Adaptive Modification of Saccade Size Produces Correlated Changes in the Discharges of Fastigial Nucleus Neurons

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Scudder, Charles A. and David M. McGee. Adaptive modification of saccade size produces correlated changes in the discharges of fastigial nucleus neurons. J Neurophysiol 90: 1011–1026, 2003; 10.1152/jn.00193.2002. Saccade accuracy is known to be maintained by adaptive mechanisms that progressively reduce any visual error that consistently exists when the saccade ends. We used an experimental paradigm known to induce adaptation of saccade size while monitoring the neural correlates of this adaptation. In rhesus monkeys where the medial and lateral recti of one eye were surgically weakened, patching the unoperated eye and forcing the monkey to use the weakened eye induced a gradual increase in saccade size in both eyes until the viewing, weak eye almost acquired the target in one step. Subsequent patching of the weakened eye gradually reversed the situation, so that the saccades in the viewing, normal eye decreased from an initial overshooting to normal. In the caudal fastigial nuclei of unadapted monkeys, neurons typically exhibit an early burst of spikes that is correlated with the onset of contraversive saccades and a later burst of spikes that is correlated with the termination of ipsiversive saccades. Comparing the discharges of the same fastigial neurons recorded before and during adaptation, this basic pattern did not change, but some parameters of the discharges did. The most consistent changes were in the latency of the burst for ipsiversive saccades, which was positively correlated with saccade size (1.28 ms/deg), and in the number of spikes associated with contraversive saccades, which was also positively correlated (0.55 spikes/deg). The former was more important when saccade size was decreasing, and the latter was more important when saccade size was increasing. Based on current knowledge of the anatomical connections of fastigial neurons, as well as on the effects of cerebellar lesions and on recordings in other structures, we argue that these changes are appropriate for causing the associated changes in saccade size.

INTRODUCTION

Because saccades have too short a duration for vision to guide the eye to its target, saccade accuracy must be maintained over the long term by mechanisms that assess saccade error at the end of each saccade and modify subsequent movements. The existence of such adaptive mechanisms has been demonstrated in patients with paresis of the extraocular muscles in one eye (Abel et al. 1978; Kommerell et al. 1976; Optican et al. 1985) and in monkeys with surgically induced paresis (Optican and Robinson 1980; Scudder et al. 1998). Because of the conjugate oculomotor command conveyed to both eyes, eye movements are necessarily smaller in the paretic, “weak” eye than in the normal eye. When the normal eye is monocularly viewing, the subject makes saccades to visible targets accurately, but when the subject is forced to use the weakened eye by patching the normal eye, saccades initially undershoot the target. However, saccades gradually increase in size until they are nearly accurate. When the patch is switched and the normal eye is used again, saccades in this eye initially overshoot the target, but adaptive mechanisms gradually restore normal accuracy. The ability to adapt saccade size has also been experimentally shown by displacing the target during the time that the human or monkey subject is generating a saccade that would have acquired the target (“intrasaccadic target steps”; Deubel et al. 1986; McLaughlin 1967; Miller et al. 1981; Scudder et al. 1998; Straube et al. 1997). Initially, saccades land near the original target and miss the displaced target, but adaptation of saccade size and/or direction gradually produces saccades that land near the displaced target.

A variety of evidence has led to the belief that the cerebellum participates in the control of saccade size and direction. Lesions of the posterior vermis that include lobule VII, especially unilateral lesions, result in saccades that are markedly dysmetric (Aschoff and Cohen 1971, 1972; Barash et al. 1999; Optican and Robinson 1980; Ritchie 1976; Selhorst et al. 1976a,b; Takagi et al. 1998). Saccade size may differ from target displacement by a factor of 2, indicating that the cerebellar signals have a potent effect on the saccadic burst generator located in the brain stem. Similar, transient deficits are produced in monkeys and cats by local inactivation of the target area of lobule VII axons, that is, the caudal fastigial nucleus. Inactivation of this part of the nucleus by cooling (Vilis and Hore 1981) or by injection of the GABA agonist, muscimol, results in saccades to the contralesional side that are hypometric and saccades to the ipsilesional side that are hypermetric (Goffart and Pelisson 1994, 1998; Robinson et al. 1993). Finally, microstimulation of lobule VII slightly before or during contralaterally directed saccades has the ability to foreshorten these saccades (Keller et al. 1983; Ohtsuka and Noda 1991b).

Anatomical and physiological data support the hypothesis that saccade size might be controlled by the cerebellum and, moreover, have suggested ways that this might occur. Retrograde and anterograde tract tracing has shown that fibers from the caudal fastigial nucleus project mainly contralaterally to the pontine and mesencephalic reticular formations as well as to the superior colliculus (Batton et al. 1977; Gonzalo-Ruiz et al. 1988, 1990; Kurimoto et al. 1995; May et al. 1990; Sato and...
Noda 1991). Efferent terminals seem to target the specific areas where saccade-related neurons are located (Noda et al. 1990; Scudder et al. 2000). These neurons include the premotor “saccadic burst neurons,” that is, excitatory burst neurons (EBNs) and inhibitory burst neurons (IBNs), as well as interneurons, that is, long-lead burst neurons (LLBNs) and midline omnipause neurons (OPNs). EBNs, IBNs, and LLBNs exhibit a vigorous burst of spikes preceding and during ipsiversive saccades, whereas OPNs exhibit a cessation (pause) in their tonic firing at the same time (cf. Fuchs et al. 1985; Scudder et al. 2002). As discussed in more detail later, the OPNs make inhibitory connections with EBNs and IBNs (Curthoys et al. 1984; Nakao et al. 1980) and are thought to permit the discharge of these premotor burst neurons by the cessation of tonic firing. Therefore OPNs probably control both the onset and termination of premotor bursts. Given that saccade size is determined by the number of spikes in these burst neurons (Kaneko et al.1981; Keller 1974; Scudder et al. 1988; Strassman et al. 1986a,b; van Gisbergen et al. 1981), control of either the burst frequency and/or the burst duration would bring about control of saccade size. The brain-stem connections of caudal fastigial neurons are therefore well suited for this function.

Extracellular recording of cells in the caudal fastigial nucleus have revealed further clues about how the cerebellum might control saccade size. Saccade-related cells are found in a circumscribed area, which Noda and colleagues have called the fastigial oculomotor region (FOR), and exhibit a burst of spikes that precedes the onset of contraversive saccades by an average 10–19 ms (Fuchs et al. 1993; Ohtsuka and Noda 1990, 1991a). The range of burst leads is large but, nonetheless, the discharges seem well timed to affect the discharges of the premotor burst neurons (EBNs and IBNs) on the contralateral side while these latter neurons exhibit their maximal bursts (in their “on-direction”; cf. Fuchs et al. 1985). Because the vast majority of cerebellar nuclear projections to the pons appear to be excitatory (Angaut and Sotello 1989; Kitai et al. 1976; Schwarz and Schmitz 1997; Verveer et al. 1997), one hypothesis is that the burst of FOR neurons during contraversive saccades contributes to the on-direction burst in contralateral EBNs and IBNs, and therefore to the production of force in agonist motoneurons and the reduction of force in antagonist motoneurons, respectively. An effect on the onset and/or offset of the OPN pause is also possible. FOR neurons also exhibit a more delayed burst during ipsiversive saccades that seems to be best correlated with the end of the saccade. Ohtsuka and Noda (1991a) report that the burst for individual neurons begins at a fairly fixed interval before saccade end that averaged 31 ms, regardless of saccade size. By the contralateral projection, this late burst could augment the late off-direction discharges of EBNs and IBNs (Scudder et al. 1985; van Gisbergen et al. 1981). Augmenting the off-direction discharges would have the effect of “braking” the saccade (Ohtsuka and Noda 1991a). However, the tight relation of the FOR-neuron burst to saccade end would seem to require a more secure mechanism, that is, indirect control of all burst neurons by affecting the resumption of OPN firing.

Fastigial neurons also project to the superior colliculus and could affect saccade size by this pathway. However, there are conflicting data regarding the strength of this projection (reviewed by Scudder et al. 2002) and whether the projection is just to the “fixation neurons” (Munoz and Wurtz 1993) in the rostral colliculus (May et al. 1990) or is more widespread (Batton et al. 1977; Gonzalo-Ruiz et al. 1988, 1990; Kurimoto et al. 1995).

Given that mechanisms are available for cerebellar control of saccade size and that these mechanisms do exert powerful effects on saccade size, it stands to reason that the cerebellum could mediate the adaptive processes described above. Nonetheless, evidence for this hypothesis is meager. The fact that the saccadic dysmetrias produced by chronic cerebellar lesions are enduring and are not corrected by adaptation argues for this hypothesis. Goldberg et al. (1993) extended this conclusion by showing that monkeys with large electrolytic lesions including the fastigial nuclei had no capacity to change saccade size when subjected to intrasaccadic target displacements. Optican and Robinson (1980) combined large lesions of the monkey posterior cerebellum with muscle weakening in one eye. Monocular viewing with the normal eye resulted in enduring hypometria, as expected from other binocular studies, but monocular viewing using the weakened eye did not produce sufficient dysmetria for a critical test.

The current study attempted a direct test of the hypothesized role of the cerebellum in saccade adaptation by searching for the neural correlates of that adaptation. The discharges of neurons in the caudal fastigial nucleus of our monkeys were recorded extracellularly during ongoing adaptation produced by alternately patching a surgically weakened or normal unoperated eye. Our approach was to correlate a variety of FOR-neuron discharge parameters with saccade size as it changed to reveal those discharge parameters that were modified in a repeatable manner. We applied this approach consistently because the hypothesis is that adaptation functions to reduce the amplitude error (i.e., change saccade size) regardless of the precise neural mechanisms that mediate the change. As noted above, possible mechanisms include those that modulate EBN and IBN burst frequency and those that modulate burst duration, which also has the effect of modulating saccade duration. In fact, our results show that FOR-neuron discharges change during adaptation in multiple ways that can modify EBN and IBN burst frequency and duration, albeit not always in ways that maintain normal saccade amplitude–duration relationships.

A preliminary report based on a smaller sample of neurons has appeared as an abstract (Scudder 1998).

METHODS

Three juvenile rhesus monkeys were used in these experiments. All procedures were approved by the Institute Animal Care and Use Committee and conform to guidelines issued by the National Institutes of Health.

Surgery

Monkeys were surgically prepared for eye movement recording during two aseptic procedures in which they were deeply anesthetized with halothane (1.5% in oxygen/nitrous oxide) after induction with ketamine. In the first surgery, a magnetic search coil was sutured to the sclera of the right eye and three acrylic lugs for the stabilization of the head were implanted as described previously (Scudder et al. 1998). The front lug also served as the receptacle for a metal stalk that held the eye patch. After training (see following text), monkeys underwent a second surgery to weaken the eye muscles of the left eye, to implant a search coil in the left eye, and to implant a recording...
chamber directed at the fastigial nuclei. The medial and lateral recti were detached from the globe and cut to about two-thirds their normal length. A length of absorbable suture bridged the gap between the cut end of each muscle and the original attachment of its tendon to help control the place where the cut muscle would reattach to the globe. The second search coil was implanted in the same manner as the first. The 20-mm-diameter recording chamber was placed in a craniotomy over the midsagittal plane. It was aimed 5–7 mm posterior to ear-bar zero and angled 20° posteriorly from stereotaxic vertical. The recording chamber was attached to the bone with self-tapping screws and dental acrylic. The chamber was filled with antibiotic gel and covered with a cap. For the duration of the experiments, the antibiotic gel was replaced daily and the dura cleaned with cotton swabs.

Behavioral apparatus and experimental tasks

Experiments began 3–4 wk after the second surgery. They were conducted in a dimly illuminated soundproof booth with the monkeys seated in a primate chair and their heads restrained. Surrounding their heads were two orthogonal pairs of magnetic induction coils that were used in conjunction with the implanted search coil for the measurement of eye movements (CNC Engineering). Eye movement signals were calibrated by having the monkey alternately fixate stationary targets at ±15° horizontal and vertical eccentricity.

Monkeys viewed a red, 0.3° target spot projected onto a textureless white screen formed into a vertically oriented quarter cylinder and situated 75 cm in front of the monkey. The target spot was generated by a laser diode and deflected by an X-Y mirror galvanometer system (General Scanning) under computer control (PDP 11/73). The computer determined the target location, monitored eye movements, and dispensed applesauce reward when on-target conditions were met. For training, food-deprived monkeys were required to fixate the target spot within an error “window” of 6° in all directions to receive a dollop (about 0.1 ml) of applesauce. As performance improved, the error window was reduced to 2° and monkeys were required to fixate ≥1.5 s after an on-target saccade.

One pattern of 16 possible targets located along 8 equally spaced directions on 8°- and 15°-radius circles and with a central fixation point was used to collect information about the relation between the size of saccades and the size and direction of saccades. The fixation point and any of the pseudorandomly chosen peripheral target locations were alternately illuminated so that the monkey made saccades to and from the fixation point in each of 8 directions. A 1.3- to 2.0-s period of fixation triggered the illumination of the next target. A second pattern consisting of two possible target locations separated horizontally by 20° was used to collect all data relating to adaptation of saccade size and the correlated changes in FOR neuron discharges. This pattern was used because it produced the most rapid adaptation (Scudder et al. 1998) and thereby maximized the probability of obtaining significant changes in a short period of time.

Long-term and short-term adaptation of saccade size was produced by forcing the monkey to view the world through the eye having surgically weakened eye muscles. Vision in the normal unoperated eye was blocked using an opaque rigid patch that mated with a receptacle attached to the front acrylic lug on the monkey’s head. Reverse adaptation (recovery) was produced by patching the weak eye. Monkeys were never allowed to experience binocular vision, either during the experiments or when housed in the animal facility. By long term, we mean that the monkeys would wear the patch on the same eye every day for 1 wk, beginning on a Friday. When recordings began the following Monday, the monkey had had sufficient time that saccades in the viewing eye could reach an asymptotic value of saccadic gain (saccade amplitude/target-step amplitude; Scudder et al. 1998), which we will call the initial state. When a suitable neuron was isolated (see following text), data from about 200 saccades were collected using first the circular target pattern and then the two-target linear pattern. The eye patch was then switched so the monkey viewed through the unadapted eye and data were again collected using the two-target linear pattern. Further data from 100 to 200 saccades were collected 20 min after switching the patch, and every 10–20 min thereafter as the saccadic system adapted to the new viewing condition. A few neurons were isolated long enough that adaptation slowed as saccade gain approached its asymptotic value for the particular viewing eye (0.8–0.95; Scudder et al. 1998). When this occurred, the target was then stepped intrasaccadically to produce additional visual error. If the monkey was viewing with the weakened eye, the target was stepped in the forward direction 3–4° (15–20% of the initial target step); if the monkey was viewing with the normal eye, the target was stepped in the backward direction 3–4°.

If the neuron was lost after only a brief period of isolation (<20 min of adaptation), the patch was switched back to cover the original eye and we attempted to isolate a new neuron. If isolation was maintained for a longer time and then lost, the patch was switched to the original eye and the remainder of the experiment was used to return saccade size to its initial state. Regardless, the monkey was returned to its cage with the patch on the original eye so that saccade gain would return to the same initial state for the experiment the next day. After 1 or 2 wk of such sessions, the patch would be placed over the original viewing eye on Friday afternoon so that the monkey would enter the lab adapted to viewing with the opposite eye during the next set of experiments.

Neuronal recording

Neuronal action potentials were recorded with commercially available 0.005-in. tungsten microelectrodes with 15-μm exposed tips (Micro Probe, Potomac, MD). Electrodes were loaded into a 24/21-gauge concentric cannula assembly that protected the electrode as both were lowered into the brain and through the tentorium cerebelli. The outer 21-gauge cannula was 8 mm shorter than the inner 24-gauge cannula so that only the latter penetrated the tentorium. Electrodes were driven the last 10-mm to the fastigial nucleus with a Trent-Wells motorized hydraulic microdrive.

Neurons exhibiting discharges related to saccadic eye movements were encountered 0.7–2.0 mm lateral to the midline in the most caudal 1–2 mm of the fastigial nucleus. The majority of neurons exhibited a burst of spikes during saccades, and some had very pronounced bursts (peak rates >500 spikes/s), which served as an unambiguous marker for the area. Preliminary data were collected for all isolated saccade-related neurons using the circular target pattern. Units selected for recording during adaptation had to have had excellent, stable isolation throughout the preliminary data collection. Neurons were also required to have a saccade-related response of ≥20 spikes/s, and to have a stronger response during horizontal saccades than during vertical saccades. Neurons failing the latter criteria were rejected under the supposition that they might function to control vertical and not horizontal saccades. Neurons meeting these criteria were tested during short-term adaptation using the procedures described above.

Data collection and analysis

Neuronal signals were conventionally amplified and filtered (0.2–10 kHz). Most data were digitized on-line. Spikes were converted to TTL pulses with a simple Schmitt trigger, and were given a time stamp to the nearest 0.1 ms. The 4 eye channels (horizontal and vertical eye position for both eyes) as well as the 2 target channels were sampled every 4 ms. Data were also binary-encoded for storage on VCR tape (Vetter 4000A). Two cells were digitized off-line using the same program, but using the taped backup data. Seven other cells were digitized off-line, and spikes were detected in software using DataWave Experimenters Workbench. Temporal resolution for spike occurrence was again 0.1 ms, and the sampling rate for the eye and target channels was 4 ms.

Neuronal discharge parameters and saccade metrics were computed.
from the digitized data using an interactive program similar to that used previously (Scudder et al. 1988). The user manually scrolled the data and placed a cursor near desired saccades. The computer (Pentium-based) found peak velocity and independently searched backward and forward in time for the first point where eye position reached that occurring during fixation before and after the saccade, respectively. Temporal resolution was improved by fitting the 4 adjacent persaccadic samples with a second-order polynomial with the vertex forced through the steady-state eye position. The time coordinate of the vertex was taken as the start or end of the saccade. The computer marked these points and the user accepted them or manually marked those that were in error (errors were usually in the vertical channel where eye velocity could change direction in the middle of a horizontal saccade). The user manually marked the approximate start and end of bursts and/or pauses in the neuronal discharges. The computer used the spike succeeding (preceding) the first mark as the onset of a burst (pause), and the spike preceding (succeeding) the second mark as the end of the burst (pause). From these marks and the eye positions at these marks, the computer determined the amplitudes of the horizontal and vertical saccadic components, and horizontal and vertical component durations. The computer also determined latency from saccade onset to burst onset, burst duration, and other discharge parameters. Because the firing rate of FOR neurons was frequently above the resting level at saccade termination, and because subsequent spikes obviously cannot affect the size of the terminated saccade, only spikes occurring between burst onset and saccade termination were included in the computation of number of spikes, average frequency (number of spikes/duration), and peak frequency. The last was defined as the average frequency of the three consecutive spikes spanning the shortest time interval.

As noted by Fuchs et al. (1993), burst onset could not always be marked with high reliability. In these cases, burst onset was determined from averaged instantaneous frequency data. The interval between successive spikes was assigned a frequency value equivalent to the reciprocal of the interval. Frequency was averaged across saccades by aligning all data on saccade onset. Burst onset was defined as the time when averaged frequency crossed the criterion of one third the difference between resting rate and peak burst frequency. For a given unit, the frequency criterion was determined from the data at the start of adaptation, and this same absolute value was applied to data acquired at all subsequent times. Measurements obtained with this method usually differed by a few milliseconds from the averaged discharge latency, but determinations at different times during adaptation were almost always in the same rank order for the two methods. Among neurons with well-defined burst onsets, the changes in burst onset during adaptation were nearly identical for the two methods. Similarly, burst end was poorly defined for some units and a graphical method was again used. Burst end was defined as the time when firing rate had dropped to 40% of the difference between peak rate and resting rate.

Saccades were excluded from the statistical analysis if the reaction time was too short (<70 ms) or too long (>600 ms), if the monkey was not initially on target (± 1.5°), or if the saccade was clearly not directed at the target. Saccades were also excluded if their durations exceeded 3.5 times the average value reported by Fuchs (1967) for a given size, or if the saccade size was 3.5 SDs away from the mean for the particular data set (about 0.3% of the data). Averaged saccade metrics (e.g., amplitude) and discharge parameters were always computed separately for leftward and rightward saccades. Measurements were statistically compared using Student’s t-test, and 2-tailed P values reported.

Data on saccade metrics after long-term adaptation were collected in association with the 28 neurons included in this study as well as with neurons that were not isolated long enough to be included. Means for each neuron were computed, and the average and SD of these means are reported. Preadaptation means and SDs of the discharge parameters (first section of RESULTS section) were obtained using the 20° target steps. Therefore some data were collected with the monkey adapted long term to using the normal eye and other data were collected with the monkey adapted long term to using the weak eye. The average saccade size for the combined data was 23.1 ± 4.4° (SD). Linear correlations were obtained between discharge and saccade parameters under two different circumstances, and the difference is important for understanding our findings. In the first circumstance, data were collected before short-term adaptation using the circle task, and the correlations describe how the discharges respond as saccade size and duration vary both naturally and to different size target steps. In the second, data were obtained during short-term adaptation, and the correlations describe how the discharges respond as saccade size changes because of adaptation. The process of obtaining the latter correlations are described more fully in the RESULTS.

Plots of average eye position versus time and averaged discharge rate were generated for illustrations. Instantaneous frequency was computed as described above, and eye position and frequency traces were aligned on saccade onset and averaged. Each data point corresponds to one 4-ms sample interval.

Anatomy and histology

At the completion of all experiments, monkeys were deeply anesthetized and perfused through the heart with buffered saline followed by buffered 4% paraformaldehyde. The fixed brain was sectioned coronally and sections were processed for neuroanatomical tracers (to be reported separately) and counterstained with Neutral Red. We confirmed that electrode tracks passed through the caudal pole of the fastigial nucleus, but we did not attempt to plot the location of recorded cells on individual tracks.

RESULTS

A total of 127 saccade-related neurons encountered in the caudal fastigial nucleus met the criteria for prolonged recording during adaptation of saccade size (see METHODS). Of these, only 28 met the additional criteria of being isolated long enough for the saccade size to change ≥5%. This report focuses on these 28 neurons: 18 from monkey M, 7 from monkey S, and 3 from monkey G. Eighteen neurons were recorded during size increases, whereas 10 were recorded during size decreases.

General features of included neurons: preadaptation data

The neurons used in this study were generally similar to those reported elsewhere (Fuchs et al. 1993; Ohtsuka and Noda 1990, 1991a). Averaged data from a typical neuron are illustrated in Fig. 1 for 20° horizontal target steps. All the neurons exhibited a burst of spikes during contraversive saccades that began on average 4.2 ± 8.1 ms (SD, n = 28) before the onset of saccades averaging 23° (see METHODS). Although other investigators have emphasized the early lead of this burst (18.5 ms, Ohtsuka and Noda 1991a; 10.5 ms, Fuchs et al. 1993), the burst began after saccade onset in 25% of our sample. In fact, one monkey (S) had a predominance of such neurons, with a mean lead of −3.7 ms. The peak discharge, which averaged 229 spikes/s for the full sample, nearly always occurred during the saccade. Some neurons appeared to have two bursts: one near saccade onset, and a second smaller burst before saccade end. For 7 neurons, the burst nearly always (>85% of saccades) ended before the saccade ended, whereas for 7 other neurons, including that in Fig. 1, the burst nearly always (>85%) ended later than the saccade. The remaining 14 units...
Neural correlates of saccade adaptation

In the majority of neurons, behavior was in between.

Between saccade start and burst onset (burst lag) was nearly invariant, but there were 2 other neurons where the interval between saccade start and burst onset (burst lag) was nearly invariant. In the majority of neurons, behavior was in between.

Exhibited intermediate behavior, with some bursts ending before and some later than the saccade. For the whole sample, the average end of the burst occurred at about the end of the saccade. The burst was preceded by a 20–50% diminution in firing rate in 8 units and was followed by a diminution in firing in 6 units. Overall, these discharge patterns fit within the “burst,” “pause-before-burst,” and “burst-before-pause” types described by Fuchs et al. (1993). A small number of neurons that exclusively paused were also encountered, but are not included in this report.

Adaptation of saccade size

The process of adapting saccade size using the appropriate patching of the paretic or normal eye is illustrated for monkey “M” in Fig. 2, A–D. Initially (Fig. 2A), monkeys wore the patch over the weak eye and viewed the target with the normal eye. Target steps elicited saccades in the normal eye (top traces) that accurately acquired the target, but saccades measured in the nonviewing weak eye were approximately half the size of the target step (bottom traces). After recording initial saccade and neuronal-discharge data, the patch was switched to cover the normal eye. Figure 2B illustrates typical eye movements recorded immediately thereafter. Saccades in the (now viewing) weak eye were still severely hypometric, thereby requiring multiple corrective saccades to finally acquire the target. Simultaneously, the initial saccade measured in the (nonviewing) normal eye was still roughly equal to target displacement (dotted line). Saccade size measured in both eyes began increasing immediately (Scudder et al. 1998) and changed measurably over 20 min. Saccade size in the weak eye ultimately reached an asymptotic value that undershot the target (Scudder et al. 1998), but this value was not achieved over the period that FOR neurons remained isolated. Long-term asymptotic horizontal gains measured in the viewing weak eye in monkeys M, G, and S were 0.85, 0.95, and 0.90, respectively. The saccade in Fig. 2C exhibits this long-term adapted gain. Horizontal gain measured in the nonviewing normal eye was about 1.8. For 10 of the neurons, this was the initial state of adaptation. Switching the patch to cover the weak eye produced the eye movements illustrated in Fig. 2D. Saccade size was initially the same as that measured in the previous panel (Fig. 2C), so that saccades measured in the viewing normal eye severely overshot the target. Saccade size decreased more rapidly than saccade size previously increased. Long-term patching of the weak eye resulted in eye movements comparable to those illustrated in Fig. 2A. Although this readaptation to use of the normal eye is operationally a “recovery,” we caution that this word carries mechanistic implications that we believe do not.

**FIG. 1.** Averaged discharges of typical saccade-related fastigial nucleus neuron illustrated for rightward saccades (top) and leftward saccades (bottom). Neuron was recorded in left nucleus, so rightward movement (illustrated as upward) is contraversive and leftward movement is ipsiversive. For both top and bottom panels, averaged horizontal position of viewing weak eye (H.Eye), spike rasters for first 12 saccades, and averaged firing rate (FR) are illustrated. For averaging, saccades were aligned on saccade onset (thin vertical line). Neuron has burst onset times and peak frequencies typical of sample, but burst durations are longer than average.

Overall, burst lag was significantly correlated with saccade duration in 24 neurons, but on average, increased 0.55 ± 0.27 ms (SD, n = 28) for every 1-ms increase in saccade duration (average r = 0.68, range 0.07–0.98). This slope is considerably less than the 1.0 ms/ms slope stipulated by Ohtsuka and Noda. The variability about this relation (square-root of the error variance) was 9.0 ms (range 2.4–22.9).

Ipsiversive burst lag was also correlated with saccade size (1.22 ± 0.71 ms/deg, n = 28), but less well than with saccade duration (average r = 0.56, range 0.04–0.94). Thus the dependency on size could be a byproduct of the correlation between saccade size and saccade duration.

The ipsiversive burst was preceded by a full cessation of firing in 13 units, and a significant reduction (e.g., 50%) in another 7. The firing rate at the end of the saccade remained elevated above the resting rate in most of the neurons (22 of 28), and this was followed by a diminution or outright pause in firing in 6 units. Overall, these discharge patterns fit within the “burst,” “pause-before-burst,” and “burst-before-pause” types described by Fuchs et al. (1993). A small number of neurons that exclusively paused were also encountered, but are not included in this report.
apply to short-term adaptation of saccade size. The vertical component of the saccades changed negligibly during the patch-switching paradigm.

In the long term, increases in saccade size produced by viewing with the weak eye were accomplished by increases in saccade duration and increases in saccade velocity. Measurements were made in the normal eye, and data from rightward and leftward saccades, which were somewhat but not significantly different, were combined. Long-term increases in saccade size for 20° target steps averaged 11.5° and were accompanied by an increased duration of 29.3 ms (67.7 ± 8.0 to 97.0 ± 13.7) and an increased peak velocity of 43°/s (548 ± 45 to 591 ± 68). These differences were significantly different (P < 0.02, n = 51). The change in duration was the dominant factor in increasing saccade size; the 62% change in saccade size was accomplished with a 43% increase in duration and an 8% increase in velocity. Adapted and unadapted “main sequence” parameters (Bahill 1975) were compared for 10° and for 15° saccades in the normal eye (values of maximal overlap for adapted and unadapted saccades using the circular target pattern). Adapted saccades had slightly, but significantly, smaller durations and velocities. For instance, unadapted and adapted durations for 15° saccades averaged 57.7 ± 5.5 (n = 45) and 50.9 ± 6.7 (n = 55) ms, respectively, whereas unadapted and adapted peak velocities were 519 ± 41 and 491 ± 42 deg/s. The smaller saccade durations and velocities associated with saccades of the same size imply that the basic shape of the velocity profiles must have changed.

Short-term changes in saccade size (those occurring during recording sessions) were smaller than the long-term changes. For the 18 gain-increasing experiments, saccade gain (weak eye) began at around 0.61 (range 0.43–0.76) and increased to 0.69. Saccade size (normal eye) began at an average 22.5° and increased by 1.3–10.6°, with a mean increase of 4.3°. Saccade size began at a value >20° because the muscle weakening produced nonlinearities in the orbit (Scudder et al. 1998) and because adaptation had been attempted before the successful recording in some electrode penetrations. For the 10 gain-decreasing experiments, saccade size began at an average 25.5° and decreased by 1.3–13.2°, with a mean decrease of 6.3°. All changes were statistically significant at P < 0.01 or better.

As in the long term, short-term changes in saccade size were usually accomplished by changes in saccade duration and peak velocity, although there was considerable variability. In some cases, for instance, saccade duration changed negligibly and/or saccade velocity did not change or changed in the “wrong” direction (velocity decreased as size increased). In these cases, the shape of the velocity profiles must have changed during adaptation. To illustrate this, we plotted the averaged velocity profiles of rightward saccades recorded during a session in which saccade size, but not duration or peak velocity, had increased after 40 min of adaptation (Fig. 3). The 11% increase in saccade size was accomplished by a relative increase in velocity during the deceleration phase of the saccade. Similar results were obtained in two more conditions from two neurons where saccade duration and peak velocity changed negligibly (leftward and rightward saccades were separately averaged for a total of 56 conditions). For the remaining conditions, we computed the product of averaged peak velocity times aver-

![Diagram](http://jn.physiology.org/Downloaded_from/IJNphysiology.org_by_10.2307.33.1_on_August_14,2017)

**FIG. 2.** Adaptation of saccade size produced by patching of either normal or weak eye. Four stages of adaptation (A–D) are shown for typical single trials in clockwise order. Horizontal position is illustrated for visible target (Targ), normal eye (N.Eye), weak eye (W.Eye), and unseen target relative to patched eye (dotted lines). Vertical target and vertical eye positions were unchanged during adaptation. Initially, patch-covered weak eye and normal eye viewed target (A). Adaptation was initiated by switching patch to cover normal eye so that saccades in viewing weak eye were severely hypometric (B). After viewing with weak eye for a day or more, saccade size increased in both eyes (C). Finally, switching patch back to cover weak eye resulted in severely hypermetric saccades in viewing normal eye (D). Long-term adaptation to this situation produced decreases in saccade size and return to normal-sized saccades in normal eye (A).
aged duration and compared the changes in this product during adaptation to the averaged changes in saccade size. If wave-shape did not change, this product would scale directly with saccade size so that the percentage change in the product and the measured size would be equal. There was a gross inequality in 6 additional conditions; the percentage changes in this product were 2.5 to 4 times smaller than the percentage changes in saccade size. All these instances of unusually small increases in duration and peak velocity were obtained during gain-increasing experiments, and most (7/9) were obtained from one monkey (S). Both the long- and short-term data show that adapted saccade duration and peak velocity need not fall on the main sequence, and that these two parameters are not sufficient for characterizing all the changes that occur during adaptation.

Changes in discharge patterns during adaptation

Based on the possible mechanisms mentioned in the introduction by which FOR neurons might affect saccade size, the discharge onset time, discharge offset time, peak frequency, average frequency, and number of spikes were all considered important parameters to monitor during adaptation. One parameter exhibiting changes during adaptation was the burst lag for ipsiversive saccades. Because the ipsiversive burst was postulated to “brake” or truncate the saccade, earlier discharges should be associated with smaller saccades, just as they are in unadapted animals. Figure 4 illustrates this association for one neuron. Plots are averages of 54 and 44 saccades aligned on saccade onset. Before the experiment, the monkey had been wearing the patch on the normal eye so that switching the patch to the weak eye caused hypermetric saccades in the now viewing normal eye (Fig. 4, top). Saccade amplitude averaged 26 ± 1.6° in response to the 20°-target step. However, after 2 h of performing the saccadic tracking task, average saccade amplitude in the normal eye declined to 19.4 ± 1.7°, and there was a corresponding significant decrease in the average burst lag from 73.0 ± 14.5 to 60.1 ± 11.4 ms (P < 0.0001, n = 98).

To quantify the results in this and in the other neurons, burst lag was plotted as a function of saccade size for all time points where data were collected. Figure 5 illustrates 8 such plots for 8 neurons selected to show the range of the data. For neurons plotted on the right-hand side, the monkey had previously been viewing with the weak eye, and data were collected after the patch was switched so that the normal eye became the viewing eye (Gain− condition). This is like Fig. 4, where initially overshooting saccades (size > 20°) decreased in amplitude over time. Note that the size sometimes went below 19° (a normal saccade size to a 20° target) because of the use of backward intrasaccadic target steps (see METHODS). For neurons plotted on the left-hand side, the monkey had previously been viewing with the normal eye, and data were collected after the weak eye became the viewing eye (Gain+ condition). Gain increased during adaptation in these cases. Figure 5 illustrates that for some neurons, increasing saccade sizes were associated with increasing burst lags, although there were others where lag decreased. Among these is a neuron whose ipsiversive burst began before saccade onset (burst lag <0).

To compare data from neurons with different magnitudes and directions of adaptation on an equal basis, discharge data were normalized to +1° change in saccade size. This is equiva-
not significantly different from zero.

Slopes recorded during gain-decreasing (Gain−) experiments were mostly clustered around zero with slight positive mean (thick arrow). Slopes recorded during gain-increasing (Gain+) experiments, most neurons exhibited positive slopes, and the small positive average slope was gain-increasing experiments, slopes were more uniformly distributed about zero, and the small positive average slope was significantly greater than zero (Table 1). For gain-decreasing experiments, most neurons exhibited positive slope, and the mean slope was significantly greater than zero (Table 1). For gain-increasing experiments, slopes were more uniformly distributed about zero, and the small positive average slope was not significantly different from zero.

If ipsilateral burst lag exerts control over saccade duration, there should be a correlation between changes in these variables as adaptation progresses. Figure 7 shows this correlation for the sample of 28 neurons. Changes in burst lag relative to that at the start of adaptation are plotted against changes in saccade duration for all time points where data were collected. The slope of this relation was 0.64 and the correlation coefficient was 0.71 (P < 0.0001, n = 76). Some scatter is expected because ipsiversive burst lag is surely not the only determinant of saccade duration. In addition, 4 atypical “untuned neurons” (squares), to be described more fully later, almost align along

![Image](https://via.placeholder.com/150)

**FIG. 5.** Burst lag (time from saccade onset to burst onset) associated with ipsiversive saccades is plotted as function of saccade size in viewing eye for 8 representative neurons. Nonoverlapping curves were selected to show range of data. Symbols plot average lag against average size for 38–70 saccades collected at discrete intervals during adaptation. Traces to left of 20° saccade size decreased during Gain− experiments, but changed more variably during Gain+ experiments. Error bars: ±1SE of burst lag or saccade size. Most standard errors were smaller than symbol size (±1.6 ms lag, ±0.28°). SDs for 8 neurons averaged ±10.6 ms for lag, and ±1.34° for size. Neuron in Fig. 4 corresponds to uppermost plot (solid squares).

![Image](https://via.placeholder.com/150)

**FIG. 6.** Histogram of slope of regression of ipsiversive burst lag against saccade size for 28 neurons. Slopes recorded during gain-increasing (Gain+) experiments clustered around zero with slight positive mean (thick arrow). Slopes recorded during gain-decreasing (Gain−) experiments were mostly positive with significant positive mean (thin arrow).

![Image](https://via.placeholder.com/150)

**FIG. 7.** Scatter plot illustrating that changes in ipsiversive burst lag are correlated with changes in saccade duration during adaptation. Each point represents difference between lag or saccade duration measured at initiation of adaptation and that measured at subsequent time periods (e.g., 20, 40, 60 min). Data from gain-decreasing experiments are shown in light symbols and data from gain-increasing experiments are shown in dark symbols. Light and dark squares plot data from 4 “untuned” neurons that had atypical discharges (see RESULTS, last section). Change in burst lag and saccade duration are well correlated (r = 0.71, n = 76, P < 0.0001) with slope of 0.64 ms/ms.

<p>| TABLE 1. Slope of saccade and discharge parameters over saccade size during adaptation |
|---------------------------------------------|----------------|----------------|----------------|----------------|</p>
<table>
<thead>
<tr>
<th></th>
<th>All neurons</th>
<th>Gain+</th>
<th>Gain−</th>
<th>Difference (G+)−(G−)</th>
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<tr>
<td></td>
<td>n = 28</td>
<td>n = 18</td>
<td>n = 10</td>
<td></td>
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<td>Saccade duration (ms/deg)</td>
<td>2.48***</td>
<td>2.22***</td>
<td>2.93*</td>
<td>0.71</td>
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<tr>
<td>Burst lag (ms)</td>
<td>(2.16)</td>
<td>(1.60)</td>
<td>(2.96)</td>
<td>(3.46)</td>
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<tr>
<td>Number of spikes (spikes/deg−1)</td>
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<td>0.34**</td>
<td>−0.27</td>
<td>0.62**</td>
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<tr>
<td>Average frequency (spikes−1 deg−1)</td>
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<td>1.92</td>
<td>−4.33*</td>
<td>6.26*</td>
</tr>
<tr>
<td>Peak frequency (spikes−1 deg−1)</td>
<td>1.83</td>
<td>6.88**</td>
<td>−7.24*</td>
<td>14.1**</td>
</tr>
</tbody>
</table>

Values in parentheses are ± SD. Main entries are mean values of slope for n neurons. * P < 0.05; ** P < 0.01; *** P < 0.002.
increase in saccade size was a significant increase in peak burst frequency from 254 ± 42 to 277 ± 47 spikes/s \( (P < 0.02) \), and a significant increase in burst duration from 54 ± 13 to 69 ± 15 ms \( (P < 0.0001) \). The increase in burst duration was mostly produced by a later termination of the burst. Changes in burst frequency and duration collectively produced a significant increase in number of spikes from 10.5 ± 2.5 to 13.1 ± 2.4 spikes \( (P < 0.0001) \).

This pattern of changes was reflected in the sample as a whole. Burst frequencies, burst onset- and end times, and number of spikes were regressed against saccade size during adaptation, and the resulting slopes were tabulated. Figure 9A shows the most robust finding of this study: the number of spikes in the burst was positively correlated with saccade size in all but one neuron, and the mean slope \( (0.55 \pm 0.44 \text{ spikes/deg}, n = 28; \text{Table 1}) \) was highly significantly different from zero. Slopes associated with gain-increasing and gain-decreasing experiments were similar but not identical (Table 1). As in Fig. 8, changes in the number of spikes were produced by changes in burst duration and discharge frequency. Figure 9B shows that peak discharge frequency was positively correlated with saccade size in most (21/28) neurons, and the mean value of the slope was significantly greater than zero (Table 1). The mean slope for gain-increasing experiments was greater than that for gain-decreasing experiments, but not significantly \( (P = 0.25) \). Burst duration was also strongly and positively correlated with saccade size for most neurons. Figure 9C shows that the end of the burst, measured graphically or by marking individual bursts (see METHODS), was positively correlated with saccade size for 24 of 28 neurons and had a significant positive mean. A caveat is that this change in burst end did not fully contribute to the change in number of spikes because burst end occurred after the end of the saccade for about half of all bursts (the spike count was truncated at saccade end; see METHODS). So the changes in number of spikes can loosely be attributed to three factors: 1) changes in peak frequency, 2) changes in burst end for those neurons with shorter bursts, and 3) changes in saccade duration acting on those neurons with longer bursts. Finally, a fourth factor contributing to a change in number of spikes was a moderate change in burst lead (0.54 ms/deg), which was about 1/4th of the change in burst end, and in the complementary direction (increased size was associated with earlier burst onset and later burst end).

Can all neurons contribute to size changes?

This study seeks to determine whether changes that occur in the discharges of FOR neurons are appropriate for causing the changes in saccade size observed during saccade adaptation. However, it is not necessarily true that all saccade-related neurons are candidates for this function. For instance, Sato and Noda (1991) raised the possibility that some neurons preferentially or exclusively control vertical saccades by showing that some caudal fastigial neurons are retrogradely labeled from the mesencephalic reticular formation (the site of the vertical burst generator) and not the pontine reticular formation. Similarly, Noda et al. (1992) found a separation of sites in the fastigial efferent pathways of the uncinate fasciculus where microstimulation elicited vertical rather than horizontal saccades. We attempted to obviate this possible problem by pre-
selecting neurons for study. Among neurons that do project to the pontine reticular formation, not all may serve the same function. Scudder et al. (2000) found that only a fraction of fastigial neurons retrogradely labeled from the EBN and from the IBN regions were double labeled, and there was a partial separation of neurons projecting to each area. Consequently, we searched for criteria that might isolate neurons that are poor candidates for participation in the adaptation of horizontal saccades.

The discharges recorded during the circle task before adaptation were analyzed for directional characteristics using the model described earlier. That is, prototypical horizontal FOR neurons have an early burst containing more spikes for contraversive saccades and a later burst with fewer spikes for ipsiversive saccades. Two neurons had their longest lead and maximum number of spikes for downward saccades, whereas their longest lag and fewest spikes occurred during upward saccades. These two were classified as vertical neurons, and two others were classified as vertical-oblique. During adaptation, the number of spikes, burst duration, and peak frequency in the contraversive burst were all positively correlated with saccade size for all 4 neurons, and the slopes were within 1SD of the mean for the full sample. Similarly, for 3 of these neurons, burst lag for ipsiversive saccades was strongly positively correlated with saccade size during adaptation, whereas one vertical neuron exhibited negative correlations. In short, these neurons behaved much like the other 24 neurons with regard to encoding saccade size during adaptation.

Analysis based on the circle task also revealed 4 neurons that had minimal or no directional tuning based on burst latency and number of spikes. In addition, these cells had very poor (nonsignificant) preadaptation correlations between ipsiversive burst lag and saccade size or saccade duration; and finally, ipsiversive burst lag itself was close to zero or negative (the burst actually led saccade onset). These neurons would not appear to be good candidates for controlling saccade size according to the hypotheses stated in the INTRODUCTION, and in fact they were not. During adaptation, 2 of the neurons exhibited very small or negative correlations between number of spikes and contraversive saccade size, and 3 exhibited negative correlations between ipsiversive burst lag and ipsiversive saccade size. This latter point is illustrated in Fig. 10, which also illustrates the more general point that the best predictor of the change in ipsiversive burst lag during adaptation (“Lag Sensitivity”) was the absolute burst lag that was recorded at the initiation of adaptation. These variables were related with a correlation coefficient of 0.57, which is significant at \( P < 0.005 \). Other variables were not significantly correlated with change in burst lag during adaptation. In fact, the preadaptation slope of the correlation between ipsiversive burst lag and saccade size was a poor predictor of the preadaptation slope (\( r = 0.19; P > 0.3 \)).

Elimination of the 4 untuned neurons from the sample averages produced minor (<10%) changes for most variables. However, the sensitivity of ipsiversive burst lag to saccade size increased 38% to 1.77 ms/deg. Sensitivity increased for both the gain-decreasing and the gain-increasing experiments, so that the mean for the latter approached significance (\( P = 0.10 \)). The other significant change was a 44% reduction (to 1.88 spikes s\(^{-1}\) deg\(^{-1}\)) in the sensitivity of contraversive peak discharge frequency to saccade size during gain-decreasing experiments. For gain-increasing experiments, sensitivity of peak frequency increased moderately (9%), so that the difference between gain-increasing and gain-decreasing experiments approached significance (\( P = 0.07 \)). Elimination of the 4 vertical and oblique neurons produced little additional change in the average sensitivity of discharge parameters to adaptation of saccade size.

FIG. 9. Histograms of slope of regression of number of spikes (A), peak frequency (B), and burst-end (C) against size of contraversive saccades during adaptation. Mean values of slope for number of spikes and burst-end are similar for Gain \(+\) and Gain \(-\) experiments, so average of full sample is marked with single arrow. Mean values of slopes for peak frequency are not similar (Table 1), and thus are marked separately for Gain \(-\) experiments (thin arrow) and Gain \(+\) experiments (thick arrow).
DISCUSSION

This study has shown that there are several parameters of FOR-neuron discharges that change significantly as saccade size is adaptively modified. The number of spikes in the burst for contraversive saccades positively covaried with saccade size in all neurons but one, and this was in turn produced by changes in peak burst frequency and in burst duration. Ipsiversive burst lag positively covaried with saccade size in the majority of neurons, but neurons changed differently during the gain-increasing and gain-decreasing experiments. Overall, gain decreases were associated with larger changes in ipsiversive burst lag, but smaller changes in contraversive peak frequency, when compared with gain increases. This dichotomy was more evident after removal of the directionally untuned units having ipsiversive bursts that led saccade onset. Assuming that the changes in FOR discharges that we recorded are partly responsible for the changes in saccade size, as we argue later, our data suggest that short-term gain decreases are not accomplished by simply reversing the mechanism of short-term gain increases. However, a full reversal presumably occurs over the long term.

An asymmetry in the mechanisms mediating gain increases and decreases is consistent with the properties of synaptic plasticity. In the cerebellum, for instance, where plasticity exists throughout the sequence of synapses from the mossy fibers to the deep cerebellar nuclei (Aizenman et al. 1998; Armano et al. 2000; Crepel and Jaillard 1991; D’Angelo et al. 1999; Hansel et al. 2001. Morishita and Sastry 1996; Ouardouz and Sastry 2000; Salin et al. 1996), long-term potentiation and long-term depression do not always coexist at the same synapses or are more readily induced at some synapses than others. Long-term potentiation and depression at the same synapse often occur at different rates and are produced by distinctly different stimuli. Consequently, it is possible that the changes in one set of synapses that mediate gain increases are not as readily reversed, allowing a different set of synapses with more auspicious properties to initially mediate the gain decreases.

Given the dichotomy in neuronal changes during gain-increasing versus gain-decreasing experiments, we had expected to see a dichotomy in the eye movement responses, with larger changes in saccade peak velocity and smaller changes in duration for gain increases compared with gain decreases. However, no significant differences were observed. A partial explanation might be found in the change in saccade waveshape, whereby the increase in velocity found during gain-increasing experiments occurred in the epoch after peak velocity. A second explanation is that changes in peak frequency probably also affect saccade duration using mechanisms that are described later.

Apparently, not all FOR neurons participate in the modification of saccade size. The untuned neurons, whose bursts resembled the contraversive burst of other neurons in all directions, were poor candidates for controlling saccade size according to the mechanisms summarized in the introduction and described more fully later. In some ways, they behaved oppositely to the other neurons during adaptation. On the other hand, one vertical and two oblique neurons, which at first might seem to be poor candidates for controlling the size of horizontal saccades, did participate in saccade adaptation. The paradox can be resolved by noting that there are not discrete populations of horizontal and vertical FOR neurons, but rather a continuum of best directions (Fuchs et al. 1993; Ohtsuka and Noda 1991a). Consequently, many of the FOR neurons with off-vertical preferences might nonetheless project to the horizontal burst neurons in the pons in addition to projecting to vertical burst neurons in the mesencephalon. Such neurons could have adaptively altered discharges during horizontal saccades and not have altered discharges during vertical saccades because there can be separately adapted horizontal and vertical inputs from the cerebellar cortex (Deubei 1987; Noda and Fujikado 1987).

In the remaining discussion, we consider the question of whether the changes in neuronal firing we observed during adaptation might cause the changes in saccade size. The question has two parts: 1) are there plastic changes occurring in the cerebellum that produce the changes in FOR-neuron firing, or do the cerebellar signals change as a byproduct of plastic changes occurring in structures that provide input to the cerebellum, and 2) are the changes in FOR-neuron discharges appropriate and sufficient to produce changes in saccade size.

The location of plastic synapses

To address the first question, we begin by considering the possible sites that both provide input to the cerebellum and might undergo plastic changes. Figure 11 shows a simplified block diagram of the saccadic system that is based on known connections. We have ignored cortical inputs from the frontal eye fields and parietal cortex, which principally impinge on the superior colliculus and project more weakly to the brain stem (Leichnetz and Gonzalo-Ruiz 1987; Lynch et al. 1985; Stanton...
FIG. 11. Schematized diagram of relationship between cerebellum and saccadic burst generator. Command to generate saccade emanates from superior colliculus and is conveyed both to saccadic burst generator and to precerebellar relay nucleus, nucleus reticularis tegmenti pontis (NRTP). NRTP efferents ascend to cerebellum as mossy fibers and make excitatory connections with FOR neurons and with granule cells in lobule VI and VII of vermis. A weaker path originates in paramedian pontine reticular formation (PPRF) and terminates on FOR and lobule VII neurons. Granule cells excite Purkinje cells that in turn inhibit fastigial nucleus neurons. FOR neurons project back to reticular formation where they contact many of the same cells that receive input from superior colliculus. This indirect pathway from superior colliculus through cerebellum is thought to contain plastic synapses that mediate adaptive modification of saccade size and direction.

et al. 1988). The superior colliculus is therefore regarded as a nodal point for collecting inputs from the cortex and basal ganglia and, in turn, issues the immediate saccadic command to the brain-stem saccadic burst generator. The superior colliculus also projects heavily to the cerebellum by way of nucleus reticularis tegmenti pontis (NRTP) and parts of the pontine nuclei in both cats and monkeys (Batini et al. 1978; Gerrits and Voogd 1987; Gonzalez-Ruiz and Leichnetz 1990; Graham 1977; Harting 1977; Huerta and Harting 1982; Kawamura 1974; Scudder et al. 1996a; Thielert and Thier 1993). The neurons of the saccadic burst generator (EBNs, IBNs, and OPNs) do not project to the cerebellum (Strassman et al. 1986a,b), and their signals may reach the cerebellum indirectly only through the smaller pathways originating in the pontine reticular formation and in raphe pontis (Fig. 11, thin lines).

This circuitry makes it unlikely that any plastic changes occurring in the brain-stem burst generator make substantial contributions to the changes we recorded in the FOR. Thielert and Thier (1993) estimated that afferents from the medial pontine reticular formation constitute only 5% of the afferents to vermal lobule VII and VIc. In short, the feed-forward pathways from the superior colliculus to the cerebellum are substantial, whereas the feedback pathways from the brain-stem burst generator are currently speculative and at best, considerably weaker. The small size of this putative feedback pathway makes it difficult to explain how plasticity in the burst generator could produce substantial changes in the discharge of FOR neurons assuming it is combined with a much larger signal that is unchanged during the adaptation paradigm. A case in point is ipsiversive burst lag, which changed in excess of the changes in saccade duration during the gain-decreasing experiments (3.2 vs. 2.9 ms/deg; Table 1). Because OPN pause and EBN and IBN burst durations covary one-to-one with saccade duration (cf. Fuchs et al. 1985), it is hard to see how weak feedback from these neurons could cause even an equal change in burst lag, much less a greater change.

The strong inputs from the superior colliculus to the cerebellum by NRTP suggest that plastic changes occurring in the colliculus could result in changes in the discharge of cerebellar neurons, should such plastic changes actually occur. However, Frens and van Opstal (1997) found no evidence of plastic changes occurring in the colliculus during short-term adaptation of saccade size. These authors measured the discharge of neurons in the superior colliculus before and after adaptation produced by backward intrasaccadic steps of the target. For target steps of a constant size, the discharges of these neurons did not change as saccade size decreased, even though in a control experiment, they discharged less when monkeys made equivalently smaller saccades to target steps of a smaller size.

Complementing the evidence that the altered discharges are not reflections of plastic changes occurring in the brain stem or superior colliculus, there is evidence that they could be the result of plastic changes occurring in the cerebellum. Reiterating the point made in the introduction, lesions of the cerebellum produce enduring saccadic dysmetria (Aschoff and Cohen 1971, 1972; Optican and Robinson 1980; Ritchie 1976; Selhorst et al. 1976a,b; Takagi et al. 1998). If there were plastic mechanisms elsewhere in the brain, one would expect these mechanisms to correct the dysmetria created by cerebellar lesions (unless these mechanisms were completely dependent on signals from the cerebellum). Note that the adaptation that we produced in a matter of hours could change saccade size by a factor of almost 2, and that this ratio is comparable to the short-term dysmetria produced by chemical inactivation of the fastigial nuclei (Robinson et al. 1993). Hence, it is difficult to argue that cerebellar lesions produce a dysmetria so profound that it exceeds the capacity of extracerebellar plasticity to compensate. A direct test of the capacity of cerebellar-lesioned animals to adapt saccade size was made by Takagi et al. (1998) and Barash et al. (1999). Monkeys with bilateral lesions of the posterior vermis, including lobule VII, tracked a target that stepped backward intrasaccadically. Unlike in normal monkeys, this paradigm did not produce decreases in saccade size. After a number of months, monkeys did recover limited adaptive capabilities, but it seems clear that these capabilities are different from those present in cerebellar-intact animals.

Finally, another reason for believing that the plastic synapses mediating adaptation are located in the cerebellum is the extensive demonstration of cerebellar plasticity, as previously described. The wealth of plastic synapses makes it plausible that different sets of synapses mediate gain increases and gain decreases, thereby offering a ready explanation for our findings that differing neuronal changes are observed in each case.

How the observed cerebellar changes might affect saccade size

Figure 12A is a simplified illustration of the probable projections of FOR neurons to saccade-related neurons in the reticular formation. The crossed projection to burst neurons (BN) includes both EBNs and IBNs. Moreover, there is a direct
crossed projection to OPNs. These projections have been strongly suspected on anatomical grounds (Noda et al. 1990; Scuddler et al. 2000) and have been confirmed electrophysiologically (Scuddler et al. 2000). In the latter study, the FOR was activated by low-rate microstimulation, and its effects on functionally identified neurons in the brain stem were measured using poststimulus-time histograms. The vast majority of EBNs and IBNs were directly excited at latencies of 1.3–2.2 ms, and a minority of OPNs were similarly excited. These results are in accord with other anatomical and physiological data showing that all, or nearly all, cerebellar nuclear projections to the pons express excitatory neurotransmitters or are excitatory, respectively (Angaut and Sotello 1989; Kitai et al. 1976; Schwarz and Schmitz 1997; Verveer et al. 1997). Finally, we hypothesize, as have others (Fuchs et al. 1993), that there is also an indirect inhibitory projection from the FOR to the OPNs. We envision that the excitatory pathway from FOR neurons to OPNs is effective during ipsiversive saccades, and the inhibitory pathway is effective during contraversive saccades. One way this could be achieved is if the inhibitory pathway were the stronger, but was gated so that it conveyed FOR signals only during saccades in one direction. Such gating might be achieved if the interneuron in the fastigial-to-OPN pathway received crossed inhibition (e.g., from IBNs) and/or excitation from (postdecussation) superior-colliculus efferents on the same side (not illustrated).

This circuitry is adequate to explain how the changes in FOR discharges observed in the present study could modify saccade size. First, we found that increased saccade size was associated with an increased number of spikes in FOR neurons during contraversive saccades. Conversely, decreased saccade size was associated with a decreased number of spikes (positive slopes, Fig. 9A). Referring to Fig. 12A, increasing the number of spikes would directly increase the number of spikes in the on-direction bursts of EBNs and IBNs, thereby increasing the activity of agonist motoneurons and decreasing the activity of antagonist motoneurons. This would in turn increase saccade size, which is consistent with our data. A decreased number of spikes in FOR neurons would decrease EBN and IBN discharges, and decrease saccade size.

Second, we found that decreasing saccade size was associated with an earlier burst of FOR neurons during ipsiversive saccades. This earlier burst should advance the excitatory input from the FOR nucleus to EBNs and IBNs and increase the number of spikes in their off-direction discharges. The antagonist motoneurons would be excited earlier (by the EBNs), and the agonist motoneurons would be inhibited earlier (by the IBNs). Both effects would contribute to decreases in saccade size. Augmenting this effect was an increase in FOR-neuron peak frequency (Table 1; negative slope = frequency increase/size decrease). Antagonist and agonist motoneurons were not only excited or inhibited earlier, respectively, but they were excited or inhibited more. Again, this should help decrease saccade size. Curiously, the opposite changes were not seen during gain-increasing experiments. Ipsilateral burst lag in FOR neurons increased minimally, and peak frequency increased. The latter change would be expected to increase antagonist and decrease agonist activity, the opposite of that needed to increase saccade size. Evidently, ipsiversive burst lag is more susceptible to decreases than to increases, which may have a parallel in the nonreciprocal relationship between synaptic long-term potentiation and long-term depression as noted earlier.

In addition to controlling the firing rates of agonist and antagonist motoneurons, saccade size can be controlled by controlling discharge durations. Because EBN and IBN burst durations are regulated by the duration of the pause in OPN discharges, a powerful mechanism for controlling saccade size...
is to control OPN pause duration. There are both direct and indirect FOR connections that could help accomplish this.

The direct projection from the FOR to the OPNs (Fig. 12A) conveys an excitatory signal to the OPNs toward the end of ipsiversive saccades, which could assist the resumption of firing in OPNs and help terminate the saccade. Earlier bursts in FOR neurons should produce shorter OPN pauses and in turn shorter duration and smaller amplitude saccades. As noted above, this is consistent with our data. However, as also noted, the lack of changes in ipsiversive burst lag during gain increases means that this mechanism was not used in the latter case. An additional caveat is that electrophysiological data show that this pathway is weak (Scudder et al. 2000), implying that the power of this mechanism for changing saccade size is also weak.

Robinson and Fuchs (2001) questioned whether onset time of the ipsiversive burst has sufficient precision to serve as a mechanism for the control of saccade duration under any circumstances. Although onset variability was somewhat high (9 ms for a given duration), the summed discharge of all FOR neurons would be expected to be much less variable. If there are ≥250 independent neurons in the FOR of macaques (Sato and Noda 1991), the standard error of the mean onset time would be only 0.6 ms. Moreover, the argument presumes that the variability is pure noise. If the FOR is part of a feedback network that acts to reduce errors produced elsewhere in the saccadic system (cf. Scudder et al. 2002), some of the seeming variability is actually a signal that increases the precision of saccades. In short, we believe the true error of the aggregate ipsiversive burst onset is <0.6 ms, which is surely precise enough to produce accurate saccades.

In the opposite direction (i.e., during contraversive saccades), the direct excitation of OPNs by the early FOR discharge is undesirable. However, as stated previously, we hypothesize that the direct excitation of OPNs is overwhelmed by inhibition from an interneuron (Fig. 12A). The indirect inhibition of OPNs during contraversive saccades could potentially affect OPN pause duration by affecting its onset and/or termination. The finding that contraversive burst lead is positively correlated with saccade size during adaptation is consistent with the idea that earlier FOR discharges help produce earlier, and therefore longer OPN pauses. However, this mechanism is apparently not consistently used, as shown by the fact that FOR burst onset lagged contraversive saccade onset on average in one monkey, and considerably lagged saccade onset in another monkey, and considerably lagged saccade onset during large head-free gaze shifts (Brettler and Fuchs 2001). Control of the resumption of OPN firing by the termination of the FOR burst, on the other hand, is a potentially powerful mechanism that is consistent with our data. That is, the end of the contraversive burst was positively correlated with saccade size during adaptation for most neurons (Fig. 9C) for both gain increases and gain decreases.

There is yet a third mechanism by which FOR discharges might affect the duration of OPN pauses and thereby saccade size. This is illustrated in Fig. 12B, and hinges on the existence of a “latch” neuron. Although proof of such a neuron is lacking, it has long been suggested that there must be an inhibitory neuron that prevents the OPNs from firing for the duration that EBNs and IBNs are firing (cf. Fuchs et al. 1985; Robinson 1975; Scudder et al. 2002). This neuron is drawn as being different from the inhibitory interneuron that receives FOR input, but this need not be so. The putative latch neuron receives excitatory input from ipsilateral EBNs that is declining toward the end of ipsiversive (on-direction) saccades, and also possibly inhibitory input from contralateral IBNs, which is increasing. Firing of the latch neuron, which is the difference between the EBN and IBN firing rates, eventually declines to a level at which it is no longer able to inhibit firing in the OPNs. Consequently, control of the EBN and IBN firing rates by FOR neurons, as described above, also serve to control OPN pause duration. In the current data, we found increased peak firing rate and increased duration of the contraversive FOR burst in association with larger saccades during adaptation. The increased FOR discharge should produce a stronger and longer excitation of the latch neuron by the EBNs. This should, in turn, produce longer and larger saccades, which agrees with what we found. Decreased FOR firing rate and burst duration should be, and was, associated with smaller saccades.

Similarly, an earlier and larger ipsiversive FOR burst was associated with smaller saccades, consistent with a putative earlier and stronger inhibition of the latch neuron by the IBNs. A later and smaller ipsiversive burst should have been associated with larger saccades, but this was not observed in our data, as noted previously.

Finally, the caudal fastigial nucleus also projects to the superior colliculus, as noted in the introduction. The specific collicular neurons contacted by fastigial efferents are currently too uncertain to advocate specific mechanisms for the control of saccade size, but we note that powerful mechanisms may exist (cf. Scudder et al. 2002). These mechanisms could prove to be as important as those just discussed.

Quantitative assessment of FOR efficacy in the control of saccade size

Most of the observed changes in FOR discharge parameters are qualitatively consistent with the proposed mechanisms by which FOR neurons might control saccade size, but are not necessarily sufficient to cause the observed changes in size. A rudimentary way to address this issue is to compare the number of spikes in the FOR and EBN discharges during contraversive saccades. This metric is relevant because there is a direct contribution of the FOR discharge to the EBN and IBN discharges, as discussed above, and because EBN and IBN number of spikes are directly proportional to saccade size. The relation between EBN number-of-spikes and saccade size has a slope of around 1.3 spikes/deg (cf. Scudder 1988), and the same relation between FOR discharges and saccade size has a slope of 0.55 spikes/deg (Table 1). To properly compare these numbers, a correction must be made for the fact that FOR peak firing rate is about 30% of the EBN peak rate (229/s vs. 750/s).1 For instance, if the FOR provided all the input to EBNs, there would have to be a 3.3-fold amplification of FOR discharge rate, possibly achieved by heavy convergence, powerful synapses, or high EBN sensitivity to membrane depolarization. The adjusted FOR sensitivity would be 1.8 spikes/deg. This example is, of course, exaggerated because we know that EBNs also receive input from the superior colliculus and

1 The value of 229/s was obtained from the current data and represents the mean peak frequency during 23° saccades for all 28 neurons; 750/s was obtained from van Gisbergen et al. (1981) for monkey EBNs during 20° saccades.
long-lead burst neurons (reviewed by Scudder et al. 2002). A more reasonable estimation based on the finding that unilateral chemical inactivation of FOR can cause up to a 50% dysmetria (Robinson et al. 1993; C. A. Scudder, unpublished observations) would be that the FOR provides 40% of the input to EBNs. Therefore the FOR contribution to EBN firing would be 0.72 spikes/deg, which is less than the 1.3 spikes/deg needed to cause the observed changes in saccade size. It does, however, exceed a lower estimate of EBN discharge-size sensitivity (0.65 spikes/deg; computed from Table 2 in van Gisbergen et al. 1981).

The above calculation partially excludes the effect of the putative control of saccade duration by the FOR. To estimate the effect of this control on saccade size based on an evaluation of each of the three mechanisms described above would require many assumptions and modeling, which is beyond the scope of this investigation. Rather, we presuppose that the FOR can contribute the remainder of the input to EBNs and IBNs; that is, 100% – 40% = 60%. Using the measurement of van Gisbergen et al. (1981) that EBN firing rate is about 500/s just before the end of the saccade, the FOR contribution of burst duration accounts for 2.1 ms/deg × 60% × 500 spikes/s = 0.63 spikes/deg. When added to the direct contribution of FOR firing calculated above (0.72 + 0.63 = 1.35 spikes/deg), the FOR appears to have adequate power to control saccade size.

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DISCLOSURES

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