

## **Cerebellar Uvula Involvement in Visual Motion Processing and Smooth Pursuit Control in Monkey**

S. J. HEINEN AND E. L. KELLER

*Smith-Kettlewell Eye Research Institute*  
2232 Webster Street  
San Francisco, California 94115

and

*Department of Electrical Engineering and Comparative Sciences*  
*University of California*  
Berkeley, California 94720

The cerebellum has been shown to be involved in the generation of most types of eye movements. In particular, the flocculus and lobules VI and VII of the vermis, sometimes called just the posterior vermis, have been most extensively studied in this regard. Neurons have been found in both areas that code aspects of visual and motor signals important for the generation of smooth pursuit, and lesions to these areas produce pursuit deficits.<sup>1,2</sup> The posterior vermis seems to play an important role in saccade generation as well,<sup>3-5</sup> and the flocculus has been shown to be involved in the neural processing for all types of smooth eye movements including pursuit and vestibular.<sup>6,7</sup> Both the vermis and flocculus receive projections from the pontine nuclei, as well as from the nucleus reticularis tegmenti pontis (NRTP), brain stem regions that contain cells responding to visual stimuli and during oculomotor behavior.<sup>8-12</sup>

The dorsal portion of lobule IX of the vermal cerebellum (the dorsal uvula) receives at least as strong an input from visual areas of the pontine nuclei as do the posterior vermis and the flocculus.<sup>13,14</sup> Therefore the uvula might be expected to process information for the generation of visually guided eye movements as well. The uvula in rabbits has been studied for neural correlates of visual surround motion,<sup>15</sup> but no single-unit studies have previously been done to assess uvular involvement in smooth tracking or saccades. However, it has been shown that optokinetic after-nystagmus (OKAN) could no longer be suppressed or "dumped" by visual or tilt stimulation after combined nodulus/uvula lesions.<sup>16</sup>

We therefore set out to determine if the uvula plays a role in the generation of visually guided eye movements using behavioral paradigms, single-unit recording, and lesion techniques previously employed in clarifying the oculomotor relationships of the flocculus and vermis. Surprisingly we found very few cells in the uvula that responded either during smooth pursuit or for saccades. Instead, a large majority of uvular cells responded with relatively long latencies during prolonged optokinetic stimulation. In addition, our lesions to this area produced effects on pursuit different from those seen with lesions in the other two cerebellar oculomotor areas. This suggests that the uvula may not be in the direct pursuit pathway, a role hypothesized for the posterior vermis and the flocculus, but may instead have an indirect effect on the gain of other pathways actually producing smooth eye movements. The uvula then could be a structure that plays a role in the adaptive control of pursuit performance.

## METHODS

Three *Macaca fascicularis* monkeys were used for all experiments. Each was surgically implanted with a stainless steel chamber located stereotaxically over the cerebellum for single-unit recording, and a coil of wire around the globe of the eye for monitoring eye position with the search coil technique. For single-unit recording, tungsten microelectrodes were lowered into the uvula through a guard tube which pierced both the dura and the tentorium.

For reversible lesions, 10–15 microliters of lidocaine were perfused through a cannula into the uvula. If an effect on pursuit or optokinetic eye movements was found, lidocaine administration was followed by an injection of 2–4 microliters of 15 micrograms/microliter ibotenic acid.

Standard behavioral paradigms were used to assess single-unit responses and lesion effects. Animals were required to smoothly track a small visual spot which moved at constant velocity over a dim homogeneous background in four directions at speeds of 10, 20, and 40 deg/second at random, or to make saccades to the spot as it was stepped to 5-, 10-, and 20-deg locations. Water was given when animals successfully performed these tasks. Visual responses of neurons were tested by moving small spots or sweeping a large textured background across the visual field while the animal fixated. A drum with random width vertical stripes rotated around the animal at speeds of 40 or 100 deg/second provided constant-velocity optokinetic stimulation.

Eye position signals were differentiated on-line by analog hardware to produce eye velocity traces (bandwidth = 150 Hz), then desaccaded either manually or with software based on an acceleration criterion. Eye position and velocity and target position signals were sampled at 500 Hz for short visual or pursuit trials and at 100 Hz for longer optokinetic trials.

Isolated single units were classified as Purkinje cells (P-cells) if they exhibited an irregular high-frequency simple-spike discharge accompanied by the concomitant low-frequency discharge of a complex spike. It was usually possible to determine when the electrode tip was located outside Purkinje cell layers by the lack of the characteristic, irregular, high-frequency discharge of these large cells, by their wider spike durations, and the absence of complex spikes. Units recorded outside Purkinje cell layers were characterized by more regular spontaneous discharge or by the lack of discharge and by more narrow spike durations. We classified these units as mossy fiber input units although this population may have also included other cerebellar cortical cell types. For the analysis of the unit data, the raw spike trains were convolved with a Gaussian time function resulting in a spike density profile.<sup>17</sup> Modulations of this spike density function were checked for correlation with eye velocity or retinal slip during pursuit and optokinetic trials (or target motion during fixation trials). For the analysis of the optokinetic data, the latency and the time constant of any neural response modulation as quantified by the spike density profiles were measured graphically. A sample of these measures was verified by fitting the spike density function with an exponential waveform using nonlinear optimization techniques.

Following the completion of the unit recordings and the lesions, several electrolytic marker lesions were placed in the cerebellum. Unit recording sites and the sites of chemical lesion placements were reconstructed from the location of these marking lesions.

## RESULTS

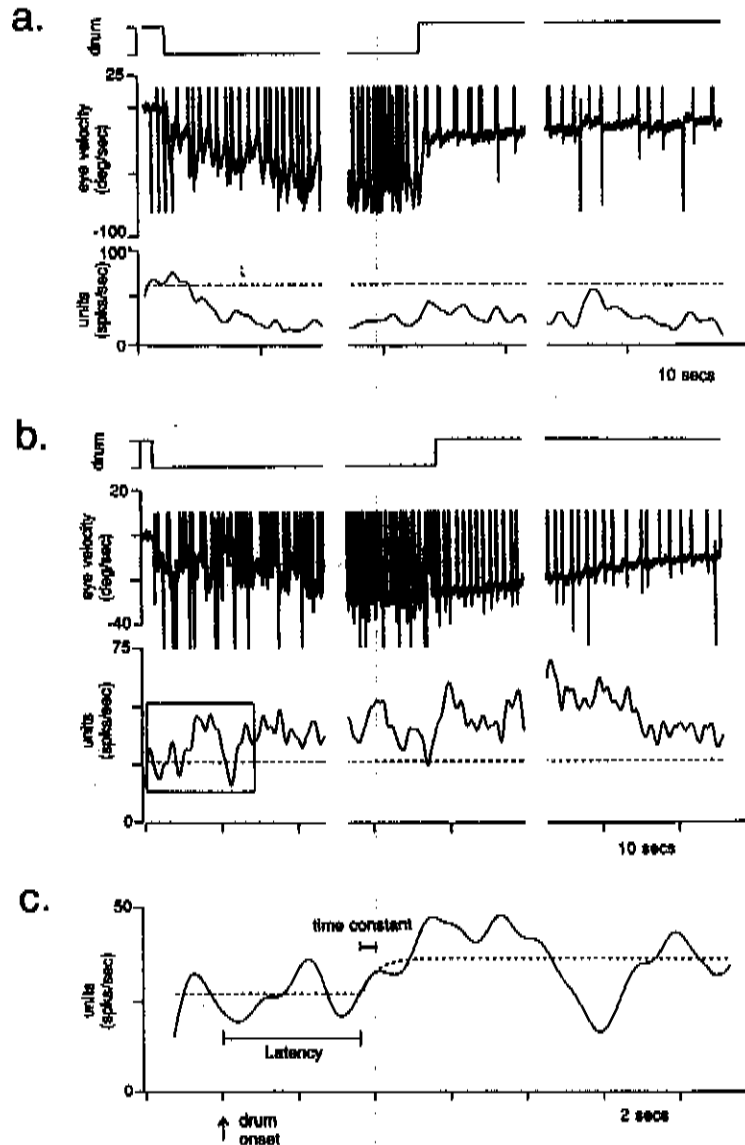
We recorded from a total 78 P-cells and 14 mossy fibers in the uvula. We were surprised to find that very few (25%) of the units recorded carried signals relating to either pursuit or visual motion of a small spot. Most of the cells that could be modulated by these behaviors exhibited a long latency response to target or pursuit onset, although a few cells had more crisp, short-latency response typical of floccular or vermal units. Most of these (33%), however, were classified as mossy fiber inputs.

By far the most robust stimulus for activating uvular P-cells was prolonged constant-velocity drum rotation. This type of stimulation could either excite or inhibit spontaneous P-cell firing rate for one direction of drum rotation, and usually produced the opposite or no change for the other direction, and this modulation usually began some time after drum onset. These cells also usually did not begin to return to their spontaneous rate until well after the drum lights were turned off following prolonged (approx. 30-second) optokinetic stimulation. FIGURE 1 shows two examples of P-cell discharge during drum rotation, one (FIGURE 1a) shows a decrease in activity following the onset of optokinetic (drum) stimulation, and the other (FIGURE 1b) an increase.

We attempted to quantify the temporal relationship of such P-cell modulation to periods of optokinetic stimulation by determining the latency and time constant of modulation with respect to both drum onset and offset. An example of the results of the curve fit applied to the cell in FIGURE 1b (enclosed box) is shown in expanded form in FIGURE 1c. A summary of the results of similar fits from all cells can be seen in FIGURE 2. The latency of the neural response to drum onset averaged 3.5 seconds, and the mean time constant of the change in neural rate was 2.0 seconds for these cells. No speed tuning was evident for this population, at least for the 40- and 100-deg/second drum rotations that we used. There also was no apparent bias for a given direction of drum rotation in terms of response for the cells recorded on one side of the uvula.

Note that there is a somewhat bimodal distribution to both the latencies and time constants shown in FIGURE 2. Some of these neurons had extremely long temporal courses in their activity, and occasionally a cell would even continue to modulate away from its spontaneous rate throughout the entire period of OKAN in contrast to the cells shown in FIGURE 1.

After the collection of all unit data, we created reversible or more permanent lesions by the infusion of lidocaine and ibotenic acid into the uvula. We were surprised to find that the biggest effect on eye movements as a result of these lesions was on the pursuit tracking ability of the monkeys. Even more surprising was the nature of this effect which was very different from that previously demonstrated on pursuit following lesions to the posterior vermis or flocculus. Our animals showed an *increase* in velocity gain in tracking contralateral to the lesion, which was most dramatic in the open-loop period of pursuit. FIGURE 3 shows averaged tracking trials at 20 deg/second in a monkey before and after a left uvular lesion was created. This animal's open-loop eye acceleration (first 100 mseconds) during rightward pursuit was 461 deg/second<sup>2</sup>, compared to its open-loop eye acceleration of 150 deg/second<sup>2</sup> before the lesion. Once steady state was reached the animals usually had a normal velocity gain, but brief periods of retinal slip continued to produce greatly exaggerated periods of eye acceleration in response to this slip. We saw evidence of this heightened open-loop gain in all three of our animals. However, one of our lesions only destroyed the tip of the most dorsal folia of the uvula, and a small portion of



**FIGURE 1.** Purkinje cell discharge during constant-velocity drum rotation. In a, cell is inhibited by leftward drum rotation at 90 deg/second. In b, another cell is excited by leftward drum rotation at 40 deg/second. Top trace, drum state (downward steps indicate leftward drum motion, p); middle trace, eye velocity (positive signifies right); bottom trace, spike density. Dashed line is spontaneous discharge. In c, boxed-in segment of b is shown expanded to illustrate nonlinear fit of response latency and time constant.

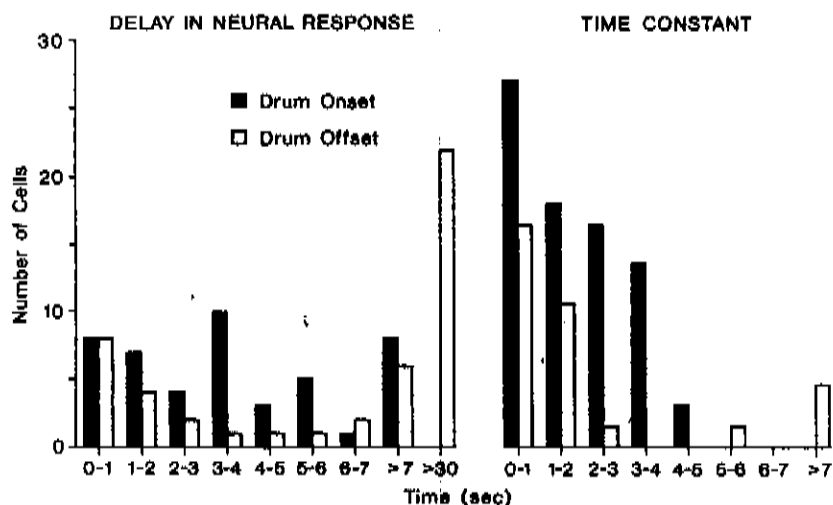


FIGURE 2. Summary of latency (left) and time constants (right) for population of Purkinje cells sampled.

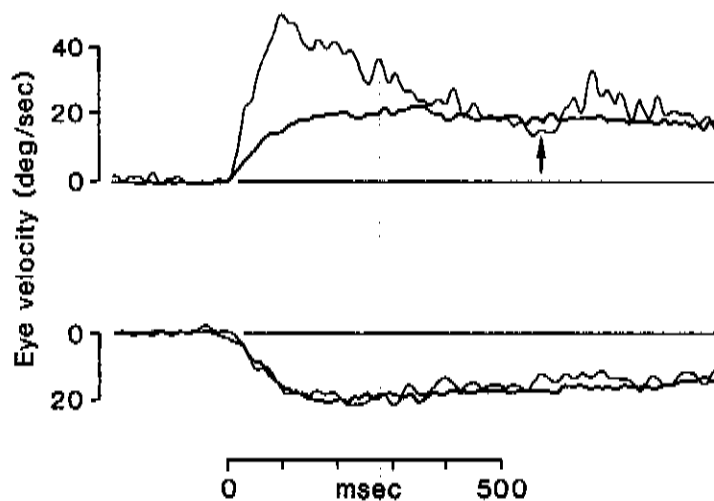


FIGURE 3. Pursuit eye velocity following left uvula lidocaine injection. At top, the animal is pursuing a target spot with a velocity 20 deg/second right. At bottom, the spot velocity is 20 deg/second left. Target motion begins about 100 msec before the zero time indication. Traces are average eye velocity responses before (thick line) and after (thin line) injection. Saccades have been removed. The arrow shows a brief period of rightward retinal slip that produced another large episode of rightward eye acceleration.

lobule VIII. In this animal the effects were minimal. In the third animal we saw a substantial increase in rightward open-loop gain with a left uvular lidocaine injection as in the first animal. Interestingly, another lidocaine and subsequent ibotenic acid lesion which affected the midline of the uvula resulted in increased open-loop pursuit response in *both* directions.

Another result of these lesions was an inability to suppress following eye movements with fixation of a small stationary spot during sweep of the large textured background. If background motion was to the right, the left uvular lesion animals were easily pulled off of the fixation point, whereas before the lesion they could almost suppress this motion totally. With background motion to the left, suppression was even better than normal. In FIGURE 4, averaged eye velocity from trials of this type for the same animal shown in FIGURE 2 is displayed, both before and after the lesion. Eye velocity for background motion to the right following the lesion was much greater than normal, as it was higher than 5 deg/second for most of the trial. To the left, eye velocity was less than normal, i.e., this animal suppressed optokinetic

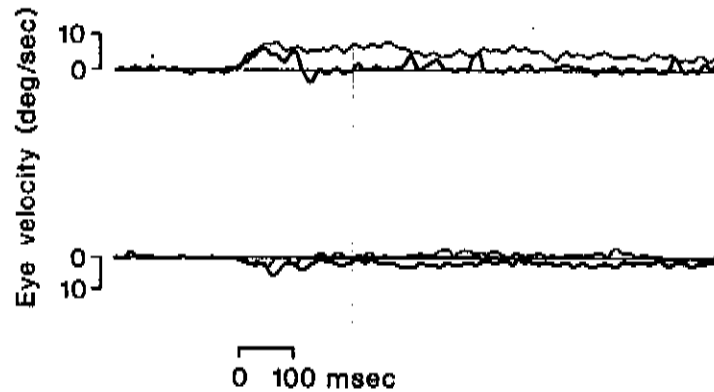


FIGURE 4. Eye velocity following left uvula lidocaine injection in suppression task. Background velocity is 20 deg/second right (top) and left (bottom). Background motion begins about 100 msec before the zero time indication. Other conventions as in FIGURE 3.

following movements better than before the lesion. Eye velocity actually switched directions and was opposite in direction to that of the background in this animal late in the trial.

Optokinetic nystagmus (OKN) and OKAN were less affected by the lesions than these other types of eye movements. For drum rotation directed contralateral to the lesion, eye velocity was almost normal during both OKN and OKAN in these animals. There was decreased OKN for drum rotation directed ipsilateral to the lesion; however we do not believe that this was due to an inability of slow eye velocity to build up during the prolonged stimulation. Our drum rotation apparatus had several peripheral fixed objects inside the drum which the animal occasionally attempted to fixate which decreased OKN even before the lesion. During these intermittent periods of attempted fixation, these objects would have become more effective following the lesion due to the monkeys' heightened suppression for this direction of optokinetic stimulation.

## DISCUSSION

In summary, some uvular units showed pursuit and/or visual motion responses resembling those found on floccular or vermis units. These were rare, however, and most responses like this that we were able to record were classified as mossy fiber input units, probably reflecting dorsolateral pontine and other visual pontine nuclei projections to the uvula. Since P-cells almost never showed this type of immediate response, the uvula must utilize visual inputs for a different purpose than does the flocculus or vermis. Uvular P-cells seem to be associated with some other process, presumably some functional concomitant of long-duration large-field visual motion. What candidates for this function can be considered?

Velocity storage is one possibility, but the time course of change of most uvular P-cells during the induction of OKN was much different than that postulated for the velocity storage mechanism.<sup>18</sup> In addition, the time course of the unit modulation seldom paralleled the decay of OKAN, probably the single best measure of the storage dynamics. Also, the eye velocity built up during OKN is stored as evidenced by the presence of rather normal OKAN in our lesioned animals.

Another possibility is that this structure is involved in the visual dumping mechanism of velocity storage as hypothesized by Waespe *et al.*<sup>16</sup> However, dumping requires a rapid visual response which we rarely find on these cells. Furthermore, our lesions restricted to the uvula have very little effect on this function. We think that visual dumping of velocity storage is probably performed more by the nodulus and perhaps the ventral folia of the uvula which were not consistently affected by our lesions.

Our suggestion as to what function the uvula may perform concerns its anatomical projections to the vestibular nucleus, both directly and via the fastigial nucleus.<sup>19</sup> The vestibular nuclei have been shown to be a structure through which pursuit signals flow, and are also the posited site of the neural integrator.<sup>20</sup> Individual vestibular neurons project directly to eye muscle motor neurons, but the state of the integrator that represents expected eye position must be coded by the bilateral activity in the vestibular nuclei on each side of the brain stem. It seems likely that this push-pull arrangement would require an active balancing mechanism to provide stable drift-free operation of this final output stage of the oculomotor system. We hypothesize that the uvula is part of this balancing mechanism. Occasionally we have noticed abnormal temporary eye drift as a result of our lesions, and cerebellar patients sometimes show a gradual decline of their gaze-paretic nystagmus during prolonged periods of eccentric fixation. However, when this is followed with attempted central fixation, they show a period of rebound nystagmus in the opposite direction.<sup>21</sup> These phenomena and the results of our lesions could be explained by the removal of inhibitory input from the uvula on the neural integrator. The uvula then appears to be a structure that aids in adaptation to abnormal periods of unbalanced oculomotor output, such as that which results during prolonged optokinetic stimulation.

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