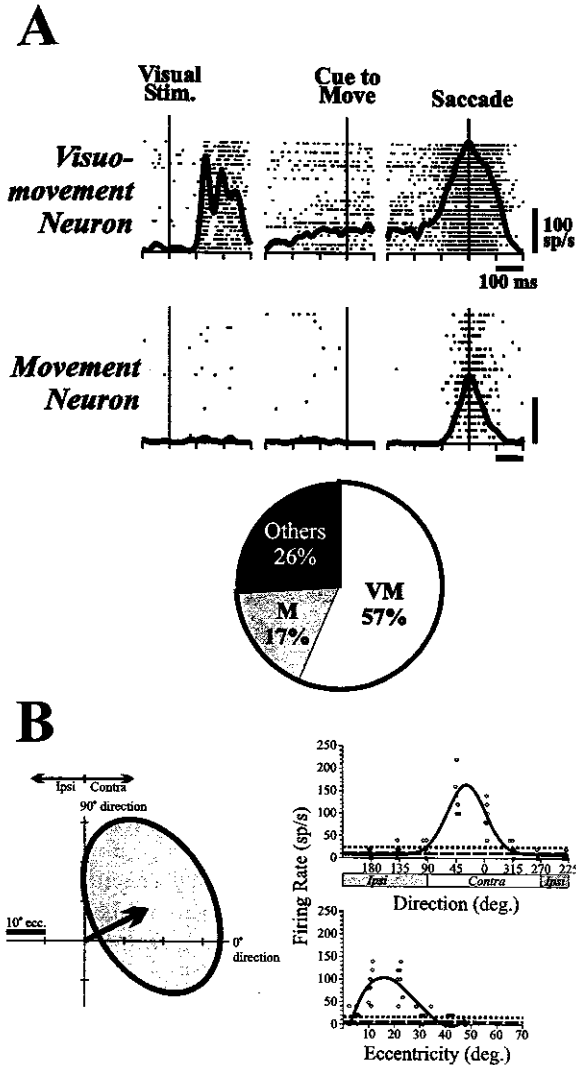


Fig. 5. Evidence satisfying Criterion 2, showing that signals in the pathway precede and spatially represent the movements. (A) Presaccadic bursts of activity recorded from MD relay neurons. Once an MD relay neuron was isolated it was studied by having the monkey perform a delayed saccade task. The monkey looked at a fixation spot, then a target (Visual Stim.) appeared in the periphery, and after a delay period of 500–1000 ms the fixation spot disappeared (Cue to Move), which was the cue to start the eye movement (Saccade) and look at the target. Shown are examples of two major types of MD relay neurons, Visuo-movement and Movement Neurons. Neurons of both types had bursts of activity beginning just prior to the saccade. The pie chart shows the percentage of each neuron type in our sample of MD relay neurons (VM, Visuo-movement Neurons; M, Movement Neurons; 'Others' include neurons with only visual responses and those with neither visual or saccadic activity). Presaccadic bursts of activity were present in 74% of

at least were positively identified as relay neurons between SC and FEF.

After studying the MD relay neurons we then examined the SC neurons that projected up to them (Wurtz and Sommer, 2000). This was done by looking for SC neurons antidromically activated from the locations of previously recorded MD relay neurons. We also identified FEF neurons that seemed to receive the signals flowing in this ascending pathway (Sommer and Wurtz, 1998). This was done by searching for FEF neurons orthodromically activated from the SC. In sum, we recorded from identified neurons all along a pathway originating in the SC, a structure crucial for generating saccades.

Criterion 2: The signals precede and spatially represent the movements

For brevity we will focus on the MD relay neurons, which represents the crucial node in the pathway. We studied their activity while monkeys made delayed saccades to visual targets (Sommer and Wurtz, 2002) and found that most of them increased their activity just before the saccade (see Fig. 5A). Of 46 neurons tested, 57% were visuo-movement neurons (having both a presaccadic burst and a visual response) and 17% were movement neurons (having a presaccadic burst but no visual response). In net, 74% of the neurons increased their activity before the saccade, on average starting their saccade-related burst 66 ms prior to the onset of movement. Note that this presaccadic initiation meant that the activity could not have resulted from proprioceptive input from eye-muscle contraction. We examined the relationship

the neurons (M+VM neurons), as indicated by the bold outline. (B) Representation of saccadic vectors by MD relay neurons. The movement field (gray oval) of an example neuron is shown at left. The neuron exhibited presaccadic bursts of activity only for saccadic vectors made from the origin into this field. The saccadic vector encoded by the peak firing of the neuron (bold arrow) was directed 27° up from horizontal and was 16° in amplitude. This vector was determined by having the monkey make various directions and amplitudes of saccades (right) and fitting the presaccadic firing rate data with Gaussians and spline curves (solid curves), respectively. Dashed lines show mean baseline activity, and dotted lines show 2 SDs above that, which was the criterion level for significance. Ipsi, ipsilateral space; Contra, contralateral space.

between the saccadic activity and the saccadic vector for 29 of the neurons, and 23 of them (79%) had distinct peaks in their movement fields, firing strongest for saccades of a certain amplitude and direction (Fig. 5B). For all tuned neurons the best direction was into the contralateral visual field.

Many MD relay neurons, therefore, have activity preceding the saccade and representing the spatial aspects of the saccade. Incidentally, nearly identical results were found for saccade-related bursts of SC neurons projecting up to the MD, consistent with our assumption that the MD relay neurons were driven in large part, if not completely, by SC neurons. These ascending saccadic bursts are excellent candidates to be corollaries of motor commands, because they are qualitatively similar to saccadic bursts exhibited by the general population of SC neurons (Sparks and Hartwich-Young, 1989) and in particular by those SC neurons identified as projecting downstream to saccadic-generating circuits (Guitton and Munoz, 1991; Munoz and Guitton, 1991; Munoz et al., 1991).

Criterion 3: Eliminating the signals does not impair movements in a simple task not requiring corollary discharge

At this point we know that signals related to impending saccades are sent from SC up to FEF. But might these signals actually be causing saccade generation through some loop involving cerebral cortex and brainstem? To answer this question we capitalized on the presence of the MD relay neurons in the ascending pathway — an experimental gift to the physiologist. By inactivating them we could specifically interrupt transmission from SC to FEF. [Directly inactivating the SC or FEF, instead, would have caused extensive unwanted effects due to perturbing the myriad other networks involving these structures, including the descending, motor-dedicated pathways to the pons; we already know that inactivating either SC or FEF impairs saccade generation itself (Hikosaka and Wurtz, 1985; Sommer and Tehovnik, 1997; Dias and Segraves, 1999).] We inactivated the MD relay neurons using muscimol, a GABA_A agonist. Muscimol inhibits neuron cell bodies, not axons (Lomber, 1999), so it

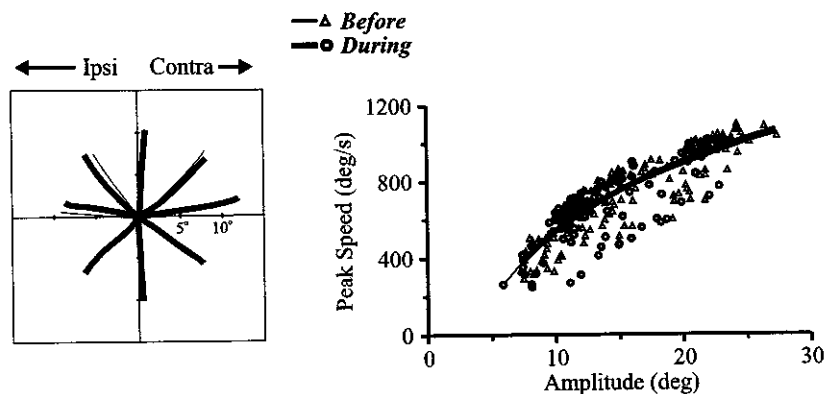
should suppress MD relay neurons without affecting transthalamic fibers passing nearby.

While MD relay neurons were inactivated, we had monkeys make single saccades to visual or remembered targets at several eccentricities and directions. Making a single saccade does not require corollary discharge information. Thus if the ascending pathway's saccade-related signals are corollary discharges, single saccades should not be affected by MD inactivation; however, if the signals instead are needed for making saccades, then single saccades *should* be impaired by MD inactivation. Figure 6A (left) shows the average trajectories of saccades made to targets at 10° eccentricity and eight directions, before versus during inactivation of MD neurons in one experiment. The monkey still made saccades, and quantification showed that the accuracy and latency of these saccades was not altered by inactivation (Sommer and Wurtz, 2002). Throughout a series of like experiments, significant changes in the accuracy and latency of single saccades were infrequent and small. To examine saccadic dynamics we plotted peak speed as a function of amplitude (referred to as the main sequence, Fig. 6A, right). There were no clear impairments during inactivation; the logarithmic fits of the values before and during the injection were not significantly different.

The significance of this *lack of effect* during MD inactivation is brought into sharper perspective by considering previous experiments in which the SC was inactivated with muscimol. Figure 6B (left) shows that during an example of SC inactivation, saccades made to the upper right quadrant were shortened and their trajectories altered. In addition, SC inactivation markedly slowed saccades (Fig. 6B, right). Similar effects have been reported for FEF inactivation (not shown; Sommer and Tehovnik, 1997; Dias and Segraves, 1999).

Thus, eliminating the saccade-related signals coursing through MD does not eliminate, or even significantly affect, the generation of single saccades in simple tasks. This supports the idea that these signals provide information about saccades but are not critical for generating them. This is in contrast to inactivation of SC or FEF, which can severely impair saccade generation presumably by shutting off descending efferents to brainstem saccade-generating circuits.

A MD Inactivation: Single saccades unaffected



B

SC Inactivation: Single saccades impaired

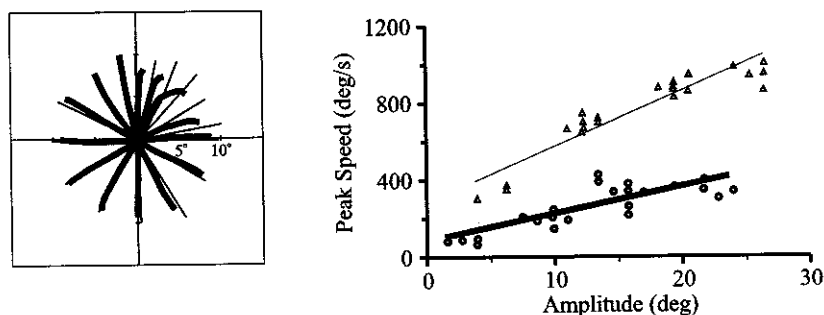


Fig. 6. Evidence satisfying Criterion 3, showing that eliminating the signals *does not* impair saccades made in a simple task not requiring corollary discharge. (A) Results of inactivating the MD relay neurons while monkeys made single saccades to visual targets. *Left*, average trajectories of saccades made in one experiment, before versus during the inactivation. Saccades traveled from the center of the screen to each of eight targets at 10° eccentricity. Inactivation did not significantly impair saccades in any direction. *Right*, graphs summarizing the dynamics of contraversive single saccades. The curves show logarithmic fits. (From data presented in Sommer and Wurtz, 2002.) (B) Analogous saccade data from an experiment in which the SC was inactivated (Hikosaka and Wurtz, 1985; Aizawa and Wurtz, 1998).

Criterion 4: Eliminating the signals disrupts movements in a task requiring corollary discharge

Many tasks can be imagined that require corollary discharge for their execution, for example tasks that require distinguishing sensations caused by self-movement as opposed to external forces or tasks that require generation of fast, complex motor acts. The task we used was the double-step task, in which the monkey had to make successive saccades to two flashed targets (Fig. 7A, left). We selected this task because it is widely used as an assay for the presence

of corollary discharge, particularly in patients with cortical lesions (Duhamel et al., 1992b). Correct execution of the second saccade (the upward saccade) requires knowledge of where the eye lands after the first (horizontal) saccade. Visual feedback indicating where the eye is after the first saccade is not available because the saccades begin after the targets disappear; additionally, the experimental room is usually in total darkness. Proprioception probably does not contribute to successful performance, because it likely has little influence in the online control of saccades (Lewis et al., 2001) and has been

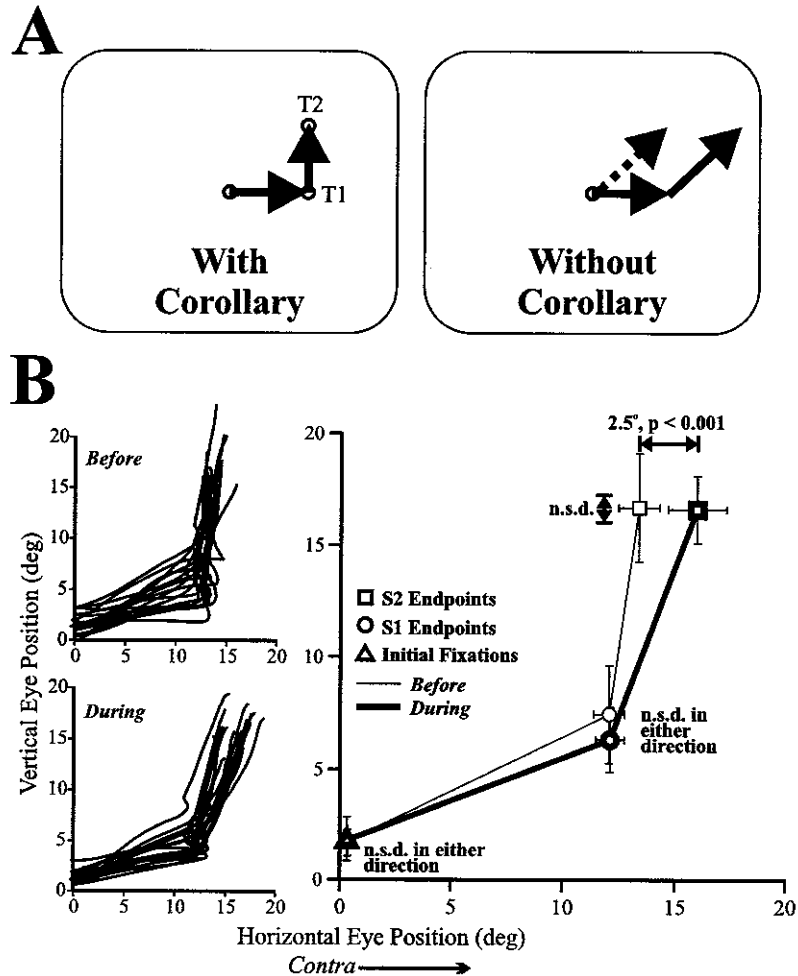


Fig. 7. Evidence satisfying Criterion 4, showing that eliminating the signals *does* impair saccades made in a task requiring corollary discharge. (A) We used the double-step task, which requires corollary discharge for correct performance. *Left*, the monkey first looked at a fixation spot (shown in gray, center of screen), which then disappeared as two targets were flashed sequentially (shown in white, T1 and T2). The monkey then made two saccades (arrows) to the target locations. Due to the reaction time of the saccades, all stimuli were gone before the saccades started. With corollary discharge intact, the first saccade would go rightward and the second saccade would go straight up from there. *Right*, without corollary discharge, the first saccade would go rightward but there would be no internal record of this. Hence the monkey would not know that its eyes are at a new position, and to complete the trial it would be expected to make the second saccade as if it were still looking at the center of the screen, i.e. the second saccade should travel diagonally (dashed arrow). Since the first saccade was in fact made correctly, however, the pattern of saccades should be as shown with the solid arrows. (B) *Left*, individual saccadic sequences from an example MD inactivation, before (*top*) and during (*bottom*) inactivation. *Right*, means (and SDs) of the initial fixation locations, first-saccade endpoints, and second-saccade endpoints for the same example. The only significant change was that predicted by loss of corollary discharge: there was a shift of second-saccade endpoints in the contraversive (rightward) direction. From Sommer and Wurtz (2002). S1, first saccade; S2, second saccade; n.s.d., not significantly different.

shown to be unnecessary for performing a similar double-step task (Guthrie et al., 1983). We discouraged memorization or preplanning of the sequences by randomizing a variety of sequences

across trials and changing the sequences between experiments.

The indicator of a loss of corollary discharge in this task is specific and quantifiable. If inactivation

totally eliminates corollary discharge (Fig. 7A, right), the monkey should make a contraversive first saccade correctly but should not have internal information that it did so. Therefore, if the monkey tries to complete the trial by looking at the second target, it should make a second saccade as if it never made the first, i.e. as if the eyes were still looking at the fixation point; hence the second saccade should be made diagonally (Fig. 7A, right, dashed arrow). But since the first saccade actually was correct (the monkey just did not know this), the second saccade will begin at the endpoint of the first target and will land to the right of the second target location (Fig. 7A, right, diagonal arrow). The indicator of lost corollary discharge therefore would be a shift of second-saccade endpoints contraversively (in this example, rightward) during inactivation. No vertical shifts should occur, however, nor any changes in the initial fixation locations or first-saccade endpoints.

Figure 7B shows the results from one injection of muscimol into MD (Sommer and Wurtz, 2002). Before inactivation the monkey made saccadic sequences correctly. Because the saccades were made in total darkness, first-saccades were shifted upward slightly (Gnadt et al., 1991). Second saccades went nearly straight up, indicating that the corollary discharge was intact. Following inactivation of MD, the second-saccade endpoints shifted contraversively (to the right) as expected if the corollary discharge was impaired. Quantitatively the second-saccade endpoints were shifted 2.5° to the right ($P < 0.001$), but not significantly vertically, during the injection. Neither the initial fixation locations nor the first-saccade endpoints were shifted significantly in either direction.

We performed seven muscimol experiments in which there were a total of 22 cases of before versus during saccadic sequence pairs to analyze (Sommer and Wurtz, 2002). In every case the principle for identifying a corollary discharge deficit was the same as in Fig. 7. In 82% of the cases (18/22) there was a contraversive shift in second-saccade endpoints, and the overall mean shift (1.12°) was significantly greater than zero. The contraversive shift in half (11/22) of the cases was individually significant. First-saccade endpoints did not exhibit a significant mean horizontal shift and neither did initial fixation locations. In the vertical direction there were no

mean shifts in any of the data. As controls we randomly interleaved trials in which the targets appeared ipsilaterally. Identical target configurations were used, but flipped across the vertical meridian. In these trials the first-saccades were ipsiversive, a direction poorly represented by MD relay neurons. Accordingly, we found no corollary discharge deficits: the mean horizontal shift for second-saccade endpoints was not significantly different from zero.

We also considered whether inactivation degraded a monkey's ability to see the second target and/or remember its location. If such deficits occurred, there should have been greater scatter of the second-saccade endpoints during inactivation, due to greater uncertainty about the second target location. This did not occur, however. If there were subtle visual or memory deficits, they did not seem to affect performance in our task.

We measured the size of the deficit by finding the percentage of the observed shift relative to that expected if the corollary were completely eliminated. In the example shown in Fig. 7B, the second-saccadic endpoints shifted 2.5° horizontally rather than the 10° as expected, and so there was a 25% deficit. Calculating this value for each experiment showing a deficit allowed us to gauge the average deficit, and overall there was a 19% impairment. There are several experimental and theoretical factors that might have contributed to the modest size of the deficit. First, we injected at only one MD site at a time, and therefore we may have left a substantial fraction of MD active. Second, we have identified *one* possible pathway for a corollary from brainstem to cortex, but we do not claim that it is the only pathway. In fact, our results might be interpreted as indicating that there are other such pathways including those relayed from cerebellum or substantia nigra to the thalamus and then to FEF (Lynch et al., 1994). Finally, it is conceivable that the monkeys exploited proprioceptive input after losing corollary discharge during inactivation. However, due to the dubious usefulness of proprioception in rapid saccadic behavior, as mentioned above, we think that the first two explanations are more likely.

In summary, signals in the pathway from SC to FEF via MD satisfy all four criteria for being corollary discharges. The signals originate from a known motor-related region, they encode the timing

and spatial parameters of upcoming saccades, their removal does not affect the generation of saccades in simple tasks, and their removal does disrupt saccades in a double-step task that requires corollary discharge.

Conclusion

We have concentrated on the pathway from SC to FEF and how the corollary discharge carried therein contributes to making accurate movement sequences. This is an example of how corollary discharge can be crucial for motor behavior, as has been explicated in computational detail lately with respect to limb movements by Wolpert and Ghahramani (2000). The other major role of corollary discharge is in analysis of sensory input, for example in our ability to perceive a stable visual scene despite the frequent rotations of our retinas due to saccades. One way in which corollary discharge might promote a sense of visual stability is by helping to remap visual receptive fields just prior to saccade initiation in the FEF (Umeno and Goldberg, 1997) and in the lateral intraparietal cortex (LIP) and other extrastriate visual areas (Duhamel et al., 1992a; Colby and Goldberg, 1999). Also, corollary discharge could help neurons, such as those in superficial SC and area MT, discriminate real visual motion from self-induced motion caused by eye movements. Note that corollary discharge signals sent to the FEF from the SC through our ascending pathway could then be disseminated via the FEF's projections to a legion of other cerebral cortical areas, including MT and LIP as reviewed by Schall (1997). Future work therefore should focus on possible sensory functions of the corollary discharge signals sent from SC to FEF. Moreover, it should be recalled that saccade-related bursts of activity, the presumed corollary discharges, were not the only kinds of signals found in the pathway from SC to FEF. The exact roles of the other signal types in this pathway, e.g. the visual responses, still need to be determined.

More generally, we would like to emphasize that the pathway we explored is only one of a number of brainstem-to-cortex pathways in primates. Another salient example is the pathway from the SC superficial layers relayed through the pulvinar to

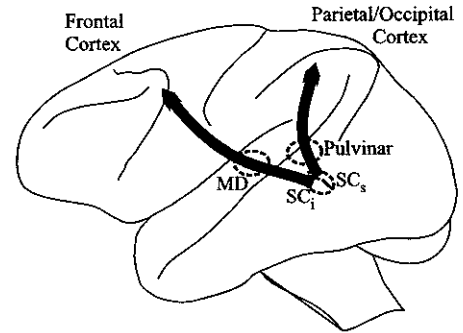


Fig. 8. Two ascending pathways from SC to cerebral cortex. One, the pathway from the SC intermediate layers (SC_i) through MD to frontal cortex, carries corollary discharges of saccadic eye movements as established by the criteria set forth in this chapter. The other pathway, from the SC superficial layers (SC_s) through pulvinar to parietal and occipital cortex, may be involved in attention, but relatively little is known about it.

extrastriate cortex (Fig. 8; reviewed by Sommer and Wurtz, in press). We have little knowledge of the contribution of this pathway to cortical function, but we do know that inactivation of pulvinar alters a monkey's performance on a task requiring a shift of attention (Petersen et al., 1987). This SC to pulvinar to extrastriate cortex pathway was the center of intense interest in considering multiple visual pathways to the cortex over 30 years ago (Diamond and Hall, 1969; Schneider, 1969), and it should clearly be revisited using techniques as discussed here.

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