

Stimulation-Evoked Eye Movements With and Without the Lateral Rectus Muscle Pulley

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Dimitrova, Diana M., Mary S. Shall, and Stephen J. Goldberg. Stimulation-evoked eye movements with and without the lateral rectus muscle pulley. *J Neurophysiol* 90: 3809–3815, 2003. First published August 27, 2003; 10.1152/jn.00622.2003. Recent studies have suggested that extraocular muscle (EOM) pulleys, composed of collagen, elastin, and smooth muscle, are among the tissues surrounding the eye. High-resolution magnetic-resonance imaging appears to indicate that the pulleys serve to both constrain and alter the pulling paths of the EOMs. The active pulley hypothesis suggests that the orbital layer of the EOMs inserts on the pulley and serves to control it. Based on anatomical data, the active pulley hypothesis also suggests that the orbital layer does not rotate the eye within the orbit; this is done by the global layer of the muscle. However, no physiological data exist to confirm this hypothesis. Here we used stimulation-evoked eye movements in anesthetized monkeys and cats before and after destruction of the lateral rectus muscle pulley by removal of the lateral bony orbit and adjacent orbital tissue. The absence of these structures resulted in increased lateral, in the primate, and medial, in the cat, eye-movement amplitude and velocity. Vertical eye movements in the cat were not significantly affected. The results indicate that these increases, confined to horizontal eye-movement amplitude and velocity, may be attributed to passive properties within the orbit. In relation to the active pulley hypothesis, we could discern no clear impact (in terms of amplitude or velocity profile of the movements) of lateral eye exposure that could be directly attributable to the active lateral pulley system.

INTRODUCTION

The recent discovery of extraocular muscle pulleys (Miller 1989) has provided an anatomical basis for a “revolutionary” re-examination of ocular motor physiology (Demer 2002). Previous examinations of human orbits characterized the orbital connective tissue as highly uniform among individuals and bilaterally symmetrical (Koorneef 1977). The more recent histological approaches have revealed a “pulley system” composed of collagen, elastin, and smooth muscle (Demer et al. 1995, 1997). Although the role of this orbital tissue in eye movements has been considered, recent advances in magnetic-resonance imaging (MRI) have suggested that some of the tissue might serve as active pulleys to help determine the effective pulling direction of each extraocular muscle (EOM) (Clark et al. 1997; Demer et al. 1995). High-resolution MRI has revealed the stability of EOM paths during changes in

gaze, and quantitative data on the location of the pulleys has been obtained indirectly based on inflections of the EOMs (Clark et al. 1997). Thus it is now hypothesized that these pulleys serve as a functional insertion for some EOM fibers and to control the EOM path during active contractions (Demer et al. 1995, 2000).

The architecture of EOM revealed a layered structure with a peripheral, orbital layer (OL) facing the orbital wall and enclosing a global layer (GL) adjacent to the globe (Porter et al. 1995). Morphological studies of EOMs described the presence of five to six muscle fiber types that exhibited a differential distribution within the orbital and global muscle layers (Porter et al. 1995; Spencer and Porter 1981). Histological studies of primate EOMs show that the fibers from the OL do not reach the tendon (Oh et al. 2001), and high-resolution MRI demonstrated the insertion of each rectus OL on its respective pulley (Demer et al. 1995). The “active pulley hypothesis” suggests that the OL inserts on the EOM pulley, whereas the GL inserts on the eyeball through the muscle tendon. Therefore it was hypothesized that the function of the OL is, instead of rotating the eyeball along with the GL, to position the pulley. It has also been suggested that the contractile force of the OL fibers is not transmitted to the main EOM tendon inserting on the globe (Demer et al. 2000). However, electrophysiological evidence appears to indicate that OL muscle fiber force is transmitted to the muscle insertion on the eye (Shall and Goldberg 1995) and that lateral transmission of force within whole skeletal muscle is not unusual (Monti et al. 1999, 2001; Trotter et al. 1995). That is, force need not be exclusively exerted, in parallel, between tendinous insertions. The prediction that the OL of extraocular muscles serves to control pulley position, but not to rotate the eyeball, does not correspond to existing physiological data.

The present experiments were designed to examine the effect of a missing lateral rectus pulley on eye movements induced by stimulation of the VIth nerve in the monkey and the IIIrd nucleus in the cat. (Different nuclei were used in monkey and cat for technical reasons—see METHODS.) This was done by surgically removing the entire lateral orbital wall and all adjacent orbital tissues. Although the existence of an orbital pulley system in cats is not yet proven, it is expected because pulleys have been found in monkeys, humans, rats, and rabbits (Demer

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2002; Demer et al. 1995, 2000; Khanna and Porter 2001). It might be expected that depriving a rectus EOM of part of its insertion (i.e., the OL's insertion on the pulley) and its functional origin (Demer 2002) would have a deleterious effect on the control of eye movement. Pulling direction might be altered, which could decrease lateral eye-movement amplitude and/or velocity. If, in contrast to the active pulley hypothesis, the OL muscle force could be transferred to the globe, the lateral eye movement could actually increase in size and/or velocity. However, such an increase could result also from changes in the passive properties of the eye system.

To confirm that any changes in the stimulation induced eye movement were due to the absence of the active lateral pulley in the primate and not to passive changes resulting from the removal of the lateral bony orbit and adjacent tissues, eye movements in directions other than to the side of the surgery were also studied in the cat. Changes in lateral eye movement could be attributed to both a damaged lateral rectus pulley and a reduction of passive orbital tissues. In contrast, possible changes in medial and/or vertical eye movement with intact pulleys of the respective muscles would suggest modification of the passive properties of the eye plant. Therefore comparison between lateral eye movements and movements in other directions would reveal the active control of the pulley by the lateral rectus muscle's OL.

METHODS

Surgical preparation

Six adult cats (2.5–3.5 kg) and two monkeys [1 Rhesus monkey (4.5 kg) and 1 *Cynomolgus* monkey (2.5 kg)] were used in the experiments. The cats were initially anesthetized with pentobarbital sodium at 45 mg/kg ip. The monkeys were premedicated with 15 mg/kg ketamine and 0.01 mg/kg glycopyrrolate administered intramuscularly and then anesthetized with pentobarbital sodium at 25 mg/kg iv into the saphenous vein. Additional doses of pentobarbital sodium were provided intravenously during the experiment to maintain deep anesthesia as assessed by the absence of blink reflex and withdrawal to digit pinch.

After topical anesthesia of the larynx with 4% lidocaine, the animals were intubated with a 3.5 to 5.0-mm endotracheal tube. The end-tidal CO₂, respiratory rate, and heart rate were continuously monitored and maintained within a normal range. Body temperature was kept at 37°C with a heating pad. An intravenous drip of lactated Ringer solution at room temperature (10 mg · kg⁻¹ · h⁻¹) was also provided.

The animal was placed in a Kopf stereotaxic frame, and a midline incision was made from the forehead to the back of the neck. An anterior parietal craniotomy was performed for placement of a stimulating electrode. Medial (4 cats) and downward (1 cat) movements of the right eye were evoked by stimulating the ipsilateral oculomotor nucleus and upward movement was evoked in one cat by stimulating the contralateral oculomotor nucleus (coordinates: A 1.5–3.5 L 0.5–2.0 D 1–2). Because of the complexity of the oculomotor nucleus, a slight shift of the electrode in this coordinate range could evoke an eye movement of different direction. The electrode location was adjusted to evoke purely vertical or horizontal eye movements. No attempt was made to evoke lateral eye movements in the cat to avoid potential confounding effects of globe retraction since the abducens nerve innervates both the lateral rectus and retractor bulbi muscles (Crandall et al. 1981). Retractor bulbi involvement influences stimulation induced lateral eye movements, by causing retraction of the globe.

Lateral eye movements were evoked in the monkeys in response to stimulation of the VIth nerve in the brain stem. The VIth nerve is

found at a coordinate of A 1.5, L 2.0 and at varying depths depending on the size of the animal (Contreras et al. 1981; Paxinos et al. 2000). Medial eye movements were not studied in the monkey since the caudal aspect of the IIIrd nucleus is only ~2 mm rostral to the exit of the VIth nerve from the brain stem, although they are at different depths. It was not technically practical therefore to stimulate both the IIIrd nucleus and VIth nerve in the same animal. In addition, the evoked eye-movement study reported on here was only the initial phase of a series of experimental protocols, using the lateral rectus muscle, to which these valuable primates were subjected during the period of their anesthesia.

After the experiment the animals were killed with an overdose of pentobarbital sodium administered intravenously. All procedures and protocols for animal care and use were approved by Animal Care and Use Committee of Virginia Commonwealth University.

Stimulation and recording procedures

All eye movements were recorded in two experimental conditions using an identical stimulation electrode location: with the orbit intact and with the lateral bony orbit and the underlying connective tissue, including the lateral rectus muscle pulley, surgically removed. We refer to this second condition as "lateral eye exposure."

Movements of the right eye were examined in response to abducens nerve (monkey) or oculomotor nucleus (cat) stimulation. A stainless steel bipolar electrode (0.2 mm tip diameter and 1.5 mm distance between the poles) with uninsulated tips was used for stimulation. Individual pulses ranged from 400 to 800 μA in intensity with 0.2-ms pulse duration. They were delivered as constant frequency trains of pulses lasting for 200 ms in a range from 50 to 220 Hz (8 different frequencies). All stimuli were produced by a programmable pulse generator (AMPI Master-8) and were delivered at 5-s intervals to assure a return to baseline. The animals were presented three trials at each frequency used.

Movements of the right eye were recorded by one or both of two methods: videotaping the eye movements in the plane of the movement with a digital camcorder (Canon Elura2) at 30 frames/s and tracing the eye movement using an eye search coil (3D eye movement monitor model EM7, Rempel Labs) at 10-kHz sampling rate. A small wooden rod (1–1.5 cm in length and weighing ~6 mg) was glued to the eyeball and served as a marker to track the movement with the video camera. The wooden marker and coil remained in place for recording with the orbit intact as well as with the lateral eye exposed.

Data analysis

The recorded eye movements were analyzed off-line. The eye-tracking marker in the digital images was selected from the background by its color intensity. The points reconstituting the marker were fit with a straight line by the least-square method (P. Dean and S. Sklavos, personal communications). The amplitude of the eye movement was calculated in relation to the initial marker position (prior to stimulus) regarded as primary position.

The eye coil system was calibrated by videotaping the eye movement for a given stimulation frequency with the above-mentioned procedure and applying this conversion to all other movements. The maximal eye displacement and velocity were measured after applying a fourth-order butterworth filter at 30-Hz cut-off frequency. An example of medial eye-movement amplitude for different stimulation frequencies measured in cat by the eye coil system and by the digital-imaging method is illustrated in Fig. 1. The mean eye-movement amplitude obtained from the digital images at 140-Hz stimulation frequency was used for calibration of the eye-coil recordings. Both methods showed similar variability of the eye-movement amplitude and the maximal angular displacements corresponded well to each other.

The eye-movement peak velocity was calculated from the eye-

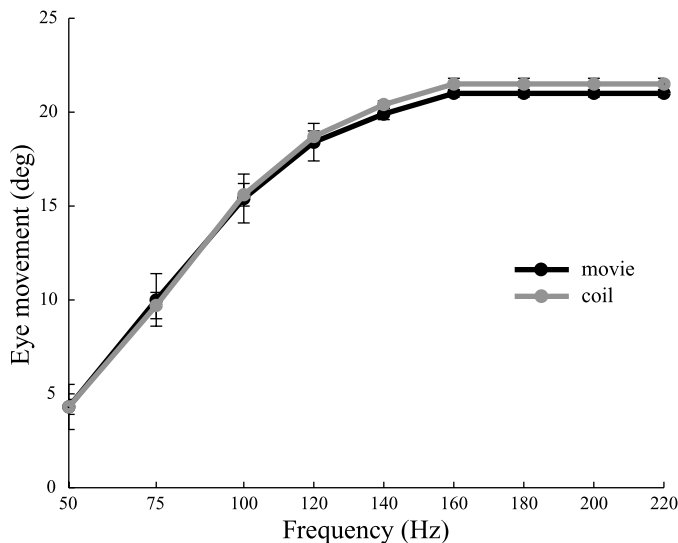


FIG. 1. Comparison of maximal amplitude \pm SE of medial eye movement at different stimulation frequencies measured with the eye coil method (gray) and with the video method in 1 experimental animal.

displacement traces recorded with the search coil (5-point method). However, no attempt was made to estimate the eye-movement velocity by the digital-imaging method because of the low sampling rate of the digital camcorder.

The effect of lateral eye exposure as well as the effect of the stimulation frequency used was estimated with ANOVA (2×8 ANOVA) at a probability level $\alpha = 0.05$, separately for each direction of eye movement. The ANOVA results are presented with the F value (degrees of freedom of the sample, degrees of freedom of the error) and the significance level P (Iversen and Nortpoth 1987) (SPSS). Values in the text and in the figures are given as means \pm SE.

RESULTS

For each direction of eye movements, higher frequency stimulation produced significantly larger eye movements in both monkey and cat [lateral: $F(8,89) = 360$, $P < 0.001$; medial: $F(8,198) = 23$, $P < 0.001$; downward: $F(8,36) = 160$, $P < 0.001$; upward: $F(8,36) = 365$, $P < 0.001$]. The maximal amplitude of eye movements in response to different frequencies of stimulation for lateral, medial, upward, and downward directed eye movements is illustrated in Fig. 2. The data established that the basic relationship between the degree of eye movement and stimulation frequency with orbit intact (Fig. 2, —) was preserved after lateral eye exposure (Fig. 2, - - -).

But lateral eye exposure did lead to an increased amplitude in both monkey lateral [$F(1,89) = 360$, $P < 0.001$, Fig. 2A] and cat medial eye movements [$F(1,198) = 22$, $P < 0.001$, Fig. 2B]. However, no significant change in cat vertical eye movements was found after lateral eye exposure ($P > 0.75$, Fig. 2, C and D).

For the whole frequency range used, the horizontal eye movements increased after lateral eye exposure with a greater absolute difference for the higher frequencies [$F(8,89) = 11$, $P < 0.001$]. For example, lateral eye movement (Fig. 2A) was increased by $7.1 \pm 0.6^\circ$ at 200 Hz compared with $0.7 \pm 0.2^\circ$ at 50 Hz. It should be noted that the 7.1° difference represents a 37% increase and the 0.7° difference represents, similarly, a 39% increase. Across all the frequencies used, lateral eye-movement amplitude in the monkey increased by an average of

$38 \pm 2\%$ of the total eye movement after lateral eye exposure. It is important to note that medially directed eye movements in the cat, after lateral eye exposure, also showed a mean increase in eye movement amplitude of $39 \pm 3\%$ across the same frequency range.

In addition to the amplitude increase in horizontal eye movements, the peak velocity was also increased for both lateral and medial directions of eye movements [$F(1,47) = 426$, $P < 0.001$ and $F(1,47) = 83$, $P < 0.001$, respectively]. Figure 3 shows examples of lateral and medial eye movements recorded with the search coil (A and B). Eye-movement velocity was calculated from such data, and one can also see that the recorded movements are quite similar in shape, except for the amplitude and rise time differences, before and after lateral eye exposure. Typical velocity profiles for lateral and medial eye movements for the same experimental conditions are illustrated in Fig. 3, C and D. Figure 4 illustrates the peak velocity for different stimulation frequencies during lateral (A) and medial (B) eye movements with the orbit intact and after lateral eye exposure. Peak velocity increases tended to get larger as stimulation frequency increased for both lateral (monkey) and medial (cat) eye movements, although the increases were more pronounced at the lower frequencies (e.g., 50 and 75 Hz) for medial movements. Across all stimulation frequencies used, the percentage increase in peak eye velocity was $24 \pm 2\%$ for lateral and $27 \pm 4\%$ for medial eye movements.

DISCUSSION

In the present study, the active role of the lateral pulley system in the control of stimulation-induced eye movements in the horizontal and vertical planes was examined. Removing the lateral orbital wall and the underlying connective tissue together with the lateral rectus pulley led to an increased amplitude and velocity of both lateral and medial eye movements (Fig. 2, A and B) but no difference in the evoked vertical eye movements (Fig. 2, C and D).

Motoneurons and pulleys

The active pulley hypothesis for pulley control by the rectus OL would require a selective activation of motor units from this layer. However, there does not appear to be electrophysiological evidence indicating selective recruitment of particular motoneurons (Fuchs et al. 1988; Scudder et al. 2002; Shall and Goldberg 1992) that might exclusively innervate the muscle pulleys. During eye movements in alert animals, all motoneurons (Scudder et al. 2002) and therefore all motor units (in both the OL and GLs of the EOMs) have been seen to participate in all types of eye movements. Also, all motoneurons show a "pulse/slide/step" (or burst/tonic) firing pattern during saccades (Scudder et al. 2002). These various neuronal firing patterns are thought to be used, in part, to overcome the resistance due to the visco-elastic properties of the orbital tissues (i.e., connective, fat, EOMs) surrounding the eye (Robinson 1964; Scudder et al. 2002). Although motor-unit electromyographic (EMG) recordings from the OL and GLs suggest a recruitment order based on muscle fiber size, no differentiation on the basis of the type of movement to which they contribute was found (Scott and Collins 1973). In this experiment, stimulation of an EOM

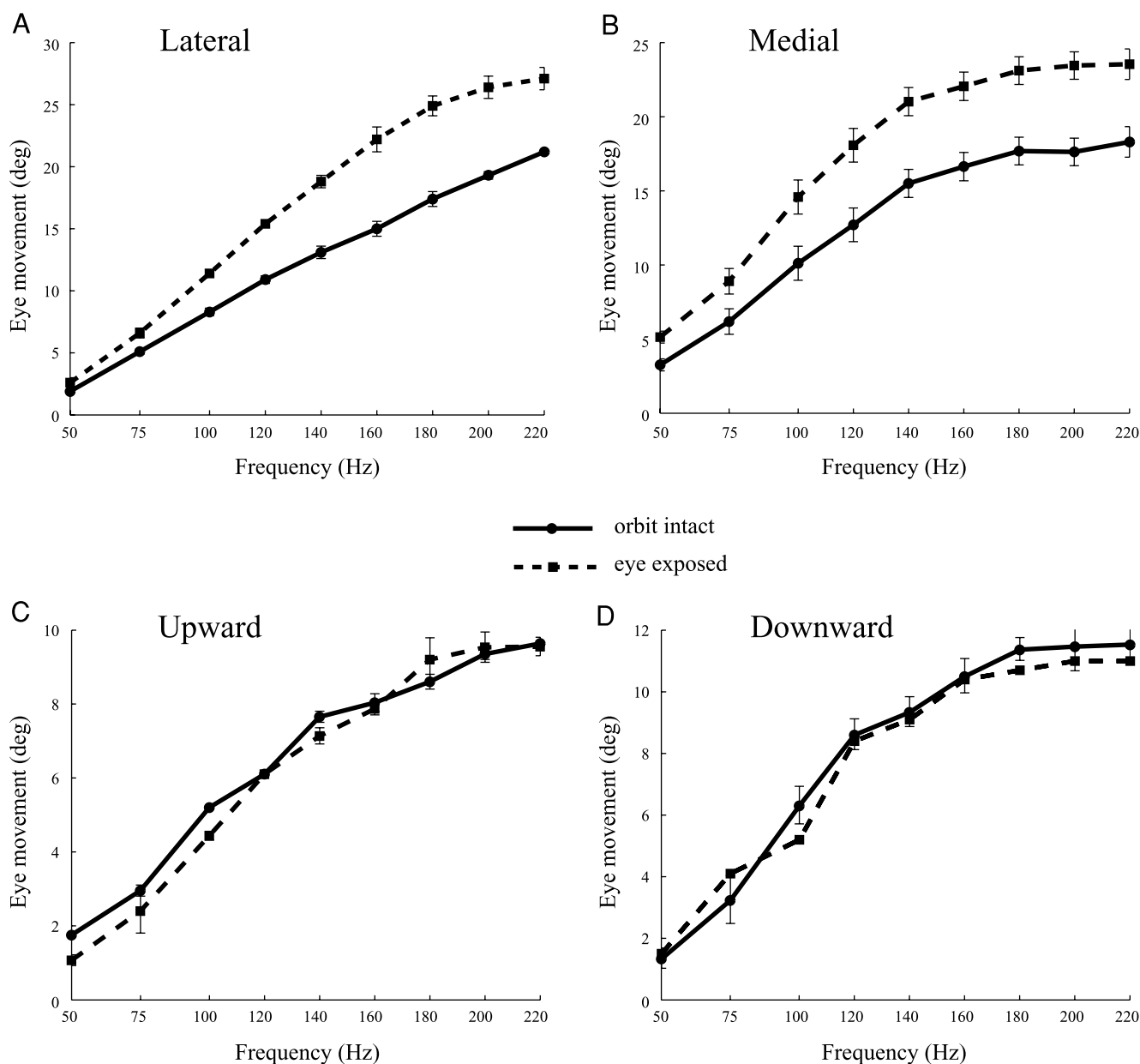


FIG. 2. Maximal movement amplitude (mean \pm SE) at different stimulation frequencies with orbit intact (—) and with lateral pulleys removed (---) during lateral (A), medial (B), upward (C), and downward (D) eye movements. The data presents results from 2 monkeys (A), 4 cats (B), 1 cat (C), and 1 cat (D).

nerve or nucleus caused activation of both OL and GL motor units simultaneously. This assures both eye rotation by the GL and pulley activation/control by the OL.

Extraocular muscle layers and pulleys

A number of studies have indicated that muscle force is distributed not only along the length of the muscle but also laterally (for reviews see Monti et al. 1999, 2001; Trotter et al. 1995). The existence of lateral force transmission as an internal characteristic of whole muscle also suggests that force generated in either the GL or OL could be transmitted to both the main tendon as well as the pulley system. Indeed, complex connections among EOM fibers have long been known in the cat (Alvarado-Mallart and Pinçon-Raymond 1976; Mayr et al.

1975), and similar serial connections, muscle fiber branching, and lateral connections have recently been confirmed in the squirrel monkey lateral rectus muscle (Shall et al. 2003). Our previous electrophysiological studies (Goldberg and Shall 1999; Shall and Goldberg 1995) showed that the force of the OL of EOMs is transmitted to the main tendon and thus would take part in eyeball rotation. The contractile properties, including twitch and tetanic force of single, lateral rectus motor units, were recorded in cat with the main muscle tendon disinserted from the globe and attached to a force transducer (Shall and Goldberg 1995). Motor units were activated by stimulation of single motoneurons in the abducens nucleus using glass micropipette electrodes. The location of each motor unit was determined by separate and simultaneous EMG recordings of activity from the OL as well as the GL. Eight of the 41 motor

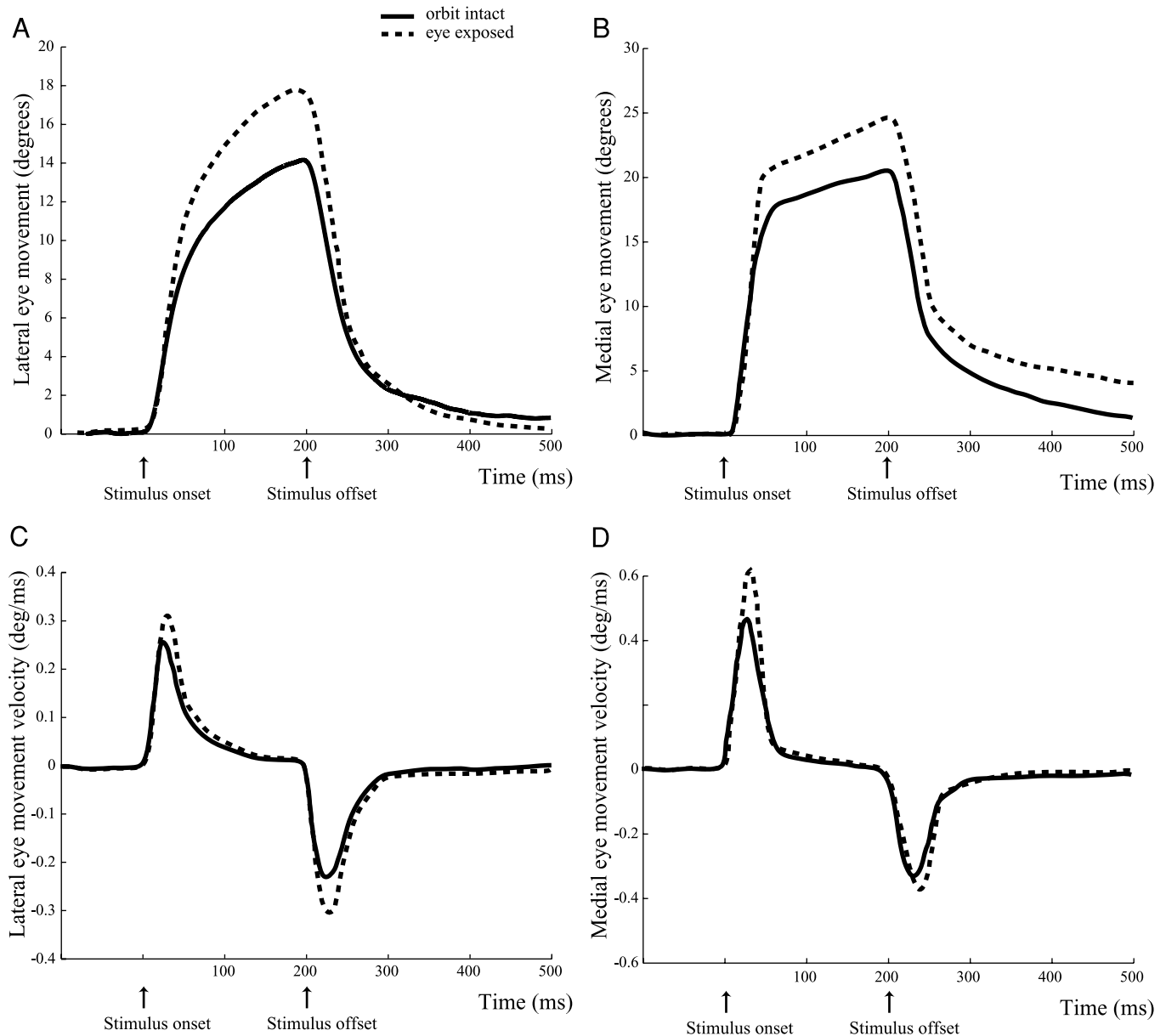


FIG. 3. Search-coil recordings of horizontal eye movements before (—) and after (---) lateral eye exposure. *A*: lateral eye movement in the monkey in response to 140-Hz stimulation of the ipsilateral VIth nerve. *B*: medial eye movement in the cat in response to 140-Hz stimulation of the ipsilateral IIIrd nucleus. *C*: velocity profile of lateral eye movement illustrated in *A*. *D*: velocity profile of medial eye movement illustrated in *B*.

units studied were confined to the OL, and 11 motor units appeared to be split between the OL and GL of the cat lateral rectus muscle. The remaining 22 units were confined to the muscle's GL. Thus despite the anatomical evidence for the insertion of the orbital fibers into pulley rather than tendon the actual physiological evidence is that the OL motor units do in fact exert force on the tendon and a possible mechanism for this would be lateral force transmission within the muscle. Also due to lateral force transmission, tension on orbital tissue surrounding the eye muscles and including the pulley may not be completely controlled by the OL alone.

Control of the pulleys

The problem of whether the pulley system is actively controlled either by EOM orbital fibers alone (Demer 2002; Demer

et al. 2000; Oh et al. 2001) or by both orbital and GLs through lateral force transmission (Goldberg and Shall 1999; Monti et al. 1999; 2001; Shall and Goldberg 1995; Shall et al. 2003; Trotter et al. 1995) is addressed further in the following text.

Pulley elimination through lateral eye exposure might result in three possible outcomes in the case of lateral eye movements in the monkey: the eye movement might remain the same because the GL is unaffected and if the orbital fibers do not impart their force to the main tendon, but to the pulley only; the eye movement might be reduced in size and/or velocity because the directional control imparted by the pulley is gone; and the eye movement might increase in size and/or velocity because the restraining tissues in the orbit have been eliminated and the OL force, originally directed to the pulley, is now delivered to the main muscle tendon through lateral transmis-

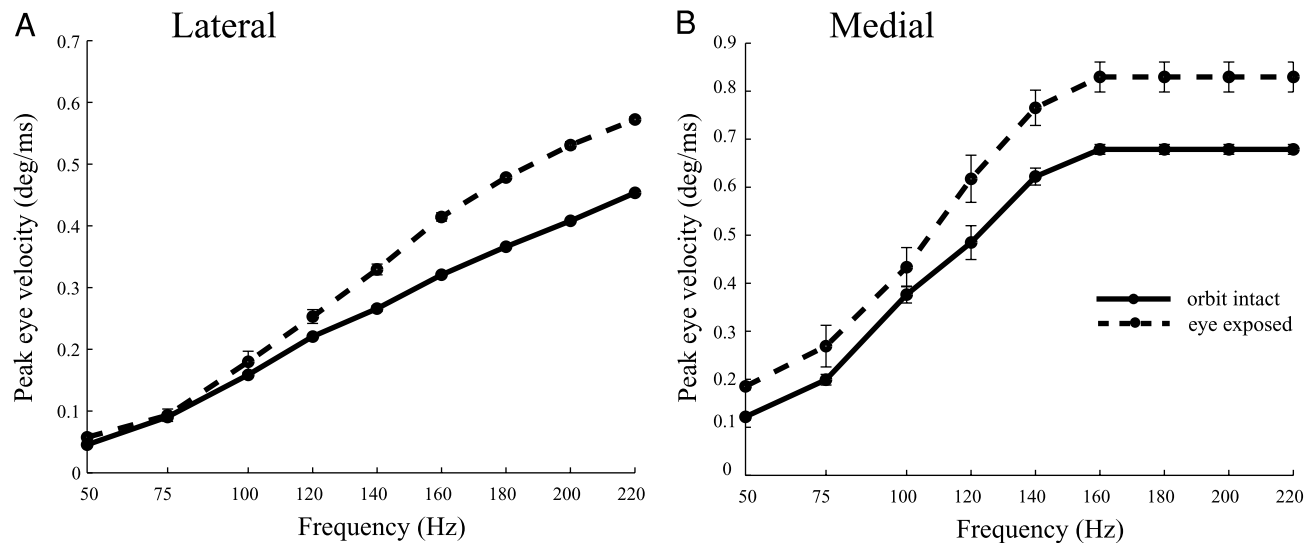


FIG. 4. Peak velocity of lateral (A) and medial (B) eye movements (mean \pm SE) at different stimulation frequencies with orbit intact (—) and with the lateral pulleys removed (---).

sion. We observed a result which is apparently consistent with the third outcome. The increase in eye-movement amplitude we observed might have been accompanied by a loss in directional stability due to the pulley's absence. This could have been reflected in the shape of the eye movement as recorded with the search coil, but shape changes were not observed.

Furthermore, we also observed a quite similar increase in eye movement amplitude and velocity for cat medial eye movements where the medial pulley is still intact. For both lateral (in the monkey) and medial (in the cat) eye movements, we observed an increase of $\sim 38\%$ in average amplitude as well as small increases in velocity after lateral eye exposure for both directions. In addition, we could discern no changes in the shape of these medial eye movements as recorded with the search coil. This data on medial eye movements, taken alone, appears to indicate that the eye can simply move more freely due to the removal, through lateral eye exposure, of the "restraining" tissues within the orbit.

One might also predict that the eye-movement amplitude and/or velocity increases observed for lateral eye movements might exceed those observed for medial eye movements. This reasoning is based on a combination of the following: OL muscle force (or the force from both muscle layers) originally directed to the pulley has become available after lateral eye exposure to provide more force to move the globe through the mechanism of lateral transmission and additionally, there would be an increase in the ease of movement without the restraining orbital tissue. But again, the amplitude and velocity increases we observed for cat medial movements were quite similar to those we observed for lateral movements in the monkey. Additionally, the pulley system remained intact medially for both the monkey and the cat. The similar effects of lateral pulley removal on lateral eye movements and movements in the opposite direction (i.e., medial) suggest the passive role of the orbital tissues in the horizontal plane. This questions the active control of the pulley by the activated lateral rectus muscle.

It is therefore also important that stimulation-evoked vertical movements in the cat remained the same before and after lateral eye exposure. The orbital tissue remained relatively

intact for those movements in the vertical plane. This further indicates that the loss of lateral orbital tissue alone played a major role in the horizontal eye movement increases that we observed in this experiment. It could be expected that in tertiary eye positions resulting from a combination of horizontal and vertical components, only the horizontal one would be affected in accordance with the present results.

It should be recalled, however, that this study used whole nerve and nucleus stimulation in anesthetized animals to evoke EOM contractions to produce eye movements that were restricted to the horizontal and vertical planes. No tertiary eye positions were examined. The stimulation used here clearly activated both orbital and global motor units simultaneously, as they are activated in saccades (Scott and Collins 1973). Nevertheless, we could discern no clear impact (in terms of amplitude, velocity, or the shape of recorded movements) of lateral eye exposure that could be directly attributable to the lateral pulley system. Perhaps future physiological studies will need to employ alert animals that are actively controlling their eye-movement system to discern the dynamic actions of the pulleys.

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DISCLOSURES

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