Compartmentalization of extraocular muscle function

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Abstract

Ocular motor diversity exceeds capabilities of only six extraocular muscles (EOMs), but this deficiency is overcome by the plethora of fibers within individual EOMs surpassing requirements of homogeneous actuators. This paper reviews emerging evidence that regions of individual EOMs can be differentially innervated to exert independent oculorotary torques, broadening the oculomotor repertoire, and potentially explaining diverse strabismus pathophysiology. Parallel structure characterizes EOM and tendon fibers, with little transverse coupling of experimentally imposed or actively generated tension. This arrangement enables arbitrary groupings of tendon and muscle fibers to act relatively independently. Coordinated force generation among EOM fibers occurs only upon potentially mutable coordination of innervational commands, whose central basis is suggested by preliminary findings of apparent compartmental segregation of abducens motor neuron pools. Humans, monkeys, and other mammals demonstrate separate, nonoverlapping intramuscular nerve arborizations in the superior *vs* inferior compartments of the medial rectus (MR) and lateral rectus (LR) EOMs that could apply force at the superior *vs* inferior portions of scleral insertions, and in the medial *vs* lateral compartments of the superior oblique that act at the equatorial *vs* posterior scleral insertions that might preferentially implement incycloduction *vs* infraduction. Magnetic resonance imaging of the MR during several physiological ocular motor behaviors indicates differential compartmental function. Differential compartmental pathology can influence clinical strabismus. Partial abducens palsy commonly affects the superior LR compartment more than the inferior, inducing vertical strabismus that might erroneously be attributed to cyclovertical EOM pathology. Surgery may selectively manipulate EOM compartments.

Mysteries of ocular motor effectors

The extraocular muscles (EOMs) and associated connective tissues are now recognized to exhibit complexities unsuspected from classical studies. For example, rectus EOMs transit connective tissue pulleys that influence EOM paths and regulate pulling directions.[1] Pulleys simplify ocular kinematics, the rotational properties of the eyes that would otherwise be unmanageable for the brain. In particular, rectus pulleys are shifted by their corresponding orbital layers to implement mechanically[2–4] Listing's Law (LL) of ocular torsion.[3,4] With head upright and stationary, LL specifies ocular cycloposition as that reached by rotation about an axis lying in a unique plane.[5] A formerly attractive belief that the brain explicitly commands LL torsion via the vertical rectus and oblique EOMs[6] was rendered untenable by findings that cyclovertical motor neurons of monkeys do not encode LL torsion during pursuit,[7] and that abducens nerve stimulation in monkeys evokes eye movements conforming to LL.[8] Rather, as systematic changes in rectus EOM pulling directions generate LL torsion,[3] activation of any whole rectus EOM must evoke an eye movement conforming to LL. However, this mechanical constraint engendered a conundrum; while the vestibulo-ocular reflex violates LL so that its velocity axis changes by one-fourth eye position, not half as for LL,[9] motor neurons controlling cyclovertical EOMs do not command the violation.[7] Put another

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way, these violations of LL by the vestibulo-ocular reflex require the generation of torsion without action of the cyclovertical EOMs. The inescapable conclusion that horizontal rectus EOMs must generate ocular torsion then motivated discovery of compartmentalization as a plausible mechanism expanding the diversity of EOM actions.[10,11] Compartmentalization has proven to be a general feature of ocular motility, and is not limited to the horizontal rectus EOMs.

Anatomic evidence for EOM compartmentalization

The roughly 20 000 fibers per human rectus EOM surpasses requirements of conventionally recognized motility,[12] and suggests that individual EOMs might execute multiple functions using specialized fiber groups. Requisite for such functional diversity is anatomic diversity of innervation to different sets of fibers. Motor nerves innervating horizontal rectus EOMs bifurcate into about equal regionally segregated intramuscular arborizations (Figure 1).[11] This was first suspected in LR because it has been thought to have a dual origin[13] arising from separate embryonic progenitors.[14] Longitudinal LR splitting can be observed by magnetic imaging resonance (MRI) in congenital cranial dysinnervation disorders, including congenital fibrosis,[15] Duane syndrome,[16] and congenital oculomotor palsy.[17] Because the fibers of the LR muscle and tendon are generally parallel, observed fissures anywhere along the EOM reflect its entire length; this is also true of the other EOMs.

Autopsies may show abducens nerve division into two or more trunks,[18,19] some widely separated at the cavernous sinus.[18] The medial rectus (MR) motor nerve also bifurcates and arborizes into nonoverlapping superior and inferior compartments of roughly equal size.[11] The feline inferior oblique is innervated by distinct medial and lateral branches that generate different contractile responses.[20] In human and monkey, the inferior oblique is also innervated in compartmental fashion by two separate motor nerve trunks.[21] Possible compartmentalization is less clear for the inferior rectus, which has a selective lateral trunk that overlaps diffuse arborization of another trunk throughout the entire EOM.[11] This implies that selective neural control of the lateral inferior rectus might be possible. However, current efforts at tracing have not identified selective intramuscular motor nerve arborization in superior rectus.[11]

The superior oblique (SO) of humans and monkeys is innervated in non-overlapping medial and lateral compartments by two divisions of the trochlear nerve[21,22] (Figure 2). The border between compartments is slightly oblique to the major axis of the elliptical SO cross-section, and thus also oblique to the border found in horizontal rectus EOMs. Although its tendon insertion is broad, SO fibers roll into cylindrical configuration passing through the trochlea and unroll posterior to the trochlea where they become contiguous with muscle fibers[21,22] (Figure 3). The medial SO compartment is contiguous with tendon fibers inserting predominantly on the equatorial sclera that would have best mechanical advantage to produce incycloduction. The lateral SO compartment is contiguous with tendon fibers inserting predominantly on posterior sclera that would have the best mechanical advantage to produce infraduction (Figure 3).

Biomechanics of compartmentalization

Another requirement for differential compartmental function is capability of EOM fiber groups transmit different forces to diverse scleral points. This is possible because EOMs and tendons are composed of parallel fiber bundles having sparse transverse interconnections. Tensile force transmission in arbitrary groupings of fibers is >90% independent of adjacent fiber groupings,[23] as
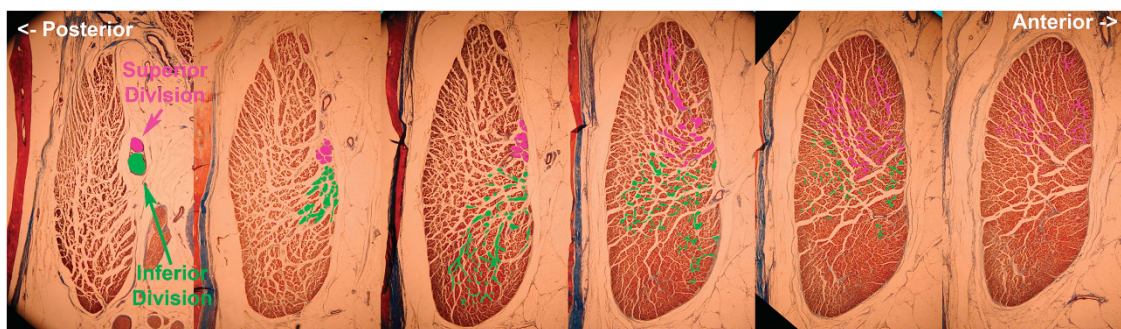

Figure 1 Inferior and superior divisions of the human intramuscular abducens nerve in the lateral rectus muscle, in serially sectioned orbit stained with Masson trichrome. Note the more posterior entry of the inferior (green) than superior (magenta) abducens division. Note lack of overlap of innervation from the two divisions among muscle fibers. Tracing and labeling of nerve branches courtesy of Roberta Costa, MD.
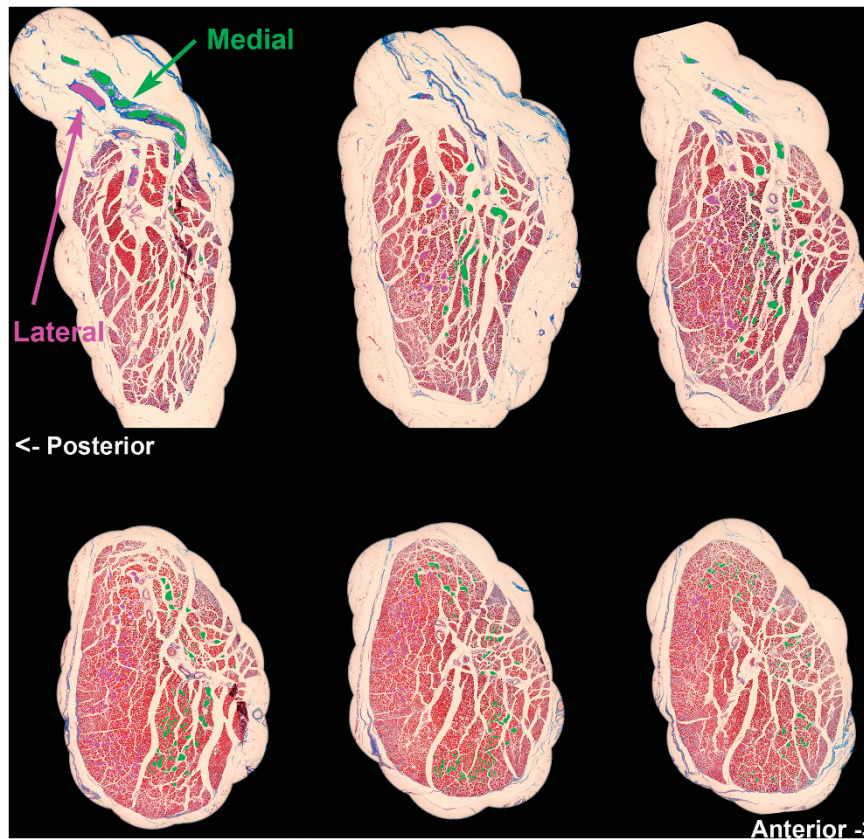
Figure 2 Lateral and medial division of the intramuscular trochlear nerve in the human superior oblique muscle, reconstructed in three dimensions from serially sectioned orbit stained with Masson trichrome. Tracing and labeling of nerve branches courtesy of Alan Le, BS.
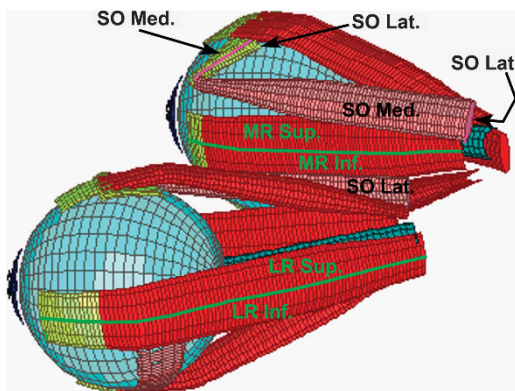

Figure 3 Rendering of globe and extraocular muscles using Orbit 1.8[29] demonstrating locations of inferior (Inf.) and superior (Sup.) compartments of medial (MR) and lateral rectus (LR) muscles, and lateral (Lat.) and medial (Med.) compartments of superior oblique (SO) muscles.

confirmed after marginal myotomy or tenotomy.[24] This supports empirically based EOM surgeries involving portions of rectus[25] or SO tendons,[26] and implies that groups of EOM fibers can transmit force independently of one another, subject only to coordination of their neural commands.

Surgeons know that transverse shifting of rectus EOM insertions imparts cyclotorsion.[27,28] Estimates are obtainable from biomechanical modeling of differential tension across the transverse extent of an EOM tendon insertion. Computational simulation using the *Orbit 1.8* (Eidactics, San Francisco, CA, USA) model suggests such shift could redirect 13–15% of LR force to vertical action, and (depending upon assumptions) 16–22% to cycloduction.[29] Compartmentalization could plausibly generate the torsion to explain LL violations during the vestibulo-ocular reflex.

Functional anatomy of compartmentalization

There is a roughly equal ratio of inferior compartment to total LR transverse dimension in those ∼20% of cases where structural demarcations are evident,[30] consistent with postmortem nerve tracing from serial histological sections showing the ratio varying from 0.4 to 0.6.[11]

Mechanical engineering concepts facilitate understanding compartmental EOM function. In arbitrary materials, applied force (stress) is related to

deformation (strain). Reasoning that mechanical strain reflects EOM force defined in proportion to undeformed dimensions, contractility can be measured by deformation of morphological indices. During contraction, total EOM volume[31] and peak cross-section increase, and the peak shifts posteriorly,[32] usually ~2 mm.[33] Practical contractility indices are obtained from coronal plane cross sections; the most robust is posterior partial volume (PPV), computed in the four contiguous posterior image planes.[33] Change in PPV closely correlates with duction for horizontal rectus EOMs.[33] Correlations for maximum cross-section are almost as strong.[33] Since anatomic demarcation between the inferior and superior LR compartments is not observable in most individuals, and is almost never observable for the MR, MRI studies have somewhat arbitrarily divided these EOMs into inferior and superior halves bisecting their greatest transverse dimensions. For both LR and MR, the inferior compartments defined in this manner is slightly larger than the superior compartment.[10] It should be recognized that misattribution in MRI studies of function of one compartment to the opposite EOM compartment would obscure or reduce intercompartmental functional differences, but never artifactitiously create functional differences that do not in fact exist.

High-resolution MRI was used to investigate activity in horizontal rectus EOMs of humans during asymmetrical convergence to a monocularly aligned near target, and compared with a wide range of conjugate gaze from abduction to adduction. Both inferior and superior LR compartments, and the inferior MR compartment, exhibited similar contractility during both convergence and conjugate adduction. But, the superior MR compartment exhibited three-fold the contractility in adduction as in convergence. Uniquely, the superior MR compartment was significantly more contractile than the other compartments during conjugate duction. Contractility in conjugate gaze was 100% greater in the superior MR compartment and 50% greater in the MR inferior compartment than in the corresponding LR compartments, defying expectation that MR and LR forces should balance. In contrast to MR, LR contractility did not differ between convergence and adduction, but contractility in the superior MR compartment in convergence was only about one-third that in adduction.

These observations illuminate a paradox: contractility of the superior MR compartment contractility unaccountably exceeds the superior LR compartment in conjugate gaze, but the two are balanced during convergence. Abducting forces of cyclovertical EOMs cannot account for these findings. During the convergence, there is a simultaneous SO relaxation and inferior oblique contraction;[34] their horizontal actions would cancel. These findings argue for

contributions by nonstriated EOM mechanisms, possibly including autonomically innervated smooth muscle in pulley suspensions.[35–37]

During ocular counter-rolling, MRI in normal volunteers showed significant contractile PPV changes in the inferior but not superior LR compartments, and borderline contractile changes in superior MR but not inferior compartment.[10] These differential compartmental changes presumably contribute to cyclotorsion.[10] Differential compartmental changes in PPV were absent in vertical rectus EOMs.[10]

During vertical duction, MRI has also demonstrated significant contractile changes in maximum cross-section and PPV of the superior MR compartment, without changes in the inferior MR compartment, or in either LR compartment.[38] Differential compartmental MR contractility might thus augment vertical duction.

Vertical fusional vergence

Compartmental function of normal subjects has been studied using MRI during vertical fusional vergence induced by a monocular 2Δ base up prism requiring monocular infraduction without fellow eye rotation.[39] There was significant differential compartmental contraction in the LR indicated by PPV change. There was clear evidence of difference contractility in the SO compartments, with significant contraction of the lateral SO compartment contralateral to the prism, and paradoxical relaxation of the medial SO compartment ipsilateral to the prism. Differential LR and SO contractile behavior during vertical fusional vergence suggest that the EOM mechanisms that normally compensate for vertical heterophoria are highly complex, presumably because of the necessity to regulate horizontal and torsional eye orientation.

Compartmental brainstem control

Differential compartmental behavior of EOMs requires control by selective motor neuron pools. The A and B groups of MR motor neurons in the oculomotor nucleus are widely separated by the vertical rectus and inferior oblique motor neurons.[40] Both version and vergence signals are observed in MR and LR motoneurons.[41] The abducens nucleus has cyclovertical premotor inputs, including vestibular inputs from vertical eye movement pathways.[42] Selective injection of orthograde and retrograde neural tracers into the inferior and superior divisions of the abducens nerve have provided evidence for topographical segregation of motor neuron pools to the two LR compartments in monkey.[43] There might plausibly exist topographic segregation of brainstem motor neuron pools innervating specific regions of individual EOMs.

The possible exception to this scheme is the SR, for which no anatomical or functional evidence for selective compartmental control has yet been adduced.

Compartmental EOM pathology

Denervated human EOMs exhibit atrophy of cross-section and volume, and loss of contractile thickening.[44] About 30% of abducens palsy cases exhibit selectively greater atrophy of the superior than inferior LR (Figure 4), usually with ipsilesional hypotropia suggesting preserved inferior compartment function.[45] It has been proposed that many patients with paretic abduction deficiency have selective superior compartment LR weakness because of a selective superior division abducens pathology.[45] Selective vulnerability of the superior LR to neuropathy might be related to division of the intracavernous abducens nerve into multiple trunks that reunite distally,[18] so that compressive or ischemic processes could easily be selective within the LR. Of the 79 clinical cases of isolated LR palsy, 57% also exhibited hypertropia that increased in abduction in 80% of cases, suggesting relationship to residual LR contraction.[46] Since unexplained cyclovertical strabismus typically motivates costly neuroophthalmic investigations,[47] elucidation of cyclovertical effects of horizontal rectus palsy would often avert unnecessary diagnostic testing, as well as inappropriate surgeries. Surgical repair of only the diseased and not normal portion of an EOM is already technically feasible, if only the situation could be diagnosed. Partial tenotomy has been practiced empirically for treatment of vertical strabismus[48] and A and V pattern strabismus,[49] and regional surgery on the SO tendon to selectively manipulate the vertical *vs* torsional actions.[50] Consequently, wide dissemination of a clear understanding of the roles of horizontal rectus compartments in human strabismus could improve strabismus diagnosis and treatment.

Figure 4 Coronal magnetic resonance images of the left and right orbits demonstrating selective atrophy of the superior compartment of the left lateral rectus (LR) muscle in compartmental abducens palsy.

Conclusion

The parallel fiber anatomy of EOMs and tendons, as well as peripheral neuroanatomy of intramuscular innervation, enable portions of several EOMs to execute differing oculorotary actions. Although an EOM such as the LR may have classically been regarded as a anatomically and physiologically 'monolithic,' under some circumstances one EOM may function as two different, albeit closely apposed muscles with distinct neural control, distinct functions (Figure 3), and distinct susceptibilities to pathology (Figure 4). Further investigation of the functional anatomy of EOM compartments will be useful in diagnosis and treatment of strabismus.

Conflict of interest

The author declares no conflict of interest.

Acknowledgements

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