RICHARDSON LECTURE

Adaptive Control of Eye Movements: Clinical Implications

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Abstract: This paper is directed primarily to clinicians who diagnose and treat patients with neurological disorders. It is an attempt to illustrate that even with modern imaging technology and other advances in laboratory testing, a thorough understanding of neurophysiology and its anatomical substrate still plays an important role in the diagnosis and management of patients with neurological diseases. One area in neurophysiology in which there has been great progress in the last few decades is the ocular motor system. Particular interest has been focused on the ways that the brain can adapt to lesions, and more specifically, how the ocular motor system keeps itself calibrated in the face of normal development and aging as well as in response to disease and trauma. Since disorders of eye movements are such common and often dramatic manifestations of neurological disease it seems appropriate to bring some of the newer concepts in ocular motor physiology to the "bedside".

Résumé: Contrôle adaptative des mouvements oculaires: implications cliniques. Cet article s'adresse principalement aux cliniciens qui posent le diagnostic et instituent le traitement des patients présentant des troubles neurologiques. Nous tentons d'illustrer que, même avec l'imagerie moderne et le progrès dans les techniques de laboratoire, une parfaite compréhension de la neurophysiologie et de son substrat anatomique joue encore un rôle important dans le diagnostic et le traitement des patients atteints de maladies neurologiques. Un des domaines de la neurophysiologie qui a progressé considérablement dans les dernières décennies est le système moteur oculaire. On a porté un intérêt particulier sur la façon dont le cerveau peut s'adapter à une lésion et, plus précisément, comment le système moteur oculaire conserve sa calibration face au développement normal et au vieillissement ainsi qu'à la maladie et au traumatisme. Comme les troubles des mouvements oculaires sont des manifestations très fréquentes et souvent dramatiques de la maladie neurologique, il semble approprié d'attirer l'attention des cliniciens sur les nouveaux concepts physiologiques de la motricité oculaire.

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Eye Movements: A paradigm for the Study of the Control of Movement

The ocular motor system has served as a particularly useful model for many motor physiologists trying to understand the mechanisms by which the brain controls movement. Eye movements are relatively stereotyped; easily classified into subtypes by functional requirements and behavioral characteristics; and both the sensory stimuli that lead to eye movements and the consequent eye movements themselves are readily measured and hence amenable to rigorous quantitative analysis.[1] Furthermore, since movements of the eyes are unencumbered by changing mechanical loads, no stretch reflex, in the conventional sense, is required. Hence, in both motor and premotor structures, the discharge rate of many of the neurons that appear to be related to eye movements can often be closely tied to the position of the eye or, when the eye is moving, to its velocity or acceleration. For these reasons, we know much about the central structures and the pathways that carry signals related to eye movements as well as about the nature of the information processing that allows for the transformation of sensory stimuli into the correct ocular motor response.

Function of Eye Movements

The function of eye movements is related solely to the requirements for good vision. In primates, who have the highest density of retinal cone receptors in the macula, eye movements are specifically related to the needs of the fovea. Eye movements can be divided into two general types, those that bring images of objects of interest onto the fovea and those that keep them there. *Saccades*, the rapid eye movements that are used to quickly change the line of sight, bring the image of an object of interest onto the fovea in as brief a time as possible. *Vergence* movements, although slower, serve a similar function; they bring the images of a single object onto the foveae of both eyes

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at the same time allowing for stereopsis. In more natural circumstances, when the point of regard is to be moved both across the visual field and in depth, vergence movements and saccades are combined and the change in alignment is much faster than one would predict from the speed of pure vergence movements when made alone.

Once new images are brought to the fovea they must be kept there quietly for enough time (perhaps a hundred ms or so), for the visual system to be able to analyze the new information and to determine the location, motion and shape of the object of interest. Hence a number of systems have evolved to keep images on the fovea and to keep them relatively still. We use *vestibular* (and optokinetic) eye movements to compensate for any motion of the head; this allows one to see and move at the same time. *Pursuit* movements allow one to keep the images of objects that are moving in the environment on the fovea. *Vergence* movements allow one to keep the images of an object of interest on both foveae at the same time. There may also be a special *fixation* system that serves the purpose of keeping the eyes still in the orbit.

A Need for Adaptation

For optimal visual-ocular motor performance, the movements of the eyes must be appropriate to the visual and vestibular stimuli that drive them. More specifically, the output – the motor response – must be correctly calibrated for the input – the sensory stimulus from the visual, vestibular or auditory systems. Otherwise, ocular motor performance would be incorrect, that is dysmetric, and lead to the potentially dire consequences of a degraded visual sense. Thus, the brain has developed a number of adaptive mechanisms that detect erroneous motor performance and then recalibrate the motor response to a given sensory stimulus in order to eliminate the dysmetria.

Open-loop systems: saccades

The need for long-term calibration is particularly evident when there are no means to correct for inaccuracies in performance during the movements themselves. For example, saccades are so fast that once the saccade has started, there is not enough time for any new visual information to be used to alter the saccade trajectory before it is finished. Saccades in this sense are characterized as open-loop or ballistic eye movements and any mistake in performance can not be corrected in mid-flight. Of course, the high speed and brief duration of saccades has an advantage. Since visual acuity is degraded when images move across the retina at speeds of more than just a few degrees per second, it makes sense to make saccades as fast as possible, to limit the time when we cannot see. But if the eye movement is not accurate at the end of its course, that is, if the image has not been brought to the fovea, a corrective saccade must be made to complete the task. This results in a delay in the time for the visual sense to be able to identify and analyze the new visual information brought to the fovea. The brain tolerates small degrees of saccadic dysmetria, usually on the order of a degree or two, but larger degrees of saccadic dysmetria are disadvantageous. Thus, the brain has developed mechanisms to detect errors in saccade performance and then to recalibrate the relationship between the sensory input – the distance of the image of the object of interest from the fovea, the so-called retinal error – and the motor output – the saccade size – in order to bring this sensorimotor reflex back into proper register.

Open-loop systems: vestibuloocular reflex

The slow phases of the vestibuloocular reflex (VOR), which compensate for head movements, are also described as open-loop, in the sense that the output of the reflex – the slow phase – does not influence the input, the head movement. Furthermore, any dysmetria of the slow phase, which would lead to motion of images on the retina during head movements, cannot be immediately eliminated using visual information. The typical head movements made during normal behavior are so brief and fast that there is not enough time for visual inputs (which require up to 100 ms of processing time before they can be translated into a motor response) to influence the trajectory of the vestibular slow phase. Thus, the first 100 ms of output of the vestibuloocular reflex is open-loop in the same sense that saccades are open-loop, with no possibility that visual feedback can alter performance in the early, but critical period of time when the eye movement is initiated.

These considerations lead to the general concept that even so-called "closed-loop" eye movements, such as smooth pursuit and vergence movements, which are usually slow enough and last long enough to be helped by visual feedback during their elaboration, are still open-loop for the roughly 100 ms it takes for any change in visual information to influence the motor output. These closed-loop systems, too, require methods for calibration of the response during the period when they must be functioning open-loop, by virtue of the delay inherent in the processing of new visual information.

Implications of Adaptation for Neurology

We have reviewed the rationale for a need for mechanisms that provide for adaptive control of eye movements. Here, we will concentrate on the implications of such adaptive capabilities for clinical neurology. First, it is important to remember that unless one sees a patient within the first few *seconds* of the onset of a neurological insult, be it from trauma, ischemia, etc., one not only observes the initial effects of the lesion itself but also the attempts of the brain to compensate for the deficit. Thus, to interpret findings on neurological examination correctly and to localize and identify the cause of a neurological problem accurately, one must be aware of how the adaptive mechanism might have altered and hence masked the primary effects of the neurological lesion. Secondly, one must also be able to recognize that what are appropriate adaptive responses in certain circumstances may mimic other neurological lesions in other circumstances and lead to confusion as to the localization of the lesion. Thirdly, normal adaptive mechanisms may act on centrally-induced ocular motor malfunctions and lead to a different type of ocular motor disorder than that produced by the lesion itself. Fourthly, brain lesions may affect the adaptive mechanisms themselves and lead to inappropriate or uncalled-for adaptation that can produce a disorder in its own right. As a corollary, if the adaptation mechanism itself is deprived of the

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sensory information on which it bases the need to make a change in motor performance, errors can creep into motor behavior as if the adaptive mechanism itself were malfunctioning. Finally, a thorough knowledge of adaptation may help the physician to speed the recovery of the patient by virtue of prescribing medications or the correct programs of physical therapy to promote the adaptive process.

Here, we illustrate these various implications of adaptation with examples that occur in the everyday practice of neurology, and in this way encourage the neurologist to use what both the clinical and basic science laboratory have provided for clinicians in a concrete and meaningful way for patients.

Abduction Nystagmus of Internuclear Ophthalmoplegia

As a first example of how adaptation affects the clinical presentation of a neurological disorder, consider the abducting nystagmus that occurs with unilateral internuclear ophthalmoplegia.[2] Internuclear ophthalmoplegia (INO) is a classic neurological syndrome and is typically characterized by a loss or slowing of adduction on the side of the lesion with a dissociated nystagmus in the other, abducting eye. The cause of the adduction weakness is clear: an interruption of the fibers that arise from the internuclear neurons within the abducens nucleus and then ascend in the medial longitudinal fasciculus (MLF) to impinge upon the medial rectus subdivision of the ocular motor nucleus, and so subserve adduction of the eye during conjugate movements. The origin of the abducting nystagmus in the opposite eye, however, is unclear; many speculative hypotheses have been proposed to account for it. Important in understanding the possible mechanisms for the abducting nystagmus in INO is the recent experimental observation in the monkey that with an acute INO, created by anesthetizing MLF fibers with lidocaine, there is a marked weakness of adduction but no abducting nystagmus in the contralateral eye.[3] This experimental finding implies that the abducting nystagmus of INO is due either to involvement of parts of the nervous system outside the MLF or is a secondary phenomenon, perhaps as part of an adaptive response to compensate for the adduction weakness of the other eye.

Abduction nystagmus as an adaptive response

We examined the adaptive hypothesis for abducting nystagmus in a patient with a unilateral INO.[4] Our line of thinking was that for some reason, possibly "ocular dominance" or a subtle difference in the visual acuity between the two eyes, the patient preferentially used her paretic eye for fixation and so had optimized innervation to meet the needs of the eye with the adduction weakness. Assuming that the patient habitually "viewed" with the paretic eye, even with both eyes open, the central adaptive mechanisms would use visual information from the paretic eye to determine if saccades were accurate. Hence, because saccades made by that eye were dysmetric (undershooting the target) , the brain would recalibrate the relationship between saccadic innervation and retinal error in an attempt to increase the speed and improve the range of adduction of that eye. Because of Hering's law of innervation – which states that the innervation for conjugate eye movements goes equally to both eyes – any improvement in adduction of the paretic eye would have to be made at the expense of an inappropriate increase in innervation for abduction to the contralateral eye, which itself had no weakness.* Thus, the patient would develop an abducting nystagmus in the contralateral eye that would actually reflect a change in innervation, that is, in conjugate innervation, that would have been made in order to improve the performance of the paretic, adducting eye.

When eye muscles become weak, any change in innervation to overcome that weakness requires that the phasic and the tonic component of saccadic innervation be adjusted in different proportions.[5] While such a mismatch in phasic-tonic innervation would be correct for the weak, adducting eye of INO, it would be incorrect for the strong abducting eye, and cause the abducting eye both to overshoot the target and to drift back following the saccade. This would produce a nystagmus-like pattern.

We tested this adaptation hypothesis explicitly by requiring the patient to ignore visual information from the dominant eye (by having her habitually wear a patch in front of the paretic eye) and use instead the visual information from the eye that had the abducting nystagmus as the stimulus to the mechanism that adjusts saccade innervation. Indeed, upon wearing a patch for five days the abducting nystagmus had disappeared. Thus, she had again altered conjugate saccadic innervation to meet the needs of the habitually viewing eye. As expected, the disappearance of the abducting nystagmus was at the expense of the paretic eye on adduction. Its innervation had become decreased so that adduction by the paretic eye became slower. These clinical findings – slower adduction but without abducting nystagmus – presumably reflected the initial and basic effect of the MLF lesion per se, without adaptation.**

Thus, when viewing under natural circumstances our patient had developed an abnormality in her normal eye – the abducting nystagmus – which in fact was only abnormal in the sense that it reflected the action of an adaptive response that was actually improving the function of the eye that the patient depended upon for seeing.

This case history illustrates an important principle when evaluating any patient with disconjugate ocular motor performance and especially with a dissociated nystagmus. One must always ask if the abnormality observed in one eye is, in fact, a reflection of an adaptive response that is working to improve the performance of the other eye. The clinical circumstance in which this principle is most commonly applied is the patient with a unilateral peripheral muscle palsy who, for some reason, usually ocular dominance, fixes with the paretic eye. Just as the patient with INO, a nystagmus develops in the opposite eye. Such patients are usually misdiagnosed as having a central ocular motor disorder. Thus, one must determine if a patient with a

*Hering's law is not immutable and there are also mechanisms by which the relative innervation to the two eyes can be adjusted. Nevertheless, in this patient the adaptive process appeared to ignore information about dysmetria from the contralateral eye and solely altered conjugate innervation based on the needs of the visually dominant but paretic eye.

**Conjugate adaptation is certainly not the only mechanism for the abducting nystagmus observed with INO. A dissociated gaze-evoked nystagmus, greatest in the abducting eye, due to a lesion that affects more than just the MLF, is another frequent mechanism and there may be others. But, whenever there is a dissociated nystagmus, adaptation should always be considered as a possible mechanism.

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muscle palsy and other, seemingly central ocular motor signs, has a strongly dominant eye that is habitually used for fixation, as this may be the clue to the nature of any abnormality in the other eye.

Abnormal Saccades in Ocular Myasthenia Gravis

Another example of an adaptive response to a peripheral muscle weakness, which also masquerades as a central ocular motor disorder, occurs in patients with ocular myasthenia gravis. We observed a dramatic example of such a process in a woman with myasthenia gravis. Before edrophonium, the patient had a markedly restricted range of horizontal eye motion – perhaps to a maximum of 10-15 deg – but within that range the eye movements themselves were relatively fast. It was as if she could generate the initial portion of the saccade at a high speed but then ran out of gas, presumably due to the neuromuscular fatigue that occurs with myasthenia gravis. In fact, myasthenic saccades can appear to be faster than normal because they may be truncated in mid-flight due to intrasaccadic fatigue, and so have a peak velocity that would be appropriate for a much larger saccade.

After edrophonium our patient showed a striking response. First, the range of eye motion became full. Secondly, and even more dramatically, she became unable to fix upon a target that was located straight ahead. She made extremely large saccades, back and forth about the fixation target, with an intersaccadic interval of several hundred ms between each saccade. This saccade oscillation slowly died out as the effect of the edrophonium dissipated. These large, uncalled for, back and forth saccades about a fixation target are known as *macrosaccadic oscillations* and are a classic cerebellar eye sign. They represent an extreme degree of saccadic hypermetria; the relationship between saccade size and target displacement becomes so large that the patient cannot make a saccade small enough to acquire the target.

The cerebellum and myasthenia gravis

What can be the explanation for this cerebellar eye sign appearing with edrophonium? Much as was the case for the patient described above with abducting nystagmus and INO, the answer lies in an adaptive increase in the amplitude of saccadic innervation for a given target displacement, in an attempt to overcome the peripheral muscle weakness. In this patient with myasthenia gravis, however, the increase was so great that when the myasthenic neuromuscular block was relieved suddenly, restoring muscle strength close to normal, the eyes markedly overshot the target and began to oscillate back and forth about it. Normally, it takes hours to days for an adaptive recalibration of saccadic innervation in response to muscle weakness to take place. Thus, in the face of the immediate restoration of muscle power, which negated the need for any increase in saccadic innervation, the adaptive mechanism could not "deadapt" fast enough to restore saccadic accuracy. Hence, the persistent saccadic hypermetria and the macrosaccadic oscillations.

Indeed, one can visualize that the saccadic system in patients with myasthenia gravis is undergoing a constant change in its calibration as the degree of block at the neuromuscular junction fluctuates, both with activity and with the waxing and waning of levels of anticholinesterase medications. So, the macrosaccadic oscillations in myasthenia gravis are indeed a classic cerebellar eye sign but in this case an eye sign not of pathology in the cerebellum but a sign that the cerebellum itself had changed the saccadic innervation – retinal error relationship in an attempt to eliminate the dysmetria created by the peripheral muscle weakness. In fact, the finding of macrosaccadic oscillations, both in patients with cerebellar disease and also in patients with ocular myasthenia who respond to edrophonium, is indirect evidence that the cerebellum must play a role in the adaptive calibration of saccadic innervation.[6]

Saccadic hypermetria as a diagnostic sign of myasthenia

Finally, there is one other direct clinical application of this "edrophonium effect" on saccades in patients with ocular myasthenia. Because even the smallest degree of saccadic overshoot usually necessitates a backward corrective saccade, which is easily discerned at the bedside even when it is only on the order of a degree or two, the presence of even the slightest degree of saccadic hypermetria can be inferred from the appearance of backward corrective saccades. A change in saccade metrics as small as 10% can be easily confirmed at the bedside by inspection, whereas a 10% change in eye movement range or in eye alignment is difficult to detect without sophisticated recording techniques. This makes the detection of saccadic hypermetria an extremely sensitive way of confirming a positive response to edrophonium.

Finally, one should also recall the importance of determining which is the habitually viewing eye, as what was discussed above with respect to INO also applies to myasthenia gravis. In myasthenia, fluctuations in ptosis may determine which eye is used for habitual viewing, and hence influence any effects of adaptation on saccades.

Recovery Nystagmus

Recovery nystagmus, a "wrongway" nystagmus occurring during the phase of recovery from a unilateral labyrinthine loss, has a pathophysiology analogous to the macrosaccadic oscillations that occur in myasthenic patients given edrophonium. In the case of recovery nystagmus, a patient with a paretic labyrinth (for example, due to an attack of Ménières syndrome or neurolabyrinthitis) develops a nystagmus with slow phases directed toward the paretic ear. Central mechanisms, however, attempt to null this nystagmus by developing a slow-phase bias in the opposite direction (toward the good ear). This bias probably develops in several stages with a rapid (minutes) but partial immediate response and then a more long-term, enduring response lasting for hours or days. If function is suddenly restored in the paretic labyrinth, as can occur with Ménières syndrome, the previously appropriate adaptation will suddenly become excessive, creating a new central imbalance in vestibular tone, and lead to a nystagmus with slow phases toward the unaffected ear. This nystagmus can be misinterpreted as arising from a new lesion on the previously intact side, though it is in fact is a sign of recovery – recovery with which the adaptive mechanism can not keep pace. This sequence of events is equivalent to the immediate ameliorative effect of anticholinesterase

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medications in myasthenia gravis and the development of saccadic hypermetria.

Evaluation of Vestibular Function in Patients Who Wear Spectacles

The correct interpretation of the results of vestibular function tests – both at the bedside and in the laboratory – also depend upon a knowledge of any adaptive responses that might occur if a patient habitually wears corrective spectacles.[20] Corrective spectacles (but not contact lenses), because of their magnification effect, induce a need for a readjustment in the amplitude of the vestibuloocular reflex (VOR). If one is farsighted and wears a hyperopic (plus) correction, the amplitude of the VOR must increase. Likewise, if one is nearsighted and wears a myopic (minus) correction, the amplitude of the VOR must decrease. Normal subjects who wear spectacles do indeed show such adaptive changes. Take, for example, the patient who habitually wears a farsighted spectacle correction. During ophthalmoscopy, if the patient (without wearing glasses) rotates the head back and forth, the optic nerve head (and the rest of the retinal landmarks) will oscillate in phase with the head motion whereas normal subjects who do not wear glasses will show no such movement of the optic nerve head during head rotation. In the case of the patient who wears spectacles the oscillation of the optic nerve head is a sign of adaptation and can be taken as evidence that the patient has a capability – presumably cerebellar in origin – for adapting to abnormalities of the amplitude of the VOR. Recognition of these effects of wearing spectacles may be particularly important when one wants to interpret the presence of a seemingly hyperactive or hypoactive VOR, on the basis of either bedside or laboratory testing. Hyperactive vestibular responses are usually taken as a cerebellar eye sign but this would not necessarily be the case in a patient who habitually wears a farsighted correction. Likewise, hypoactive vestibular responses are usually taken as a sign of a bilateral peripheral vestibular loss but this would not necessarily be the case in a patient who habitually wears a nearsighted correction.

Periodic Alternating Nystagmus

Periodic alternating nystagmus (PAN) is an eye movement disorder that reflects the actions of a normal adaptive mechanism acting upon a centrally-induced ocular motor malfunction.[13] PAN is an infrequent but characteristic ocular oscillation in which there is a sustained horizontal jerk nystagmus that changes direction every few minutes. It is a central form of vestibular nystagmus and is associated with lesions in the posterior fossa and particularly in the cerebellar nodulus.[14]

Short-term VOR adaptation

PAN can be best understood by considering two normal vestibular mechanisms. The first is that which produces the so-called reversal phase of vestibular nystagmus. If one rotates a normal subject at a constant speed in the dark, a nystagmus is induced that slowly dies away with a time constant (the time for an exponential function to decay to 37% of its initial value) of about 20 sec. The nystagmus, however, does more than simply die out; it often reverses direction, leading to a sustained nystagmus, albeit with slow phases of relatively low speed, lasting for several minutes. This is called the *reversal phase* of rotational nystagmus. A similar reversal phase occurs following a caloric-induced nystagmus, and also following head-shaking induced nystagmus.[15]

The reversal phase of vestibular nystagmus is thought to reflect the action of a short-term adaptive mechanism that attempts to nullify any sustained unidirectional nystagmus. Under natural circumstances, a sustained unidirectional nystagmus would almost always be due to a pathological process producing a static imbalance in vestibular tone. The adaptive mechanism generates a counteracting slow-phase bias in the direction opposite to that of the slow phase of the spontaneous nystagmus, in an attempt to nullify the spontaneous nystagmus. During artificial vestibular stimulation that produces a sustained unidirectional nystagmus, such as with a caloric or a constant-velocity rotational stimulus, the adaptive mechanism "assumes" that the induced nystagmus is pathological and attempts to nullify it. The corrective action of this adaptive process is then reflected in the reversal phase that appears when the primary nystagmus dies out. This reversal-phase mechanism is one of the ways by which the central nervous system attempts to hold the eye still in the face of an acute unilateral vestibular imbalance.*

Velocity storage

The second mechanism that underlies the pathophysiology of periodic alternating nystagmus is so-called *velocity storage*. The concept of velocity storage arose from the observation that the duration of the nystagmus that occurs during a constant velocity rotation of the head in the dark is much longer than would be expected from the mechanical characteristics of the cupula and endolymph.[17] In other words, the return of the cupula toward the primary position, owing to its elastic restoring properties, is much quicker than the decay of the behaviorally induced nystagmus. Similar considerations apply to the discharge rate of primary vestibular afferents, which is a direct reflection of the position of the cupula, as it, too, decays much more quickly than does the actual nystagmus. In other words, there must be a mechanism, presumably residing within the vestibular nuclei, that perseverates the activity entering the brain stem on primary vestibular afferents such that the actual nystagmus lasts beyond that predicted from peripheral labyrinthine activity. This mechanism has been termed *velocity storage* and functionally serves to improve the range of frequencies (and especially the low-end frequencies) over which the vestibuloocular reflex can render a faithful representation of actual head velocity.**

*Another way in which the brain can attempt to nullify a sustained unidirectional nystagmus is by producing a superimposed, direction-changing, gaze-evoked nystagmus which would act to counteract the spontaneous unidirectional nystagmus and, in at least one field of gaze, lead to a position of the eye in the orbit in which the nystagmus is minimized or absent.[16] This presumably is also the mechanism that underlies Alexander's classification of nystagmus in which the slow-phase velocity of nystagmus is greatest when the eyes are displaced in the orbit in the direction of the quick phase.

**The concept of velocity storage has important practical implications for clinical vestibular testing. The state of velocity storage is usually reflected in the time constant of the vestibular response to a constant velocity rotation (or equivalently, to the phase lead measured at low frequencies of sinusoidal oscillation). Unilateral complete peripheral lesions typically produce a decrease in the value of the time constant to between 7-10 secs (with greater than 10 sec being normal) and with bilateral peripheral lesions the time constant is often less than 7 sec. Thus, measurement of the time constant of the VOR, which reflects the state of the velocity-storage mechanism, is useful, especially in patients with unexplained dysequilibrium or vertigo who have little else to find on clinical examination. While caloric testing may give the same information, the wide range of normal values with caloric testing and occasionally technical difficulties often make results of rotational testing valuable in this circumstance.

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PAN and the cerebellar nodulus

Important to the process of velocity storage is the cerebellar nodulus, which has been shown to influence velocity storage and in particular to inhibit it such that removal of the nodulus leads to a vestibular nystagmus that, in response to a constant-velocity rotation, lasts much longer than normal.[14] One can thus envision that if inhibition upon velocity storage were completely removed, any induced vestibular nystagmus might not just be perseverated more than expected but could actually lead to instability such that the nystagmus would begin to increase in velocity in a runaway fashion.

Pathophysiology of PAN

How do we put this information together to understand PAN? We must invoke two processes. First, a lesion in the cerebellar nodulus leads to uninhibited velocity storage and a consequent runaway vestibular nystagmus. Second, the short-term adaptive, reversal-phase mechanism attempts to nullify any sustained unidirectional spontaneous nystagmus by producing a bias oppositely directed to the primary nystagmus. The two mechanisms combine to produce the rhythmic periodic reversals of nystagmus that characterizes PAN. The velocity-storage mechanism causes the eyes to run away in one direction and the short-term reversal phase mechanism causes the eyes to turn around and run away in the other. This hypothesis was tested analytically with a computer model and indeed PAN could be nicely simulated with the above underlying assumptions.[13]

PAN and GABA

One further important point is that the inhibition of the velocity-storage mechanism by the nodulus appears to be mediated by GABA-B receptors.[18] About 15 years ago it was shown that baclofen, a GABA-B agonist, abolished periodic alternating nystagmus.[19] The mechanism almost certainly reflects the replacement, by baclofen, of the missing, nodulus-mediated, GABA-B inhibition upon the velocity-storage mechanism.

Eye Movements of the Blind

Patients with congenital blindness characteristically have abnormal eye movements including nystagmus and poor fixation[7] and a failure to develop a normal vestibulo-ocular reflex.[8] They also lack a conscious sense of where their eyes are in their orbit. This is not surprising, since, without visual feedback, there is no way (or reason) for the eye movement system to development its repertoire of finely-tuned visual and vestibular ocular motor reflexes. But patients with acquired blindness, too, may show a deterioration of the calibration and precision of their eye movements leading to unstable fixation and nystagmus. Even in patients with monocular loss of vision the eyes are no longer properly yoked during saccades, and the blind eye may develop oscillations.[9] Monkeys, too, develop similar disturbances of eye movements several months after an experimental ablation of both occipital lobes producing cortical blindness.[10]

In these various cases, the abnormalities of eye movements look much like those of patients with cerebellar lesions, with a variety of types of fixation deficits including spontaneous nystagmus, difficulties holding eccentric gaze and a "wandering null" as the position of gaze in which there is no nystagmus drifts about.[11] The most likely reason for these findings is that the cerebellum, which normally maintains ocular motor calibration, is deprived of its sources of information, i.e., the error signals, about the state of motor function. While visual deprivation does not cause abnormal eye movements in the immediate period following blindness, it can in the long term, because of the need in all of us for recalibration due to the spontaneous fluctuations in activity within the various brain stem circuits that mediate ocular motor reflexes. Thus, our adaptive mechanisms are constantly at work, using visual and perhaps proprioceptive information to keep themselves apprised of what is required to maintain the exquisite calibration necessary for optimal visuomotor behavior.

Finally, adaptation to lesions is, at least to a certain extent, a dynamic process. Consider the compensation that occurs to restore dynamic vestibular performance (stable gaze during head movements) after unilateral labyrinthectomy. Such adaptation may be slowly lost at a later date if the visual error signals that initially drove the recalibration become unavailable.[12] This may be a possible explanation for a recurrence of symptoms in patients who had compensated for a peripheral vestibular loss in the past, but then lose sensory inputs later in life. Thus, adaptation is both a dynamic and a fragile process, requiring continuous feedback to sustain optimal motor performance.

Promotion of Recovery After Loss of Labyrinthine Function

Activity and recovery of vestibular function

As a final example, I would like to discuss promotion of adaptive responses in human patients with unilateral or bilateral loss of labyrinthine function. About 15 years ago, Lacour and colleagues made an extremely important observation.[21] They studied recovery of otolith-spinal reflexes in animals who had undergone experimental unilateral labyrinthectomy. In one group of animals, they allowed normal motor behavior after the labyrinthine lesion and in the other group the animals were restrained so that they could not move about normally for a period of 1-2 weeks after the labyrinthine lesion. After this period of restraint they were allowed normal activity. Lacour et al. found that the animals that had been restrained after labyrinthectomy recovered more slowly and never to the same degree as the monkeys that were allowed normal activity immediately after the labyrinthine lesion.

Visual inputs and VOR adaptation

We performed similar experiments, looking at the effects of visual input on recovery of the vestibulo-ocular reflex after experimental unilateral labyrinthectomy in monkeys.[12] We found that monkeys placed in the dark for a period of five days after the labyrinthine lesion showed no recovery of dynamic VOR function (i.e., amplitude and symmetry of the slow-phase response to head rotation). When finally allowed normal vision, dynamic VOR function began to recover but at a lower rate than in the labyrinthectomized monkeys that had immediate normal visual experience. In contrast, the effect of visual deprivation had no effect on the decrease in spontaneous nystagmus that occurred after unilateral labyrinthine loss. In other words, visual experience after unilateral labyrinthine loss is critical for the restoration of the dynamic performance of the VOR but not for

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the static rebalancing between the vestibular nuclei that eliminates spontaneous nystagmus. Also recall the experiments described above related to blindness. Monkeys that had undergone occipital lobectomy months after recovery from a unilateral labyrinthectomy slowly lost the adaptive recalibration of dynamic vestibular function that had occurred immediately following the unilateral labyrinthectomy.[12]

Implications for treatment

What are the practical implications of these experimental findings? First, it seems that the worst recommendation that a physician can make to a patient after a unilateral loss of vestibular function – for example, due to acute vestibular neurolabyrinthitis or following vestibular nerve section – is to tell the patient to go into a dark room, take a sedative, keep one's eyes closed and not move about until one feels better. In actual fact, adaptation should be encouraged and the patient needs to be informed of the need for movement (of course, to the limits of what the patient can reasonably tolerate). Sedation should be avoided; antiemetic medications should be carefully chosen for minimal sedative effects. One should remember that this approach is designed for a patient with a relatively fixed static lesion in which case adaptation will be the major mechanism of recovery. In contrast is the management of a patient who has an acute unilateral vestibular paresis due, for example, to an attack of Ménières syndrome. In such a patient recovery is usually based on mechanical factors, presumably repair of the rupture in the membranous labyrinth, with restoration of the normal electrolyte composition of the perilymph bathing the vestibular nerve. It would not be inappropriate to sedate such patients and instruct them to lie quietly, as they should recover within a short period of time on their own. Obviously, the mechanism of the loss of vestibular function will determine the need for and the type of adaptation, and the type of therapy.

Recovery from bilateral loss of labyrinthine function

Similar considerations apply to bilateral loss of labyrinthine function. A variety of mechanisms are available for compensating for bilateral vestibular loss but the mechanism that is invoked depends upon what function is left.[22] If there is a paresis but not a paralysis of peripheral labyrinthine function, therapy should attempt to promote labyrinthine-ocular motor reflexes by potentiating the central response to weak peripheral inputs. On the other hand, if there is no residual labyrinthine function, physical therapy designed to promote labyrinthine-ocular reflexes would be counterproductive, and instead one should encourage either the development of new strategies (such as preprogramming of compensatory slow phases in anticipation of head movements) or potentiation of what are rudimentary, vestigial reflexes in normal human subjects but can serve a useful function in patients who have no labyrinthine function. An example would be the cervicoocular reflex, the neck-eye loop, which is barely functional in normal human subjects but can be considerably potentiated and then used to generate compensatory slow phases in patients who have no labyrinthine function. Specific exercise programs, in which a patient's head is passively rotated faster and faster, and the patient is encouraged to read progressively smaller print, might help to potentiate the cervicoocular reflex. Likewise, exercises in which the patient is instructed to rapidly move the head and eyes between different objects in the visual field might encourage the ability to preprogram compensatory slow phases in anticipation of a change in gaze associated with a head movement.

Conclusions

We have discussed a number of examples in which a knowledge of the adaptive process allows one to interpret a patient's clinical findings correctly, to help localize the neurological lesion accurately and to plan any therapeutic intervention rationally. To recapitulate some of the main practical points:

1) When a patient has a dissociated or monocular nystagmus together with an ocular muscle weakness it is important to determine if the patient preferentially fixes with one eye, and if so, which eye, so that the effects of any adaptive responses on the other eye can be properly interpreted. Patients with ocular myasthenia gravis may show a number of unusual and sometimes bizarre eye signs. They usually reflect the combination of fatigue at the neuromuscular junction, even intrasaccadic fatigue, as well as adaptive responses. Small changes in saccadic accuracy in response to edrophonium may be easily seen at the bedside and are a useful diagnostic sign.

2) Recovery nystagmus, after a unilateral labyrinthine lesion, reflects a mechanism analogous to that which accounts for the abnormal saccades induced by edrophonium in ocular myasthenia. Central adaptation can not "deadapt" fast enough in the face of a sudden restoration of peripheral labyrinthine function, leading to a transient recurrence of nystagmus that appears to emanate from a new lesion in the normal ear.

3) Eye movement abnormalities of the blind may resemble those seen in patients with cerebellar disease, probably because normal adaptive responses depend upon a cerebellar mechanism that, in blind patients, is deprived of the necessary error signals to maintain long-term ocular motor calibration.

4) Periodic alternating nystagmus, an unusual and characteristic eye oscillation, reflects the actions of two very normal mechanisms – velocity storage, which perseverates peripheral labyrinthine inputs to improve the range of frequencies over which the VOR can function, and short-term vestibular adaptation, which attempts to nullify any sustained unidirectional vestibular nystagmus. It is the lesion in the cerebellar nodulus that leads to the disinhibition of velocity storage that produces the sustained oscillations of PAN. The loss of inhibition from the nodulus can be supplanted with the GABA-B agonist, baclofen, which stops periodic alternating nystagmus.

5) The results of vestibular function tests must be interpreted in the context of whether or not a patient habitually wears a spectacle correction since that, in itself, can lead to an increase or decrease in the amplitude of the VOR, and should not be interpreted as due to cerebellar or bilateral labyrinthine dysfunction, respectively.

6) Programs of physical therapy for vestibular dysfunction should be tailored to the specific cause of the vestibular loss and the amount of residual function. In patients with acute unilateral loss of function, early activity may be essential to assure optimum recovery. Furthermore, adaptation to labyrinthine lesions is fragile. Continuous exposure to the error signals that provided the initial adaptive drive is necessary to maintain the adaptive state.

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