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## Failure of the oculomotor neural integrator from a discrete midline lesion between the abducens nuclei in the monkey

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Recent anatomical studies indicate that axons of neurons in the vestibular nuclei, projecting to the contralateral abducens nuclei, cross the midline at the abducens level. These axons then give off collaterals to the contralateral vestibular and prepositus nuclei that may be important for the neural integrator that converts eye-velocity to eye-position signals. We disrupted a subset of these commissural projections by making a small midline lesion between the abducens nuclei in a monkey. The vestibulo-ocular reflex and saccades were still present post-lesion, indicating that premotor drive was intact, but the lesion produced severe post-saccadic drift, indicating failure of the neural integrator. We conclude that commissural projections crossing at the abducens level may be important for oculomotor integration.

Primate eye movement commands are initially encoded as an eye-velocity signal. For example, neurons in the vestibular nuclei carry head-velocity signals that serve as eye-velocity commands to execute the vestibulo-ocular reflex (VOR) [2]. Also, saccadic eye velocity is encoded by reticular burst neurons [17]. Motoneurons, however, carry both eye velocity *and* position commands during all types of eye movements [7]. The eye-position command is derived from the eye-velocity command by a neural network known as the oculomotor neural integrator [15].

Current evidence indicates that the oculomotor neural integrator for horizontal eye movements resides jointly in the medial vestibular nuclei (MVN) and nuclei prepositus hypoglossi (NPH), bilaterally. Single unit studies reveal that many neurons carry eye-position as well as eye-velocity signals in primate MVN [6] and NPH [13]. Excitotoxin lesions of both MVN and NPH in monkey produce, among other deficits, total inability to maintain eccentric gaze following saccades due to severe post-saccadic drift [3]. This indicates a complete failure of the oculomotor neural integrator. Similarly, electrolytic lesions of MVN and/or NPH produce integrator failure in cat [5].

Recent models suggest that neural integration is

brought about via inhibitory commissural interactions between the MVN-NPH complexes (MVN/NPH) bilaterally [4, 9]. Mutual inhibition creates positive feedback loops that could allow MVN/NPH neurons to persevere (integrate) eye-velocity commands to produce eye-position commands. However, commissurotomy by midline section at the level of MVN/NPH in cat did *not* result in an integrator deficit [5]. This result would seem to oppose the hypothesis that integration in the oculomotor system is subserved by commissural interactions.

Anatomical studies illustrate that axons of MVN neurons projecting to the contralateral abducens nuclei cross the midline at the abducens level, and then give off a collateral to the contralateral MVN/NPH [12]. These collaterals may form the commissural loops that are critical for neural integration. More posterior midline lesions, made at the MVN/NPH level as in cat [5], would fail to disrupt these commissural loops. Conversely, more anterior lesions at the abducens level would not only disrupt these commissures but remove part of the oculomotor drive to abducens from MVN as well. The purpose of this study was to make a small, discrete midline lesion between the abducens nuclei to see if it could produce a measurable deficit of the oculomotor neural integrator without totally disrupting premotor drive. Because this lesion is difficult to reproduce precisely, preliminary data, if only from one monkey, are worth communicating.

The adolescent rhesus monkey was prepared for

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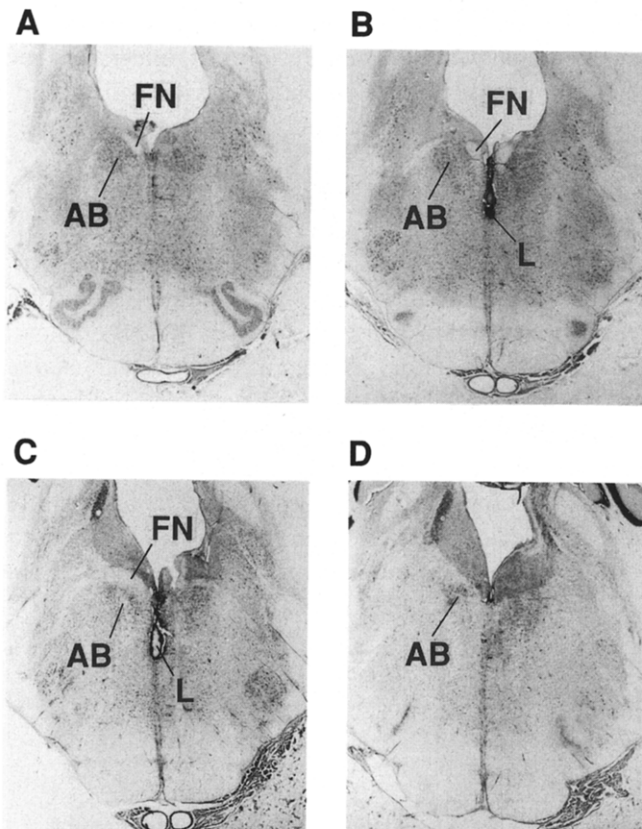


Fig. 1. Discrete, electrolytic lesion of the midline in a rhesus monkey. The midline lesion was located roughly midway between the rostral and caudal poles of the abducens nuclei, and had an approximately columnar shape about 4 mm deep and 1 mm in diameter. The sections begin at the caudal pole of the abducens nuclei (A), and progress from there in 0.48 mm steps (B–D). Landmarks include the abducens nuclei and the genuae of the facial nerve. The right medial periaqueductal nucleus was damaged by a mechanical lesion made one week *after* the electrolytic lesion. The track of a marking pin inserted at the time of sacrifice can be seen on the right side of the brainstem (C). AB, abducens nucleus; FN, genu of the facial nerve; L, midline lesion.

chronic eye movement and single unit recording. Aseptic surgery was performed under anesthesia. A coil of teflon coated wire was implanted under the conjunctiva of the left eye [10], and its leads were passed subcutaneously to a connector at the top of the head. A stainless-steel, cylindrical recording chamber was mounted over a trephine hole in the occiput on the midline. The axis of the chamber was tilted 25° back from vertical in the sagittal plane and stereotaxically directed toward the region of the MVN/NPH and abducens nuclei, according to the atlas of Smith et al. [16] (lateral 0.0 mm, posterior 4.0 mm, dorsal 0.0 mm). Stainless-steel screws were fastened to the skull as anchors, and a pedestal for immobilizing the head, the eye-coil connector, and the recording chamber were cemented to the skull and screws using dental acrylic.

Eye position was recorded using the magnetic search

coil technique [8]. Single unit recordings were made from the abducens nuclei using tungsten microelectrodes advanced from a guide tube. Abducens motoneurons were identified by their characteristic ‘singing’ discharge, as heard on an audio monitor, that correlated closely with horizontal eye movements. By making many penetrations in grid formation, a stereotaxic map, relative to the recording chamber, of both abducens nuclei was constructed.

A discrete electrolytic lesion, having a roughly columnar shape approximately 4 mm deep and 1 mm in diameter, was made on the midline between the abducens nuclei. This was done by positioning a tungsten microelectrode using the stereotaxic map, and advancing it into the brainstem in five 1 mm steps. At each step anodal current was passed at 100  $\mu$ A for 1 min. Eye movement evaluation commenced immediately after the last (5th) burn. One week after this lesion was made, the monkey was perfused with formalin, its brain was removed and frozen sections were cut at 40  $\mu$ m and stained for Nissl substance. The lesion is shown in Fig. 1.

During experiments, the monkey was seated in a primate chair which could be rotated about the vertical axis. Vestibular stimuli were delivered by rotating the chair by hand at an approximately constant velocity for 30 s and abruptly stopping it. Horizontal spontaneous saccades and post-rotatory nystagmus in the dark were recorded before and after the lesion shown in Fig. 1. Eye position and chair tachometer signals were digitized on-line for subsequent analysis.

The effects of this lesion on gaze-holding following spontaneous saccades in the dark are shown in Fig. 2. One day prelesion, the monkey exhibited some deficit in gaze-holding due to damage from repeated microelectrode and guide tube penetrations into the brainstem. (The last single-unit experiment occurred 53 days before integrator function was evaluated.) This neural integrator deficit appears as an exponential drift back to primary position following all spontaneous saccades (Fig. 2A). Several eye position decays were fit with a single exponential and the time constants were averaged. The prelesion integrator time constant was  $6.1 \pm 1.0$  s (S.E.M.) ( $n=11$  drifts). In comparison, the integrator time constant is about 20 s in normal humans [1].

The midline lesion produced pronounced post-saccadic drift and a spontaneous nystagmus to the left (Fig. 2B). The combination of leftward spontaneous nystagmus and an integrator deficit resulted in curved slow phases, and shifted the null point from the normal, primary position (0°) to almost 40° to the left. Following each saccade (or nystagmus fast-phase), eye-position decayed exponentially toward the null point. With the null point shifted from zero, the integrator time constant

can be determined by fitting the decay of eye *velocity* with a single exponential [3]. The lesion reduced the integrator time constant to  $0.5 \pm 0.1$  s (S.E.M.) ( $n=9$  drifts). This result indicates that destroying a subset of the commissural fibers crossing the midline at the abducens level can reduce the time constant of the neural integrator by an order of magnitude. This result supports the hypothesis that integration is subserved by commissural interactions among MVN/NPH neurons.

A leaky integrator will cause the eyes to drift centripetally at a rate that is roughly proportional to the angle of eccentric deviation [3]. Vestibular eye velocity, whether spontaneous or induced, will be corrupted by this drift at eccentric eye positions, but can be accurately measured as the eye passes through zero. The lesion shown in Fig. 1 produced a spontaneous nystagmus of over  $40^\circ/s$  to the left. Spontaneous nystagmus abated af-

ter 5 (Fig. 2C) and 10 min (Fig. 2D) post-lesion, and was compensated within 30 min. In contrast, integrator time constant recovered little during this period and even after 1 week post-lesion had only increased to  $3.3 \pm 0.3$  s (S.E.M.) ( $n=5$  drifts).

Although direct projections from the MVN to the contralateral abducens nuclei were probably also disrupted by the lesion, the VOR could still be elicited either side by head rotation in the dark. Post-lesion VOR with abductive slow-phases is shown in Fig. 3B,D. Slow-phases of post-rotatory nystagmus were also curved due to the integrator deficit (Fig. 3B). The peak response gain of the VOR, corrected for integrator leak and spontaneous nystagmus, did not appear to decrease after the lesion. This suggests that the lesion did not significantly disrupt premotor vestibular drive. Vestibular inputs to the abducens nuclei not affected by the lesion may have

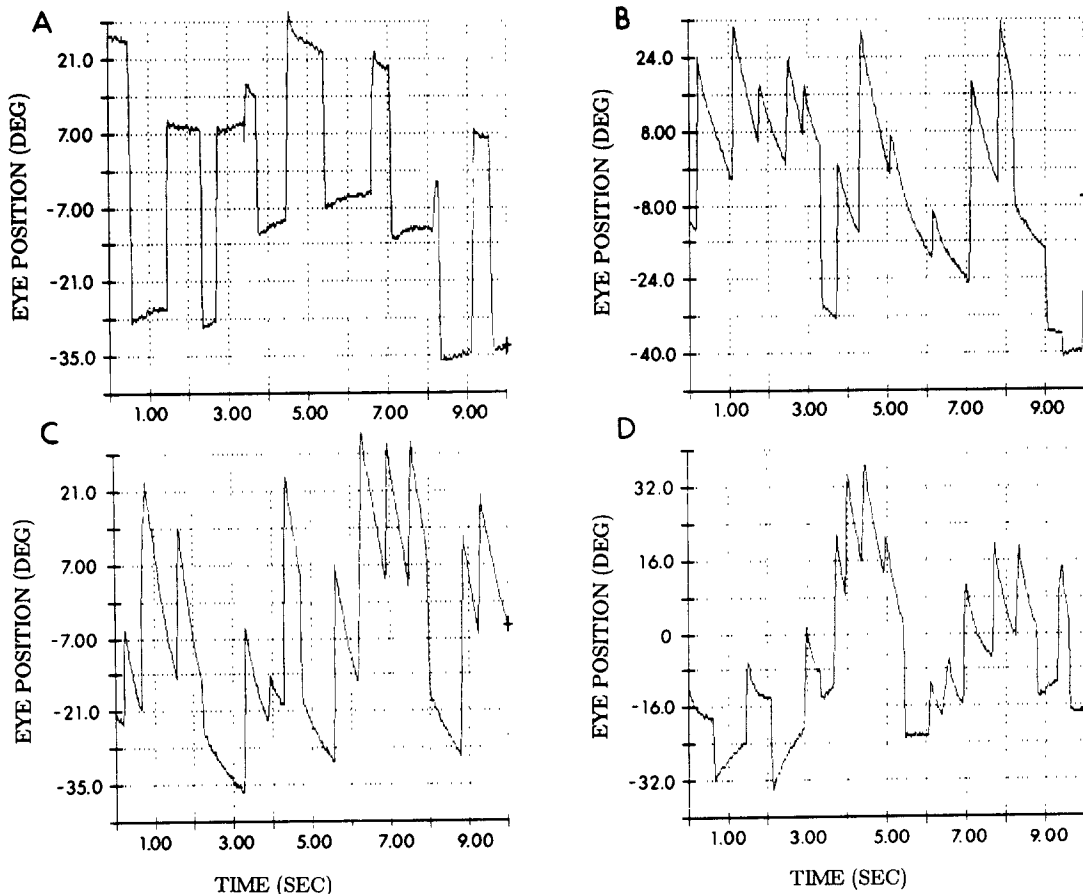


Fig. 2. Effects of the midline lesion on gaze-holding following spontaneous saccades in the dark. Horizontal eye position in degrees is plotted against time in seconds; eye positions to the right of zero are positive. A: 1 day prelesion, gaze-holding was partially impaired due to damage from repeated microelectrode penetrations. The neural integrator time constant was about 6 s. B: immediately post-lesion, the monkey exhibited a spontaneous nystagmus of  $40^\circ/s$  to the left, and the integrator time constant was decreased to about 0.5 s. The combination of spontaneous nystagmus and the integrator deficit resulted in curved slow phases and a shift of the eye position null point from zero to almost  $40^\circ$  to the left. C: approximately 5 min after the lesion, spontaneous nystagmus abated but the integrator time constant had not increased. D: approximately 10 min after the lesion, spontaneous nystagmus decreased to  $30^\circ/s$  and the null point shifted back to about  $10^\circ$  left. The integrator time constant, however, had still not increased. Note the increased exponential drift back to the null point following all spontaneous saccades in D as compared to A.

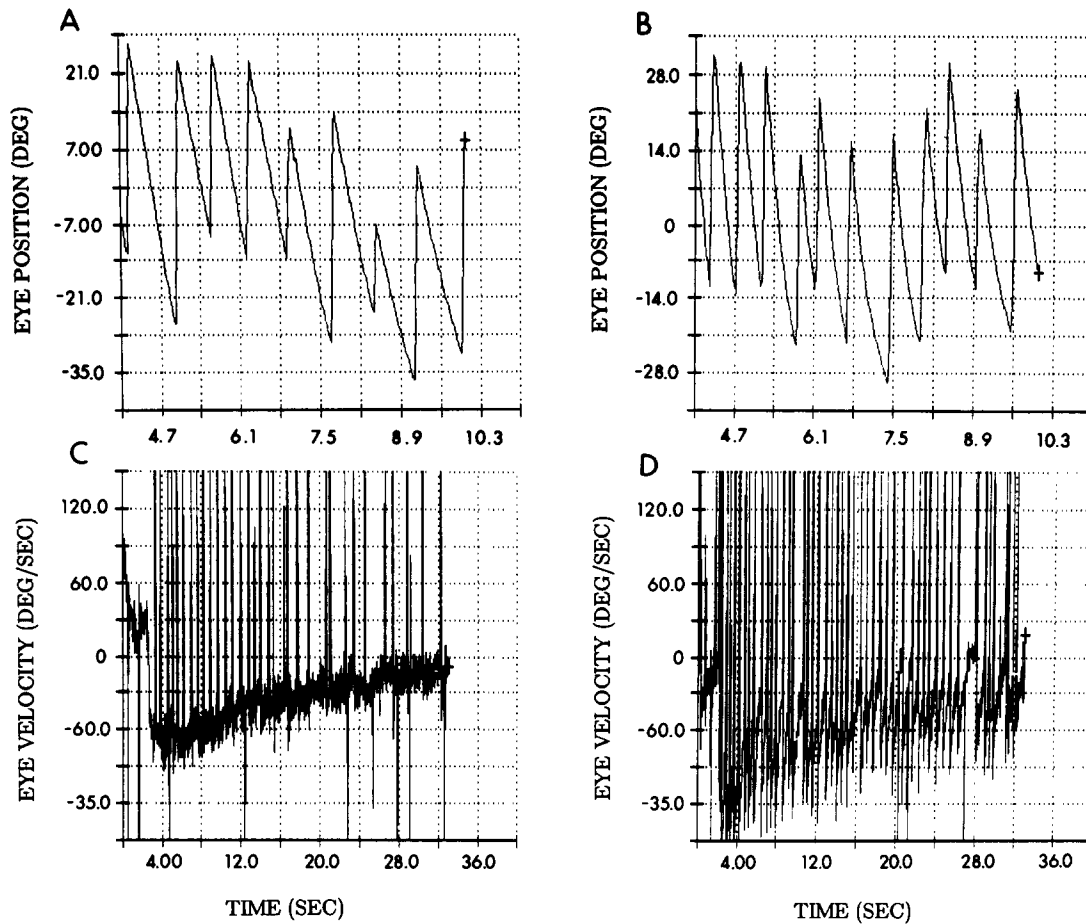


Fig. 3. Effects of the midline lesion on post-rotatory nystagmus in the dark. Horizontal eye position in degrees (A,B) and velocity in degrees/second (C,D) is plotted against time in seconds; rightward eye positions and velocities are positive. Time coordinates in A and B correspond to those in C and D, respectively. A: before the lesion, slow-phases of post-rotatory nystagmus were straight. C: horizontal VOR time constant, measured by fitting slow-phase eye velocity with a single exponential, was 18 s. B: following the lesion, nystagmus slow-phases were curved, indicating an integrator deficit. This deficit, combined with spontaneous nystagmus, resulted in larger changes in individual slow-phase velocities. D: horizontal VOR time constant, measured from the decay of slow-phase eye velocity corrected for the integrator deficit and spontaneous nystagmus, was decreased to 10 s by the lesion.

included remaining fibers from MVN, and fibers from the ventral lateral vestibular nuclei and NPH, bilaterally [11]. Vestibular inputs to the oculomotor nuclei coursing in the ascending tract of Deiters [12] were probably also spared. The lesion did not produce any noticeable deficits in adduction, indicating that it did not eliminate internuclear fibers from the abducens to the oculomotor nuclei [18].

The dominant time constant of the horizontal VOR was measured by fitting the eye velocity decay of one post-rotatory response with a single exponential. Eye velocity was recorded each time the eye passed through zero and corrected for spontaneous nystagmus. The horizontal VOR time constant was reduced from 18 (Fig. 3C) to 10 s (Fig. 3D) as a result of the lesion, and did not recover with time post-lesion. This result indicates that midline lesions at the abducens level can also reduce velocity storage, which prolongs the VOR time constant

beyond that of the semicircular canals [14]. However, this lesion affected velocity storage to a lesser degree than neural integration. More posteriorly placed lesions, that were actually in the left MVN just off the midline, and made approximately one hour after the midline lesion shown in Fig. 1, completely abolished velocity storage, reducing the VOR time constant to about 6 s. These MVN lesions also reduced VOR gain.

Simulations of a version of the neural integrator model proposed by Cannon et al. [4] were run to determine the effects of commissurotomy. In this version, model MVN/NPH neurons driven from one vestibular input were segregated on one side of the brainstem. Thus the lateral inhibitory connections between the neurons on either side corresponded to vestibular commissures. Sectioning of a single commissural connection produced an integrator deficit similar to that following removal of one neuron [4]. Cutting one commissural fiber also un-

balanced the network and resulted in spontaneous nystagmus. This indicates that midline lesions can also produce spontaneous nystagmus if an unequal number of oppositely directed commissural fibers are disrupted. Such will inevitably occur in making incomplete, discrete lesions of the commissures, and probably accounts for the spontaneous nystagmus produced by the lesion shown in Fig. 1.

In summary, some MVN neurons which project to the contralateral abducens nuclei send off collaterals to the contralateral MVN/NPH that cross the midline at the abducens level [12]. Disruption of a subset of these projections by discretely lesioning the midline between the abducens nuclei produces a profound integrator deficit without blocking premotor drive. These preliminary results suggest that commissural collaterals of vestibular projections crossing at the level of the abducens nuclei may be important for neural integration in the oculomotor system.

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