THE ROLE OF THE CEREBELLUM IN VOLUNTARY EYE MOVEMENTS

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Abstract  In general the cerebellum is crucial for the control but not the initiation of movement. Voluntary eye movements are particularly useful for investigating the specific mechanisms underlying cerebellar control because they are precise and their brain-stem circuitry is already well understood. Here we describe single-unit and inactivation data showing that the posterior vermis and the caudal fastigial nucleus, to which it projects, provide a signal during horizontal saccades to make them fast, accurate, and consistent. The caudal fastigial nucleus also is necessary for the recovery of saccadic accuracy after actual or simulated neural or muscular damage causes horizontal saccades to be dysmetric. Saccade-related activity in the interpositus nucleus is related to vertical saccades. Both the caudal fastigial nucleus and the flocculus/paraflocculus are necessary for the normal smooth eye movements that pursue a small moving spot. By using eye movements, we have begun to uncover basic principles that give us insight into how the cerebellum may control movement in general.

INTRODUCTION

Cerebellar lesions do not abolish movements, but they make them slow, inaccurate, rough, and variable. Previous findings have suggested that the cerebellum compensates for different loads and muscle lengths, improves movement accuracy and smoothness, and increases movement speed and consistency. These functions affect movement as it is occurring, so we consider them part of the cerebellum’s “moment-to-moment” or short-term role. In addition to its short-term influence on movements, the cerebellum also plays a longer-term role, adapting motor commands gradually over many movements to compensate when motor commands produce consistently inaccurate movements. Motor commands may cause consistently inaccurate movements as we age or when trauma or physical disability, such as weakened muscles, changes the consequences of a command.

In this review, we describe the short- and long-term role of the cerebellum in the control of movement in primates by considering its influence on voluntary eye
CEREBELLAR CONTROL OF SACCADIES

Saccades are the voluntary rapid eye movements that move our eyes from one visual target to another. During saccades, the eyes rotate very quickly (up to >500° per s) and the movements are very brief (often <50 ms). This brevity maximizes the number of targets viewable and minimizes the saccadic transit time during which vision is impaired. Because saccades are so brief, there is not enough time for visual feedback to guide them to their targets. Thus, the brain must specify the command for a saccade before it starts. As we show below, the cerebellum helps modify this command and thus is critical for making saccades that are fast, accurate, and consistent from moment-to-moment and for maintaining their accuracy in the long term.

Saccade-Related Posterior Medial Cerebellum

Location

Most of what we know about the cerebellum’s role in saccades comes from study of the saccade-related part of the posterior lobe vermis, i.e. the oculomotor vermis (Noda & Fujikado 1987), and the part of the fastigial nucleus to which it projects. The oculomotor vermis is the region within which Purkinje cells (P-cells) and background activity discharge a burst of spikes during saccades and from which one can elicit saccades by stimulating with current trains of <10 µA (Noda & Fujikado 1987). This area includes vermal lobule VII and, in some monkeys, the most posterior folium or two of lobule VI. Axons of P-cells in the oculomotor vermis terminate densely in a small oval region (1.5–2 mm A-P and ~1 mm D-V) in the caudal part of the ipsilateral fastigial nucleus (CFN) and less densely in the rostral fastigial nucleus (Yamada & Noda 1987). Neurons in the rostral fastigial nucleus do not respond with saccades and are not considered further here ( Büttner et al 1991).

Role in the Moment-to-Moment Control of Saccades

Effects of Lesions

When the caudal fastigial nucleus is disabled saccades are inaccurate, slow, and abnormally variable in size and speed (Vilis & Hore 1981, Robinson et al 1993). Normal saccades have gains, the size of the saccade divided by the distance to its target, of nearly 1.0. After the CFN on one side of the cerebellum is inactivated by an injection of the GABAa agonist muscimol, ipsiversive saccades are too large (gain, ~1.2–1.9) and contraversive saccades are too small (gain, ~0.6–0.8). In addition, saccade gains are more variable than normal (e.g. standard deviations for saccades to 10° horizontal targets are 1.2–4.8 times normal). Saccades to vertical targets curve strongly, ending 2°–9° to the left of their targets.

In addition to being dysmetric, both ipsilateral and contralateral saccades are slower than normal saccades of the same size. For example, after unilateral CFN
inactivation, a 15° ipsiversive saccade reaches only ~84% of the velocity of a normal 15° saccade. Contraversive 15° saccades achieve velocities that average ~73% of normal for 15° saccades (Robinson et al 1993). After unilateral CFN inactivation, saccade velocities not only are abnormally slow, they are also much more variable than normal. Correlation coefficients of the relation of velocity and size typically drop from 0.95 to 0.39 (Figure 8A in Robinson et al 1993).

The dysmetrias produced by unilateral CFN inactivation suggest that each saccade is missing a contraversive component and that the net affect of saccade-related CFN activity on one side is to drive the eyes toward the contraversive side. Consistent with this interpretation, electrical stimulation of the CFN elicits saccades with large contraversive components (Noda et al 1988).

Humans with damage to one fastigial nucleus, or a lateral medullary stroke thought to reduce ipsilateral CFN activity (Wallenberg’s syndrome) (Waespe & Wichmann 1990), exhibit saccade abnormalities like those of monkeys with unilateral CFN inactivation. For example, in five Wallenberg’s patients, ipsiversive saccades to the lesioned side overshot by 33% and contraversive saccades undershot by 21.4% (Waespe & Baumgartner 1992).

Bilateral CFN inactivation in monkeys makes saccades in all directions too large (mean gain of saccades to 10° horizontal and vertical targets is 1.33 and 1.25, respectively) (Robinson et al 1993). Although their endpoints show abnormal scatter, saccades to vertical targets do not curve horizontally. Again, horizontal saccade velocities are slower and more variable than normal.

**Effects of Vermal Lesions** Lesions of the oculomotor vermis also impair saccades. After such lesions, both leftward and rightward saccades were between 20% and 30% hypometric (Barash et al 1999). Also, postlesion gains were at least twice as variable as normal (Barash et al 1999, Takagi et al 1998). Average saccade gain returned to normal within 3–12 months after the lesion but remained as variable as it was immediately after the lesion (Barash et al 1999). Evidently, a mechanism outside the medial cerebellum slowly restores mean saccade gain to normal, but no mechanism outside the medial cerebellum can restore saccade consistency. After vermal lesions, horizontal saccades in some monkeys were ~30% slower than normal. Humans with infarctions that include the posterior vermis exhibit hypometria of both leftward and rightward saccades (Vahedi et al 1995).

In summary, without the CFN, the remaining saccade machinery produces symmetric, slow saccades that lack their normal stereotypy. The hypometria and low velocity of saccades contraversive to a unilateral lesion suggest that CFN activity helps accelerate contraversive saccades. The hypermetria of ipsiversive saccades suggests that CFN activity helps decelerate ipsiversive saccades. We now see that the activity of CFN neurons is consistent with this suggestion.

**Saccade-Related Unit Activity in the CFN** Unlike burst neurons elsewhere in the saccadic system, the vast majority of CFN neurons discharge a burst of action potentials for nearly every saccade, whatever its direction or size (Ohtsuka & Noda...
However, for saccades of the same size and direction, there is a considerable variability in burst lead, firing frequency, and burst duration. Bursts in CFN neurons begin an average of $\sim 8$ ms before small saccades in any direction. For contraversive saccades, there is little change in this timing as saccade size increases. For ipsiversive saccades, however, the burst occurs later for larger saccades, so that for a $20^\circ$ saccade, the burst begins after saccade onset but before saccade end. For saccades $\sim 10^\circ$ or larger, CFN neurons usually burst earlier for contralateral than for ipsilateral saccades. This pattern of burst timing suggests that the bursts are associated with the beginning of contraversive saccades and the end of ipsiversive ones (Ohtsuka & Noda 1990, 1991; Fuchs et al 1993).

CFN neurons not only are active during targeting saccades, they also respond during the fast phases of optokinetic nystagmus (Helmchen et al 1994) and during spontaneous saccades in the light (Fuchs et al 1993, Helmchen et al 1994). There is disagreement as to whether they do (Helmchen et al 1994) or do not (Ohtsuka & Noda 1992) respond during spontaneous saccades in the dark. Also, the role of the CFN might be clarified by characterizing its activity during a richer variety of voluntary gaze shifts, such as express, memory-guided, and self-paced saccades. Finally, because CFN inactivation produces dysmetria of both the head and eye components of free-head gaze shifts in cats (Goffart & Pélisson 1994), primate CFN neurons should also be examined during gaze shifts with the head unrestrained.

Although there is general agreement on the dependence of CFN burst timing on saccade direction, there is disagreement about how strongly other burst attributes are related to saccade metrics. For example, Ohtsuka & Noda (1991) report that burst and saccade durations are very well correlated ($R = 0.85–0.97$). In contrast, our lab finds a much lower correlation ($R = \sim 0.6$) for our entire population of CFN neurons (Fuchs et al 1993). Because some of our neurons exhibit correlation coefficients above 0.8, perhaps Ohtsuka & Noda saw higher correlations because they limited their analysis to 19 well-behaved neurons in their sample of 96. In general we find that the properties of saccade-related bursts in CFN neurons are loosely related to saccade properties. In particular, the same saccade may be accompanied by a brisk burst on one trial and little, if any, discharge on the next.

In summary, the dependence of burst timing on saccade direction is consistent with the CFN inactivation data. For contraversive saccades, the burst occurs early in the saccade, providing a contraversive drive to help accelerate it. Without this drive, the saccade falls short. Later in the saccade, neurons in the other CFN, i.e. ipsiversive to the direction of the saccade, discharge a burst that delivers a drive opposite to the direction of the saccade to slow the movement. Without this late burst, the saccade does not decelerate as quickly as normal and overshoots. The CFN discharge somehow also makes the saccades more consistent or repeatable. How this is accomplished is currently a mystery.

**Saccade-Related Unit Activity in the Posterior Vermis** Most (71%) oculomotor vermis P-cells exhibit saccade-related bursts for either ipsiversive or contraversive saccades or both (Ohtsuka & Noda 1995). For ipsiversive saccades, P-cell bursts begin before saccade onset and fall off abruptly in the last half of the saccade.
This fall-off of inhibitory P-cell activity could cause a rebound depolarization in cerebellar nuclear neurons (Aizenman & Linden 1999), perhaps promoting the onset of late bursts in CFN neurons for ipsiversive saccades. For contraversive saccades, P-cell bursts begin before or early in the movement, peak near its middle, and continue past saccade end (Ohtsuka & Noda 1995). This pattern could help produce the postburst pauses that occur in ∼19% of CFN cells. About 18% of P-cells pause for contraversive saccades. Pause timing is variable from saccade to saccade, with the average mean lead time of 17.5 ms (Ohtsuka & Noda 1995). These pauses begin sharply and so could, if synchronized across many P-cells, trigger the early bursts in CFN neurons for contraversive saccades. In general, however, we cannot account entirely for the saccade-related responses of CFN neurons by using only P-cell activity. Specifically, it is not yet clear how the brain produces the bursts that CFN neurons discharge before contraversive saccades (but see the next section). Signals from the frontal eye field (FEF) and superior colliculus (SC) on one side would have to reach the ipsilateral CFN. These anatomical connections exist. The FEF (Stanton et al 1988) and the SC (Harting 1977) project to subdivisions of the ipsilateral pontine nuclei that, in turn, project to the ipsilateral, as well as contralateral, CFN (Noda et al 1990). We schematically represent a connection between the right SC and the right CFN in Figure 1.

How Does the CFN Influence the Saccade Machinery? CFN cells project to brain-stem regions containing saccade-related premotor neurons. A schematic of the brain-stem generator for horizontal saccades is shown in Figure 1 (Fuchs et al 1985). The burst-tonic firing pattern of abducens motor neurons for an ipsiversive saccade and its subsequent fixation position is produced by a velocity signal from excitatory burst neurons (EBNs) in the ipsilateral paramedian pontine reticular formation and a position signal from the nucleus prepositus hypoglossi in the medulla (not shown). The pause in activity associated with contraversive saccades is caused by inhibitory burst neurons (IBNs) in the contralateral medullary reticular formation. Both IBNs and EBNs are inhibited during fixation by steadily firing omnipause neurons (OPNs) in the pontine raphe, which must be inhibited to trigger a saccade to occur. Both a desired change in gaze command required by the EBNs and the trigger signal to the OPNs is thought to be provided by the SC.

Anatomical (Noda et al 1990) and recording (Scudder et al 2000) evidence indicates that the CFN projects contralaterally to EBNs, IBNs, and OPNs. Because IBN inputs to motor neurons are crossed but EBN inputs are not, CFN activity could help accelerate the eyes contralaterally via either projection (for details, see Fuchs et al 1993). If it does, there will be late off-direction bursts in IBNs, EBNs, and abducens motor neurons. Indeed, most EBNs exhibit a weak late burst for off-direction saccades (e.g. Strassman et al 1986), and ∼30% of IBNs do (Scudder et al 1988) but abducens motoneurons do not (Fuchs et al 1988). CFN neurons also send a large projection to the ventrolateral region of the contralateral thalamus (Noda et al 1990), a pathway whose role has yet to be investigated.

The CFN apparently receives information with timing appropriate to produce late bursts for ipsiversive saccades and early bursts for contraversive saccades. The
Figure 1  Highly schematic representation of the transient elements of the brain-stem saccade burst generator (shaded box) and its inputs from the superior colliculus (SC) and the cerebellum (dashed lines). Cerebellar output via the caudal fastigial nucleus (CFN) influences the excitatory burst neuron (EBN), inhibitory burst neuron (IBN), and omnipause neuron (OPN). Filled synaptic terminals indicate inhibitory synapses; open terminal symbols mark excitatory synapses. Other abbreviations: MN, motor neuron.
early bursts may originate in the SC because SC neurons burst before contraversive saccades. In addition to the SC’s projection to the contralateral burst generator, it also projects to a subdivision of the ipsilateral pontine nuclei (Harting 1977) that projects bilaterally to the CFN (Noda et al 1990). If the early bursts in CFN neurons in fact originate in the SC, signals from SC neurons on one side must reach the CFN on the same side. Perhaps the pathway from the SC to the ipsilateral CFN, as shown in Figure 1, carries these signals.

**CFN Models** Current models have attempted to incorporate the CFN into the saccade circuitry. Most past circuits of the saccade burst generator have used a classical control systems model with a local feedback loop that compares actual with commanded saccade amplitude at the EBN. Employing such a model and adding the CFN influence at the EBN, Dean (1995) was able to produce saccades whose size, velocity, acceleration, and deceleration were quantitatively similar to those observed after CFN inactivation.

In a recent model touted to have more predictive power (Lefèvre et al 1998, Quaia et al 1999), the oculomotor vermis generates a motor error signal, shaped by feedback from the brain-stem saccade generator and signals from the SC. This error signal, in turn, activates a specific topographic locus in the CFN corresponding to the saccade to be generated. As the saccade progresses, activity in the CFN contraversive to the saccade direction moves from the activated site medially. Near the end of the saccade, the activity crosses the midline into the other CFN, and the bursts produced there activate IBNs to inhibit activity in motoneurons and end the saccade. This model also accurately simulates the abnormalities in saccade velocity, size, and direction after bilateral CFN inactivation. Unfortunately, the predictions of the model (Quaia et al 1999) that CFN neurons are topographically organized by desired saccade displacement and that some CFN cells should burst only for saccades greater than a certain amplitude are not substantiated by single-unit recordings (Ohtsuka & Noda 1991, Fuchs et al 1993). Furthermore, demonstrating a topographic organization of any sort in the CFN would be impossible because of its compact size.

**CFN Role in Saccade Adaptation**

**Effects of Lesions** Normally primates can adapt the size of their saccades. For example, when damage to the medial longitudinal fasciculus in humans (Doslak et al 1980) or the eye muscles in monkeys (Optican & Robinson 1980) causes hypometric saccades, both primates gradually increase saccade gain toward normal. We can simulate saccade dysmetria to elicit adaptation by rapidly moving a target spot during each saccade so that the saccades seem to miss their target (McLaughlin 1967). This technique causes adaptive changes in saccade size in both humans and monkeys. Adaptation is substantially complete within \(~100\) saccades in humans (Miller et al 1981, Deubel et al 1986) and \(~1000\) saccades in monkeys (Straube et al 1997a).
Lesions that include the posterior medial cerebellum seem to abolish the ability to adapt saccades. After removal of the medial cerebellar cortex and nuclei, monkeys no longer could eliminate the dysmetria caused by weakened eye muscles (Optican & Robinson 1980). After a large electrolytic lesion of the medial and interpositus nuclei, a monkey could not adapt to backward-moving targets (Goldberg et al 1993). After ablations of large parts of the oculomotor vermis, monkeys were unable to adapt either to backward- (Takagi et al 1998) or forward-moving targets (Barash et al 1999). Also, humans with Wallenberg’s syndrome were unable to adapt the size of their saccades to backward-moving targets (Waespe & Baumgartner 1992). Finally, we demonstrated that bilateral inactivation of the CFN alone impaired a monkey’s ability to reduce its saccade gain (Robinson et al 2000).

Despite this last result, it would be premature to conclude that the CFN was necessary for saccadic gain adaptation. Perhaps adaptation occurred upstream from the inactivated CFN but could not reach the motor neurons through the anesthetized CFN output. To test this possibility, we inactivated the CFN bilaterally in two monkeys and confirmed that there was no reduction in saccade gain after >1000 overshooting saccades in each direction. The animal was then placed in the dark for 10 h so that it would have no visual targets until the muscimol dissipated. After the muscimol dissipated, saccades were hypometric, which suggests that adaptation had occurred during CFN inactivation and that adapted signals could influence saccades once the CFN was able to relay them to the brain stem (Robinson et al 2000).

**CFN Changes During Saccade Adaptation**

To alter saccade amplitude, CFN neurons possibly could increase or decrease their burst rates or alter the timing of the burst relative to saccade onset or end. Adaptation appears to use both mechanisms. Some neurons in the CFN increase their burst frequency and duration during adaptations that decrease the size of ipsiversive saccades (FR Robinson, CT Noto, AF Fuchs, unpublished data). Another study did not observe changes in the firing rate of CFN neurons during saccade adaptation but did observe changes in burst timing (Scudder 1998).

**The Site of Saccade Adaptation**

Our preliminary data indicate that the site of saccade adaptation is upstream from the CFN. Sites that have been considered include the SC, the FEF, and the oculomotor vermis. After saccade gain was reduced with intrasaccadic target movements, electrical stimulation at sites in either the FEF (Edelman & Goldberg 1995) or the SC (Fitzgibbon et al 1986) elicited the same saccades as before adaptation, which suggests that adaptation occurs upstream of both structures. On the other hand, adaptation produces no shift in the topographic map of saccade amplitude in SC neurons, which suggests that each site in the SC continues to command the same saccade after adaptation as before (Frens & van Opstal 1997). This finding indicates that a signal must be subtracted from the SC saccadic command signal at a downstream site. Potential sites include the oculomotor vermis, which receives a heavy SC input via the
dorsolateral pontine nucleus and the nucleus reticularis tegmenti pontis, and also the
brain-stem saccade generator (Figure 1). Because the cerebellar cortex has been
implicated in other kinds of oculomotor learning, such as vestibuloocular reflex (VOR) adaptation (e.g. Ito & Kano 1982), a parsimonious suggestion is that it also is involved in saccade adaptation.

Unresolved Issues

Why is There Little Evidence of Eye Position Signals in CFN Units When Lesion Data Suggest a Position Sensitivity in Saccade Deficits?

Cerebellar lesions that include the oculomotor vermis (Ritchie 1976) or the CFN (Vilis & Hore 1981) cause saccade dysmetrias whose size depends on initial eye position. Centrifugal saccades are smaller than centripetal saccades. This is also true in human patients with infarcts that include the posterior vermis (Vahedi et al 1995). These observations led to the proposal that the output of the posterior medial cerebellum normally compensates for initial eye position so that centrifugal and centripetal saccades are nearly the same size. After bilateral inactivation of the CFN, we also found that centrifugal saccades to 20° targets were 79% of the size of centripetal saccades. Others, however, found no difference in the size of centrifugal and centripetal saccades (Ohtsuka et al 1994). Furthermore, the discharge of CFN neurons has either only a weak (Fuchs et al 1993) or no (Ohtsuka & Noda 1991, Ohtsuka et al 1994) relationship with initial eye position.

What is the CFN’s Influence on Gaze Position?

Unilateral CFN inactivation in monkeys with their heads restrained causes the eyes to aim ∼1°–2° to the side of the target in the direction of the inactivated CFN (Robinson et al 1993). Monkeys consistently move their eyes away from the target by a distance equal to this offset when the target spot moves to fall on the fovea. This offset is too small to account for the ipsiversive saccade hypermetria after unilateral CFN inactivation. For example, after unilateral CFN inactivation, two monkeys overshot 10° targets by an average of 5.6° but their mean ipsiversive offset was only 1.2° (Robinson et al 1993).

In contrast to a head-fixed monkey, a cat with its head unrestrained exhibits a 10°–20° ipsiversive offset of gaze after unilateral CFN inactivation. Ipsiversive gaze shifts of any size overshoot their targets by the size of the offset, i.e. the offset accounts completely for ipsiversive gaze hypermetria. If a target appears directly ahead, the cat will shift its gaze to look 10°–20° ipsiversive of the target (Goffart & Pélisson 1998). Contraversive gaze movements are different, undershooting by an amount that depends on the size of the saccade, so that a gain of 0.25–0.68 (depending on the experiment) accounts very well for this hypometria.

We currently do not understand why CFN inactivation causes an ipsilateral offset, why animals work to maintain it, or why this offset is so much larger when
the head is not restrained. Goffart & Pélisson (1998) propose that the output of the CFN on each side helps to determine perceived heading direction in the ipsiversive field.

**How does Variable Activity in the CFN Make Saccades More Consistent?**

Evidently CFN bursts make saccades more consistent, although the bursts themselves are quite inconsistent in their onset time, burst duration, peak frequency, and number of spikes for nearly identical saccades (Fuchs et al 1993). Saccade-related CFN neurons project directly to burst neurons in the premotor saccade-generating network (Scudder et al 2000), whose activity is machine-like in its consistent relationship to saccade metrics.

There are two general proposals about how the variable activity in the CFN could reduce saccade variability. The first asserts that the saccadic system outside the cerebellum, e.g. the SC, provides the burst generator with variable commands but that CFN output to the burst generator varies to complement this variability exactly, thereby producing consistent saccades (Robinson 1995). This interpretation leads immediately to the question of how the cerebellum can produce the appropriate complementary signal. One possibility is that the cerebellum receives an efference copy of each saccade that tailors CFN output to keep saccades on the right trajectory and to end them on target (Lefèvre et al 1998).

The second proposal asserts that although the output of individual cerebellar cells is variable, their combined activity reliably specifies some feature of each saccade. Indeed, Thier et al (2000) demonstrated that although the activity of any single Purkinje cell in the oculomotor vermis poorly represents saccade timing, the average activity of many such cells accurately specifies the end of a saccade.

**Saccade-Related Posterior Interpositus Nucleus and Dorsal Paraflocculus**

Neurons in the ventrolateral corner of the posterior interpositus nucleus (VPIN) and the adjacent limb of the lateral nucleus discharge a burst of action potentials for nearly every saccade (Robinson et al 1996). For most VPIN neurons, the burst occurs during acceleration of downward saccades and deceleration of upward saccades. Bilateral inactivation of the VPIN deprives all saccades of a downward component, i.e. all saccades end above their targets. However, inactivation also reduces upward acceleration and downward deceleration, indicating that VPIN activity also provides an upward drive. Therefore, current data indicate that some VPIN neurons drive the eyes downward during saccades and others drive them upward, but the downward drive predominates (Robinson 2000).

Despite the apparent similarities between the CFN’s influence on the horizontal component of saccades and the VPIN’s influence on the vertical component, there are two noteworthy differences. First, CFN inactivation causes vertical saccades to become hypermetric. In contrast, VPIN inactivation has relatively little effect on the size of horizontal saccades. Second, after unilateral CFN inactivation,
saccades to vertical targets curve dramatically toward the side of the injection. After bilateral VPIN inactivation, however, saccades to horizontal targets travel a straight trajectory to a point above their target. Therefore, the CFN and VPIN do not simply provide the same signals for saccades with orthogonal vectors.

Other Saccade-Related Regions of the Cerebellum

**Basal Interstitial Nucleus**  
The basal interstitial nucleus (BIN) of the cerebellum is a broad flat collection of neurons on the roof of the ventricle, ventral to the lateral and interpositus cerebellar nuclei (Langer 1985). BIN neurons exhibit a burst of action potentials for saccades in every direction (Takikawa et al 1998). These bursts begin an average of 16 ms before the start of visually guided saccades and end 33 ms before the saccade ends. BIN activity is correlated with the duration of the saccade but not with the saccade’s size or speed. Takikawa et al (1998) suggest that BIN neurons may contribute to the onset of the pause in OPNs but could not help sustain that pause until saccade end because their bursts end well before.

**Lateral Nucleus**  
Although there has not yet been a systematic exploration of the dentate nucleus, it may be involved with saccade generation because its caudal portion projects, via a relay in the thalamus, to the saccade-related part of the FEF (Lynch et al 1994).

**CEREBELLAR CONTROL OF SMOOTH PURSUIT**

**General Properties of Smooth Pursuit**

The objective of smooth-pursuit eye movements is to reduce the slip of a visual image over the fovea to velocities that are slow enough to allow clear vision. Smooth pursuit is most highly developed in primates, where it has been studied by requiring them to track a small target spot, usually moving with one of two patterns. Sinusoidal motion tests smooth pursuit in the steady state but allows considerable prediction (Leung et al 2000). To determine how the smooth-pursuit system responds to unpredictable target motion, investigators use a target that steps in one direction before moving at constant velocity in the opposite direction, i.e. step-ramp motion (Rashbass 1961). If the target crosses the initial fixation point at approximately the primate’s saccadic reaction time (≈200 ms), the eye will accelerate smoothly to acquire the target. The initial ≈40 ms of acceleration is relatively unaffected by target speed and serves only to start the eye in the correct direction. Acceleration between 40 and ≈100 ms depends strongly on the target’s velocity, position, movement direction, and contrast (Lisberger et al 1987). Thereafter, visual feedback can help guide pursuit. After the eye acquires the target, it moves at nearly target velocity, so retinal image motion is quite low. If retinal slip is eliminated completely by stabilizing the target on the retina, smooth pursuit continues, which suggests that once begun, smooth pursuit is driven by a “velocity memory” and not a visual signal (Morris & Lisberger 1987).
Eye velocity often oscillates during ramp tracking. These oscillations disappear when the target is stabilized on the retina (Lisberger et al 1987), and their period can be altered by altering the time between eye and target movement (Goldreich et al 1992). Therefore, the oscillations are under visual control (and not just the result of instabilities of an internal feedback loop with a ∼100-ms visual delay). In summary, the smooth-pursuit system requires predominantly visual signals to drive eye acceleration and oculomotor signals to control maintained pursuit.

Smooth-Pursuit Adaptation

The cerebellum has been implicated in adaptation of the gains of both the VOR (e.g. Lisberger 1988) and saccades (see above). Both these movements are so fast that visual feedback can not guide them; thus, adaptation is necessary to reduce persistent visual slip (VOR) or saccadic dysmetria. In contrast, smooth pursuit is slow enough to employ visual feedback to compensate for movement deficits due to neuronal or muscular failure. Therefore, it would seem unnecessary for the smooth-pursuit system to have the capability to adapt. Nevertheless, it does.

In three of four patients with unilateral oculomotor palsies, one week of viewing with the impaired eye caused the acceleration of the normal eye to increase (Optican et al 1985). Presumably this is a consequence of increased neural drive, which goes to both eyes, to compensate for the sluggish movements of the paretic eye. This adaptive increase in acceleration occurred between about 40 and 100 ms of pursuit onset. During maintained tracking, adapted patients often displayed substantial oscillations, which suggests an increase in the effect of image slip on eye motion.

As with saccade adaptation, pursuit adaptation can be elicited in normal subjects by manipulating target motion. Subjects track a ramp target that starts at one speed and, after a brief period of smooth pursuit, assumes either a higher or lower speed. After 20–30 min of such double-speed tracking, two thirds of normal subjects showed significant changes in eye velocity starting 100–200 ms after pursuit onset (Fukushima et al 1996). When this double-speed method was used on monkeys, the largest pursuit adaptation occurred in the first 50–80 ms after the onset of smooth pursuit after about 200 trials (Kahlon & Lisberger 1996). In summary, smooth-pursuit adaptation in humans and monkeys develops after the initial direction-only component of pursuit, i.e. after ∼40 ms. However, adaptation in humans appears to occur somewhat later in pursuit acceleration than it does in monkeys. Whether this reflects a difference in experimental technique or in the species is currently unclear.

Cerebellar Lesions Implicate Two Separate Areas in Smooth Pursuit

In 1973, Westheimer & Blair (1973) made the anecdotal observation that animals with complete cerebellectomies tracked a sinusoidally moving horizontal target with only saccadic eye movements. However, because there was no quantification of the deficit, it is unclear whether their monkeys retained any smooth-pursuit capability. Subsequent smaller lesions revealed that the profound smooth-pursuit deficit that Westheimer and Blair described was the result of damage to at least
two separate cerebellar subregions: the flocculus/ventral paraflocculus and the posterior medial cerebellum.

Bilateral ablation of the flocculus and the ventral paraflocculus caused a 33% reduction in horizontal, steady state, smooth-pursuit gain (eye velocity/target velocity). During steady state tracking, any deficit is ameliorated by visual feedback, so this deficit is equivalent to \( \sim 90\% \) reduction in open loop gain (Zee et al 1981). In addition to their pursuit deficit, monkeys could not hold their eyes at an eccentric location, and there was a centripetal, exponential drift with a time constant of \( \sim 1.6 \) s in the first few weeks after surgery. The ablation had no effect on saccade metrics. Finally, there was no consistent effect on the gain of the VOR (Zee et al 1981). These data indicate that the flocculus participates in smooth pursuit and also helps regulate the gaze-holding integrator.

The second cerebellar area involved with smooth pursuit is the posterior medial cerebellum, including the cerebellar vermis (lobule VIc and all of VII) (Noda & Fujikado 1987) and the fastigial nuclei to which these vermal P-cells project. In addition to the saccadic dysmetria discussed above, muscimol inactivation of the monkey CFN produces \( \sim 30\% \) reduction in gain of both contraversive and downward sinusoidal pursuit, with little effect on ipsiversive or upward pursuit (Robinson et al 1997). When both fastigial nuclei are inactivated, the deficits in contraversive and downward pursuit are larger and upward, and ipsiversive pursuit becomes slower [but not apparently in humans (Büttner et al 1994)].

In contrast to the effect of floccular lesions, there is no deficit in gaze holding. As after flocculus lesions, the VOR appears normal (Kurzan et al 1993) and VOR suppression, believed by some to be a smooth-pursuit capability, is impaired. Surgical ablation of the vermis, including lobules IV–VI and parts of VII and VIII, caused a 30%–40% reduction of simian sinusoidal smooth-pursuit gain (Keller 1988). Damage to the cerebellar vermis of humans also causes smooth-pursuit deficits (Furman et al 1986, Pierrot-Deseilligny et al 1990, Vahedi et al 1995). More lateral cerebellar lesions also affect smooth pursuit (Straube et al 1997b). Indeed, smooth-pursuit–related activity has been found in monkey interpositus nucleus, to which the laterally placed dorsal paraflocculus projects (Robinson & Brettler 1998). Information about these possible lateral cerebellar smooth-pursuit areas is currently sparse and is not considered further.

In the following sections we consider which aspects of the smooth-pursuit response the CFN and the flocculus/paraflocculus might control. Currently, there is substantial evidence on their roles in the moment-by-moment control of pursuit but little concerning their roles in pursuit adaptation.

**Flocculus/Ventral Paraflocculus**

**Sinusoidal Target Tracking**

Different investigators have described firing patterns during different tracking tasks, so cerebellar neurons have not been tested under a set of standard conditions. However, most studies agree that the simple spike activity of the vast majority of floccular P-cells is modulated during smooth pursuit of a small target (Miles et al
Most of these cells respond best to either horizontal (ipsiversive) or vertical (mostly down but with a small contraversive component) pursuit directions (Lisberger & Fuchs 1978; Krauzlis & Lisberger 1994, 1996; Stone & Lisberger 1990a; Fukushima et al 1999; Leung et al 2000). During pursuit of a sinusoidally moving target in a unit’s best direction, firing rate modulation is roughly sinusoidal (Stone & Lisberger 1990a) and is in phase with and increases monotonically with eye velocity. Many of the cells with smooth-pursuit sensitivity also respond to whole body oscillations even when eye movements are suppressed, increasing their activity for head rotation in the same direction that elicits the best smooth-pursuit response. The sensitivities to head and eye movements often are quite similar, so when the eyes move opposite to the head during the VOR or when a rotating animal fixes a target stationary in space, these units show little or no modulation in their activity. In this paradigm, eye position relative to space, i.e. gaze, remains fixed, so neurons with this behavior have been designated gaze-velocity P-cells. Most units with horizontal best directions apparently have gaze-velocity characteristics (but see Belton & McCrea 1999).

In contrast, most of the P-cells with vertical-preferred pursuit directions have unequal sensitivities to head and eye velocity and may even have different vestibular- and pursuit-preferred directions. Therefore, they continue to exhibit modulation when the oscillating monkey tracks a target that remains stationary in space. During pursuit, most tend to fire in phase with eye velocity, but some fire in phase with eye position (Fukushima et al 1999). In the vertical system, therefore, there appears to be a continuum of P-cell types reflecting a range of vestibular sensitivities. P-cells with horizontal- and vertical-preferred directions are intermixed within the flocculus/ventral paraflocculus (Krauzlis & Lisberger 1996).

P-cells also discharge complex spikes, which are elicited by the climbing fiber input from the inferior olive. Complex spike rates also are modulated during sinusoidal pursuit. For those ipsiversive and downward gaze-velocity P-cells with robust complex-spike modulation, complex-spike firing increased during contraversive and upward pursuit (Stone & Lisberger 1990b). When averages of eye and target velocity were triggered on the occurrence of complex spikes, a transient impulse of visual image motion was detected ~100 ms before the complex spike. Consistent with this data, an increase in climbing fiber spikes also occurred 100 ms after initiation of contraversive or upward ramp target motion for horizontal and vertical gaze-velocity P-cells, respectively. Because the complex spike causes a brief decrease in simple spike activity, its occurrence would facilitate the decrease of simple spike activity that is required to drive contraversive or downward tracking in response to image motion due to imperfect pursuit. Indeed, the visual climbing fiber responses seem more likely to occur during active pursuit than as a result of passive background motion (Stone & Lisberger 1990b). However, any climbing fiber influences are infrequent because of their very low modulation rate; thus, it seems unlikely that the complex spike is involved with immediate on-line control of smooth pursuit. Perhaps, as has been suggested for the VOR, the climbing fiber signal serves as an error signal to drive smooth-pursuit adaptation (see below).
Step-Ramp Target Tracking

To parse out the signals that effect P-cell firing, most investigators have used a step-ramp target motion, which allows separation of smooth pursuit and the accompanying unit activity into an initial directional component (first 40 ms), an open loop component that responds to target acceleration (40–100 ms), and a maintained component when eye velocity is similar to target velocity (>100 ms). Step-ramp stimuli have only been used to evaluate gaze-velocity neurons.

In the preferred smooth-pursuit direction, most P-cells exhibited a burst of simple spike firing during eye acceleration and a sustained rate during maintained pursuit. In general, the burst begins after smooth-pursuit onset and reaches its maximum near the end of acceleration (Stone & Lisberger 1990a). Discharge frequency then settles down to a lower steady rate associated with constant-velocity smooth pursuit (Stone & Lisberger 1990a, Krauzlis & Lisberger 1994). As expected from the sinusoidal tracking data, the steady firing rate increases with velocity increases in maintained pursuit. A reduction in firing rate often occurs during smooth-pursuit acceleration in the nonpreferred direction.

Because of the intimate relation of smooth pursuit with the target movement that generates it (Lisberger et al 1987), it is difficult to sort out what the simple spike discharge of P-cells is related to. After using different step-ramp combinations to dissociate eye and image motion, Krauzlis & Lisberger (1991) successfully simulated the associated discharge patterns by using visual signals to drive pursuit acceleration to change eye velocity and an eye movement signal to sustain it. Although several arguments are consistent with the contention that the burst accompanying pursuit acceleration is not solely oculomotor, no single experiment has conclusively demonstrated its visual origin (Stone & Lisberger 1990a). Frank visual responses to movement of either a small spot or the background while a monkey is fixating occurred in a small percentage of gaze-velocity P-cells (Noda & Warabi 1987, Stone & Lisberger 1990a). Stabilization of the target on the retina during maintained tracking did not change the firing of most P-cells, which supports the existence of an underlying eye-velocity signal during the maintained phase of smooth pursuit (Stone & Lisberger 1990a).

The simple spike discharge of P-cells, in turn, has the requisite characteristics to match nicely the dynamic load presented by the oculomotor plant (Krauzlis & Lisberger 1994). Therefore, the flocculus is thought to transform visual inputs to provide the dynamic but not the static (Shidara et al 1993) signals required to generate smooth pursuit. This conclusion seems at odds with the observation that the burst of most P-cells begins after smooth-pursuit onset. On the other hand, stimulation of the flocculus elicits smooth pursuit at latencies ranging from ~10 to 20 ms (Belknap & Noda 1987, Shidara & Kawano 1993, Lisberger & Pavelko 1988), and modeling of flocculus signals driving the brain-stem smooth-pursuit apparatus requires a burst lead of 9 ms (Krauzlis & Lisberger 1994). Perhaps the small minority of P-cells with early bursts are sufficient for pursuit initiation.

In conclusion, destruction of gaze-velocity P-cells probably accounts for the smooth-pursuit deficits produced by flocculus removal.
Sensitivities of Other Purkinje Cells

In addition to those P-cells that discharge with eye velocity, a minority have saccade and/or position-related simple spike activity. For some, their pause or burst is well timed with saccade onset and offset (Noda & Suzuki 1979b). However, none of the saccade-related activity appears to be important because ablation of the flocculi and paraflocculi has no effect on saccade metrics or accuracy (Zee et al 1981). The steady discharge of some P-cells is tightly related to eye position (Noda & Suzuki 1979a). A small number of P-cells with eye position sensitivity have also been reported by others (Miles et al 1980). It is possible that the loss of these cells could account for the gaze-holding deficit produced by flocculectomy (Zee et al 1981).

Neural Correlates of Pursuit Adaptation

In the double-speed paradigm, ~25% of flocculus P-cells showed changes in simple spike firing appropriate for the resulting smooth-pursuit adaptation (Kahlon & Lisberger 2001). Whether climbing fiber discharge could guide smooth-pursuit learning was unclear.

Posteriomedial Cerebellum

Oculomotor Vermis

Lying among the P-cells in the oculomotor vermis with simple spike activity related to saccades are others that discharge simple spikes during sinusoidal smooth pursuit (Sato & Noda 1992, Suzuki et al 1981, Suzuki & Keller 1988). At least half of these cells discharge in phase with head velocity and the velocity of a small spot that moves through a second spot on which the monkey is fixating (Suzuki & Keller 1988). Because almost half of these P-cells responsive to head, eye, and image motion preferred the same directions for all three motions and roughly, across the population, had the same velocity sensitivities, it has been suggested that such vermal P-cells provide signals related to target velocity. No study has yet described the vectorial directional preferences of these P-cells. Unlike flocculus P-cells, the discharge of vermal P-cells waxes and wanes considerably from cycle to cycle under identical tracking and target motion conditions. Like flocculus P-cells, many of the vermal P-cells with smooth-pursuit sensitivity also show bursts or pauses in activity with saccades.

Because of the paucity of pursuit-related units in their survey of the oculomotor vermis, Sato & Noda (1992) opined that the vermis is primarily concerned with saccades. In their hands, stimulation of the vermis with low currents produced only saccades (Noda & Fujikado 1987). However, more recently, Krauzlis & Miles (1998) have shown that electrical stimulation of the vermis can produce either saccades or smooth-pursuit eye movements, depending on stimulation frequency and whether the eyes are fixating or pursuing a moving target. The evoked pursuit movements are ipsiversive and occur with a latency of 10–20 ms.

Unfortunately, there are no recordings during step-ramp tracking, so the timing of P-cell discharge to response initiation is not known. Nor do we know if changes in firing occur preferentially during the acceleration or sustained velocity phases.
of pursuit. Finally, there are no studies concerning climbing fiber responses in the oculomotor vermis during smooth pursuit.

**Caudal Fastigial Nucleus**

Some CFN neurons exhibit a modulation in firing rate when a monkey makes smooth eye movements in pursuit of a moving target (Büttner et al 1991, Fuchs et al 1994). For 72% of the neurons, the pursuit direction that elicits the most vigorous modulation is contraversive and/or downward; most of the remainder prefer ipsiversive and/or upward motion. Based on the phase of the modulation during sinusoidal pursuit, 80% of cells with contraversive/downward–preferred directions discharge most during smooth-pursuit acceleration, whereas those with the opposite-preferred directions discharge most during smooth-pursuit deceleration. These data suggest that the CFN helps accelerate the eyes during contraversive pursuit and decelerate them during ipsiversive pursuit. This interpretation is consistent with the deficits reported after CFN inactivations (Robinson et al 1997). Firing patterns during step-ramp pursuit reveal that many CFN neurons could initiate contraversive eye acceleration because their burst-sustained discharge precedes pursuit onset by >25 ms (Fuchs et al 1994). Finally, almost every CFN neuron with pursuit sensitivity also responds during yaw or pitch rotation. Most have unequal sensitivities to eye and head velocity, with some more sensitive to eye and others more sensitive to head velocity. Therefore, the apparent gaze- or target-velocity sensitivity of vermal P-cells is not reflected in the discharge of individual CFN neurons.

Like vermal P-cells, the discharge patterns of CFN cells display considerable trial-to-trial variation. Some CFN cells (~30%) with smooth-pursuit sensitivity also discharged a burst of spikes with saccades.

**Summary**

Based on current evidence, it is difficult to assign the flocculus or the posteriomedial cerebellum unique roles in the control of smooth pursuit. Both have neurons with a variety of burst-sustained discharge patterns during step-ramp pursuit. However, the bursts of a majority of CFN neurons lead pursuit onset, whereas the bursts of most floccular P-cells occur after pursuit is underway. Therefore, the CFN could be more important in pursuit initiation and the flocculus could serve to maintain it. The fact that floccular neurons respond to velocities >100° per s and CFN neurons to velocities of only 20°–60° per s seems consistent with this suggestion. However, the observation that bilateral CFN inactivation does not consistently delay pursuit onset (Robinson et al 1997) may argue against it.

All CFN cells and many floccular P-cells have vestibular as well as pursuit sensitivities. However, it is unclear, even in the flocculus, where many cells have equal head- and eye-velocity sensitivities, that gaze velocity is the controlled variable, especially when the head is free to rotate (Belton & McCrea 1999). Many flocculus P-cells and CFN cells respond for both smooth pursuit and saccades. Because smooth-pursuit cells in the CFN are in the immediate vicinity of saccade cells that
discharge during eye acceleration, it has been suggested that the CFN provides signals to help accelerate both saccades and smooth-pursuit movements (Fuchs et al. 1994). However, a similar role seems unlikely for the flocculus, where bilateral removal does not affect saccade metrics, which suggests that those saccade-related bursts have no impact downstream. With regard to the likelihood that these two structures could have a significant impact on smooth pursuit, floccular efferents impinge on neurons that are only one or two synapses from motor neurons. On the other hand, CFN efferents have no apparent smooth-pursuit target in the brain stem (Noda et al. 1990). Furthermore, the activity of CFN cells waxes and wanes from trial to trial, a potentially problematic attribute for precision control. Floccular P-cell activity is considerably more reliable. In conclusion, deficits after lesions leave little doubt that the flocculus and posteriomedial cerebellum are required for accurate smooth pursuit, but we need more information to determine whether each structure indeed has a specific role in the generation of smooth pursuit.

Unresolved Issues

Do the Flocculus and the Posterior Vermis/CFN Account for all of the Cerebellum’s Influence of Smooth Pursuit?

We can answer this question directly by testing a monkey’s ability to produce pursuit after simultaneous inactivations of the flocculus and the CFN.

How does Pursuit-Related P-Cell Activity in the Oculomotor Vermis Shape the Discharge of CFN Neurons?

To answer this question the timing of P-cell discharges should be examined with step-ramp target motion to allow comparison with activity recorded under similar conditions in the CFN. Again, it would be informative to design an experiment that would separate the direct mossy fiber inputs to the CFN from those routed through the vermis.

Does the CFN also have a Role in Smooth-Pursuit Adaptation?

To examine this issue, the CFN first could be inactivated pharmacologically to determine whether adaptation to double-speed targets indeed is affected. If so, CFN smooth-pursuit units could be recorded while adaptation was occurring.

CEREBELLAR ROLE IN VERGENCE

In addition to their role in saccades and smooth pursuit, the CFN and VPIN also influence vergence movements. Some CFN neurons increase their firing rates during the near response, i.e., convergence and increasing accommodation (Zhang & Gamlin 1996). Inactivating the CFN with muscimol reduces the speed and size of convergence (Gamlin & Zhang 1996). Of the CFN neurons that respond with convergence, 63% also discharge during saccades (Zhang & Gamlin 1996). We think these saccade-related neurons are the same ones we have characterized
because the saccade-related part of the CFN is so small. The fact that many CFN neurons respond to both saccades and convergence raises the possibility that these neurons play an important role in coordinating saccade and vergence movements, which occur together when targets are at different distances from the viewer.

Some VPIN neurons, in contrast, increase their firing rates during the far response, i.e. divergence and decreasing accommodation (Zhang & Gamlin 1998). These cells are in the same area as those with saccade-related responses, but none discharges with saccades. CFN and VPIN output may mediate vergence movement in humans as well because a patient with damage to his superior cerebellar peduncle, which carries cerebellar output, exhibited an almost complete absence of vergence eye movements (Ohtsuka et al 1993).

Clearly, we need much more information before our understanding about the cerebellum’s role in vergence movements approaches that of its role in saccades and smooth pursuit.

CONCLUSION

Studies on the behaving monkey reveal that the cerebellum is necessary for the production of both accurate saccades and smooth-pursuit eye movements. Evidence is also accumulating for a cerebellar role in vergence eye movements. The neurons underlying the modification of these various eye movements have been localized and their behavior has been documented during the short-term control of individual movements. With this information, we can now evaluate the role of the cerebellum in long-term motor adaptation or learning. We can consider such fundamental issues as how neuronal discharge reflects behavioral adaptation, what might be the role of climbing fibers, and where are the synapses that undergo change during learning. Using the oculomotor system in this way, we may reveal mechanisms that are fundamental to the cerebellar control of all voluntary movements.

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