Reviews

EOM Pulleys and Sequelae: A Critical Review

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Purpose. The discovery of extraocular muscle (EOM) pulleys resolved long-standing issues in oculomotor physiology, revived interest in EOM function generally, and led to several new theories. We describe the pulley concept of Miller and Demer (M-D Pulleys) and briefly review evidence, distinguishing this well-supported notion from the Active Pulley Hypothesis (APH) and the EOM Compartments hypothesis, and critically reviewing the methodologies and evidence on which the latter are based.

Methods. We analyze evidence on mechanical independence of individual EOM fibers, implications of nerve tracing for functional independence of EOM layers and compartments, validity of image-based methods of assessing EOM contraction, and data analysis issues.

Conclusions. M-D Pulleys are well-supported by several lines of evidence from several labs. The APH, which predicts relative movements of EOM lamina sufficient to alter muscle actions, has been effectively disproved. The width-wise articulations of EOM Compartments, in contrast, might produce significant contractile oculorotary force gradients across muscle tendons, although existing evidence is unconvincing. We suggest how this hypothesis could be effectively tested.

Keywords: extraocular muscle pulleys, Active Pulley Hypothesis, extraocular muscle compartments, extraocular MRI

Orbital connective tissues perform a complex function once thought to require the brain: extraocular muscle (EOM) pulleys, condensations of connective tissue elastically stabilized to the orbital wall, solve the problem of controlling 3-dimensional (3D) eye rotation according to Listings Law.[1–4] This discovery was unexpected in a field that supposed extraocular anatomy and muscle actions to be basically understood, stimulated research in anatomy, physiology, mathematical analysis and modeling, and prepared ground for further theorizing.

We review the pulley concept of Miller and Demer,[1,5,6] and distinguish it from related proposals that followed. The Active Pulley Hypothesis (APH) and the notion of independently controlled EOM Compartments are then discussed, and their evidence is reviewed.

Longitudinally-Dragged EOM Pulleys

Condensations of midorbital connective tissue stabilized relative to the orbit and determining muscle paths were predicted by biomechanical modeling,[1,7,8] and confirmed by magnetic resonance imaging (MRI) before and after muscle transposition surgery.[1,5] Subsequent imaging studies estimated pulley positions and movements,[9–11] immunohistochemical studies showed that elastin and smooth muscle were concentrated in pulley tissues,[12–14] electron microscopic studies revealed an unusual, cross-layered structure,[15] and studies in nonhuman species showed that pulleys were evolutionarily conserved.[12,16]

Neurophysiologists had long assumed that Listing's Law (the kinematic principle that determines torsion for each gaze position), and coping with noncommutativity of 3D rotation (such as how independent horizontal and vertical gaze centers could control nonadditive rotation) must be implemented in the brainstem, although no such center could be found.[17–20] Mathematical analyses then showed that EOM pulleys could solve these problems mechanically, in the orbit.[2–4]

Demer and colleagues observed that rectus muscles could not slide freely through their connective tissue pulleys because they were attached on their orbital faces,[21] such that the pulleys would be dragged longitudinally with the contracting and relaxing muscles while remaining stabilized in other directions, and showed that this arrangement extended pulley kinematic functions to nonprimary gaze positions.[6,22] Originally named "Pulleys of Miller,"[23–25] we propose to recognize the contribution of Demer's group by calling these longitudinally-dragged connective tissue structures Miller-Demer Pulleys (M-D Pulleys).

Compelling confirmation of M-D Pulley kinematics was provided by Ghasia and Angelaki,[26] who showed that cyclovertical motoneurons do not modulate their firing during eccentric pursuit as would be necessary if the brainstem implemented Listing's Law, and by Klier et al.,[27,28] who stimulated the abducens nerve and nucleus downstream of any neural circuit that might implement Listing's Law and found that eye movements nevertheless had Listing kinematics, demonstrating that extraocular mechanics, that is M-D Pulleys, were capable of implementing Listing's Law without neural assistance.

However, Demer et al.[6] went beyond these data to claim support for the APH, the notion that orbital layer (OL) EOM fibers controlled pulley positions independently of global layer (GL) fibers, which rotated the eye. The APH was never plausible in its strong form,[29] and nerve tracing, microanatomy, immunohistochemistry, and experimental surgical manipulations have since rendered it untenable. The subsequently proposed notion of EOM Compartments, in contrast, remains a

viable, if unproven, hypothesis. We review the evidence on both theories.

APH and EOM Compartments

The APH is the claim that orbital and global EOM layers independently control longitudinal pulley position and globe rotation, respectively. The EOM Compartments hypothesis proposes that the two half-width parts of most muscles are independently controlled, thereby endowing, for example, horizontal recti with vertical and torsional actions. Together, these ideas distinguish actions, not of six EOMs, but of some 17 independent extraocular "mini-muscles" (11 GL compartments and six OLs). Such complication of the oculomotor plant must be justified with clear evidence that the proposed mini-muscles have independent neural control and sufficient mechanical independence to function differentially.

Mechanical Independence of EOM Fibers

The APH was born of the well-known microanatomic fact that mammalian EOMs generally have a thin layer of small myofibers facing the orbital wall, with different type distribution than the bulk of the muscle (the GL). The microanatomic study of Lim et al.[21] usefully describes the merging of OL connective tissue with adjacent pulley tissue, but then struggles to characterize this fusion of neighboring connective tissues as a "tendon." In support of fiber independence, they report being unable to find the myomyous junctions linking adjacent fibers that are reported commonly in EOMs of many species, including human,[30–33] which failure may have been due to their reliance on muscle cross-sections or their use of formalin-fixed tissue, which suffers significant shrinkage, breaking protein crosslinks and creating artefactual spaces.

From in-vitro experiments on bovine EOM, Shin et al.[34,35] report that differential passive stretching of OL or GL, and chemically-induced contraction of GL, were almost completely uncoupled from unmanipulated layers. They also stretched lateral halves of muscles, corresponding to compartments suggested by nerve tracing (see below), and found similarly weak coupling to the unstretched halves. Interestingly, Shin et al.[34] found that *any* group of EOM fibers was only loosely coupled to adjacent fibers, which is to say that the particular division into compartments suggested by nerve tracing was not found.

The extraordinary fiber independence reported by Shin et al. could be due to epimysium having been stripped off, damaging the connective tissue matrix that normally couples fibers,[36] and to the experimental procedure itself, in which connective tissues joining adjacent fibers were subjected to shear forces far exceeding those they normally sustain. A related study of tendon fiber independence[37] drew a similar, independent critique, complaining that muscle samples had been denuded of "key surrounding structures" and subjected to supraphysiologic forces, also citing surgical Z-tenotomy data inconsistent with fiber independence.[38] If EOMs were composed of parallel independent fibers their total force would be the sum of forces of the individual fibers, which several lines of evidence show is not the case.[33,39–41]

McLoon et al.[36] showed that epimysium, perimysium, and endomysium of human EOMs form a dense and continuous collagen matrix, with no separations between any muscle regions, limiting relative fiber movements of any kind. Alan B. Scott (personal communication, 2018) sought to selectively ablate OL to weaken primary position forces without impairing eccentric gaze or saccades, but could find no natural laminar cleavage in the horizontal recti of cats, rabbits, or monkeys, even with sharp dissection and laser ablation. It generally is accepted that neither histologic sections[21] nor MRI[42] show any boundary or separation between OL and GL.

The finding of Maas and Sandercock[43] that the connective tissue matrix of skeletal muscles permits small fiber movements, but not large, potentially damaging ones, suggests a clarifying distinction: differential contractile *forces* can be developed across a muscle's width, but substantial differential *movements* cannot. Thus, EOM Compartments might function by producing a force gradient across the tendon, balancing opposing forces isometrically, whereas the APH implausibly requires relative movements of OL and GL sufficiently large to translate pulleys and alter the actions of muscles passing through them.

Innervational Independence of Layers and Compartments

Different oculomotor functions generally are associated with distinct brainstem nuclei or regions, but the anatomic studies cited in support of EOM Compartments only traced motor axons downstream of the entry into their muscles. Absent full axon tracing (e.g., using brainstem lesioning, stimulation, or retrograde tracers) there is no evidence that the branches identified contain axons from distinct brainstem centers. It has been shown only that the abducens nerve, the medial rectus (MR) and inferior rectus (IR) divisions of the oculomotor nerve, and the trochlear nerve bifurcate as they enter, and then branch to fill more-or-less separate regions of their respective muscles.[44–46]

These nerve tracing studies are at the root of the EOM Compartment notion, but what do they imply about function? Arborization is a fractal process in which a compact trunk branches out to fill a large volume while preserving its basic structure. Trees arborize to expose leaves to sunlight, and bronchi to increase contact of air from the trachea with circulating blood. Motor nerves traverse long distances in compact bundles, and then branch repeatedly to synapse effectively throughout the volumes of target muscles. Once a trunk branches into, say, left and right limbs, the starting points of subsequent branchings already tend to be lateralized. To minimize inefficient overlap with domains of neighboring branches that would occur with such purely random growth, active processes exist, such as molecular self-avoidance, that help achieve "innervational tiling."[47] Branching into nonoverlapping neighborhoods is an efficient way to fill space and does not imply differential function.

How do the nerve tracing studies bear on the APH and its assumption of independent OL and GL control? Although anatomically separate nerve branches do not imply independent control, an intermixed nerve supply does mean that independent control is impossible. Earlier studies showed that many abducens motor neurons innervate OL and GL,[48,49] and now, Peng et al.[44] and da Silva Costa et al.[45] report finding no separation of nerve branches to OL and GL in any muscle. The absence of neural support for independent control clearly disconfirms the APH.

Posterior Partial Volume (PPV) Does Not Measure Muscle Contraction

The neurophysiologic studies needed to demonstrate differential functioning of mini-muscles have not been done. In their place, we are offered MRI measurements of Posterior Partial Volumes. Are PPVs reliable measures of EOM contraction, or indeed measures of muscle contraction at all?

When an EOM contracts, its maximum cross-section (MaxCS) increases, so that a reasonable measure of contraction

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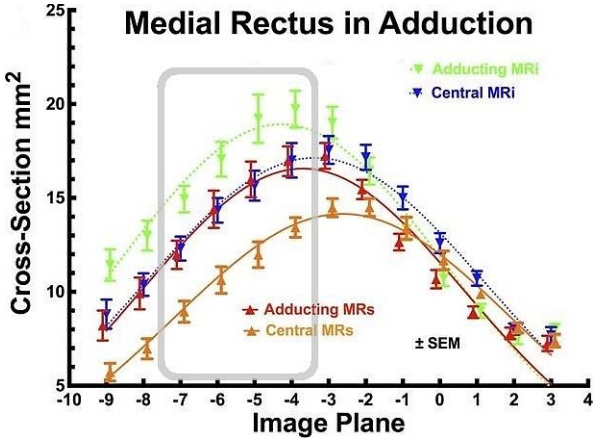

Figure 1. PPV is a complex measure. As the MR contracts and the eye adducts, the data of Clark and Demer[50] show MaxCS increasing and tissue distributions moving posteriorly (*blue* => *green* and *yellow* => *red*), the movement causing more anterior tissue to enter the ROI than posterior tissue leaves. Compounding this problem, the ROI is referenced to the G-OJ (*Image Plane 0*), which moves anteriorly in adduction (see Fig. 2), so that posterior tissue movement is exaggerated, and contraction is doubly overestimated. Redrawn with permission from Demer et al.[50]

would be the volume of a few MRI slices centered on MaxCS. However, MaxCS also moves posteriorly with contraction,[1,50] and this movement must be tracked to avoid conflating different contractile states with different parts of the muscle. A MaxCS-centered region of interest (ROI) also would have a defined location in any gaze position for any muscle that had a MaxCS, and as the muscle contracted volume would flow, so to speak, similarly into both ends, making such a measure robust to positioning errors.

PPV, in contrast, was defined as the volume in an 8 mm thick ROI posterior to MaxCS in central gaze. It was chosen from many candidate measures for its high correlation with duction.[51,52] Therefore, PPV is a measure of eye position, not of muscle contraction. Eye position results from contractile and elastic actions of multiple muscles and elastic tissues, and is not interchangeable with the contractile state of an individual muscle. Indeed, nontrivial mathematical models are needed to relate the two.[8,53,54]

Clark and Demer[52] summarize the centrality of their PPV measurements: "Using change in PPV as the measure of contractility, differential compartmental activity has been demonstrated for the LR during ocular counterrolling,[56] for the MR during asymmetric convergence,[50] and for the LR, inferior rectus (IR), and superior oblique (SO) during vertical fusional vergence." [57]

What does PPV actually measure? Admittedly, it reflects not only contractile thickening of the muscle, but also the contraction-related posterior movement of its MaxCS[51] (Fig. 1). Unhappily, the ROI is defined relative to the globe-optic nerve junction (G-OJ),[51,52] which moves anteriorly in eccentric gaze (Fig. 2). When we introduced orbital MRI to study muscle function,[1] resolution was insufficient to resolve the orbital apex and it was necessary to reference the G-OJ, but thanks to improvements in resolution, such unstable orbital referents have long been obsolete. A consequence of using a G-OJ referent is that in experiments using gaze to determine contractile state, the part of the muscle analyzed is contingent on gaze. Offered as a general measure of muscle contraction, PPV actually measures duction, is complexly contaminated, and is vulnerable to error and bias due to the critical positioning of its ROI.

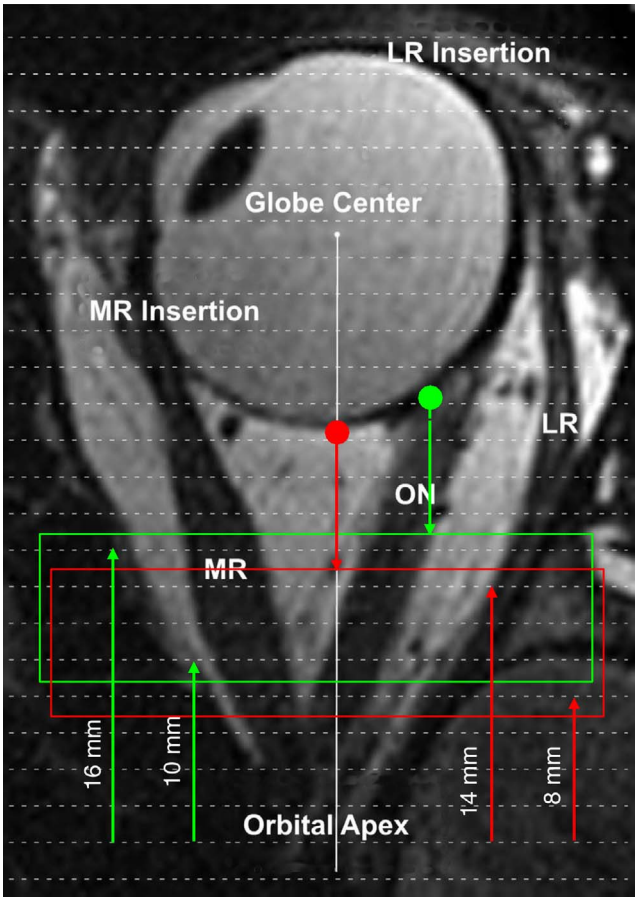

Figure 2. PPV sampling depends on eye position. For the adducted gaze pictured, the ROI (*green box*) referenced to the G-OJ (*green dot*) encloses four MRI slices (*horizontal dashed lines*, separated by 2 mm), located 10 to 16 mm anterior to the orbital apex. In central gaze, the G-OJ moves to the *red* dot and the ROI to the *red box*, sampling different parts of muscles and introducing a systematic gaze-related sampling error. Redrawn with permission from Clark and Demer.[55]

MRI Quantification Issues

Muscles visualized by MRI must be manually segmented (outlined) because judgment is required to distinguish adjacent nerves, vessels, connective tissues, and bone. Since introducing MRI techniques to study human EOMs in vivo,[1] we have learned that bias must be controlled with multiple readers from whom experimental conditions are obscured.[58] No such controls are described in MRI studies from the Demer lab.

Although scan planes generally cut muscles obliquely, the Demer lab calculates muscle volumes by multiplying slice areas by slice thickness, without correcting projection errors, and then stacking these blocks to estimate volume.[51] This process introduces errors that could have been avoided using well-described methods (Fig. 3).[58]

Published images illustrate the difficulty of unbiased segmentation. Figure 4, for example, shows an image from Clark and Demer's[52] study of vertical duction, in which it is clear that the shape change claimed in the MR cross-section is the result of biased segmentation.

In an experiment involving head tilt, Clark and Demer[56] measured ocular counterrolling relative to the interhemispheric sulcus, a soft tissue referent likely to be unstable with head tilt, and which can be seen in Figure 5 to have misaligned orbits in the two tilt conditions, creating the appearance of counterrolling where there was actually little or none. Because

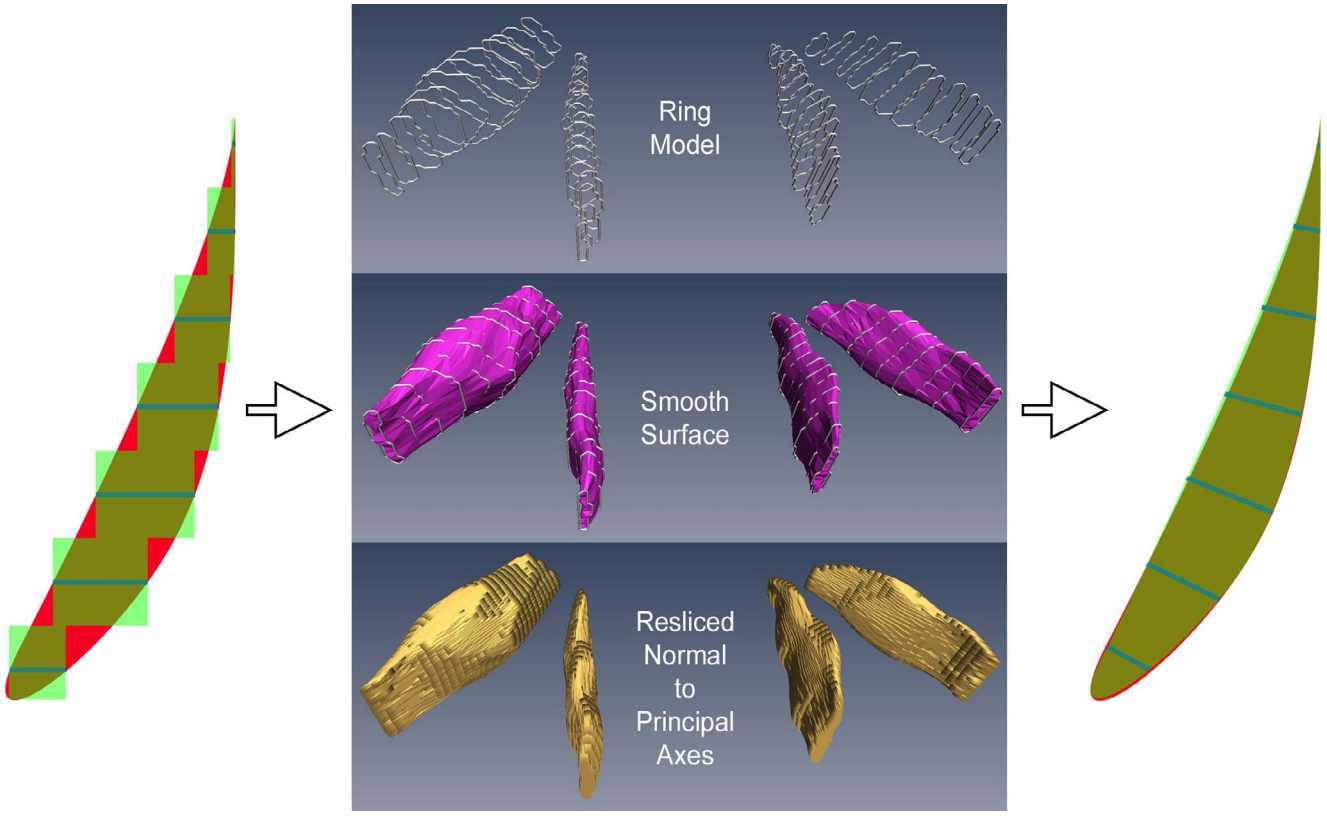

FIGURE 3. MRI volume calculation. *Left*: Muscle paths are not straight and scan planes are not generally perpendicular to the muscle's long centerline, so simply stacking individual slice "blocks"[51] gives a poor estimate (*green*) of muscle volume (*red*). *Center*: Both problems can be solved by stacking slice *contours* to form a ring model, fitting a smooth surface, and reslicing normal to the midline.[58] *Right*: This 3D reconstruction technique estimates true cross-sections with high longitudinal resolution.

the head tilt manipulation evidently failed, this experiment provides no support for compartmental contraction during ocular counterrolling.

Clark and Demer[59] offered an alternative to existing biomechanical strabismus models, which likened eye muscles to inextensible bicycle chains, and supported it with an MRI study claiming to show that the globe's axis of rotation was highly eccentric. However, the analysis was so clearly mistaken[60] that the published paper was retracted. The representative MRI image shown[59] is worrisome on its own, picturing a globe with geometric center far from the point marked "globe center," and a distance between global landmarks before rotation different from after, which cannot be correct unless the globe changed shape.

Cause or Effect?

Changes in the shapes of EOM cross-sections have been assumed to reflect differential contraction of compartments and to be causal with respect to eye position, but are more parsimoniously explained as passive consequences of eye movement. When a muscle (or any such soft object) bends "sideways" (e.g., vertical eye rotation for horizontal recti), tissue on the outside of the curve distributes along a lengthened path, reducing its cross-section, and tissue inside the curve "bunches-up," increasing its cross-section. Therefore, observed cross-sectional shape changes are likely a result of eye movement, occurring precisely because the muscle is not contracting differentially to relax outside fibers and take-up slack inside. Midorbital M-D Pulleys sharpen and confine the bend to a small region, increasing the "stretching-bunching" difference, and predicting that the asymmetry would be seen only in slices through pulleys, but not elsewhere (Fig. 6). Clark and Demer[56] dismiss the relevance of passive changes in cross-section.

Sampling Bias

Studies from the Demer lab typically use multiple eye movement types, eye positions, mini-muscle segmentations and measures of contraction to generate many potential comparisons. These are evaluated with *t*-tests and correlations to find those yielding the largest differences, which then are reported as either confirming and extending previous claims or as suggesting new and unexpected EOM capabilities. However, simple pairwise contrasts give correct error rates only for single hypotheses stated before analysis. Multiple a-posteriori tests on complex data sets—referred to as "data dredging" or "p-hacking"—are problematic, because as the number of comparisons increases, so does the probability of finding a "significant difference" by chance where none exists. There are many ways the multiple comparison problem might have been dealt with.

Clark and Demer,[52] for example, collected data in central and six eccentric gaze positions. Some comparisons pooled all infraductions, others all supraductions, and still others changes from maximum infraduction to maximum supraduction. A small 4% compartmental PPV difference pooled across infraductions is reported for LR, although there was no difference across supraductions or across maximal gaze changes (which included infraductions), and nevertheless,

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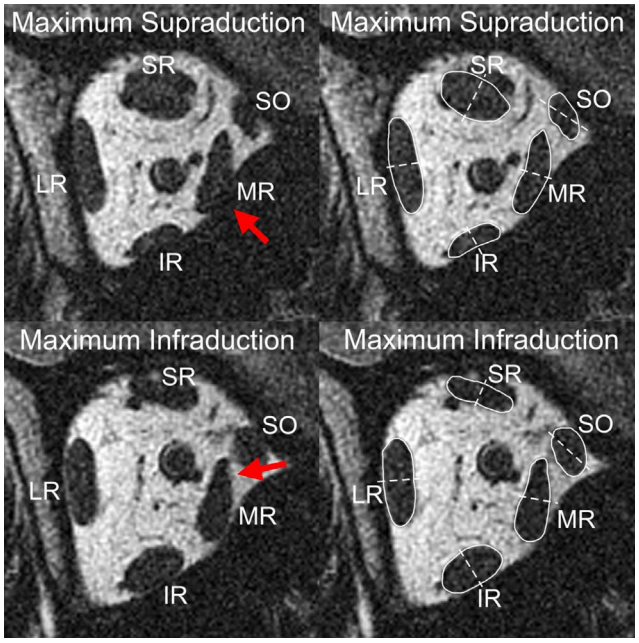

Figure 4. Biased image segmentation. Clark et al.[52] present these image segmentations as evidence that, from supraduction (*top-right*) to infraduction (*bottom-right*), the inferior part of MR enlarges differentially because compartment MR_I contracts more than MR_S. However, the raw images on the left clearly show that the supposed shape change is an artifact of excluding MR_I tissue where it abuts the curved orbital wall in the upper image, and excluding MR_S tissue in the less clear lower image (*red arrows*). EOM compartment theory would also predict $LR_I > LR_S$ but this is not seen, and no explanation is given. The "stretching-bunching" theory (see text), in contrast, might explain that the LR pulley inflection fell outside of the slices shown. Redrawn with permission from Clark and Demer.[52]

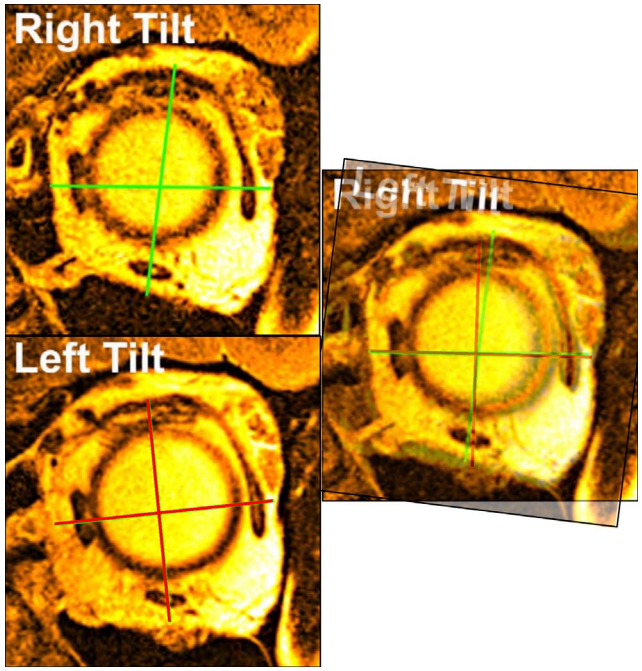

Figure 5. Biased image comparison. *Left*: Images, modified from Clark and Demer,[56] aligned by the interhemispheric sulcus and claiming to show the pulley array counterrolling against head tilt, are rotationally misaligned. *Right*: The "left tilt" image is rotated to align the two images on the visible orbital bone, showing that there was actually little or no counterrolling.

was taken as support for EOM Compartments and the broad conclusion that all EOMs have complex actions.

Clark and Demer[52,56] wished to show differential compartmental contraction during ocular counterrolling and vertical duction. Although nerve tracing[45,46,61] predicts particular compartment boundaries, they created multiple segmentations—12 in the case of the SO—with the expressed aim of finding the "most likely intercompartmental border," but actually finding segmentations yielding the largest differences, regardless of whether they corresponded to nerve tracing predictions.[52] These differences were then tested with paired comparisons.

Conclusions

- Nerve tracing, experimental surgical manipulations, and connective tissue studies—given that relative movements and not just force gradients are required—have effectively disproven the APH.
- Nerve tracing raises the possibility that LR, MR, SO, and possibly IR might have differentially controlled half-width compartments, and it is possible that they strain the connective tissue matrix sufficiently to exert differential oculorotary forces at their tendons, although there is no good evidence that they do so.
- MRI studies from the Demer lab use incorrect measures of muscle contraction that are dominated by artifacts, use statistics that do not reasonably account for overall error rates, show evidence of bias, are unconvincing about cause and effect, and lack confirmation from other labs.
- It is unwarranted to state as if proven that eye position is controlled by some 17 extraocular mini-muscles, and to urge tests, diagnoses, and treatments on the basis that it is.[62–64]

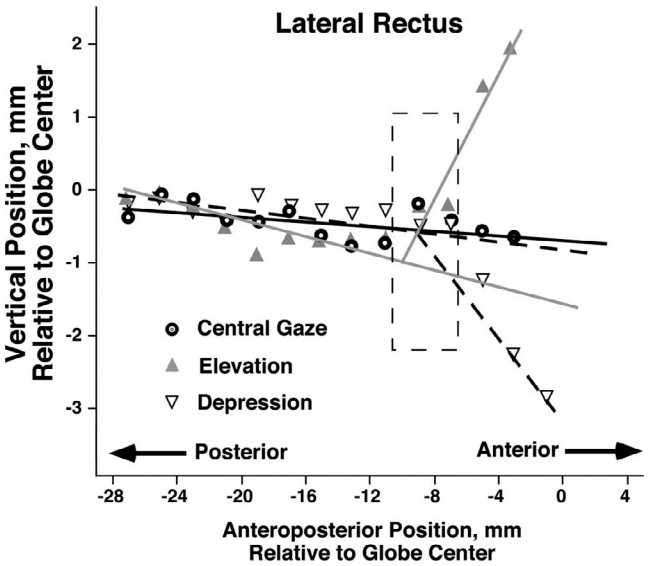

Figure 6. Sharp deflection of muscle path due to pulleys. Positions of area centroids of the LR relative to globe center are shown as a function of vertical gaze. The muscle's path bends sharply in elevation and depression at the location of the pulley (*dashed box*). Passive changes to the shape of the muscle's cross-section would be confined to the region of the pulley. Redrawn with permission from Clark et al.[11]

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Future Directions

The EOM Compartments hypothesis remains viable, though unproven. EOMs certainly develop elastic force gradients across their tendons, which helps stabilize eye position,[7,8,65] and it is possible that they develop contractile force gradients as well. Testing this idea would require new studies with better design and analysis:

- To establish that EOM motor nerve branching is functionally significant, tracing must extend back to the motor nuclei. Brainstem lesioning and stimulation studies should be performed, and effects on putative compartmental contractions measured.
- Techniques must be used that specifically measure muscle contraction, uncontaminated by muscle movement or eye rotation, and robust to variation in ROI position. We described the desirable properties of an imaging measure that tracks MaxCS. Direct measurement with force transducers is another possibility.[66,67]
- It is essential to control bias and error in quantifying orbital MRI images. We found it sufficient to have images segmented by three trained readers who are naive about experimental conditions. When the three reads are not consistent, all are repeated.[58]
- MRI studies must distinguish passive muscle cross-section shape changes due to "stretching-bunching" from hypothetical changes due to differential compartmental contraction. This could be done by taking advantage of the fact that the former would be confined to the region of the pulleys.
- Experiments must be designed so that potential comparisons are clear in advance, and are amenable to analysis using acceptable statistical methods.

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Letter to the Editor of IOVS From Joseph L. Demer and Robert A. Clark Regarding Joel M. Miller, "EOM Pulleys and Sequelae: A Critical Review"

This letter responds to the recent review by Joel M. Miller,[1] purportedly refuting the active pulley hypothesis (APH) of ocular kinematics, and criticizing with panoramic scope the methods and findings of publications from our research group.

Dr. Miller himself was prescient in his 2007 review, entitled "Understanding and Misunderstanding Extraocular Muscle Pulleys," when he wrote: "We will find that most critiques of pulley theory are incorrect, being based on gross misunderstanding or directed at abandoned hypotheses."[2] That statement is unfortunately characteristic of Dr. Miller's own 2019 review.[1]

The core of the APH, as Demer first articulated it in 2000[3] and elaborated in the Friedenwald Lecture paper in 2003[4] is that the orbital layer (OL) of each rectus extraocular muscle (EOM) inserts on that EOM's pulley and shifts the pulley posteriorly during EOM contraction. This notion, which Miller later termed the concept of "coordinated pulley control," does not require any relative shift at all between each EOM's OL and oculorotary global layer (GL), as Miller clearly stated in his 2007 review when he wrote:

> There is nothing in the notion of coordinated active pulleys about independent control or differential motion of orbital and global lamina. Laminar distinctions are merely references to known anatomy. Nothing about coordinated APH kinematics would change if all fibers were coupled to both the pulley sleeve and the sclera.[2]

It is thus more than puzzling that Miller's 2019 review absolutely contradicts his foregoing statement with the assertion that "The absence of neural support for independent control (of OL and GL) clearly disconfirms the APH."[1] Although Demer's initial publication of the APH also offered up the possibility of differential pulley position control of to implement the non-Listing's kinematics of the vestibulo-ocular reflex, Demer quickly abandoned that view, as Miller acknowledged in his 2007 review.[2] In this context, Miller is remarkably erroneous in his assertion in the 2019 review that "…the APH implausibly requires relative movements of OL and GL sufficiently large to translate pulleys and alter the actions of muscles passing through them." It seems that Miller's review has rather baldly misrepresented the APH, as Demer proposed it and Miller correctly explained it in 2007,[2] to make the astonishing claim that the APH has now been disconfirmed.

Even if mechanical independence among all EOM fibers were required to sustain the APH (And just to be absolutely clear, laminar independence is not required at all to implement Listing's law.), what is the quality of the evidence cited in Miller's 2019 review to exclude any independence? Miller's review casually dismissed extensive functional studies from the Demer laboratory showing minimal lateral force transmission among arbitrary groups of bovine EOM muscle[5] and tendon[6] fibers during external loading, and EOMs actively contracting ex vivo.[7] The basis for this dismissal of the only existing functional evidence on the question is speculation about possible effects of removing epimysium connective tissues external to EOMs prior to mechanical testing,[8] and a letter to a journal editor alleging use of excessive tensile forces during testing.[9] The epimysium is synonymous with the muscle capsule, which in cow is a small fraction of 1 mm thin, relative to the thick 5- to 10-mm transverse dimensions of a bovine EOM. It is simply implausible to propose that the necessary, careful dissection of the thin external muscle capsule fundamentally disturbed internal connective tissue coupling among all of the many thousands of fibers deep within the EOM, or that removal of the thin external capsule somehow surrounding both layers destroyed Miller's putative, tight mechanical connection between GL and OL. For tensile testing, the Demer laboratory uses force sensors on frictionless air bearings capable of resolving 0.02 mN (2-mg force) tension applied to EOM or tendon.[7] Because all specimen force loading was monitored as it gradually increased from zero, there was no chance of missing coupling effects that might exist only at low force.

Miller's 2019 review asserts that differential contractile forces can develop across an EOM's width, yet somehow substantial differential movements cannot occur. The meaningfulness of such distinction depends on the definition of "substantial." The concept of muscle "contraction" necessarily implies some shortening, somewhere and on some scale. Different muscle fibers that contract differently, as due to different recruitment threshold, or fiber type, or laminar insertion, must shorten differently during activation, and therefore could not in principle be monolithically united to all other fibers while exerting, as Miller implies, significant differential forces. The magnitude of differential movement need not be very large to be physiologically important. For example, a 1-mm differential movement in a typical rectus EOM 40 mm long would only represent a 2.5% differential, yet might plausibly mediate a physiologically significant vergence eye rotation. The Demer laboratory has published a series of papers demonstrating by magnetic resonance imaging (MRI) the existence of differential compartmental function in EOMs under a wide variety of conditions, and carefully compared a range of MRI metrics indicating EOM contractility, including both posterior partial volume (PPV) and maximum cross sectional area. The Demer laboratory published a systemic comparison indicating that all measures reflect contractility and typically concord, but that PPV is most robust.[10] Our analysis was not subject to the confound alleged in Figures 1 and 2 of Miller's review; we consistently assigned image plane numbers relative to the location of the globe-optic nerve junction (G-ONJ) in central gaze. Moreover, many of our MRI studies, for example involving ocular counterrolling[11,12] and various forms of vergence,[13–16] involve zero or sufficiently small horizontal or vertical eye rotations that cause no material change in anteroposterior position of the G-ONJ at all,

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and thus could not have been confounded in the way Miller so broadly alleges. No scientific technique is free of limitations and artifacts, but the quantitative measures we have used in our more than 105 peer-reviewed research publications applying MRI to the ocular motor system have applied adequate methodology to support the APH and the compartmentalization hypothesis. We have performed much self-replication in the process, supporting the robustness of the findings. Space does not permit specific refutation of every individual criticism offered by Miller's wide-ranging review, but we are confident that none of them undermines our conclusions as published.

Miller extended his review to allege lack of rigor, broadly suggesting various implied biases and statistical inadequacies, and lack of confirmation of "studies from the Demer lab."[17] All of our experimental studies did undergo critical peer review, mainly by journals such as *IOVS* and *Journal of Neurophysiology*, which was not the case for the "personal communication" and letters to the editor upon which Miller relies to argue for refutation of the APH. The lack of "confirmation" of our work should not be understood, as might be erroneously implied from Miller's review, to be disconfirmation; rather, no other laboratory has attempted these demanding experiments, so no one should assume as Miller implies that the experiments have been improperly performed or interpreted. In his conclusion, Miller seems to demand a standard of experimental design appropriate to a clinical trial of a drug or device, for example including only testing explicit a prior hypothesis and analysis by multiple observers. Miller's own work typically, and that of the studies upon which his new review relies, have not conformed to the stringent standard he advocates for multiple analysts[18,19] or robust statistical adequacy in a large number of subjects.[18,20] But to be fair to the field, ocular motor physiology is exploratory basic science and not a clinical trial, such that many experiments, such as those in nonhuman primates, are so costly and time-consuming that very large sample sizes and rigid prospective protocols are seldom possible. And the reader should also keep in mind that the alternative to the current, imperfect body of scientific data is continued conceptualization of the ocular motor system through intuition, assumptions, and untested dogma.

Miller's review concludes with suggestions for future directions for study of EOM compartmentalization. We agree that it would be valuable to perform anatomical and functional studies of possible segregated motor neuron pools in the brainstem for control of the OL and GL, and for transverse EOM compartments. Our preliminary work in this area, although suggestive, is as yet insufficient for publication. We would welcome the entry of primate ocular motor laboratories into this important area of investigation, and hope that Miller will join in this effort. We have recently adopted increasing levels of automation for analysis of MRI studies of EOM function, and are investigating artificial intelligence for image segmentation. However, absence of such methods does not disconfirm the APH, which remains not only tenable, but the only explanation for fundamental ocular motor physiology such as Listing's law.[4]

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Author Response: Letter to the Editor of IOVS From Joseph L. Demer and Robert A. Clark Regarding Joel M. Miller, "EOM Pulleys and Sequelae: A Critical Review"

The Active Pulley Hypothesis, as I use the term, and as Demer and colleagues normally do, was described in their article, "Evidence for Active Control of Rectus Extraocular Muscle Pulleys,"[1] which proposed that each rectus muscle was functionally two independent muscles, one of which (the global layer [GL]) was inserted in the sclera to rotate the globe, and the other (the orbital layer [OL]) was inserted in and translated the pulley to alter the oculorotary action of the GL passing through it. The diagrammatic representation from that paper[1] (top half of Fig. 10), which has appeared in many versions since, is reproduced here (Figure). The APH is a *functional* hypothesis, not merely a statement about anatomy, and it proposes both mechanical and innervational independence of OL and GL. To claim otherwise, as Demer and Clark do in the main argument of their letter,[2] is to mislead.

One finding the APH sought to explain was the non-Listing "quarter angle" kinematics of the vestibulo-ocular reflex (VOR). Implausible relative laminar movements in the order of a half centimeter were proposed, but only when it was shown mathematically that no differential pulley movements could account for VOR kinematics,[3] did we get the narrowly drawn admission that the APH did not explain "steady state VOR during low frequency head rotation."[4] The original APH concept has otherwise been maintained across dozens of publications, for example:

- "The APH proposes that OL and GL fibers are under at least partially differential central neural control and have distinct mechanical actions."[5]
- "The APH suggests that pulleys, comprised of connective tissue rings encircling rectus EOMs, are translated by the EOMs' fibers while global layer fibers insert on the eye to rotate it. Anteroposterior locations of rectus pulleys are thus neurally controlled."[6]
- "If substantial coupling were demonstrated between EOM compartments during active contraction, the biomechanical basis of the APH . . . would be undermined."[7]

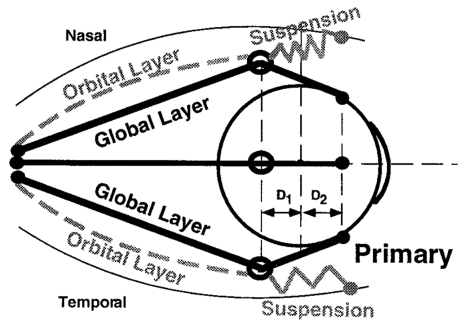

Figure. Reprinted with permission from Demer JL, Oh SY, Poukens V. Evidence for active control of rectus extraocular muscle pulleys. *Invest Ophthalmol Vis Sci.* 2000;41:1280-1290. © 2000 ARVO

The APH must entail laminar shear in the order of millimeters if the OL-controlled pulley is to significantly modify GL actions, but experimental surgical manipulations, connective tissue studies, and common sense suggest that this is unlikely, and, indeed, such relative movements are not seen. Although in vitro studies of bovine EOM claim near-complete fiber independence, researchers from other laboratories consider those findings to be experimental artifacts. It has long been known that many motoneurons innervate both OL and GL, and the recent failure to find separate nerve branches to OL and GL of any muscle[5] imply that independent control is impossible.

In an earlier review[8] I argued that anatomic findings from the Demer laboratory,[1,9,10] which had come under attack because of their association with the APH, could be accepted regardless of whether there was differential OL-GL movement. To make the point, I defined "Coordinated Active Pulleys" as the *null version* of Demer's hypothesis, in which different fiber types were innervated to contract as a unified whole, as in any heterogeneous muscle. If Demer and Clark now wish to claim that this is what they mean by "APH," they must admit there is nothing distinctively "active" about it, that their many efforts to demonstrate mechanical and innervational independence were unmotivated, and that the APH is a theory empty of content. Identifying the APH with its null version is simply a backhanded way to admit that it has been effectively disproven.

To forestall further confusion and obfuscation, I've urged that the fundamental and well-supported EOM pulley concept be referred to as "longitudinally-dragged pulleys" to highlight its passive mechanics, or "M-D pulleys," to reference its developers.[11]

PPV Does Not Measure Muscle Contraction

The Demer laboratory infers muscle contraction from MRI data. Muscle volume in a region of interest (ROI) centered on the point of maximum cross-section (MaxCS) in such images would be a reasonable measure of muscle contraction,[11] but the method they use, posterior partial volume (PPV), being both complexly contaminated and vulnerable to bias, is not as follows:

- PPV has no basis as a measure of muscle contraction apart from its correlation with duction, and duction has a nontrivial relationship to muscle contraction.[11]
- Instead of measuring the muscle thickening that's closely related to contraction, PPV admittedly[12] is contaminated by contraction-related movement of muscle tissue that causes different parts of a muscle to be measured in different contractile states. Failure to track MaxCS also makes PPV highly sensitive to choice of ROI, and so, vulnerable to bias[11] (Fig. 1).
- Additionally, the ROI used to compute PPV is referenced to the globe-optic nerve junction, which moves with gaze so that comparisons of muscle cross-sections in different gazes are actually compar-

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isons of different MRI slices imaging different parts of the orbit[11] (Fig. 2).

None of these issues are substantively addressed in Demer and Clark's letter.[2]

Force and Movement

Isometric muscle contraction, in which tension increases but length is fixed, is commonly distinguished from isotonic contraction, in which a muscle shortens under constant tension. Given the implausibility of intramuscular *shearing movements* in the order of millimeters required by the APH (the pulley is supposed to move sufficiently to alter the pulling direction of the GL passing through it), it is helpful to notice that the EOM compartments hypothesis requires only a *force gradient* across a muscle's width, which might be balanced isometrically by opposing forces, such as those of an antagonist muscle. This distinction (force gradients verses movement gradients) is one reason the theory of EOM compartments remains viable and the APH does not.[11]

Biased MRI Quantification

Demer and Clark[2] did not comment on our critique of their MRI methodology, the poor quality of which is surprising, given its centrality to their work:

- Their measurements have unstable referents—the globe-optic nerve junction and the interhemispheric sulcus—that introduce systematic errors by their movements under experimental manipulations.[11]
- Simply stacking MRI slabs is a poor way to estimate volumes. Better methods are readily available[11] (Fig. 3).
- Biased analyses, clearly evident in published images, raise general concerns about the reliability of their data[11] (Figs. 4 and 5).[13]

Cause or Effect?

Demer and Clark[2] did not comment on our suggestion that changes in the shape of a muscle's cross-section were better explained by bending around its pulley than by differential compartmental contraction.

Scientific Validity

Demer and Clark suggest that conceptual confusion, invalid statistics, biased image interpretation, generally poor methodology, and absence of independent confirmation are quibbles that don't apply to their "exploratory basic science." All shortcomings, they suggest, are offset by voluminous publication. But articles from the Demer laboratory are unusually abstruse, and readers likely skim them uncritically, supposing they must be true because of their complexity, apparent thoroughness, and the authority of the investigators, failing to see that beneath the surface, they are broadly defective.

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