THREE DIMENSIONAL DISORDERS OF GAZE AND BINOCULAR ALIGNMENT
AFTER BRAINSTEM AND OCULAR MOTOR NERVE LESIONS

by

Agnes Ming-Fong Wong, MD, FRCSC

A thesis submitted in conformity with the requirements
for the degree of Doctor of Philosophy
Institute of Medical Science
University of Toronto

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ABSTRACT

The effects of paralytic strabismus and neural lesions on ocular motor systems were investigated. Patients with sixth, fourth, and third nerve palsy, as well as skew deviation caused by brainstem or cerebellar lesions were studied. The vestibulo-ocular reflex (VOR) and saccades in three axes of rotation were investigated using the magnetic search coil technique. The effects of paralytic strabismus and neural lesions on Listing's and Donders' laws, which specify torsional eye position, were also studied.

Monocular adaptive changes in the VOR were demonstrated; in sixth nerve palsy, horizontal VOR gains are not only decreased during abduction, but also during adduction of the paretic eye, without a conjugate decrease in gains of the non-paretic eye. Similarly, in fourth nerve palsy, VOR gains are not only reduced during incyclotorsion, depression and abduction, but also during excyclotorsion, elevation and adduction of the paretic eye, while VOR gains in the non-paretic eye remain normal. In third nerve palsy, VOR gains are not only decreased during adduction and excyclotorsion, but also during abduction and incyclotorsion of the paretic eye, without a conjugate decrease in gains of the non-paretic
eye. This monocular adaptation is attributed to retinal slip differences between the two eyes.

Monocular adaptation was also identified in the saccadic system. In mild and moderate sixth nerve palsy, saccade peak velocities in the paretic hemifield of motion are normal in the paretic eye, without a conjugate increase in peak velocities in the non-paretic eye. This selective adaptation is also visually driven; it allows both eyes to reach a target in the paretic hemifield of motion rapidly and simultaneously.

During saccades and fixation, *acute* peripheral sixth and fourth nerve palsy violates Listing's law, whereas *chronic* palsy obeys it, indicating that neural adaptation can restore Listing's law even when the eye muscle remains abnormal. Patients with skew deviation caused by brainstem or cerebellar lesions have abnormal ocular torsion in both eyes, providing evidence that elements of the neural pathway that enforce Listing's law traverse the regions of the brainstem and cerebellum that are damaged in skew deviation.
ACKNOWLEDGMENT

I would like to thank members of my Program Advisory Committee, Dr. Dianne Broussard, Dr. James Sharpe, and Dr. Douglas Tweed, for their comments on previous drafts of the thesis.

I would also like to thank Dr. Douglas Tweed, Dr. R. David Tomlinson and the late Mr. Phat Nguyen for their advice and technical assistance.

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<th>Description</th>
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<td>3D</td>
<td>three-dimensional</td>
</tr>
<tr>
<td>AC</td>
<td>anterior semicircular canals</td>
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<tr>
<td>AMPA</td>
<td>alpha-amino-3-hydroxy-5-methyl-4-isoxalone propionate</td>
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<td>ATD</td>
<td>ascending tract of Deiters</td>
</tr>
<tr>
<td>BC</td>
<td>brachium conjunctivum</td>
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<tr>
<td>CCW</td>
<td>counterclockwise</td>
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<td>cNRTP</td>
<td>caudal nucleus reticularis tegmenti pontis</td>
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<tr>
<td>CNS</td>
<td>central nervous system</td>
</tr>
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<td>CROM</td>
<td>cervical range of motion</td>
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<td>CT</td>
<td>computerized tomography</td>
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<td>CW</td>
<td>clockwise</td>
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<td>esodeviation</td>
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<td>ET</td>
<td>esotropia</td>
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<td>frontal eye field</td>
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<td>FOR</td>
<td>fastigial oculomotor region</td>
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<tr>
<td>FTNs</td>
<td>floccular target neurons</td>
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<td>GABA</td>
<td>gamma-aminobutyric acid</td>
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<td>HC</td>
<td>horizontal semicircular canal</td>
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<td>HGVP</td>
<td>horizontal gaze-velocity Purkinje cells</td>
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<tr>
<td>IO</td>
<td>inferior oblique</td>
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<td>Abbreviation</td>
<td>Definition</td>
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<td>--------------</td>
<td>------------------------------------------------</td>
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<tr>
<td>IR</td>
<td>inferior rectus</td>
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<td>LHD</td>
<td>left hyperdeviation</td>
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<td>MLF</td>
<td>medial longitudinal fasciculus</td>
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<tr>
<td>$M_{\text{pred}}$</td>
<td>predicted magnification</td>
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<td>medial rectus</td>
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<td>MR images</td>
<td>magnetic resonance images</td>
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<td>MVN</td>
<td>medial vestibular nucleus</td>
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<td>NMDA</td>
<td>N-methyl-D-aspartate</td>
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<td>NOT</td>
<td>nucleus of the optic tract</td>
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<td>OCR</td>
<td>ocular counterroll</td>
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<tr>
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<td>posterior semicircular canals</td>
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<td>prisms diopters</td>
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<td>PPRF</td>
<td>pontine paramedian reticular formation</td>
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<td>rapid eye movement</td>
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<td>right hyperdeviation</td>
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xx
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<td>riMLF</td>
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<td>standard deviation</td>
</tr>
<tr>
<td>SNpr</td>
<td>substantia nigra pars reticulata</td>
</tr>
<tr>
<td>SO</td>
<td>superior oblique</td>
</tr>
<tr>
<td>SR</td>
<td>superior rectus</td>
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<td>SVN</td>
<td>superior vestibular nucleus</td>
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<td>VOR</td>
<td>vestibulo-ocular reflex</td>
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<tr>
<td>VVOR</td>
<td>visually enhanced vestibulo-ocular reflex</td>
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To Bill,

my mother, Esther, and

my late father Joseph Chung-Lam Wong
CHAPTER 1

INTRODUCTION
**Strabismus** is a common and disabling manifestation of diseases that affect the brainstem, ocular motor nerves and extraocular muscles. Common causes of paralytic strabismus include arteriosclerosis, diabetes mellitus, multiple sclerosis, and neoplasia. Clinical testing of ocular motor nerve palsies emphasizes examination of static deviations of the eyes. Studies on the dynamics of strabismus have focused on horizontal or vertical eye movements. However, the eye rotates with three degrees of freedom: it can rotate around a vertical (abduction and adduction), horizontal (elevation and depression), or anteroposterior axis (excycloduction and incycloduction). A complete and accurate understanding of strabismus therefore calls for a three-dimensional (3D) approach. The purpose of this thesis is to characterize the effects of paralytic strabismus and neural lesions on eye rotations around three axes. Patients with strabismus caused by peripheral ocular motor nerve palsy (sixth, fourth, and third nerve palsy), and brainstem and cerebellar lesions (e.g. central sixth nerve palsy, and skew deviation) are studied. Quantitative understanding of the effects of paralytic strabismus on ocular motor systems, and adaptation to it, if any, is important in diagnosing and managing this common disorder.

Palsy of the ocular motor nerves would cause abnormalities in the horizontal, vertical and torsional alignments of the eyes during fixation and eye motion. Disparity of retinal images and retinal image slip differences between the two eyes are abnormalities that challenge the repair mechanisms of the brain. We postulated that eye movements in paralytic strabismus will be manifestations of both the palsy and adaptation of the brain to the palsy. This thesis identifies deficits caused by ocular motor nerve palsy and adaptation to these deficits, in three dimensions.

The thesis is divided into an Introduction and five sections. In the Introduction, the
relevant literature is reviewed. The anatomy and function of the extraocular muscles and ocular motor nerves are first reviewed. The vestibulo-ocular reflex and the saccadic system are then examined. Evidence of monocular adaptation in these two systems are discussed. This is followed by a review of Listing’s and Donders’ laws, which govern 3D eye movements. The terminology used in strabismus is then described. Section I contains chapters on adaptations and deficits of the vestibulo-ocular reflex after sixth, fourth and third nerve palsy. Each chapter has its own set of figures, tables and references. Section II describes the dynamics of saccades after sixth nerve palsy. Section III presents evidence of adaptive neural mechanisms for Listing’s law after sixth and fourth nerve palsy, and in patients with skew deviation caused by brainstem or cerebellar lesions. Section IV deals with vertical misalignment in sixth nerve palsy and its clinical implications. Section V consists of a final discussion on the role of adaptation in paralytic strabismus, and the neural mechanisms underlying the adaptive control of 3D eye movement. Future directions are also discussed.

1.1 THE EXTRAOCULAR MUSCLES

1.1.1 Gross anatomy

The eyeball is rotated by six extraocular muscles: the medial rectus, lateral rectus, superior rectus, inferior rectus, superior oblique and inferior oblique. The action of the muscles on the globe is determined by the point of rotation of the globe, and the origin and insertion of each muscle. In addition, the tendons of the rectus muscles pass through sleeve-like pulleys that lie several millimeters posterior to the equator of the globe, approximately 10 mm posterior to the insertion sites of the muscles. These pulleys,
consisting of fibrous tissue and smooth muscle, limit side-slip movement of the rectus muscles during eye rotations and act as the functional origins of the rectus muscles.3-6

The eyeball rotates about three axes; one current convention refers to these axes as x (the roll or naso-occipital axis), y (the pitch or interaural axis), and z (the yaw or caudal-rostral axis). Rotations about the x-axis produces torsional eye movements, about the y-axis vertical movements, and about the z-axis horizontal movements. The primary action of the muscle refers to the axis about which the eye principally rotates when that muscle contracts; the secondary and tertiary actions refer to the axes about which there are lesser rotations.

The four rectus muscles arise from the annulus of Zinn at the apex of the orbit. The medial rectus inserts onto the medial side of the globe at approximately 5.3 (± 0.7) mm from the corneoscleral limbus, whereas the lateral rectus inserts onto the lateral side of the globe at approximately 6.9 (± 0.7) mm from the limbus.7-10 Since the origins and insertions of the horizontal rectus muscles are symmetric and lie in the horizontal meridian of the globe, their functions are relatively simple and are antagonistic; contraction of the medial rectus adducts the globe, while contraction of the lateral rectus causes abduction of the globe.11

The superior and inferior rectus also originate from the annulus of Zinn. The superior rectus inserts onto the globe superiorly at approximately 7.9 (± 0.6) mm from the limbus, and the inferior rectus inferiorly at approximately 6.8 (± 0.8) mm from the limbus.7-10 In addition, their insertions onto the globe subtend an angle of 23° with the straight ahead visual axis, straddling the vertical meridian of the globe. Thus, in addition to their primary actions of elevation for the superior rectus and depression for the inferior rectus, the
vertical rectus muscles also have relatively prominent secondary actions of incyclotorsion for the superior rectus and excyclotorsion for the inferior rectus, as well as tertiary action of adduction for both muscles. The relative importance of the primary and secondary actions depends on the direction of the visual axis. When the eye is abducted 23°, the superior rectus acts solely as an elevator and the inferior rectus acts solely as a depressor of the globe. When the eye is adducted 67°, then the superior rectus acts solely to incyclotort the globe and the inferior rectus acts solely to excyclotort.

The superior oblique muscle also arises from the annulus of Zinn; however, its functional origin is the trochea in the superomedial orbit. In human, the superior oblique is tendinous after it passes through the trochea. This tendon then assumes a posterolateral direction and inserts onto the superior-posterior-temporal quadrant of the globe behind the center of rotation. This vector plane subtends a 54° angle with the straight ahead visual axis. Thus, in addition to its primary action of incyclotorsion, the superior oblique also has a secondary action of depression and tertiary action of abduction. When the eye is adducted 54°, the superior oblique acts solely to depress the globe, and when the eye is abducted 36°, it acts solely to incyclotort the globe.

The inferior oblique muscle arises from the anterior medial orbital floor. It inserts onto the inferior-posterior-temporal quadrant of the globe behind the center of rotation, and subtends a 51° angle with the straight ahead visual axis. Thus, in addition to its primary action of excyclotorsion, the inferior oblique also has a secondary action of elevation and tertiary action of abduction. When the eye is adducted 51°, the inferior oblique acts solely to elevate the globe, and when the eye is abducted 39°, it acts solely to excyclotort the globe.
1.1.2 Structure of Extraocular Muscle Fiber Types

The rectus and oblique muscles exhibit two distinct layers: an outer orbital layer adjacent to the periorbita and orbital bone, and an inner global layer adjacent to the eye and the optic nerve. While the global layer extends the full muscle length, inserting via a well-defined tendon, the orbital layer ends before the muscle becomes tendinous. Each layer contains fibers more suited for both sustained contraction and brief rapid contraction. However, the orbital layer contains many fatigue-resistant twitch fibers. Six types of fibers have been defined in the extraocular muscles.12-15

In the orbital layer, about 80% are singly innervated fibers. These fibers exhibit the fast type of myofibrillar ATPase and high oxidative activity, but also appear to be capable of anaerobic activity. They have twitch capacity and are the most fatigue-resistant fibers. They are the only fiber type that show long-term effects after injection of botulinum toxin.16 The remaining 20% of orbital fibers are multiply innervated fibers. They have twitch capacity near the center of the fiber and non-twitch activity proximal and distal to the endplate band.17

In the global layer, about 33% are red singly innervated fibers, which are fast-twitch and highly fatigue-resistant. Another 33% are pale singly innervated fibers with fast-twitch properties but low fatigue resistance. Intermediate singly innervated fibers constitute about another 25% of fibers. They have fast-twitch properties and an intermediate level of fatigue resistance. The remaining 10% are multiply innervated fibers, with synaptic endplate along their entire length, as well as at the myotendinous junction, where there are palisade organ proprioceptors. These fibers show tonic properties, with slow, graded, non-propagated responses to neural or pharmacological activation.
The levator palpebrae muscle contains the three singly innervated muscle types found in the global layer of the extraocular muscles, and a true slow-twitch fiber type. The multiply innervated fiber type and the fatigue-resistant singly innervated type seen in the orbital layer are absent.

1.1.3 Function of Extraocular Muscle Fiber Types

It was suggested that different muscle fiber types subserve various eye movements; slower or vestibularly-induced eye movements were attributed to contraction of the slower tonic muscle fibers, and rapid movements were attributed to contraction of the faster twitch fibers. However, more recent studies argue against this concept, and indicate that motoneurons and muscle fibers represent a final common pathway for all oculomotor systems. Robinson proposed that the functional arrangement of muscle fiber types is related to the threshold at which motor units are recruited. In saccades and quick phases of nystagmus, all motor units are recruited and burst synchronously. There is no differential in the recruitment order of the different muscle fiber or motor unit types. However, after saccades, or in slow smooth eye movements, the recruitment of individual motoneurons into sustained discharge is eye position-dependent. Motor units containing orbital singly innervated fibers and global red singly innervated fibers are recruited first, well in the off-direction of muscle action. Those motor units containing multiply innervated fiber types are recruited next, probably near straight ahead position where their fine increments of force would be of value for fixation. The increasingly faster, but fatiguable fibers are recruited last, at positions well into the on-direction of muscle action.

Using electromyograms, Scott and Collins provided evidence of a functional
division of labor between the global and orbital layers of extraocular muscles. They found that orbital fibers are active throughout nearly the entire range of movement, but during fixation, global fibers are recruited only as the eye is called into the field of action of that muscle. This indicates that the singly innervated, fatigue-resistant orbital fibers may play a key role in sustaining eye position and maintaining extraocular muscle tone in any eye position. During saccades, both global and orbital fibers are activated, but the activity of global fibers subsequently falls, whereas activity of orbital fibers sustains. These findings are consistent with the presence of more fatigue-resistant fibers in the orbital layers.

1.1.4 Extraocular Proprioception

Although human extraocular muscles contain muscle spindles, the palisade tendon organs appear to be the primary proprioceptors. Palisade endings are mainly associated with the distal myotendinous junctions of the global multiply innervated muscle fiber type. This fiber type accounts for about 10% of global fibers and is absent from the eyelid. Extraocular muscle afferents project from these proprioceptors, via the ophthalmic branch of the trigeminal nerve and the Gasserian ganglion, to the spinal trigeminal nucleus. Proprioceptive inputs may also project centrally via the ocular motor nerves. From the trigeminal nucleus, proprioceptive information is distributed widely to structures involved in ocular motor control, including the superior colliculus, vestibular nuclei, nucleus prepositus hypoglossi, cerebellum, and frontal eye fields. Proprioceptive information is also distributed to structures involved in visual processing, including the lateral geniculate body, pulvinar, and visual cortex.
Functionally, extraocular proprioception has been implicated in a variety of roles. Proprioception may specify visual direction, modulate visual processing, and participate in binocular functions, particularly during the critical period of development of the visual sensory system. Abnormalities in proprioception may contribute to fixation instabilities in congenital nystagmus and to strabismus. Steinbach et al have shown that proprioception contributes to spatial localization and that alterations in localization can be attributed to marginal myotomy procedure, which compromises the sensory receptors. Proprioception may also participate in the control of different oculomotor systems. Its role in the control of the vestibulo-ocular and saccadic systems is discussed in sections 1.2 and 1.3 of this chapter.

1.1.5 Changes in Extraocular Muscles After Ocular Motor Nerve Palsy

After ocular motor nerve palsy, the paretic muscle lengthens, while the non-paretic antagonist muscle shortens and stiffens, in response to the change in orbital position of the globe. The changes observed in the antagonist muscle have been referred to as “contracture.” Anatomical and histological study showed that shortening or contracture of the non-paretic antagonist muscle is associated with a decrease in the number of sarcomeres, whereas lengthening of the paretic muscle is accompanied by an increase in the number of sarcomeres. In addition, denervation atrophy in the paretic muscle, and changes in orbital tissues have also been documented in paralytic strabismus.

1.2 THE OCULAR MOTOR NERVES
1.2.1 The Abducens Nerve

The abducens nucleus lies in the floor of the fourth ventricle, at the level of the lower pons. Two populations of neurons lie within the abducens nucleus: the abducens motoneurons, which innervate the ipsilateral lateral rectus muscle, and the abducens internuclear neurons, which project to contralateral medial rectus motoneurons via the medial longitudinal fasciculus.57-59 Root fibers destined for the ipsilateral lateral rectus muscle emerge from the medial aspect of the nucleus, course ventrally, laterally, and caudally through the pontine tegmentum and medial lemniscus, and emerge from the brainstem at the caudal border of the pons lateral to the corticospinal tract. The abducens nerve then courses up the ventral surface of the pons, between the pons and the anterior inferior cerebellar artery. In up to 30% of individuals, the abducens nerve may exist as two or more separate trunks that eventually fuse within the cavernous sinus.60,61

The nerve continues to ascend through the subarachnoid space along the clivus. It then pierces the dura mater, courses around or through the inferior petrosal sinus, and passes under the petroclinoid (Gruber's) ligament in Dorello's canal to enter the cavernous sinus. Within the sinus, it bends laterally around the intracavernous carotid artery and runs medial and parallel to the ophthalmic division of the trigeminal nerve. Unlike the oculomotor and trochlear nerves, the abducens nerve does not lie within the lateral wall of the sinus, but rather runs within the body of the sinus.61 Oculosympathetic fibers from the carotid plexus to the iris dilator muscle run with the abducens nerve for a short distance before joining the ophthalmic division of the trigeminal nerve. The abducens nerve enters the orbit through the superior orbital fissure 62 and passes through the annulus of Zinn. It runs within the clefts on the medial surface of lateral rectus muscle,
where it divides into about 10 filaments before finally penetrating the conal surface of the muscle at the junction of the posterior and middle thirds of the length of the muscle.

Clinically, abducens nerve palsy is the most common ocular motor paralysis. It is characterized by incomitant esotropia, which is greatest when viewing objects in the field of paretic duction. The most common cause of isolated sixth nerve palsy in patients over 50 years of age is ischemia, which occurs with greater frequency in patients with diabetes mellitus or hypertension. The abducens nerve is also predisposed to injury from head trauma because of its long course along the base of the skull and its abrupt angulation over the petrous ridge. Other causes of sixth nerve palsy include neoplasm, demyelination, mastoiditis, meningitis, inflammatory diseases, collagen vascular diseases, sarcoidosis, migraine, and Wernicke's disease. In approximately 25% of patients, the cause is unknown.

1.2.2 The Trochlear Nerve

The trochlear nucleus appears as a small compact cell group at the ventral border of the periaqueductal gray matter at the level of the inferior colliculus. It lies at the dorsal margin of the medial longitudinal fasciculus. Each trochlear nucleus sends axons to supply the contralateral superior oblique muscle. Root fibers from the nucleus pass dorsolaterally and caudally near the margin of the central gray matter, decussate completely in the anterior medullary velum (the roof of the aqueduct), and emerge from the dorsal surface of the brainstem caudal to the inferior colliculus and close to the tentorium cerebelli. It is the only crossed cranial nerve and the only one that exits on the dorsal side of the brainstem.
The trochlear nerve curves around the lateral surface of the upper pons, passing between the superior cerebellar and posterior cerebral arteries, to reach the prepontine cistern. It then runs forward on the free edge of the tentorium for 1 to 2 cm before penetrating the dura of the tentorial attachment and entering the cavernous sinus. Within the lateral wall of the sinus, the trochlear nerve lies below the oculomotor nerve and above the ophthalmic division of the trigeminal nerve. It then crosses over the oculomotor nerve and receives filaments from the carotid sympathetic plexus. The nerve enters the orbit through the superior orbital fissure above the annulus of Zinn in company with the frontal and lacrimal branches of the ophthalmic division of the trigeminal nerve. It divides into several small fascicles that penetrate the superior oblique muscle on its superolateral surface about 9 to 10 mm from the orbital apex.

Clinically, fourth nerve palsy accounts for most cases of acquired vertical strabismus. It is characterized by ipsilateral hypertropia, which increases during adduction, depression, and head tilt toward the side of the lesion. The most common known cause of fourth nerve palsy in adults is trauma. The long intracranial course of the trochlear nerve and its proximity to the bony orbital wall predispose it to injury from head trauma. Vascular diseases, including hypertension, atherosclerosis, and diabetes, account for approximately 20% of cases. Other causes include neoplasm, collagen vascular diseases, herpes zoster ophthalmicus, aneurysm, hydrocephalus, and encephalitis. In approximately 30% of patients, the cause is unknown.

1.2.3 The Oculomotor Nerve

The oculomotor nucleus is a paired structure that lies at the ventral border of the
periaqueductal gray matter; it extends rostrally to the level of the posterior commissure and caudally to the trochlear nucleus. It sends motor fibers to the medial rectus, superior rectus, inferior rectus, inferior oblique, and levator palpebrae muscles. It also carries parasympathetic fibers to the pupillary constrictor muscle and the ciliary body. Within the somatic portion of the oculomotor nucleus, there is a topographic localization of motor neurons that can be traced to the individual ocular muscles. The subnuclei lie in a long column and are arranged in the order: medial rectus - inferior rectus - superior rectus - inferior oblique from rostral to caudal. Subnuclei of the inferior and medial rectus and inferior oblique are paired and innervate muscles on the ipsilateral side. The superior rectus subnuclei are located medially on each side of the midbrain. Their fibers cross the midline, passing through the subnucleus on the opposite side to join axons from other oculomotor subnuclei on that side. Motor neurons that innervate the levator muscle of both sides lie in a single subnucleus in the dorsal midline. Parasympathetic innervation for the pupil originates in the Edinger-Westphal nucleus.

The fascicular portion of the oculomotor nerve extends through the midbrain; it passes ventrally through the medial longitudinal fasciculus, the tegmentum, the red nucleus, the medial part of the substantia nigra, and finally emerges as a series of rootlets in the interpeduncular fossa on the medial aspect of the cerebral peduncle. These rootlets immediately converge to form the oculomotor nerve trunk, which lies between the superior cerebellar and posterior cerebral arteries.

The nerve passes forward, downward, and laterally through the subarachnoid cistern and runs medial and slightly beneath the free edge of the tentorium. It continues lateral to the posterior communicating artery and below the temporal lobe uncus, where
it runs over the petroclinoid ligament, medial to the trochlear nerve and just lateral to the posterior clinoid process. It pierces the dura mater at the top of the clivus as it enters the lateral roof of the cavernous sinus, slightly above and medial to the abducens nerve.\(^6^0\)

Within the cavernous sinus, the third nerve lies initially above the trochlear nerve, and here it receives sympathetic fibers from the carotid artery. As it leaves the cavernous sinus, it is crossed superiorly by the trochlear and abducens nerves, and it divides into the superior and inferior divisions. Both divisions pass through the superior orbital fissure\(^6^2\), and enter the orbit within the annulus of Zinn. The smaller superior oculomotor division runs lateral to the optic nerve and ophthalmic artery, and supplies the superior rectus and levator palpebrae muscles. The larger inferior oculomotor division branches in the posterior orbit and supplies the medial rectus, inferior rectus, and inferior oblique muscles, and the ciliary ganglion.\(^7^1\)

The clinical manifestation of third nerve palsy varies, depending on the point of axonal interruption. Nuclear lesion is rare and results in unilateral third nerve palsy with contralateral superior rectus weakness and bilateral ptosis.\(^8^1\) Complete third nerve palsy results in an ipsilateral exotropia and hypotropia, ipsilateral ptosis and a fixed dilated pupil. Partial third nerve palsy is more common, and its clinical characteristics correlate with lesions at various sites along the course of the nerve.

The most common causes of third nerve palsy in adults are ischemia and aneurysms, each accounting for approximately 20% of cases.\(^6^3, 6^5, 6^6, 6^8, 6^9, 8^2, 8^3\) Trauma and tumors each account for another 10% to 15% of cases.\(^6^3, 6^5, 6^6, 6^8, 6^9, 8^2, 8^3\) Other causes include meningitis, encephalitis, Hodgkin's disease, herpes zoster, temporal arteritis, collagen vascular disease, Paget's disease, and acquired immunodeficiency syndrome.\(^6^5-7^0\)
In about 20% of cases, the cause is unknown.\textsuperscript{83, 65, 66, 68, 89, 82, 83}

A common sequel of oculomotor nerve palsy is aberrant regeneration. The clinical signs of aberrant regeneration include abnormal lid and pupillary movements. Most commonly the lid elevates during adduction or depression of the eye. Other common patterns include depression of the lid on abduction, and pupillary constriction on adduction or depression of the eye, while direct pupillary light reaction is absent. All these combined movements are due to cocontraction of muscles innervated by the third nerve. Aberrant reinnervation of the oculomotor nerve may occur after trauma\textsuperscript{84}, aneurysm\textsuperscript{85, 86}, congenital third nerve palsy\textsuperscript{87}, migraine\textsuperscript{88} or as a complication of neurosurgery.\textsuperscript{89} If aberrant regeneration is encountered without a history of preceding oculomotor palsy, then slowly growing intracavernous meningioma\textsuperscript{90, 91} or carotid aneurysm\textsuperscript{92} is likely, though sometimes no cause can be found.\textsuperscript{93} Aberrant regeneration almost never occurs with diabetic third nerve palsy.\textsuperscript{94}

1.3 THE VESTIBULO-OCULAR REFLEX

The vestibulo-ocular reflex (VOR) stabilizes retinal images during head movements. It has two components, one angular and one linear. The angular VOR is elicited during head rotations by stimulation of the cupulas in the semicircular canals, and produces horizontal (about the yaw or caudal-rostral axis), vertical (about the pitch or interaural axis) and torsional (about the roll or naso-occipital axis) eye movements. The linear VOR is activated during head translations by stimulation of the otolith receptors in the maculae of the utricle and saccule, and produces horizontal eye motion (heave, along the interaural axis), vertical motion (bob, along the dorsal-ventral axis) and vergence motion (surge,
along the naso-occipital axis).

The ratio of the output of the reflex (the speed of smooth eye movement in one direction) to the input of the reflex (the speed of head movement in opposite direction) is its gain. VOR gain varies with frequency of head motion, and must approximate 1.0 to prevent slippage of retinal images. At frequencies that correspond to most natural head rotations (0.5 - 5 Hz), horizontal and vertical VOR gains are close to -1.0. If the gain is too much above or below its ideal value of unity, a target image remains off the fovea, although it may be transiently stable on the retina. The eyes and head must also be 180° out of phase. This normal phase difference is designated zero, by convention. If there is a phase lead of the eyes before the head or a phase lag behind it, the target image is never stationary on the retina. An abnormal gain or phase of the VOR causes visual blur and oscillopsia.

1.3.1 The Horizontal Angular VOR Pathway

A three- to four-neuron arc underlies each semicircular canal-extraocular muscle reflex. Primary afferents of the horizontal VOR pathway originate from the horizontal (lateral) canals. Stimulation of a horizontal canal by ipsilateral head acceleration results in deviation of both eyes away from the side of the canal. The semicircular canals on each side work in a reciprocal push-pull fashion. When the head moves to the right, the ampullary nerve of the right horizontal canal is stimulated by deflection of its cupula, and the left horizontal canal nerve is inhibited by deflection of its cupula.

The horizontal angular VOR is served by two projections (Figure 1-1). The first is a direct excitatory projection from the horizontal canal to second-order neurons in the
medial vestibular nucleus (MVN). Axons of these second-order neurons then project to the contralateral abducens nucleus. Two populations of neurons lie within the abducens nucleus: the abducens motoneurons, which innervate the lateral rectus on that side, forming a three-neuron arc, and the abducens internuclear neurons, which axons cross the midline and ascend within the medial longitudinal fasciculus (MLF) to innervate the medial rectus motoneurons in the oculomotor nucleus on the opposite side.\textsuperscript{57-59} The internuclear pathway to the medial rectus muscle is a four-neuron reflex and is thought to be the most important VOR pathway to the medial rectus muscle. They also transmit saccadic and pursuit eye movement signals to the medial rectus.\textsuperscript{99,100}

A second direct excitatory pathway arises from the horizontal canals to second-order neurons in the lateral vestibular nucleus. Axons of these second-order neurons project to the ipsilateral abducens nucleus without synapsing. They ascend through the ascending tract of Deiters (ATD) to the ipsilateral medial rectus subnucleus.\textsuperscript{101,102}

1.3.2 The Vertical and Torsional Angular VOR Pathway

Primary afferents of the vertical and torsional angular VOR pathway originate from the anterior and posterior canals. When one anterior (or posterior) canal is stimulated, the posterior (or anterior) canal in the opposite labyrinth is inhibited. One anterior canal excites the ipsilateral superior rectus muscle and the contralateral inferior oblique muscle \textsuperscript{103}, resulting in dysconjugate elevation and contralateral torsion of the upper poles of both eyes (Figure 1-2A); elevation of the ipsilateral eye is greater than that of the contralateral eye and torsion of the contralateral eye is greater than that of the ipsilateral eye.\textsuperscript{104} At the same time, the anterior canal sends reciprocal inhibitory signals
to the antagonistic ipsilateral inferior rectus and contralateral superior oblique muscles\textsuperscript{105,108} (Figure 1-2B).

One posterior canal excites the ipsilateral superior oblique muscle and the contralateral inferior rectus muscle\textsuperscript{107} (Figure 1-2C). Thus, one posterior canal activates dysconjugate depression and contralateral torsion of the upper poles of both eyes; depression of the contralateral eye is greater than that of ipsilateral the eye and torsion of the ipsilateral eye is greater than that of the contralateral eye.\textsuperscript{104} Reciprocal inhibition is conveyed from the posterior canal to the antagonistic ipsilateral inferior oblique and contralateral superior rectus muscles\textsuperscript{105,108} (Figure 1-2D).

Stimulation of both anterior canals by downward head acceleration activates the upward angular VOR, whereas stimulation of both posterior canals by upward head acceleration activates the downward angular VOR. Stimulation of the anterior and posterior canals on one side during ipsilateral head roll activates the torsional angular VOR, so that the upper poles of the eyes roll toward the contralateral shoulder.

\textbf{1.3.3 Dynamic and Static Head Roll}

\textit{Dynamic head roll.} During head roll, compensatory eye movements are generated by the torsional VOR, which is mediated predominantly by the vertical semicircular canals. The dynamic torsional VOR gain typically ranges from 0.4 to 0.7\textsuperscript{2,109-113}, and are considerably lower than its horizontal or vertical counterparts. In human and other frontal-eyed animals, dynamic head roll produces predominantly torsional eye movement with a small vertical disjunctive component.\textsuperscript{2,114,115} This is in contrast to lateral-eyed animals, who have predominantly dysjunctive vertical eye movement with a small
torsional component during head roll.\textsuperscript{116,117} The vertical disjunctive movements serve to align the visual axes along the earth-horizontal plane.

The central pathway of the torsional VOR is known to be the same among vertebrates, with the anterior and posterior semicircular canals linked to specific vertical recti and oblique muscles by three-neuron arcs (see above).\textsuperscript{118} However, the insertions and lines of action (the pulling directions) of these muscles, and hence their secondary and tertiary actions relative to the eyes (Table 1-1), are different in species with different interocular angles.\textsuperscript{11} The different combinations of primary, secondary and tertiary actions of the vertical recti and oblique muscles explains the difference in compensatory eye movements observed in frontal-eyed and lateral-eyed animals during head roll.\textsuperscript{11}

**Static head roll.** Sustained head roll evokes compensatory changes in torsional eye position, called "static ocular counterroll", that are mediated mainly by the otolith-ocular reflex from inputs of the utricles.\textsuperscript{119} In lateral-eyed animals, static head roll causes a disjunctive, vertical deviation that acts to hold the visual axis of each eye parallel to earth's horizon. Direct stimulation of the utricular maculae in lateral-eyed animals, such as the guinea pig, produces upward or upward-torsional movements in the ipsilateral eye, and downward or downward-torsional movements in the contralateral eye.\textsuperscript{120} In contrast, in frontal-eyed species including humans, static head roll produces primarily torsional movements with contraversive roll of the upper poles of the eyes. Direct stimulation of one utricular nerve in cats produces predominantly incyclotorsion with a small elevation and adduction of the ipsilateral eye, and predominantly excyclotorsion with a small depression and abduction of the contralateral eye.\textsuperscript{121} In humans, static counterroll (OCR) gain ranges from 0.10 to 0.24, depending on target distance.\textsuperscript{2,108,122}
Central otolith-ocular connections are less well studied than those for angular VOR. In cats, horizontal utricular responses are elicited by mono- or di-synaptic projections to the ipsilateral abducens nucleus that excite the ipsilateral lateral rectus motoneurons, and to internuclear neurons that project via the MLF to the contralateral medial rectus subnucleus (Figure 1-3A). These effects are opposite in direction to the effects of stimulating the vestibular nerve from the ipsilateral horizontal semicircular canal. Polysynaptic pathways from the utricle cross the midline to excite the contralateral trochlear motoneurons, which innervate the superior oblique muscle on the side of the utricle, and they inhibit ipsilateral inferior oblique motoneurons to relax the ipsilateral inferior oblique muscle (Figure 1-3B). Stimulating different parts of the utricular macula may evoke pure upward, downward or lateral eye movements. Stimulation of one utricular nerve results in vertical ocular divergence and contralateral ocular torsion—the ipsilateral eye elevates, the contralateral eye depresses, and the upper poles of both eyes rotate to the opposite side. Stimulation of the saccular nerve activates both the lateral vestibular nucleus and the y-group of the vestibular nuclei, both of which participate in the generation of vertical smooth eye movements.

Brainstem or acute peripheral vestibular lesions that disrupt the otolith inputs causes the ocular tilt reaction, a triad of dysjunctive vertical deviation (skew deviation), ocular torsion and head tilt. Skew deviation is a vertical misalignment of the visual axes caused by a disturbance of supranuclear inputs. It is a vestige of the vertical divergence of the eyes that occurs in lateral-eyed animals. In fact, during static head roll in normal human subjects, a change in vertical alignment of the eyes was reported during binocular viewing in one study; however, the hypertropia was small (up to 3.6° for a 20° head roll),
and varied idiosyncratically with viewing distance. In general, during viewing of a distant target (7.2 m), a right head tilt was associated with a left hyperdeviation, and a left head tilt with a right hyperdeviation. The reverse was observed during viewing of a near target (20 cm): a right head tilt was associated with a right hyperdeviation, and a left head tilt with a left hyperdeviation.

1.3.4 Neurotransmitters in the VOR

Excitatory transmission between first and second order vestibular neurons is probably effected by glutamate and by substance P. Both NMDA (N-methyl-D-aspartate) and AMPA (a-amino-3-hydroxy-5-methyl-4-isoxalone propionate) glutamate receptors are involved. Acetylcholine receptors, both nicotinic and muscarinic, are found in the medial vestibular nucleus, and acetylcholine facilitates transmission between first and second order neurons. Cholinergic second order vestibular neurons transmit movement related information to the flocculus, uvula and inferior olivary nucleus.

Glutamate acts as a neurotransmitter in excitatory VOR pathways and its AMPA receptors are likely responsible for transmission to abducens nucleus motoneurons, but glutamate NMDA receptors are also found on abducens motoneurons. Aspartate and glutamate are the excitatory neurotransmitters utilized by abducens internuclear synaptic endings, whose burst-tonic activity conveys vestibular information related to eye position to medial rectus motoneurons. For activity related to head velocity in the ascending tract of Deiters, glutamate is the excitatory neurotransmitter to medial rectus motoneurons.

Glycine and GABA (γ-aminobutyric acid) are inhibitory transmitters in the vestibular nuclei. Glycine is the inhibitory transmitter for the horizontal VOR, acting at the abducens
nucleus. On the other hand, GABA mediates inhibition for the vertical VOR on GABA<sub>A</sub> receptors of neurons of the trochlear and oculomotor nuclei.\textsuperscript{129}

1.3.5 Habituation and Adaptation of the VOR

The VOR is a phylogenetically old brainstem reflex. It can nevertheless be modified to meet prevailing environmental circumstances. These modifications may occur acutely or after several days to weeks, and are classified as habituation and adaptation.

1.3.5.1 VOR habituation

Although vision is the stimulus for many adaptive changes of VOR performance, the VOR may also show habituation, a reduction of response after repetitive stimulation in complete darkness. Habituation is most evident after repeated constant-velocity or low-frequency continuous oscillations.\textsuperscript{131-133} The functional significance of habituation is uncertain, although it may contribute to eliminating the spontaneous nystagmus that occurs after a unilateral labyrinthine lesion. Removal of the nodulus and uvula in monkeys prevents habituation and reverses it once it has occurred.\textsuperscript{134}

1.3.5.2 VOR adaptation to visual stimuli

Adaptive changes in the VOR occur in response to different visual stimuli. The VOR is an open-loop system, meaning that receptors in the labyrinth that provide input to the reflex receive no information about eye movements, the output of the reflex. The angular VOR has a latency of action of 7-15 msec\textsuperscript{135,136}, whereas visually mediated eye movements are initiated with latencies of > 70 msec.\textsuperscript{137} The short latency within which
the VOR operates means that immediate visual inputs is not available to the reflex because of slow visual processing. In the absence of feedback, the brain must continuously monitor the effectiveness of its VOR. Visual error signals provide the stimuli for long-term adaptive changes of the VOR.

When normal subjects wear magnifying (or miniaturizing) glasses, VOR gain increases (or decreases) within 15 minutes. The retinal slip caused by magnifying (or miniaturizing) glasses increases (or decreases) the amplitude of eye movement relative to that of head movement. Myopic subjects who habitually wear minus lenses have lower VOR gains, whereas hyperopic subjects who wear plus lenses have higher gains than emmetropic subjects. Individuals who wear contact lenses show no changes in VOR gain because they do not cause rotational magnification. The prismatic effect or rotational magnification induced by spectacle adaptation can be calculated using the formula:

\[ M_{\text{pred}} = \frac{40}{40 - D} \]  

where \( D \) is the lens power in diopters and \( M_{\text{pred}} \) is the predicted magnification. For example, a hyperope who habitually wear a +10 D spherical lenses has an \( M_{\text{pred}} = \frac{40}{40 - 10} = 1.3 \). This means that while wearing +10 D, a VOR gain of 1.3, instead of 1.0, is required to prevent the visual scene from moving on the retina during head rotations.

More dramatic changes in VOR occur when subjects wear reversing prisms or glasses that laterally invert the world, right to left, such that head turns cause the environment to appear to move in the same direction as the head turn itself. When normal subjects wear reversing prisms for two days, a large reduction of VOR gains is observed. After three to four weeks of vision reversal, VOR gains and phase actually reverse; head rotations cause eye movements in the same direction, so that retinal images
are once again stabilized.\textsuperscript{142}

Cross-axis adaptation also occurs in the VOR. When the head is rotated horizontally (about the yaw axis) while visual display is synchronously rotated vertically (about the pitch axis), after a short training period, horizontal head rotations in darkness elicit vertical eye movements.\textsuperscript{143} In the early stages of adaptation, the VOR changes that develop may rapidly reverse in the absence of continuous visual input.\textsuperscript{144} However, the changes that occur after 1-2 weeks of altered visual input persist for some time even when the altered visual stimulation is discontinued.\textsuperscript{142} These persistent changes reflect the plasticity of the VOR and are important in the repair of altered visual input to the VOR or damage to the reflex by aging or disease.

1.3.5.3 Proprioception and VOR adaptation

Proprioceptive signals from extraocular muscles (EOM) may also contribute to VOR adaptation. Using the artificial vestibulo-ocular reflex (artificial VOR) technique \textsuperscript{43, 45, 47, 49}, in which movement of one eye is controlled by a opaque suction contact lens, EOM afferent signals from one eye have been shown to modify the VOR in the other eye in decerebrate or alert pigeons. When, during sinusoidal head rotation, the movement of one eye is limited such that the imposed eye velocity is slower than head velocity, VOR gains in the other eye increase.\textsuperscript{45, 47, 49} Conversely, when the imposed eye velocity is faster than head velocity, VOR gains in the other eye decrease.\textsuperscript{45, 47, 49} These effects are observed immediately after the movement of one eye is controlled, suggesting that EOM afferent signals participate in moment-to-moment control of the VOR. Further supports came from single units recordings in the reticular formation, vestibular and ocular
motor nuclei during artificial VOR in decerebrate pigeons; response activities of these neurons are inversely correlated with imposed eye velocity.\textsuperscript{145} In addition, sectioning of the ophthalmic branch of the trigeminal nerve, which carries proprioceptive signals from the EOM to the spinal trigeminal nucleus, abolishes this effect on VOR gains from imposed eye movements.\textsuperscript{146-148}

1.3.5.4 Role of the cerebellum in VOR adaptation

The flocculus and adjacent paraflocculus in the cerebellum are important for VOR adaptation. The flocculus receives bilateral, mossy fiber inputs, primarily from the vestibular nuclei and nucleus prepositus hypoglossi (NPH), but also from the pontine nuclei and nucleus reticularis tegmenti pontis (NRTP).\textsuperscript{149,150} It also receives inputs from the contralateral inferior olivary nucleus via climbing fibers \textsuperscript{149,150}, and from the cell groups of paramedian tract, which may relay an efference copy of eye movement.\textsuperscript{151} Floccular Purkinje cells supplement vestibular nucleus neurons in generating the VOR \textsuperscript{152}, regulate the phase of VOR \textsuperscript{153,154}, and participate in the adaptive control of the VOR.\textsuperscript{155} The flocculus in turn projects to the ipsilateral vestibular nuclei, including the floccular target neurons (FTNs), which are thought to play an important role in vestibular adaptation. The flocculus also projects to the y-group, and the basal interstitial nucleus of the cerebellum.\textsuperscript{156}

Experimental lesions of the flocculus and paraflocculus produce small changes in VOR gain.\textsuperscript{134,157,158} However, the ability to adapt VOR gain in response to visual demands is abolished.\textsuperscript{143,155} Humans with cerebellar disease also show abnormalities in VOR adaptation.\textsuperscript{159-161}
Based on Marr's and Albus' general hypotheses of cerebellar learning, Ito postulated that the cerebellar cortex of the flocculus is the site of motor learning for VOR adaptation. According to this hypothesis, retinal error signals of an inadequate VOR are relayed through the nucleus of the optic tract (NOT), to the inferior olivary nucleus, and thence via the climbing fibers to the Purkinje cells in the flocculus. By comparing this visual information with the vestibular inputs relayed by mossy fibers and the parallel fibers of the granule cells, the efficacy of the synapses between the parallel fibers and Purkinje cells are modified, such that Purkinje cells can make appropriate changes in the VOR via their projections to a subset of second-order neurons in the vestibular nucleus called flocculus target neurons (FTNs). However, Ito's flocculus hypothesis cannot account for all the experimental data in primates. A more recent model proposed by Lisberger suggests that the sites of motor learning lie both in the brainstem VOR pathways and in the vestibular inputs to the flocculus and ventral paraflocculus of the cerebellum. Changes in the gain of VOR can be achieved by changing in the gain of vestibular inputs to the FTNs in the brainstem, and by changes in the time course of vestibular inputs to the horizontal gaze-velocity Purkinje cells (HGVP) in the cerebellar cortex.

1.3.6 VOR in Paralytic Strabismus

Although the behavior of the VOR in normal humans has been the subject of extensive investigations, little is known about the VOR in patients with ocular motor nerve palsy. Leigh and Zee studied a patient with unilateral sixth nerve palsy. They found asymmetric horizontal VOR gains in the paretic eye during rotation in darkness and during
non-paretic eye viewing in light. During paretic eye viewing, the amplitude of movements of the occluded non-paretic eye increases, which is attributed to saccades. Averbuch-Heller et al.\textsuperscript{122} investigated the change in torsional VOR in patients with skew deviation caused by brainstem lesions, and reported abnormal dynamic and static torsional VOR.\textsuperscript{122} Owing to their small sample size, however, they\textsuperscript{122} were not able to demonstrate any specific pattern of change. These investigations\textsuperscript{94, 170, 171} are also limited by their one-dimensional approach to this 3D reflex. In Section I, we investigate patients with sixth, fourth and third nerve palsy, and identify deficits and adaptations of the VOR in three dimensions.

1.4 THE SACCADIC SYSTEM

Saccades are rapid eye movements that quickly redirect the eye such that an image of an object is brought to the fovea. They include both voluntary and involuntary changes of fixation, the quick phases of vestibular and optokinetic nystagmus, and the rapid eye movements that occur during rapid eye movement (REM) sleep.

1.4.1 Characteristics of Saccades: Saccadic Velocity, Amplitude and Waveform

Saccades show a relatively invariant relationship between the peak velocity and the amplitude of the movement. The larger the amplitude, the higher the peak velocity (Figure 1-4). This amplitude-peak velocity relationship is called the main sequence, which can be used to identify eye movements as saccades.\textsuperscript{172} The values of most normal subjects fall within a relatively limited range.\textsuperscript{173, 174} The peak velocity of saccades varies from 30 to 700 deg/sec, and their duration varies from 30 to 100 msec for movements 0.5
to 40 deg in amplitude.\textsuperscript{172} The peak velocity saturates for larger amplitude saccades. A commonly used equation to describe main sequence relationship is:

$$ P = V (1 - e^{-A/C}) $$

where $P$ is peak velocity at any point on the curve, $V$ is asymptotic peak velocity, $A$ is saccade amplitude, and $C$ is a constant.\textsuperscript{175}

Saccades may be horizontal, vertical, oblique, or torsional. Saccadic velocity is influenced by the direction of the movement, and by the initial and final orbital positions. Centripetal (toward the center) and abducting saccades tend to be faster than other saccades, but the differences are minimal.\textsuperscript{176} Saccades are about 10% slower when made in complete darkness.\textsuperscript{177,178}

For a typical normal saccade, the eye accelerates rapidly, reaching its peak velocity between 1/3 and 1/2 of the way through the movement.\textsuperscript{179} The eye then gently decelerates but usually stops relatively abruptly. Occasionally, in normal persons, the eye drifts for a few hundred milliseconds after the initial portion of the horizontal saccade is finished. Such postsaccadic drifts are called glissades.\textsuperscript{180} They are considered to represent a mismatch between the sizes of the pulse and step innervations that produce saccades (see below). If the pulse portion is too large for a given step, glissadic overshoot occurs; if the pulse is small relative to the step, glissadic undershoot occurs.\textsuperscript{181} Glissades can be conjugate (correcting for undershoot of the target), disconjugate (compensating for divergence during the saccade), or purely monocular. Glissades occur more frequently in fatigued persons.\textsuperscript{172}

\subsection*{1.4.2 Neurophysiology of Saccadic Eye Movements}

The innervational changes during saccades consist of two components. A pulse
of innervation consists of a high frequency burst of phasic activity in agonist motoneurons. Phasic contraction of the agonist muscle overcomes viscous drag in the orbit, and is responsible for the rapid eye movement. Once the eye has been brought to a new position, agonist motoneurons assume a new, higher than resting level of tonic innervation, constituting saccadic step of innervation, which holds the eye in its new position against orbital elastic recoiling forces. The saccadic step, an eye position command, is created from the pulse (an eye velocity command) by a neural network that integrates, in the mathematical sense, conjugate eye-velocity commands into the appropriate position-coded information for the ocular motoneurons. For horizontal movements, this neural integrator is located in the medial vestibular nucleus and adjacent nucleus prepositus hypoglossi, and for vertical and torsional movements, it resides in the interstitial nucleus of Cajal and vestibular nucleus.

For each position of the eye, there is a specific step discharge rate of agonist motor units and a reciprocally lower step discharge rate of their antagonist motor units. Thus, the ocular motor control signal for saccadic eye movement is a pulse and a step of innervation. Both the pulse and the step must be of the correct amplitude and appropriately matched for the eyes to be moved rapidly from one position to another and held steady at the end of the movement. The pulse does not actually have an abrupt offset before the step change in activity of eye muscles. Instead, there is a gradual decline (called a slide) in muscle torque after the saccade lands the eye at the position specified by the step in the orbit. This slide may result from a gradual transition from the high frequency discharge of motoneurons during the pulse to a lower frequency discharge for the step. The innervation for a saccade then consists of a pulse-slide-step.
Two classes of neurons are critically important for the generation of saccades: burst neurons and omnipause neurons. Burst neurons are divided into excitatory and inhibitory types. Excitatory burst neurons are in turn divided into medium-lead burst neurons and long-lead burst neurons. Medium-lead burst neurons generate the immediate premotor command for the saccadic pulse. They reside in the pontine paramedian reticular formation (PPRF) for horizontal saccades, and in the rostral interstitial nucleus of the medial longitudinal fasciculus (riMLF) in the mesencephalon for vertical and torsional saccades. Medium-lead burst neurons discharge at a high frequency to motoneurons, 8 to 15 msec before and during saccades, but are silent during fixation, pursuit, vestibular and optokinetic eye movements. Long-lead burst neurons are located predominantly in the rostral PPRF and are thought to activate the medium-lead burst neurons. They discharge irregularly for up to 100 msec before and during saccades, and may encode saccade direction.

Omnipause (pause) neurons lie in the nucleus raphe interpositus in the pons. They discharge continuously except immediately prior to and during saccades, and are thought to tonically inhibit the medium-lead burst neurons during fixation and smooth eye movements. When a saccade is called for, the omnipause cells are inhibited, possibly by long-lead burst neurons, which leads to activation of the medium-lead burst neurons and generation of saccades. Inhibitory burst neurons are activated at the same time by the excitatory medium-lead burst neurons. Inhibitory burst neurons inhibit the motoneurons to antagonist muscles just before and during saccades.

1.4.3 Brainstem Pathways for the Generation of Saccades
For horizontal saccades, medium-lead burst neurons project directly to the ipsilateral abducens nucleus and internuclear neurons. The latter project to the contralateral medial rectus subnucleus via the medial longitudinal fasciculus (MLF). Medium-lead burst neurons also project to ipsilateral inhibitory neurons, which send their axons across the midline to the contralateral abducens nucleus to inhibit contralateral abducens motoneurons and internuclear neurons during ipsilateral saccades.\textsuperscript{196, 199} In addition, medium-lead burst neurons also project to the medial vestibular nucleus and adjacent nucleus prepositus hypoglossi \textsuperscript{184-196}, where the step of tonic innervation is generated.

For vertical and torsional saccades, medium-lead burst neurons project directly to motoneurons in the oculomotor and trochlear nuclei. Inhibitory burst neurons probably reside within the riMLF.\textsuperscript{200, 201} Medium-lead burst neurons also send axons collaterals to the interstitial nucleus of Cajal, which is the eye velocity-to-position neural integrator that generates the step of innervation for vertical and torsional saccades.

1.4.4 Neurotransmitters for the Saccadic Premotor neurons

Omnipause neurons utilize glycine to inhibit excitatory burst neurons. They are inhibited by serotonin and probably by $\gamma$-aminobutyric acid (GABA) and glycine.\textsuperscript{202} Glycine is also the transmitter of inhibitory burst neurons. The transmitters of horizontal excitatory medium-lead and long-lead burst neurons have not been determined; however, glutamate and aspartate are the probable synaptic transmitters of vertical excitatory medium-lead burst neurons.
1.4.5 Cerebral Control of Saccadic Eye Movements

The cerebral hemispheres initiate saccades by sending trigger signals to the omnipause neurons in the pons. They also send signals of desired saccade amplitude and direction. The parietal eye field (PEF) and the frontal eye field (FEF) in the cerebral cortex participate in the control of saccades. The PEF initiates visually-guided saccades and projects to the ipsilateral superior colliculus and to the FEF. The FEF initiates volitional and visually-guided saccades, and projects to the superior colliculus (SC) via the PEF and directly to brainstem presaccadic structures. The supplementary eye field receives input from the PEF and projects to the FEF, SC and brainstem presaccadic structures. It may play a role in directing voluntary saccades to specific positions in the orbit (craniotopic coordinates).

The FEF also project to the caudate nucleus, which send inhibitory projections to the nucleus substantia nigra pars reticulata (SNpr). The SNpr in turn send inhibitory projections to the superior colliculus. The SNpr tonically discharges during fixation, and when it pauses, it disinhibits the SC which discharges before and during voluntary and visually evoked saccades. Thus the FEF has a powerful two-pronged effects on the SC, one direct and the other through the caudate and Snpr.

Together, the FEF and SC form an obligatory route for saccadic commands originating in the cerebrum, because ablation of both the FEF and SC, but not either alone, causes severe deficits in the generation of saccades. The FEF and SC project to the contralateral PPRF and riMLF. Each FEF and SC generates contralateral horizontal saccades, whereas vertical and torsional saccades require simultaneous activity of both frontal eye fields or both superior colliculi.
1.4.6 Cerebellar Control of Saccadic Eye Movements

The cerebellum regulates the size of saccades, and participates in the repair of saccade inaccuracy. The vermis, paravermis, the fastigial nucleus, and the flocculus are particularly important for the control of saccadic eye movement.\textsuperscript{217} Lobules VI\textsubscript{c} and VII of the cerebellar vermis receive mossy fiber from the PPRF, NPH, vestibular nuclei, nucleus reticularis tegmenti pontis (NRTP) and pontine nuclei.\textsuperscript{218, 219} They, like other cortical regions, also receive climbing fibers from the inferior olivary nucleus.\textsuperscript{218} Purkinje cells in the dorsal vermis discharge before saccades.\textsuperscript{220, 221} This "oculomotor vermis" in turn projects to an ellipsoidal region in the caudal fastigial nucleus, the fastigial oculomotor region (FOR)\textsuperscript{218}, which is important for the control of saccade accuracy and consistency.\textsuperscript{217, 222, 223} Because the vermis does not project directly outside the cerebellum, the signals present in the FOR determine the effect of cerebellar vermis on saccades. In addition to receiving inhibitory inputs from Purkinje cells of the dorsal vermis, the FOR receives projections from the frontal eye fields and superior colliculus, via the NRTP.\textsuperscript{224} Projections of the fastigial nucleus decussate within the cerebellum and enter the uncinate fasciculus, which courses along the dorsolateral border of the brachium conjunctivum, to reach the brainstem. Within the brainstem, FOR projections terminate onto burst neurons, omnipause neurons, and the rostral pole of the superior colliculus.\textsuperscript{224, 225}

The effects of cerebellar lesions on the adaptability of the central nervous system (CNS) to saccade accuracy have been investigated by surgical weakening of the horizontal rectus muscles of one eye in monkeys.\textsuperscript{217} With the unaffected eye patched, the initial hypometric saccades made by the viewing affected eye gradually became
normometric after three days, indicating that the CNS can compensate for peripheral weakness. Total cerebellectomies, however, created an enduring saccadic hypermetria and postsaccadic drift in the unaffected eye, and abolished all adaptive capability for both the pulse and pulse-step mismatch.217 Lesions of the vermis, paravermis and the fastigial nuclei created an enduring saccadic hypermetria without postsaccadic drift in the unaffected eye, indicating that these structures are responsible for the adaptive control of the pulse of innervation.217,226 On the other hand, monkeys with floccular lesions are able to generate saccades with normal velocities and accuracy, but they have an enduring postsaccadic drift, indicating that the flocculus and paraflocculus are responsible for matching the pulse and step so that the eyes do not drift after saccades.157,227

1.4.7 Proprioception and Saccadic Control

The role of EOM proprioception in the control of saccadic eye movements is uncertain. After bilateral sectioning of the ophthalmic branch of the trigeminal nerve in monkeys, saccades made to remembered visual targets were accurate, even after the eyes were driven to a new position by electrical stimulation of the superior colliculus just before the saccade.228 Gauthier and Vercher 44 measured the amplitude of human horizontal saccades in the viewing eye, while the non-viewing eye was either allowed to move freely or held immobile in an eccentric position. No differences were found in saccade amplitudes in the viewing eye, whether the non-viewing eye was free or immobile. Together, these findings 44,228 suggest that EOM afferents may not participate in the control of saccades.

There is, however, experimental evidence indicating that EOM proprioception may influence saccadic control.37,44,46,48 Using a method similar to Gauthier and Vercher 44 but
with movement of the non-viewing eye impeded near the straight ahead position in humans, Knox et al \(^{229}\) found a consistent decrease in saccade amplitudes in the viewing eye, which they interpreted as an attempt by the saccadic system to maintain conjugacy. Proprioceptive deafferentation results in worsening of ocular alignment and saccade conjugacy in monkeys. \(^{37}\)

Lewis et al \(^{48}\) examined the contributions of proprioceptive and retinal afferents to the suppression of postsaccadic drifts induced by unilateral weakening of a vertical eye muscle. They \(^{48}\) found that when binocular fusion is not possible, retinal slip information from both eyes is an adequate stimulus to promote disconjugate adaptation of postsaccadic drifts. When fusion is made possible by wearing disparity-reducing prism, either retinal disparity or retinal slip could be the dominant visual error signal used to modify postsaccadic drifts.\(^{48}\) Proprioceptive deafferentation of the paretic eye alters the amplitude, velocity and time constant of post-saccadic drifts in that eye \(^{48}\); however, it does not influence visually mediated adaptation of postsaccadic drifts.\(^{48}\)

### 1.4.8 Dynamics of Saccades in Paralytic Strabismus

Information about saccadic abnormalities in paralytic strabismus is sparse. Using electroculography and a limbal sensing device, Metz et al \(^{230}\) reported on 2 of 12 patients with lateral rectus palsy. They \(^{230}\) found that in a patient with unilateral left lateral rectus palsy, the paretic left eye made "slow and drifting" leftward saccades but "rapid and sharp" rightward saccades, whereas the normal eye made rapid saccades in both directions. Similar observations were reported in patients with medial rectus palsy and unilateral sixth nerve palsy.\(^{94,176,231-233}\) However, they were either single case reports or small case series
and the effects of palsy were not systematically investigated or compared with normal controls. In Section II, we investigate the dynamics of saccades in three dimensions in patients with sixth nerve palsy, and examine how horizontal saccades made by the paretic and non-paretic eyes vary with the eye used for fixation, the direction of movement, eye position in the orbit, and severity of palsy.

1.5 MONOCULAR ADAPTATION IN THE VESTIBULO-OCULAR REFLEX AND THE SACCADIC SYSTEM

Hering suggested that the brain circuitry controlling gaze consists of two systems, one for conjugate movements, the other for vergence. Conjugate control operates in the vestibulo-ocular, saccade, smooth pursuit and optokinetic systems. Premotor neurons encode common signals to both abducens motoneurons and internuclear neurons in the abducens nucleus. The abducens motoneurons innervate the ipsilateral lateral rectus, while the internuclear neurons innervate the medial rectus motoneurons in the contralateral oculomotor nucleus. Electrical stimulation of the caudal PPRF, where the excitatory burst neurons reside, generates ipsiversive saccades. Unilateral lesions of the PPRF create ipsiversive horizontal saccadic palsy. For upward and torsional eye movements, common premotor signals are sent to the oculomotor subnuclei that drive the contralateral superior rectus and ipsilateral inferior oblique muscles (see Figure 1-2A). For downward and torsional movements, common signals are relayed to the trochlear nucleus, which innervates the contralateral superior oblique muscle, and to the oculomotor subnucleus that innervates the ipsilateral inferior rectus muscle (see Figure 1-2C).

Because neuronal connectivity is suitable for conjugate motion, it might be
presumed that only conjugate plasticity is possible. This is supported by observations in monkeys \textsuperscript{217} and humans \textsuperscript{176,240} with ocular motor nerve palsy. When the non-paretic eye was patched, saccade amplitude of the paretic eye in the paretic hemi-range of motion became more normal \textsuperscript{176,240}; however, conjugate saccades in the non-paretic patched eye became excessively large.\textsuperscript{176,240}

\subsection{1.5.1 Evidence of Monocular Adaptation}

Experiments on monkeys and humans have shown that the ocular motor systems are capable of selective, monocular adaptation. \textsuperscript{170,171,241,242} Disconjugate ocular motor adaptation has been demonstrated in normal humans \textsuperscript{243,244} and monkeys \textsuperscript{245} in response to image disparity induced by anisometropic spectacles \textsuperscript{243} or prisms.\textsuperscript{245} Disconjugate saccades and pursuit are generated to compensate for disparate retinal errors produced by the optical displacement of images.\textsuperscript{243,244}

By patching one eye of five normal adult monkeys for one week, Virre et al \textsuperscript{241} demonstrated small and consistent changes in saccades and VOR of the occluded eye only. A change, usually a decrease, in the saccadic step magnitude and VOR gain was observed in the occluded eye. When the patch was removed, normal function was restored within one day in the previously occluded eye without any change in the non-occluded eye. In healthy humans, after patching one eye for three days, saccadic undershoot, postsaccadic drift, as well as up-and down-shoot in adduction were observed only in the occluded eye.\textsuperscript{242} These changes disappeared rapidly after binocular vision was restored.\textsuperscript{242}

In another experiment \textsuperscript{170}, tenectomy of the medial and lateral recti of one eye was performed on six monkeys. After the tenectomy, when the normal eye was patched, a
conjugate increase in saccadic magnitude and VOR gain was observed in both eyes. In accord with Hering's law, saccadic magnitude and VOR gain of the seeing tenectomized eye returned to pre-tenectomy values, while those of the normal occluded eye became excessively large. However, when the patch was removed so that neither eye was patched, a selective decrease in saccadic magnitude and VOR gain to pre-tenectomy values was observed only in the normal eye, while those of the tenectomized eye remained at pre-tenectomy values. Subsequent re-patching of the tenectomized eye produced a selective return of deficits in that eye over a period of several days.

In another study, surgical weakening of one of the horizontal recti of one eye was performed by either recession or tenotomy on six monkeys.\textsuperscript{171} The affected eye was patched immediately after the surgery for one week. When the patch was removed, a selective increase in saccadic magnitude and VOR gain was observed in the affected eye, while those of the normal eye remained at control values. These observations suggest that both the saccadic and vestibulo-ocular systems are capable of selective adaptation of neural innervation to a single eye, in response to peripheral neuromuscular deficits.

1.5.2 Sites for Monocular Adaptation

One possible site where changes in neural drive to each eye could occur independently is at the level of motoneurons. Selective adaptation might be achieved by changing the sensitivity of each motoneurons pool to innervation from premotor neurons. The cerebellum, which mediates such adaptive changes, may have direct projections to ocular motoneurons.\textsuperscript{246} Using the Nauta method for tracing Wallerian degeneration, Carpenter and Strominger\textsuperscript{246} concluded that cerebello-oculomotor fibers from all part of
the dentate nucleus project to the inferior rectus subdivision of the contralateral oculomotor nucleus, whereas fibers from ventral portions of the dentate nucleus project to the superior rectus subdivision of the contralateral oculomotor nucleus. However, using the more modern retrograde tracer technique, afferents from the dentate nucleus to the oculomotor nucleus are not identified.

Supranuclear neural circuitry is not exclusively conjugate. For example, for saccades, different populations of burst neurons mediate a pulse of innervation to each eye. In monkeys, 79% of premotor excitatory burst neurons in the caudal pontine paramedian reticular formation that were thought to encode conjugate velocity commands for saccades, actually encode monocular commands for either the ipsilateral or contralateral eye. Similarly, different populations of vestibular neurons provide innervation to the horizontal muscles of each eye. In addition to a major excitatory horizontal VOR pathway which mediates conjugate eye movements via the contralateral abducens nucleus and internuclear neurons, a second direct excitatory horizontal VOR pathway exists. This second pathway originates from the ventral lateral vestibular nucleus, ascends through the ascending tract of Deiters to the ipsilateral medial rectus subdivision of the oculomotor nucleus. In addition, neurons in the feline medial vestibular nucleus (MVN) are activated antidromically only by local stimulation of the contralateral abducens nucleus. Another group of MVN neurons are activated only by stimulation of the ipsilateral medial rectus motoneurons pool, but not by stimulation of contralateral abducens nucleus.

1.5.3 Role of Cerebellum in Monocular Adaptation

The cerebellum plays important roles in adaptive control of saccades.
and the VOR, including disconjugate control. Experimental inactivation of the deep cerebellar nuclei (including the fastigial nucleus) causes disconjugate saccadic dysmetria, such that both saccade magnitude and peak velocity differ in the two eyes. Patients with cerebellar degeneration or dysgenesis also show disconjugate dysmetria during and immediately after horizontal or vertical saccades, although brainstem circuits are not spared in spinocerebellar degenerations or malformations. The flocculus regulates conjugate VOR responses; unilateral lesions of the rabbit flocculus cause different VOR gain changes in the two eyes.

1.5.4 Monocular Adaptation after Ocular Motor Nerve Palsy

Monocular adaptation in human after ocular motor nerve palsy has not been previously investigated. In Sections I and II, we investigate patients with sixth, fourth and third nerve palsy, and identify monocular adaptations of the VOR and saccades in three dimensions.

1.6 LISTING’S AND DONDERS’ LAWS

During fixation, saccades and smooth pursuit, the eye rotates freely in the horizontal and vertical dimensions, but torsion is constrained. This restriction on ocular torsion is described by Donders’ and Listing’s laws. Donders’ law states that horizontal and vertical positions of the eye determine the torsional angle. Donders’ law does not specify what torsional angle the eye assumes, but only that there is a unique torsional angle for each gaze direction. Listing’s law is a special case of Donders’ law which quantitatively specifies the torsional angle for each gaze direction. It states that, when the
head is fixed, there is an eye position called primary position, and that the eye assumes only those orientations that can be reached from primary position by a single rotation about an axis in a plane called Listing's plane \(^1\); this plane, furthermore, is orthogonal to the gaze line when the eye is in primary position.

Listing's law is illustrated in Figure 1-5. The eye at the center is in primary position and the plane of the paper is Listing's plane. All the eye orientations drawn with solid lines accord with Listing's law, because they can be reached from the primary position by rotating about axes (black lines) in Listing's plane. But the position drawn with dashed lines at the top center violates Listing's law, because the rotation to that orientation from primary position has its axis (white line) tilted out of Listing's plane.

Figure 1-5 also shows that Listing's law implies Donders' law: for any direction of gaze, there is only one torsional position assumed by the eye, and this does not depend on the path taken to that gaze direction. For example, the eye positions drawn with solid and dashed lines at top center both correspond to the same upward gaze direction, but the torsional position drawn in solid lines is the only eye position for that gaze direction that fits Listing's law.

1.6.1 Coordinate System for Listing's law

Listing's law can be expressed using different coordinate systems.\(^{254,257-261}\) The Helmholtz's coordinate is particularly useful in presenting binocular data.\(^{261}\) In this system, an eye position is decomposed into a series of three sub-rotations. Starting from primary position: first a torsional rotation through angle T about the line of sight, then a horizontal rotation through angle H about a head-fixed vertical axis, and finally a vertical rotation
through angle $V$ about the interaural axis. Expressed in Helmholtz coordinates, Listing's law says that:

$$ T = -HV/2 \quad (3) $$

where all angles are given in radians (not degrees). Positive directions for angles $T$, $H$ and $V$ are clockwise, right and up, respectively, all from the subject's point of view. Equation (3) is actually not precisely equivalent to Listing's law, but it is a very close approximation; within $30^\circ$ of primary position, the discrepancy is less than $0.1^\circ$.\textsuperscript{262}

The direction of torsion is defined from the subject's point of view, by convention. Rotation of the upper pole of the iris towards the subject's right shoulder was designated as clockwise (CW), whereas rotation of the upper pole of the iris towards the subject's left shoulder was designated as counter-clockwise (CCW).

As equation (3) makes clear, Listing's law requires that the Helmholtz-torsional angle of the eye vary as a function of horizontal and vertical eye position. Figure 1-6 depicts the torsional positions of the eye, represented by thin black lines with respect to the vertical meridian, in different combination of horizontal and vertical eye positions, as viewed by the examiner. If the eye is $30^\circ$ down and $30^\circ$ left (bottom right panel), then the eye (thin black line) rotates $7.9^\circ$ (0.14 rad) counterclockwise, with respect to the vertical meridian (dashed line). In other words, Listing's law specifies quantitatively the degree of ocular torsion for any given horizontal and vertical eye position. Any torsion that differs from that specified by equation (1) means that Listing's law is violated.

1.6.2 Functional Significance of Listings' Law

The functional significance of Listing's law is uncertain. Herring \textsuperscript{234} and
Helmholtz\textsuperscript{1} proposed that it optimizes certain aspects of image flow across the retina, thereby simplifying the neural processing of visual information. As optical flow depends on the eye's motion relative to space, both theories tacitly assume that the eyes rotate relative to space in the way dictated by Listing's law. But, in fact, it is eye rotation relative to \textit{head} that follows Listing's law, whereas, owing to head movement, eye rotation relative to \textit{space} does not\textsuperscript{263-265}. Thus, theories based on optical flow likely cannot explain Listing's law.

Fick and Wundt proposed that Listing's law enhances motor efficiency by minimizing the rotational eccentricity of the eye.\textsuperscript{1} Minimizing eccentricity may reduce the elastic recoiling force acting on the eye, and therefore reduce the work load on the eye muscles. Or, it may bring the eye the same advantage that staying near the center court brings a squash player, namely swift and flexible responses to incoming stimuli. By ensuring that all gaze shifts toward and away from primary position are made along the shortest path, Listing's law permits quick responses to unpredictable targets that may appear from any direction.

1.6.3 Implementation of Listing's Law: Neural and Mechanical

Listing's law holds during fixation, saccades and smooth pursuit, but fails during sleep\textsuperscript{266,267} and vestibulo-ocular reflex (VOR)\textsuperscript{268}. Its failure shows that the eye muscles are capable of violating Listing's law, so it is not the muscles but the neural commands driving fixation, saccades and pursuit that constrain the eye to obey the law.\textsuperscript{255,269} The muscles may, however, be arranged in a way that simplifies the brain's work in implementing Listing's law\textsuperscript{3,6,270-274}, as in the "active-pulley hypothesis"\textsuperscript{6}, where
contraction of the *global* layer of the rectus muscle rotates the globe, while contraction of
the *orbital* layer displaces the connective-tissue sleeves, or 'pulleys', which direct the paths
of the muscles. The implementation of Listing's law might be simplified by shifting the
position of the pulleys.\textsuperscript{6,272}

Brain circuits responsible for enforcing Listing's law have not been located. A major
neural pathway underlying saccadic eye movements involves the superior colliculus\textsuperscript{275-277},
which sends saccadic signals to the medium-lead burst neurons in the pontine paramedian
reticular formation (PPRF) and the rostral interstitial nucleus of the medial longitudinal
fasciculus (riMLF).\textsuperscript{278,279} These burst neurons, in turn, project to the extraocular
motoneurons, the final common pathway for all eye movements.\textsuperscript{278,279} Electrical stimulation
and three-dimensional recordings in alert monkeys have shown that the superior colliculus
generates saccades that fit Listing's law.\textsuperscript{280} Stimulation of the medium-lead burst neurons
in the caudal PPRF and riMLF evokes abnormal saccades that violate Listing's law.\textsuperscript{281}
These findings suggest that the circuitry implementing Listing's law is downstream from
the superior colliculus and upstream from the medium-lead burst neurons.

The caudal nucleus reticularis tegmenti pontis (cNRTP), which lies ventral to the
rostral PPRF, receives inputs from the superior colliculus and projects to the dorsal vermis
and caudal fastigial nucleus.\textsuperscript{224,282} Electrical stimulation of the cNRTP elicits ipsiversive
saccades with a small torsional displacement, which brings the eye out of Listing's plane,
and a torsional saccadic reset in the opposite direction which brings the eye back to
Listing's plane.\textsuperscript{283} Inactivation of the cNRTP results in an absence of torsional saccadic
reset, such that the eye remains out of Listing's plane.\textsuperscript{283} This indicates that the cNRTP
participates in stabilization of Listing's plane against torsional errors of the saccadic
system. Torsional pulsion of saccades (torsipulsion), consisting of torsional fast eye movements away from the side of lesion (from examiner's viewpoint) induced during saccades downward or away from the side of lesion, has been recorded in patients with lateral medullary infarction. Torsional blips, consisting of torsional fast eye movements followed by slow exponential drifts towards the initial torsional eye position during horizontal and vertical saccades, were reported in a patient with an infarct involving the dorsolateral medulla and the cerebellum. These findings indicate that neurons in the lateral medulla participate in torsional control that implements Listing's law.

The cerebellum may also implement three dimensional control of eye motions. In addition to receiving inhibitory inputs from Purkinje cells of the dorsal vermis, the fastigial nucleus of the cerebellum receives projections from the frontal eye fields and superior colliculus, via the NRTP. Projections from the caudal part of the fastigial nucleus ascend in the brainstem to innervate the medium-lead burst neurons, which generate horizontal, vertical and torsional saccades. The caudal part of the fastigial nucleus also projects to the dorsolateral pontine nuclei and participates in the control of smooth pursuit. The influence of NRTP on three dimensional control of eye movements may depend on its cerebellar projections. The torsional pulsion of saccades seen in lateral medullary syndrome may be caused by interruption of olivocerebellar climbing fibers, leading to increased activity of vermis Purkinje cells and inhibition of the underlying fastigial nucleus.

1.6.4 Listing's and Donders' laws in Paralytic Strabismus and in Skew Deviations
Listing's law has been studied extensively in monkeys\textsuperscript{267, 290-293} and normal humans\textsuperscript{254, 255, 258, 259}. Little is known as to whether Listing's and Donders laws are obeyed after ocular motor nerve palsy. Haustein\textsuperscript{294} described three patients before and after recession of one of the oblique muscles. Immediately after surgery, the operated eyes continue to obey Listing's law, with shifts of Listing's primary positions\textsuperscript{294}. Within a few weeks, Listing's primary positions of the operated eyes return to their original positions, while those of the non-paretic eyes remain normal throughout the entire period\textsuperscript{294}. Melis et al\textsuperscript{295} studied a patient who had congenital esotropia and two previous strabismic surgeries. They\textsuperscript{295} found that Listing's law was obeyed, but the orientation of the Listing's planes of the two eyes varied, depending on which eye was fixating.

Bergamin et al\textsuperscript{296} reported on a subject with an acquired unilateral fourth nerve palsy. They\textsuperscript{296} found that both eyes of this patient obeyed Listing's law, with Listing's planes rotated temporally in the paretic eye and nasally in the non-paretic eye. The orientation of Listing's plane was also studied in four other patients with unilateral fourth nerve palsy who underwent a contralateral inferior oblique recession\textsuperscript{296}. Prior to surgery, all four patients had a temporal rotation of Listing's plane in the paretic eye\textsuperscript{296}. After surgery, there was an increase in temporal rotation of Listing's plane in patients with congenital palsy, and a decrease in temporal rotation in patients with acquired palsy\textsuperscript{296}.

To date, no study has been performed to assess systematically whether Listing's and Donders laws are obeyed after ocular motor nerve palsy, or after brainstem or cerebellar lesions. Investigation of patients with ocular motor abnormalities and neural lesions might reveal important information on the mechanisms underlying Listing's law. In Section III, we investigate patients with unilateral sixth and fourth nerve palsy, as well as
brainstem and cerebellar lesions, to determine whether Listing's and Donders' laws are obeyed during fixation and saccades. Our results indicated adaptive neural mechanisms for Listing's law, and demonstrated the brain regions that form part of the neural pathway that implements Listing's law.

1.7 STRABISMUS TERMINOLOGY

The term *strabismus* is derived from the Greek word *strabismos* (to squint, to look obliquely). The term is used in many ways, and thus has different implications depending on its application. In this thesis, strabismus means ocular misalignment.

*Orthophoria* is the ideal condition of ocular balance; in reality, it is seldom encountered, as the majority of individuals have a small heterophoria (see below). By definition, orthophoria indicates that the oculomotor apparatus is in perfect equilibrium so that both eyes remain aligned in all positions of gaze and at all distances of fixation even when binocular fixation is disrupted, such as during occlusion of one eye.

The term *heterodeviation* refers to ocular alignment that differs from the ideal orthophoria. *Heterophoria* is a latent deviation that is controlled by binocular fixation so that under normal binocular vision the eyes remain aligned. *Heterotropia* is a deviation that is manifest during attempted fixation with both eyes.

There are a variety of heterophoric and heterotropic deviations. If the visual axes converge, the condition is called esophoria (for latent deviation) or esotropia (for manifest deviation). If the visual axes diverge, the condition is known as exophoria or exotropia. Hyperphoria or hypertropia occurs if one visual axis is higher than the other. A right hyperphoria or hypertropia is a deviation in which the visual axis of the right eye is higher
than that of the left.

Strabismus may be comitant or incomitant. In comitant strabismus, the magnitude of deviation is the same in all directions of gaze and does not depend on the eye used for fixation. In incomitant strabismus, the deviation varies in different direction of gaze. Most incomitant strabismus is paralytic or restrictive. The deviation is largest when the eyes turned in the direction of the paralytic or underacting muscle. The deviation in incomitant strabismus also varies with the eye used for fixation. When the normal eye is fixating, the amount of misalignment is called the primary deviation. When the paretic eye is fixating, the amount of misalignment is called the secondary deviation. The secondary deviation is larger than the primary deviation in incomitant strabismus.

Weakness of a muscle can be classified as a paralysis or paresis. If the action of a muscle is completely abolished, the condition is a paralysis or palsy; if the action of a muscle is impaired but not abolished, it is called a paresis. The terms palsy and paresis are often used interchangeably in clinical settings and in neurologic practice. In this thesis, the term palsy is used to denote a partial or a complete impairment of muscle action.
1.8 FIGURES AND TABLES
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Figure 1-1. The angular VOR pathway from horizontal semicircular canal (HC) to medial rectus (MR) subnucleus of the oculomotor nucleus (III) and to the abducens nucleus (VI). Excitatory second-order vestibular neurons project to the medial rectus subnuclei through the medial longitudinal fasciculus (MLF) and the ascending tract of Deiters (ATD). Axons of the ATD actually course through the abducens nucleus without synapse (not shown). The abducens nucleus contains motoneurons to the lateral rectus muscle (LR), and internuclear neurons that project through the opposite MLF to the medial rectus subnucleus of that side. LVN, lateral vestibular nucleus; MVN, medial vestibular nucleus. (Adapted from Sharpe JA, Johnston JL. The vestibulo-ocular reflex: Clinical, anatomic and physiologic correlates. In: Sharpe JA, Barber HO eds. Vestibulo-ocular Reflex and Vertigo. New York: Raven Press; 1993:15-39.)
Figure 1-2. Direct vertical vestibulo-ocular projections from the vertical semicircular canals. A. Excitatory afferents from the anterior semicircular canals (AC) synapse in the superior vestibular nucleus (SVN), and their signals are relayed via the brachium conjunctivum (BC) to the contralateral oculomotor subnuclei that drive the ipsilateral superior rectus (SR) and contralateral inferior oblique (IO) muscles. B. Inhibitory afferents from the anterior semicircular canals synapse in the SVN, and their signals are relayed via the medial longitudinal fasciculus (MLF) to the ipsilateral trochlear nucleus, which innervates the contralateral superior oblique (SO) muscle, and to the ipsilateral oculomotor subnucleus that innervates the ipsilateral inferior rectus (IR) muscle. C. Excitatory afferents from the posterior semicircular canals (PC) synapse in the medial vestibular nucleus (MVN), and their signals are relayed via the MLF to the contralateral trochlear nucleus, which innervates the ipsilateral superior oblique (SO) muscle, and to the contralateral oculomotor subnucleus that innervates the contralateral inferior rectus (IR) muscle. D. Inhibitory afferents from the posterior semicircular canals synapse in the SVN, and their signals are relayed via the MLF to the ipsilateral oculomotor subnuclei that drive the ipsilateral inferior oblique (IO) and contralateral superior rectus (SR) muscles. (Adapted from Ghelarducci B, Highstein SM, Ito M. Origin of the preoculomotor projections through the brachium conjunctivum and their functional roles in the vestibulo-ocular reflex. In: Baker R, Berthoz A eds. Control of Gaze by Brainstem Neurons. Amsterdam: Elsevier/North-Holland; 1977:167-175.)
Figure 1-3. Diagram of connections from the utricle to extraocular muscles in the cat. Connections to horizontal recti muscles (A) and to oblique muscles (B). Solid lines indicate short-latency (mono- or di-synaptic) circuits. Dotted lines indicate long-latency (polysynaptic) circuits. Open circles are excitatory projections. Filled circles are inhibitory projections. LR, lateral rectus; MR, medial rectus; SO, superior oblique; IO, inferior oblique; III, oculomotor nucleus; IV, trochlear nucleus; IV, abducens nucleus; MLF, medial longitudinal fasciculus; VN, vestibular nucleus. (Adapted from Uchino Y, Sasaki M, Sato H, Imagawa M, Suwa H, Isu N. Utriculoocular reflex arc of the cat. *Journal of Neurophysiology* 1996; 76:1896-1903.)
Mean peak velocity
Velocity range

Peak Velocity (deg/sec)

Saccade amplitude (deg)
Figure 1-5. The nine orientations drawn in solid lines accord with Listing's law, because they are attainable by rotating from primary position (center) about axes lying in Listing's plane (the plane of the paper). The position drawn in dashed lines at top center does not fit Listing's law because the rotation to this position from primary position occurs about an axis that is tilted out of primary position. (Adapted from Tweed D, Vilis T. Geometric relations of eye position and velocity vectors during saccades. Vision Research 1990; 30:111-127.)
Figure 1-6. Torsional positions of the eye, as represented by thin black lines with respect to the vertical meridian, in different combination of horizontal and vertical eye positions, as viewed by the examiner. If the eye is 30 deg down and 30 deg left (bottom right panel), then the eye (thin black line) rotates 7.9 deg (0.14 rad) counterclockwise, with respect to the vertical meridian (dashed line). CW, clockwise from the subject's reference; CCW, counterclockwise from the subject's reference. (Adapted from Somani RAB, DeSouza JFX, Tweed D, Vilis T. Visual testing of Listing's law during vergence. Vision Research 1998; 38:911-923)
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SECTION I

THE VESTIBULO-OCULAR REFLEX IN THREE DIMENSIONS
CHAPTER 2

ADAPTATIONS AND DEFICITS IN THE VESTIBULO-OCULAR REFLEX

AFTER SIXTH NERVE PALSY
2.1 SUMMARY

**Purpose:** The effects of paralytic strabismus on the vestibulo-ocular reflex (VOR) have not been systematically investigated in humans. The purpose of this study is to analyze the VOR in patients with unilateral peripheral sixth nerve palsy.

**Methods:** Twenty-one patients with unilateral peripheral sixth nerve palsy (6 severe, 7 moderate, 8 mild) and 15 normal subjects were studied. Subjects made sinusoidal ± 10° head on body rotations in yaw and pitch at approximately 0.5 and 2 Hz, and in roll at approximately 0.5, 1 and 2 Hz. Eye movement recordings were performed using magnetic scleral search coils in each eye in darkness and during monocular viewing in light. Static torsional VOR gains, defined as change in torsional eye position divided by change in head position during maintained head roll, were also measured.

**Results:** In all patients, horizontal VOR gains in darkness were decreased in the paretic eye in both abduction and adduction, but remained normal in the non-paretic eye in both directions. In light, horizontal visually enhanced VOR (VVOR) gains were normal in both eyes in moderate and mild palsy. In severe palsy, horizontal VVOR gains remained low in the paretic eye during viewing with either eye, while those in the non-paretic eye were higher than normal when the paretic eye viewed. Vertical VOR and VVOR were normal, but dynamic and static torsional VOR and VVOR gains were reduced in both eyes in all patients.

**Conclusions:** In darkness, horizontal VOR gains are reduced during abduction of the paretic eye in all patients, as anticipated in sixth nerve palsy. Gains are also reduced during adduction of the paretic eye, suggesting that innervation to the medial rectus has changed. After severe palsy, vision does not increase abducting or adducting horizontal
VVOR gains to normal in the paretic eye, but causes secondary increase in VVOR gains to values above unity in the non-paretic eye, when the paretic eye fixates. In mild and moderate palsy, vision enhances the VOR in the paretic eye but causes no change in the non-paretic eye, suggesting a monocular readjustment of innervation selectively to the paretic eye. Vertical VOR and VVOR gains are normal, indicating that the lateral rectus does not have significant vertical actions through the excursions that we tested (±10°).

Reduced torsional VOR gains in the paretic eye can be explained by the esotropia in sixth nerve palsy. Torsional VOR gain normally varies with vergence. We attribute the reduced torsional gains in the paretic eye to the mechanism that normally lowers it during convergence. The low torsional gains in the non-paretic eye may be an adaptation to reduce torsional disparity between the two eyes.
2.2 INTRODUCTION

Sixth nerve palsy is the commonest ocular motor nerve palsy. Clinical testing of strabismus emphasizes static deviations; little information is available about the effects of paralytic strabismus on eye movement dynamics such as during the vestibulo-ocular reflex (VOR). Adaptive changes in the VOR occur in response to different visual stimuli. Disconjugate VOR adaptation has been elicited in monkeys in response to anisometropic prisms and experimental weakening of the horizontal recti muscles. Here, we investigated patients with unilateral peripheral sixth nerve palsy to assess their VOR and its adaptation, if any, to abduction palsy. As anticipated, horizontal VOR was weak in the paretic eye in the direction of palsy. Reduced horizontal VOR gains of the paretic eye in the direction opposite to the palsy, and reduced gains in the torsional dimension in both eyes, were also identified. These findings provide evidence of monocular, neural adaptations in humans with peripheral neuromuscular deficits.

2.3 METHODS

Clinical assessment and imaging studies

Twenty-one patients with unilateral peripheral sixth nerve palsy were recruited from the Neuro-ophthalmology Unit at the University Health Network. A complete history was taken, and detailed ophthalmic and neurologic examinations were performed, recording the duration and age of onset of diplopia, the presence or absence of risk factors for ischemia (diabetes mellitus and hypertension), and associated neurologic symptoms and signs. The magnitude of strabismus was measured objectively using the prism and cover test, and subjectively using the Maddox rod and prism test (see Chapter 9 for details).
When indicated, appropriate tests were performed to rule out myasthenia gravis, thyroid ophthalmopathy, other orbital diseases, or intracranial lesions.

Ranges ofduction was estimated independently by two examiners (AW and JAS) who graded the abduction defect as the estimated percentage of the normal abduction in the other eye. Based on the abduction defect, patients were classified into three groups: mild (81-95% of normal range of abduction), moderate (51-80%), and severe (≤50%).

Serial axial and sagittal T1- and T2-weighted magnetic resonance (MR) images with gadolinium enhancement were obtained (slice thickness = 5 mm) for all patients under 50 years of age and those with other neurologic signs. In this investigation, computerized tomography (CT) images of the head with contrast were obtained in all patients with ischemic risk factors and for patients over 50 years of age, although CT imaging is not our standard practice for such patients. If CT was normal, patients were followed at about 3 months. Those without improvement of their sixth nerve palsy at 3 months and those with an abnormal CT scan were further investigated with MR imaging.

Eye movement recordings

Experimental protocol. With one eye occluded, subjects viewed a red laser spot of 0.25° in diameter, rear-projected onto a uniformly gray vertical flat screen 1 m away from the nasion. Subjects made active sinusoidal ± 10° head on body rotations in yaw to elicit the horizontal VOR, and in pitch to elicit the vertical VOR, at approximately 0.5 and 2 Hz. Torsional VOR was elicited by head rotation in roll at approximately 0.5, 1 and 2 Hz. Head movements were paced by a periodic tone. The maintenance of desired amplitude and frequency of head movements was encouraged by placement of the examiner’s hands
on each parietal area of the subject's skull. The procedure was performed in light with one eye viewing to elicit visually-enhanced VOR (VVOR), and repeated with the other eye fixating and the fellow eye occluded. The VOR was then recorded in complete darkness while subjects were instructed to fixate on an imaginary earth-fixed target.

To measure the static torsional VOR, patients fixated on the center target with one eye occluded as we measured their ocular responses to static head rolls of about 30° toward each shoulder, as measured with a search coil. The procedure was then repeated with the other eye fixating and the fellow eye occluded, and also in total darkness.

**Recordings of eye movement and calibration.** Positions of each eye were simultaneously measured by a 3-dimensional magnetic search coil technique, using a 6 ft (183 cm) diameter coil field arranged in a cube (CNC Engineering, Seattle, Washington). In each eye, the patient wore a dual-lead scleral coil annulus designed to detect horizontal, vertical, and torsional gaze positions (Skalar Instrumentation, Delft, Netherlands). Phase detectors employing amplitude modulation as described by Robinson provided signals of torsional gaze position within the linear range. Head position was recorded by another coil taped to the subject's forehead. Each subject's head was centered in the field coils. Horizontal and vertical eye movements were calibrated with saccades to steps of the laser target. Head and torsional eye movements were calibrated by attaching the scleral coil to a rotating protractor. Torsional precision was about ± 0.2°. There was minimal crosstalk; large horizontal and vertical movements produced deflections in the torsional channel of less than 4% of the amplitude of the horizontal and vertical movement. Any coil slippage was assessed by monitoring offsets in torsional eye position signal during testing. Consistency of calibrated positions after each eye movement
provided evidence that the coil did not slip on the eye. Eye position data were filtered with a bandwidth of 0 to 90 Hz and digitized at 200 Hz. They were recorded on disc for off-line analysis. Analog recordings were also displayed in real time by a rectilinear thermal array recorder (Model TA 2000, Gould Inc., Ohio).

**Data analyses.** In one dimension, the input (head velocity) and output (eye velocity) of the VOR are regarded as scalar quantities (i.e. real number), and the reflex is characterized by its gain, which is the ratio of eye velocity to head velocity. In most natural head rotation, however, the input and output of the VOR are not scalars but three-component vectors (the angular velocity vectors of the head and eye), having not only magnitudes but also directions. Thus, a more complete characterization of the VOR requires a description, not only of the relative sizes of eye and head velocities, but also of their relative directions; that is, the axes about which the eye and the head rotates.

The VOR, however, can be treated as one dimensional if head rotation occurs around only one axis. For example, during pure horizontal head rotation (that is, around the earth-vertical axis), the vertical and torsional components of the three-component rotation vector become zero. In this situation, the velocity of rotation can be derived by differentiation of position data. In this study, whereas horizontal, vertical and torsional *head* positions were measured simultaneously, *gaze* position data was measured in one dimension. That is, horizontal *gaze* positions were recorded during horizontal head motion, vertical *gaze* positions during vertical head motion and torsional *gaze* positions during head roll. Pure head rotation around one axis was approximated by analyzing only data where the other two axes showed less than 1 deg variation from baseline (Figure 2-1A).
Eye position was derived by subtracting head position from gaze position signals. Fast phases of vestibular nystagmus were identified by a computer program using velocity and acceleration criteria. Results of fast-phase identification were edited on a video monitor, allowing the operator to verify cursor placement for fast-phase removal. Eye positions between 80 msec before and after the identified fast-phases were removed and the gaps were replaced with quadratic fits. Their average slopes were used to calculate the contribution of the ongoing slow phase during the fast phase. The offset due to the fast phase was then removed and the ongoing slow phase was interpolated to yield a cumulative trace of eye position.

Using position data, each cycle of rotation was identified by marking adjacent peaks with opposite direction, and the frequency was computed. Using a least square sinusoidal fit, eye and head positions were fitted with one cycle, and the phase and amplitude were computed. The ratio of the amplitude of the eye and the amplitude of the head was the gain, and the difference between the phase of the eye and the phase of the head was the phase shift.

To calculate the gain in each direction, eye and head position data from each half cycle was used and reflected to form a full cycle. Each cycle was then fitted using a least square sinusoidal fit, and the gain was computed for each direction. In addition, we plotted head velocity against eye velocity, and performed a linear regression for each direction. The slopes of the fitted lines were the gains, and the results were comparable to those computed by the least square sinusoidal fit technique (Figure 2-1B).
To account for the prismatic effect or rotational magnification induced by spectacle adaptation\textsuperscript{,13}, horizontal and vertical VOR gains were adjusted in subjects who habitually wore corrective spectacles by using the formula:

$$M_{\text{pred}} = \frac{40}{(40 - D)}$$  \hspace{1cm} (1)

where $D$ is the lens power in diopters and $M_{\text{pred}}$ is the predicted magnification.\textsuperscript{,13} For example, a hyperope who habitually wear a $+10$ D spherical lenses has an $M_{\text{pred}} = \frac{40}{(40 - 10)} = 1.3$. This means that while wearing $+10$ D, a VOR gain of 1.3, instead of 1.0, is required to prevent the visual scene from moving on the retina during head rotations.

For the measurement of static torsional VOR, head and gaze position signals were sampled for 6 seconds in each of 20 positions of 30° lateral tilt. The position of the eye in the head was derived from the difference between head and gaze position signals. Head and eye positions were computed off-line over each 6-seconds period after the eye had come to a torsional resting position (defined as having angular velocity $\leq 10$ deg/sec). Responses containing blinks or rapid drifts were not analyzed. Change of torsional eye position was plotted as a function of static change of head position after roll, and a linear regression was performed. Static torsional VOR gain, defined as change in torsional eye position divided by change in head position in static roll, was calculated from the slope of the regression line.

Oculography was performed at one point in each patient's course (Table 2-1). Thus, changes from normal, rather than serial intra-subject changes, were available for analyses. Statistical analyses of horizontal, vertical and torsional VOR and VVOR gains and phase were performed using Student's t-tests, two-tailed, unequal variance. Values were defined as significant when $p < 0.05$. 

The research protocol was approved by the University Health Network Ethics Committee and followed the tenets of the Declaration of Helsinki. Informed consent was obtained from all subjects.

2.4 RESULTS

General characteristics of patients

The characteristics of the 21 patients are shown in Table 2-1. The mean age was 59 ± 17 years (median age, 64 years; range, 19 - 77 years). There were 12 men. The duration of symptoms ranged from two weeks to 96 months, with a mean duration of 16 months. Mean follow-up duration was 16 months (range, 9 - 26 months). Six patients had severe sixth nerve palsy, seven had moderate and eight had mild palsy. Nineteen patients had idiopathic, presumed ischemic, peripheral lesions and two had cavernous sinus lesions on MR imaging. Of the 19 patients with idiopathic peripheral palsy, 13 had normal MR imaging and 6 had normal CT scanning of the brain (Table 2-1). Five out of the six patients with normal CT scan had ischemic factors, such as hypertension and diabetes, and had a complete resolution of their palsy within four to six months. All patients had an incomitant esodeviation, which increased in the field of action of the paretic muscle.

Fifteen normal subjects served as controls (mean age, 52 ± 15 years; median age, 58 years; age range, 19 to 69 years; 8 women).

Horizontal VOR gain and phase

Severe sixth nerve palsy (n = 6). In darkness, horizontal VOR gains of the paretic eye were reduced symmetrically during both abduction and adduction in each (Figure 2-1)
of the 6 patients ($p < 0.01$), whereas gains of the non-paretic eye remained normal in both directions (Figure 2-2A, top graph and Table 2-2). During paretic eye viewing (Figure 2-2A, middle graph), horizontal VVOR gains of the paretic eye were low in both directions ($p < 0.01$), while VVOR gains of the non-paretic occluded eye were higher than normal controls ($p < 0.01$) (Table 2-2). During non-paretic eye viewing (Figure 2-2A, bottom graph), horizontal VVOR gains of the occluded paretic eye were reduced ($p < 0.01$), while those of the viewing non-paretic eye remained normal (Table 2-2). In light and in darkness, the mean phase differences between the eye and head positions approximated $180^\circ$, designated as zero phase shift (Tables 2-3 and 2-4).

**Moderate (n = 7) and mild (n = 8) palsy.** In darkness (Figure 2-2B and 2-2C, top graphs), horizontal VOR gains of the paretic eye during abduction and adduction were lower than normal controls ($p < 0.05$), while gains of the non-paretic eye were within normal in both directions (Table 2-2). During viewing with either eye (Figure 2-2B and 2-2C, middle and bottom graphs), horizontal VVOR gains were normal for both the paretic and non-paretic eyes in both directions (Table 2-2). Neither eye showed any significant phase shift from zero in light or in darkness (Tables 2-3 and 2-4).

**Vertical and torsional VOR gain and phase**

In all three groups of patients, vertical VOR and VVOR gains were normal in both eyes (Figure 2-3 and Table 2-5). In contrast, torsional VOR and VVOR gains were significantly reduced in both the paretic and non-paretic eyes when compared with normal controls ($p < 0.05$) (Figure 2-4 and Table 2-6). Neither eye showed any significant phase shift from zero during vertical or torsional rotation (Tables 2-3 and 2-4).
**Static torsional VOR gain**

Static torsional VOR and VVOR gains of each eye were conjugate between the two eyes in all patients, and did not differ during right eye or left eye viewing, irrespective of the severity of palsy. Static torsional VOR gains are, therefore, reported as the pooled mean of both eyes under both viewing conditions in light, and in darkness. Mean gains in patients were $0.14 \pm 0.08$ in light and $0.13 \pm 0.09$ in dark, compared with $0.21 \pm 0.10$ in light and $0.20 \pm 0.11$ in dark in normal subjects ($p < 0.01$). Nineteen (90%) of the 21 patients had significantly reduced gains in light and in dark (Z-tests, $p < 0.05$). The other two patients (one with mild and the other with moderate palsy) had lower than normal group mean gains, but they did not reach statistical significance.

**2.5 DISCUSSION**

In sixth nerve palsy, horizontal VOR gains in darkness were decreased in the paretic eye in both abduction and adduction, while those in the non-paretic eye remained normal in both directions. In light, horizontal VVOR gains became normal in both eyes in moderate and mild palsy. In severe palsy, horizontal VVOR gains remained low in the paretic eye during viewing with either eye, while VVOR gains rose to values above unity in the non-paretic eye during paretic eye viewing. Vertical VOR and VVOR were normal; however, dynamic and static torsional VOR and VVOR gains were reduced in both eyes.

Changes in the VOR in our patients, who were tested at one point in their courses, are expressed as changes from normal, rather than serial intra-subject changes. Recovery toward normal values was not determined. Abnormalities are interpreted as deficits or adaptation to those deficits.
**VOR gains during active head rotation in normal subjects**

During passive whole-body rotation, horizontal VOR gains are less than unity, with typical values ranging from 0.7 at 0.5 Hz to 0.95 at 1 Hz.\(^{14,15}\) In agreement with previous studies\(^{16-19}\), higher VOR gains were observed during active head rotation. Horizontal VOR gains during active head rotation in darkness were close to unity, while vertical VOR gains in darkness were about 0.9 in our normal subjects.

Higher VOR gains during active head motion could be explained by several influences. First, the cervico-ocular reflex might contribute. Vestibular and neck velocity signals are summed on neurons in the vestibular nuclei.\(^{20,21}\) The response of ocular motor nerve fibers to vestibular stimulation is modulated by stimulation of neck proprioceptors.\(^{22}\) However, the contribution of the cervico-ocular reflex in normal humans is negligible.\(^{23,24}\) Second, during voluntary head motion, the rotational axis of the head is displaced backward to the vertebral column, as opposed to a more head centered axis during passive whole body rotation.\(^{25}\) VOR gain increases with larger radii of rotation, since the angular VOR then receives an increasing contribution from the translational VOR.\(^{26}\) Backward displacement of the rotational axis may contribute to the higher VOR gain recorded during active head rotation. Third, modulation by pre-programmed eye movements may also account for higher VOR gain during active head motion. When labyrinthine function is lost, gaze commands become important in generating compensating, stabilizing eye movements.\(^{27}\) An efference copy of head motor commands during active head rotation could contribute to the higher gains of compensatory smooth eye movements.
**Horizontal VOR in unilateral sixth nerve palsy**

**Horizontal VOR in darkness.** During rotation in darkness, horizontal VOR gains were reduced during **abduction** of the paretic eye in all patients, as anticipated in abduction palsy. VOR gains during **adduction** of the paretic eye were also reduced. In contrast, in the non-paretic eye, VOR gains were normal during both abduction and adduction (see Figure 2-2). Apparently the innervation to the medial rectus of the paretic eye is reduced without changing the innervation to the horizontal recti muscles of the non-paretic eye.

This adjustment is likely a functional adaptation to unilateral sixth nerve palsy. Without it, the VOR would be asymmetric in the paretic eye, weak in abduction but normal in adduction. The asymmetry would drive the paretic eye farther and farther into adduction with each cycle of head rotation, soon ‘pinning’ it at its nasal limits, and aggravating the patient’s diplopia. There are several strategies that might rectify this problem. The brain could increase its innervation to the paretic lateral rectus to increase VOR gain during abduction, but this strategy is limited by the palsy itself. Or, the brain might generate abducting saccades in the paretic eye to correct for low VOR gains during abduction. However, abduction paresis would limit them. Moreover, if common premotor signals are sent to both the abducens motoneurons and internuclear neurons in the abducens nucleus (see below), the result might be unwanted adducting saccades in the non-paretic eye, taking it off its target. A better choice might be to reduce the innervation just to the medial rectus of the paretic eye, decreasing its adduction gain to make the VOR symmetrical in that eye, while leaving the VOR in the non-paretic eye intact. This is apparently the strategy that the brain uses to adapt to unilateral abduction palsy.
Orbital mechanics and VOR adaptation. Changes in normal orbital plant mechanics might contribute to the decreased VOR gains during adduction in the paretic eye. The relative contribution of agonist contraction and antagonist relaxation varies with orbital position \(^{28}\), and it may be altered when one muscle of an agonist-antagonist pair is palsied. In paralytic strabismus, "contracture" (shortening and increased stiffness) occurs in the non-paretic antagonist muscle \(^{29-32}\), while the paretic muscle lengthens in response to a change in orbital position of the globe. Anatomical and histological study \(^{33}\) showed that shortening or contracture of the non-paretic antagonist is associated with a decrease in the number of sarcomeres, whereas lengthening of the paretic muscle is accompanied by an increase in sarcomeres. \(^{33}\) In addition, denervation atrophy in the paretic muscle, and changes in orbital tissues have also been documented in paralytic strabismus.\(^ {34,35}\)

If the reduction of VOR gains in both directions was due to changes in extraocular muscle mechanics, one would predict VOR gains to remain the same during rotation in darkness or in light, and that the peak velocities of saccades would be reduced in each direction. However, our results indicate that while abducting and adducting VOR gains were decreased, they increased to normal values in light during the VVOR. In addition, although VOR gains were reduced in each direction, and although abducting peak velocities in the paretic eye were reduced, adducting peak velocities in the paretic eye were normal (see Chapter 5). Our results provide evidence that decrease VOR gains in sixth nerve palsy is not merely the result of changes in mechanical properties of the orbital plant, but due to a functional adaptation to the palsy.

Proprioception and VOR adaptation. Proprioceptive signals from extraocular muscles might contribute to VOR adaptation. When, during sinusoidal head rotation, the
movement of one eye is limited by a opaque suction contact lens (the artificial vestibulo-ocular reflex technique), such that the imposed eye velocity is slower than head velocity, VOR gains in the other eye increase immediately.\textsuperscript{36-38} Sectioning of the ophthalmic branch of the trigeminal nerve, which carries proprioceptive signals to the trigeminal nucleus, abolishes this velocity-dependent effect on VOR gains from imposed eye movements.\textsuperscript{39-41}

In our patients, horizontal VOR gains of the paretic eye are reduced in both directions, while gains of the non-paretic eye remain normal. Why, then, did we not observe similar effects as in those observed in artificial VOR experiments? Proprioceptive signals may be defective after peripheral nerve palsy. Although proprioceptive signals are generally thought to project via the ophthalmic branch of the trigeminal nerve to the spinal trigeminal nucleus, a portion may also travel to the trigeminal nucleus via the ocular motor nerves.\textsuperscript{42}

In addition, effects of muscle palsy differ from the effects of imposed movement of one eye; the paretic muscle is slack, whereas the muscle of an eye with imposed movement is taut. Furthermore, artificial VOR elicited by passive eye motion confers no functional advantage; diplopia and oscillopsia would result from motion of the fellow eye. Visual signals play a more dominant role than proprioceptive signals in the control of VOR with or without peripheral nerve palsy.

**Visually enhanced horizontal VOR (VVOR).** In darkness, the VOR functions poorly with a gain below one during passive head rotation at frequencies below 1 Hz. Vision enhances VOR gain to unity. VOR enhancement is a function of optokinetic system at very low frequencies.\textsuperscript{43} At frequencies below 1-2 Hz, smooth pursuit appears to be responsible for gain enhancement. The fixation system may also contribute to visual enhancement of the VOR.\textsuperscript{44-46}
We found that patients with mild and moderate palsy had normal horizontal VOR gains in both eyes (see Figures 2-2B and 2-2C). This visual enhancement of VOR in the paretic eye can be the result of contributions from the smooth pursuit or fixation system at the frequencies tested. In addition, visual input enhances the response of the viewing paretic eye without inappropriately raising that of the occluded non-paretic eye, providing further evidence of monocular adjustment. However, like those of another patient, VVOR gains in all of our patients with severe palsy were below normal in the paretic eye, regardless of which eye was viewing, and above normal in the non-paretic eye when the paretic eye was viewing (Figure 2-2A). In severe palsy, monocular adjustment is inadequate and the brain increases innervation conjugately to the two eyes. The increased innervation boosts the gain in the non-paretic eye to well above unity when the paretic eye is viewing, while gain of the paretic eye remains low in the face of severe weakness of the lateral rectus. To adopt a conventional term from strabismology, this constitutes a "secondary deviation" of the VOR.

Monocular adaptation in unilateral sixth nerve palsy. Hering suggested that the brain circuitry controlling eye movements consists of two systems, one for conjugate movements, the other for vergence. Conjugate control typically operates the vestibulo-ocular, saccade, smooth pursuit and optokinetic systems. Premotor neurons encode common signals to both abducens motoneurons and internuclear neurons in the abducens nucleus. The abducens motoneurons innervate the ipsilateral lateral rectus, while axons of the internuclear neurons cross the midline and ascend within the medial longitudinal fasciculus to innervate the medial rectus motoneurons in the contralateral
Thus, conjugate commands are conveyed to both the ipsilateral lateral rectus and the contralateral medial rectus muscles.

Because the neuronal connectivity appears to be conjugate in nature, it had been assumed that only conjugate plasticity is possible. However, experiments on primates have shown that the ocular motor systems are capable of selective, monocular adaptation.\textsuperscript{1, 2} For example, in monkeys, surgical weakening of the horizontal rectus muscles of one eye causes an adaptation that selectively increases saccadic and VOR gains in the affected eye, while those of the unaffected eye remain normal.\textsuperscript{1, 2} Disconjugate ocular motor adaptation has also been demonstrated in normal humans\textsuperscript{55, 56} and monkeys in response to optical devices such as anisometropic spectacles and prisms. Disconjugate saccades and pursuit are generated to compensate for the disparate retinal errors produced by the optical device.\textsuperscript{55, 56}

To our knowledge, this study is the first to demonstrate monocular adaptation of the VOR in patients with peripheral neuromuscular deficit. We found that horizontal VOR gains are selectively decreased during adduction of the paretic eye, and that horizontal visually enhanced VOR (VVOR) gains are selectively increased in the paretic eye in mild and moderate palsy, without a conjugate increase in VVOR gains of the non-paretic eye. Retinal slip difference in the two eyes is the stimulus that drives the monocular adaptation that we have identified.

Monocular adaptation might occur at the level of motoneurons, though they receive only sparse direct projections from the cerebellum, which is thought to mediate such adaptive changes.\textsuperscript{57} Another possibility is that supranuclear neural circuitry may not be purely conjugate. For example, for saccades, different populations of burst neurons
mediate a pulse of innervation to each eye. In monkeys\textsuperscript{58}, 79\% of premotor excitatory burst neurons in the caudal pontine paramedian reticular formation that were thought to encode conjugate velocity commands for saccades\textsuperscript{48-50}, actually encode monocular commands for either the ipsilateral or contralateral eye. Similarly, different populations of vestibular neurons provide innervation to the horizontal muscles of each eye. In addition to a major excitatory horizontal VOR pathway which mediates conjugate eye movements via the contralateral abducens nucleus and internuclear neurons, a second direct excitatory horizontal VOR pathway exists. This second pathway originates from the ventral lateral vestibular nucleus, ascends through the ascending tract of Deiters to the ipsilateral medial rectus subdivision of the oculomotor nucleus.\textsuperscript{58, 60} The selective change of innervation to the medial rectus muscle of the paretic eye in our patients during VOR may be through modulation of this second pathway.

The cerebellum plays important roles in adaptive control of saccades\textsuperscript{61-64} and the VOR\textsuperscript{62, 65-68}, including disconjugate control.\textsuperscript{59-71} Experimental inactivation of the deep cerebellar nuclei (including the fastigial nucleus) causes disconjugate saccadic dysmetria, such that both saccade magnitude and peak velocity differ in the two eyes.\textsuperscript{69} Patients with cerebellar dysfunction also show disconjugate dysmetria during and immediately after saccades.\textsuperscript{70} The flocculus regulates conjugate VOR responses, and unilateral lesions of the rabbit flocculus cause different VOR gain changes in the two eyes.\textsuperscript{71} Thus the cerebellum exerts selective, monocular control and may participate in the adaptation that we have identified.

\textit{Vertical VOR}
In the straight ahead position, the lateral rectus acts as a pure abductor, with no vertical or torsional actions.\textsuperscript{72,73} When the eye is in an elevated position, the lateral rectus may have a secondary component of elevation. Similarly, when the eye is depressed, it may have a secondary component of depression.\textsuperscript{73-75} Whether the eye is in an adducted or abducted position, no additional vertical or torsional components of lateral rectus actions have been observed. Vertical VOR and VVOR mean gains in our patients were normal, upward and downward, through a 20° range across the orbital mid-position.

**Torsional VOR**

Dynamic and static torsional VOR and VVOR gains, on the other hand, were reduced in all patients during rotation in light and in darkness. Other studies have reported abnormal dynamic torsional VOR gain in patients with skew deviation (three patients having increased and one having decreased gain), spasmodic torticollis (one increased and two decreased) and eighth nerve palsy (two decreased).\textsuperscript{76} These patients also had abnormal static torsional VOR gain; one patient with skew deviation had increased and another had decreased gains, one with spasmodic torticollis had increased gain, and another with eighth nerve palsy had decreased gain.\textsuperscript{76}

What is the mechanism of the reduced torsional gains in sixth nerve palsy? During dynamic head roll, compensatory eye movements are generated by torsional VOR, which is mediated predominantly by the vertical semicircular canals.\textsuperscript{77-80} The dynamic torsional VOR has a lower gain than its horizontal or vertical counterparts, typically ranging from 0.4 to 0.7, depending on the frequency of head roll.\textsuperscript{81-86} Static head roll evokes compensatory changes in torsional eye position, which are mediated by the otolith-ocular reflex from
inputs of the utricles. Static torsional VOR has a lower gain than its dynamic counterpart, ranging from 0.10 to 0.24, depending on target distance. Dynamic and static torsional VOR gains are lower when viewing a near target; this behavior contrasts with that of the horizontal and vertical VOR gains, which increase when viewing a near object. One study found a median dynamic torsional VOR gain of 0.82 during distance (7.2 m) viewing and 0.74 during near (20 cm) viewing. Median static torsional VOR gain was 0.24 during distance viewing and 0.18 during near viewing. In our study of normal subjects, we used a target at 1 m and observed a dynamic torsional VOR gain of 0.58 and static torsional VOR gain of 0.21, consistent with reported values.

It makes functional sense to reduce torsional VOR gain during near viewing. To see why, recall that torsional eye rotation is defined to be rotation about the naso-occipital axis. When one looks into the distance, the lines of sight are roughly parallel with that axis, so the torsional VOR does not affect the gaze direction; it merely turns the eyes about their own sight lines, reducing torsional image slip on the retinas. But when the lines of sight converge on a near target, they may no longer align with the naso-occipital axis, so now the torsional VOR moves the sight lines, disrupting binocular convergence. The best solution is to reduce torsional VOR gain when the eyes converge. In sixth nerve palsy, the esotropia of the paretic eye brings its line of sight out of alignment with the naso-occipital axis just as normal vergence does (Figure 2-5). The low torsional gains we found in the paretic eye may arise from the same mechanism that normally lowers torsional gain in vergence. The low torsional gains in the non-paretic eye may be an adaptation to equalize the gains in the two eyes in order to reduce torsional disparity of retinal images.
<table>
<thead>
<tr>
<th>Patient</th>
<th>Age / Sex</th>
<th>Side of lesion</th>
<th>Duration (months)</th>
<th>Abduction deficit (% normal)</th>
<th>Imaging</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (PL)</td>
<td>21 / M</td>
<td>Right</td>
<td>2 weeks</td>
<td>0% (severe)</td>
<td>Normal MRI</td>
<td>Improved after 4 mons</td>
</tr>
<tr>
<td>2 (JM)</td>
<td>46 / M</td>
<td>Right</td>
<td>2 weeks</td>
<td>0% (severe)</td>
<td>Normal MRI</td>
<td>Resolved after 3 mons</td>
</tr>
<tr>
<td>3 (KE)</td>
<td>75 / F</td>
<td>Right</td>
<td>2</td>
<td>10% (severe)</td>
<td>Normal CT</td>
<td>Resolved after 4 mons (HTN, DM)</td>
</tr>
<tr>
<td>4 (AM)</td>
<td>75 / F</td>
<td>Right</td>
<td>2</td>
<td>50% (severe)</td>
<td>Normal CT</td>
<td>Resolved after 6 mons (HTN)</td>
</tr>
<tr>
<td>5 (VI)</td>
<td>65 / F</td>
<td>Left</td>
<td>36</td>
<td>50% (severe)</td>
<td>Normal MRI</td>
<td>Idiopathic</td>
</tr>
<tr>
<td>6 (MB)</td>
<td>19 / F</td>
<td>Left</td>
<td>3 weeks</td>
<td>0% (severe)</td>
<td>MRI: Left cavernous sinus hemangioma</td>
<td>Diplopia</td>
</tr>
<tr>
<td>7 (SC)</td>
<td>66 / M</td>
<td>Right</td>
<td>3 weeks</td>
<td>80% (moderate)</td>
<td>Normal CT</td>
<td>Resolved after 4 mons (DM)</td>
</tr>
<tr>
<td>8 (JC)</td>
<td>49 / M</td>
<td>Right</td>
<td>9</td>
<td>80% (moderate)</td>
<td>MRI: Sphenoid wing meningioma with invasion of right cavernous sinus</td>
<td>Diplopia, right facial paraesthesia</td>
</tr>
<tr>
<td>9 (TH)</td>
<td>77 / M</td>
<td>Right</td>
<td>30</td>
<td>60% (moderate)</td>
<td>Normal MRI</td>
<td>Idiopathic</td>
</tr>
<tr>
<td>10 (DW)</td>
<td>65 / M</td>
<td>Left</td>
<td>98</td>
<td>70% (moderate)</td>
<td>Normal MRI</td>
<td>Idiopathic</td>
</tr>
<tr>
<td>11 (SCH)</td>
<td>50 / F</td>
<td>Left</td>
<td>24</td>
<td>80% (moderate)</td>
<td>Normal MRI</td>
<td>Idiopathic</td>
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Table 2-1 (continued). Characteristics of patients with 6th nerve palsy

<table>
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<tr>
<th>Patient</th>
<th>Age / Sex</th>
<th>Side of lesion</th>
<th>Duration (months)</th>
<th>Abduction deficit (% normal)</th>
<th>Imaging</th>
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<td>12</td>
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<td>Resolved after 6 mons (HTN)</td>
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<tr>
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<td>Normal CT</td>
<td>Resolved after 5 mons (HTN)</td>
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<tr>
<td>14</td>
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<td>4</td>
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<td>95% (mild)</td>
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<tr>
<td>17</td>
<td>64 / M</td>
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<td>Normal CT</td>
<td>Claustrophobia</td>
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<td>90% (mild)</td>
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<td>Resolved after 4 months (HTN, DM)</td>
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<td>57 / M</td>
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<td>90% (mild)</td>
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<td>Idiopathic</td>
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<tr>
<td>20</td>
<td>75 / F</td>
<td>Left</td>
<td>12</td>
<td>90% (mild)</td>
<td>Normal MRI</td>
<td>Idiopathic</td>
</tr>
<tr>
<td>21</td>
<td>54 / F</td>
<td>Left</td>
<td>60</td>
<td>80% (mild)</td>
<td>Normal MRI</td>
<td>Idiopathic</td>
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HTN, hypertension; DM, diabetes mellitus
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<tr>
<th></th>
<th>0.5 Hz</th>
<th>2 Hz</th>
<th>0.5 Hz</th>
<th>2 Hz</th>
<th>0.5 Hz</th>
<th>2 Hz</th>
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<td>Normal controls</td>
<td>0.96 (0.07)</td>
<td>0.92 (0.04)</td>
<td>---</td>
<td>---</td>
<td>1.01 (0.04)</td>
<td>0.97 (0.05)</td>
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<tr>
<td>Severe (n=8)</td>
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<tr>
<td>Paretic eye abducts</td>
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<td>0.51 (0.19)</td>
<td>0.54 (0.07)</td>
<td>0.37 (0.16)</td>
<td>0.52 (0.09)</td>
<td>0.51 (0.07)</td>
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<td>0.54 (0.11)</td>
<td>0.46 (0.08)</td>
<td>0.40 (0.12)</td>
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<td>0.56 (0.09)</td>
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<td>Non-paretic eye abducts</td>
<td>1.10 (0.12)</td>
<td>0.94 (0.10)</td>
<td>1.40 (0.08)</td>
<td>1.21 (0.04)</td>
<td>1.05 (0.12)</td>
<td>1.10 (0.09)</td>
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<td>0.98 (0.22)</td>
<td>1.36 (0.09)</td>
<td>1.30 (0.07)</td>
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<td>Moderate (n=7)</td>
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<td>Paretic eye abducts</td>
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<td>1.02 (0.10)</td>
<td>0.97 (0.06)</td>
<td>0.93 (0.14)</td>
<td>1.00 (0.20)</td>
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<td>Paretic eye adducts</td>
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<td>0.79 (0.12)</td>
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<td>0.97 (0.18)</td>
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<td>Non-paretic eye abducts</td>
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<td>0.89 (0.17)</td>
<td>1.04 (0.07)</td>
<td>1.02 (0.11)</td>
<td>1.08 (0.11)</td>
<td>1.00 (0.11)</td>
</tr>
<tr>
<td>Non-paretic eye adducts</td>
<td>0.95 (0.18)</td>
<td>0.96 (0.14)</td>
<td>1.08 (0.09)</td>
<td>1.03 (0.08)</td>
<td>1.10 (0.18)</td>
<td>0.97 (0.12)</td>
</tr>
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<td>Mild (n=8)</td>
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<td></td>
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</tr>
<tr>
<td>Paretic eye abducts</td>
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<td>0.83 (0.11)</td>
<td>1.04 (0.09)</td>
<td>0.91 (0.19)</td>
<td>1.03 (0.12)</td>
<td>0.91 (0.13)</td>
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<tr>
<td>Paretic eye adducts</td>
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<td>0.84 (0.09)</td>
<td>1.05 (0.10)</td>
<td>0.95 (0.10)</td>
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<td>Non-paretic eye abducts</td>
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<td>0.95 (0.23)</td>
<td>1.01 (0.07)</td>
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<td>0.98 (0.18)</td>
<td>0.94 (0.21)</td>
<td>1.05 (0.13)</td>
<td>0.95 (0.11)</td>
<td>1.04 (0.08)</td>
<td>0.95 (0.09)</td>
</tr>
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</table>

* p < 0.05
† p < 0.01
Table 2-3. Mean VVOR phase shift in light in patients with severe, moderate and mild sixth nerve palsy

<table>
<thead>
<tr>
<th></th>
<th>0.5 Hz Mean (SD)</th>
<th>Normal eye Mean (SD)</th>
<th>1 Hz Paretic eye Mean (SD)</th>
<th>Normal eye Mean (SD)</th>
<th>2 Hz Paretic eye Mean (SD)</th>
<th>Normal eye Mean (SD)</th>
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<tr>
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<td>3.3 (2.7)</td>
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<td>0.2 (1.8)</td>
<td>0.2 (1.8)</td>
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<tr>
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<td>2.5 (3.1)</td>
<td>2.2 (3.0)</td>
<td>---</td>
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<td>1.3 (2.1)</td>
<td>0.3 (1.1)</td>
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<tr>
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<td>0.2 (0.3)</td>
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<td><strong>Torsional VOR</strong></td>
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<tr>
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Table 2-4. Mean VOR phase shift in dark in patients with severe, moderate and mild sixth nerve palsy

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<td>Paretic eye</td>
<td>Normal eye</td>
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<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
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<tr>
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<tr>
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<td>---</td>
<td>---</td>
<td>0.9 (1.7)</td>
</tr>
<tr>
<td><strong>Vertical VOR</strong></td>
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<tr>
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<td>0.9 (2.2)</td>
<td>---</td>
<td>---</td>
<td>1.5 (2.0)</td>
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<tr>
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<td>1.9 (4.3)</td>
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<td>0.3 (0.6)</td>
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<td>---</td>
<td>0.5 (4.1)</td>
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<tr>
<td><strong>Torsional VOR</strong></td>
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<tr>
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<td>0.8 (0.9)</td>
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<td>0.9 (0.7)</td>
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Table 2-5. Vertical VOR and VVOR gains in patients with sixth nerve palsy

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<td>Dark 0.5 Hz 2 Hz Paretic eye viewing 0.5 Hz 2 Hz Non-paretic eye viewing 0.5 Hz 2 Hz</td>
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<tr>
<td>Normal controls (n=15)</td>
<td>0.90 (0.14) 0.91 (0.10) --- --- 1.07 (0.10) 0.99 (0.13)</td>
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<tr>
<td>Severe (n=8)</td>
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<tr>
<td>Paretic eye elevates</td>
<td>0.98 (0.12) 0.89 (0.09) 1.09 (0.05) 1.07 (0.05) 1.05 (0.12) 1.05 (0.11)</td>
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</tr>
<tr>
<td>Paretic eye depresses</td>
<td>0.87 (0.14) 0.88 (0.11) 1.08 (0.04) 1.06 (0.05) 1.08 (0.06) 1.07 (0.09)</td>
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<tr>
<td>Non-paretic eye elevates</td>
<td>1.00 (0.03) 0.94 (0.07) 1.09 (0.11) 1.11 (0.09) 1.10 (0.07) 1.12 (0.10)</td>
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<tr>
<td>Non-paretic eye depresses</td>
<td>0.90 (0.14) 0.94 (0.09) 1.11 (0.14) 1.09 (0.10) 1.14 (0.12) 1.12 (0.12)</td>
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<tr>
<td>Moderate (n=7)</td>
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<tr>
<td>Paretic eye elevates</td>
<td>0.83 (0.13) 0.95 (0.11) 1.09 (0.11) 1.08 (0.09) 1.10 (0.17) 1.07 (0.10)</td>
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<td>Paretic eye depresses</td>
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<td>0.81 (0.12) 0.94 (0.08) 1.06 (0.06) 1.05 (0.07) 1.08 (0.07) 1.04 (0.11)</td>
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<tr>
<td>Non-paretic eye depresses</td>
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<tr>
<td>Mild (n=8)</td>
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<tr>
<td>Paretic eye elevates</td>
<td>0.87 (0.08) 0.88 (0.15) 1.02 (0.11) 0.96 (0.12) 0.97 (0.10) 0.94 (0.10)</td>
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<tr>
<td>Paretic eye depresses</td>
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<tr>
<td>Non-paretic eye elevates</td>
<td>0.94 (0.17) 0.88 (0.20) 1.05 (0.13) 0.94 (0.14) 1.02 (0.10) 0.94 (0.13)</td>
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<td>Torsional VOR gain (SD)</td>
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<tr>
<td></td>
<td>Dark</td>
<td>Paretic eye viewing</td>
<td>Non-paretic eye viewing</td>
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<tr>
<td></td>
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<td>1 Hz</td>
<td>2 Hz</td>
<td>0.5 Hz</td>
<td>1 Hz</td>
</tr>
<tr>
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<td>0.51 (0.10)</td>
<td>0.56 (0.08)</td>
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<tr>
<td>Severe (n=6)</td>
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<tr>
<td>Paretic eye incyclotors</td>
<td>0.38 (0.11)*</td>
<td>0.39 (0.09)*</td>
<td>0.45 (0.04)*</td>
<td>0.37 (0.14)*</td>
<td>0.43 (0.08)*</td>
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<tr>
<td>Paretic eye exocyclotors</td>
<td>0.34 (0.14)*</td>
<td>0.38 (0.10)*</td>
<td>0.46 (0.05)*</td>
<td>0.35 (0.13)*</td>
<td>0.41 (0.12)*</td>
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<tr>
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<td>0.41 (0.07)*</td>
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<td>0.35 (0.14)*</td>
<td>0.41 (0.09)*</td>
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<td>0.42 (0.08)*</td>
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<td>Paretic eye incyclotors</td>
<td>0.37 (0.13)*</td>
<td>0.38 (0.12)*</td>
<td>0.41 (0.15)*</td>
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<td>0.48 (0.06)*</td>
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<td>Paretic eye exocyclotors</td>
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<td>0.39 (0.12)*</td>
<td>0.42 (0.15)*</td>
<td>0.43 (0.11)*</td>
<td>0.46 (0.06)*</td>
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<tr>
<td>Non-paretic eye incyclotors</td>
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<td>0.36 (0.13)*</td>
<td>0.43 (0.12)*</td>
<td>0.41 (0.11)*</td>
<td>0.42 (0.14)*</td>
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<td>0.45 (0.09)*</td>
<td>0.47 (0.07)*</td>
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<td>Mild (n=8)</td>
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<tr>
<td>Paretic eye incyclotors</td>
<td>0.32 (0.13)*</td>
<td>0.37 (0.11)*</td>
<td>0.43 (0.14)*</td>
<td>0.40 (0.17)*</td>
<td>0.45 (0.07)*</td>
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<tr>
<td>Paretic eye exocyclotors</td>
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<td>0.38 (0.15)*</td>
<td>0.42 (0.13)*</td>
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<tr>
<td>Non-paretic eye incyclotors</td>
<td>0.33 (0.10)*</td>
<td>0.34 (0.13)*</td>
<td>0.44 (0.14)*</td>
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<td>0.44 (0.14)*</td>
<td>0.40 (0.15)*</td>
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</table>

* p < 0.05
† p < 0.01
Figure 2-1. (A) Recordings of a patient (PL) with a severe right sixth nerve palsy during horizontal head rotation about an earth-vertical axis at 2 Hz in darkness. (B) Plots of head velocity versus eye velocity of the paretic right eye (top graph) and the non-paretic left eye (bottom graph) of the same patient. VOR gains, defined as the slopes of the lines of best-fit, were reduced in the paretic right eye in both directions (top graph), whereas gains were normal in the non-paretic left eye in both directions (bottom graph). RE, right eye; LE, left eye; unfilled squares, data during rightward movements; dashed line, line of best-fit for data during rightward movements; filled circles, data during leftward movements; solid line, line of best-fit for data during leftward movements.
Right Eye

Left gain = 0.619
Right gain = 0.420

Left Eye

Right gain = 0.912
Left gain = 0.941

Eye Velocity (deg/s)

Head Velocity (deg/s)
Figure 2-2. Mean horizontal VOR gains in patients with (A) severe, (B) moderate, and (C) mild peripheral sixth nerve palsy.
(A) Severe Sixth Nerve Palsy (n=6)

**Horizontal VOR gain (dark)**

- Normal controls
- Paretic eye adducts
- Paretic eye abducts
- Non-paretic eye abducts
- Non-paretic eye adducts

**Horizontal WOR gain (light)**

- Paretic eye viewing

**Horizontal VOR gain (light)**

- Non-paretic eye viewing
(B) Moderate Sixth Nerve Palsy (n=7)

**Horizontal VOR gain (dark)**

- Normal controls
- Paretic eye adducts
- Paretic eye abducts
- Non-paretic eye abducts
- Non-paretic eye adducts

**Horizontal VOR gain (light)**
- Paretic eye viewing

**Horizontal VOR gain (light)**
- Non-paretic eye viewing
(C) Mild Sixth Nerve Palsy (n=8)

Horizontal VOR gain (dark)

Horizontal VOR gain (light)
- Paretic eye viewing

Horizontal VOR gain (light)
- Non-paretic eye viewing
Figure 2-3. Mean vertical VOR gains in patients with (A) severe, (B) moderate, and (C) mild peripheral sixth nerve palsy.
(A) Severe Sixth Nerve Palsy (n=6)

Vertical VOR gain (dark)

Vertical VOR gain (light)
- Paretic eye viewing

Vertical VOR gain (light)
- Non-paretic eye viewing
(B) Moderate Sixth Nerve Palsy (n=7)

Vertical VOR gain (dark)

Frequency (Hz)

Vertical VOR gain (light)  
- Paretic eye viewing

Frequency (Hz)

Vertical VOR gain (light)  
- Non-paretic eye viewing

Frequency (Hz)
(C) Mild Sixth Nerve Palsy (n=8)

Vertical VOR gain (dark)

Frequency (Hz)

Gain

0.0

0.2

0.4

0.6

0.8

1.0

1.2

1.4

0.5 Hz

2 Hz

Normal controls
Paretic eye elevates
Paretic eye depresses
Non-paretic eye elevates
Non-paretic eye depresses

Vertical VOR gain (light)
- Paretic eye viewing

Frequency (Hz)

Gain

0.0

0.2

0.4

0.6

0.8

1.0

1.2

0.5 Hz

2 Hz

Normal controls
Paretic eye elevates
Paretic eye depresses
Non-paretic eye elevates
Non-paretic eye depresses

Vertical VOR gain (light)
- Non-paretic eye viewing

Frequency (Hz)

Gain

0.0

0.2

0.4

0.6

0.8

1.0

1.2

1.4

0.5 Hz

2 Hz

Normal controls
Paretic eye elevates
Paretic eye depresses
Non-paretic eye elevates
Non-paretic eye depresses
Figure 2-4. Mean dynamic torsional VOR gains in patients with (A) severe, (B) moderate, and (C) mild peripheral sixth nerve palsy.
(A) Severe Sixth Nerve Palsy (n=6)

Torsional VOR gain (dark)

Torsional VOR gain (light)
- Paretic eye viewing

Torsional VOR gain (light)
- Non-paretic eye viewing
(B) Moderate Sixth Nerve Palsy (n=7)

Torsional VOR gain (dark)

Torsional VOR gain (light)
- Paretic eye viewing

Torsional VOR gain (light)
- Non-paretic eye viewing
(C) Mild Sixth Nerve Palsy (n=8)

Torsional VOR gain (dark)

Torsional VOR gain (light)
- Paretic eye viewing

Torsional VOR gain (light)
- Non-paretic eye viewing
Figure 2-5. Changes in torsional VOR gain in orthotropia and esotropia. During roll of the head about its naso-occipital axis while the subject fixates at a target at infinity, prevention of slippage of extrafoveal retinal images requires the eyes to rotate around their visual axes (solid arrows), which are parallel to the roll axis of the head. In sixth nerve palsy, the esotropic eye rotates around its visual axis (dashed arrow) subtending an angle \( \theta \) with the roll axis of the head. The effective component of eye rotation around the roll axis of the head varies as a function of \( \cos \theta \); as the eye deviates nasally (angle \( \theta \) increases), \( \cos \theta \) decreases, such that the component of eye torsion around the roll axis of the head also decreases. Thus, both the dynamic and static torsional VOR gains decrease in esotropia. RE, right eye; LE, left eye.
Right sixth nerve palsy

RE rotation axis (orthotropia) and roll axis of head (orthotropia or esotropia)
2.7 REFERENCES


37. Fahy FL, Donaldson IM. Extraocular muscle proprioception and the vestibulo-ocular reflex (VOR) in the pigeon. J Physiol 1996;495:149P.


CHAPTER 3
ADAPTATIONS AND DEFICITS IN THE VESTIBULO-OCULAR REFLEX
AFTER FOURTH NERVE PALSY
3.1 SUMMARY

Purpose: The effects of fourth nerve palsy on the vestibulo-ocular reflex (VOR) have not been systematically investigated in human subjects. The purpose of this study is to analyze the VOR in patients with unilateral fourth nerve palsy.

Methods: Thirteen patients with unilateral fourth nerve palsy and 15 normal subjects were studied. Subjects made sinusoidal ± 10° head on body rotations in yaw and pitch at approximately 0.5 and 2 Hz, and in roll at approximately 0.5, 1 and 2 Hz. Eye movement recordings were performed using magnetic scleral search coils in each eye in darkness and during monocular viewing in light. Static torsional VOR gains, defined as change in torsional eye position divided by change in head position during static roll, were also measured.

Results: Dynamic torsional VOR (in darkness) and visually enhanced VOR (VVOR) gains of the paretic eye were decreased during incyclotorsion and excyclotorsion, whereas gains in the non-paretic eye were normal. Vertical VOR gains of the paretic eye in darkness were decreased during elevation and depression; they were normal in the non-paretic eye. In light, vertical VVOR gains were normal in both eyes. Horizontal VOR gains of the paretic eye in darkness were decreased during abduction and adduction, whereas horizontal gains in the non-paretic eye were normal. In light, horizontal VVOR gains were normal in both eyes. Static torsional VOR and VVOR gains of the paretic eye were reduced during incyclotorsion, as anticipated from paresis of the superior oblique whose primary action is incyclotorsion; they were normal during excyclotorsion. In the non-paretic eye, static torsional VOR and VVOR gains were normal.
Conclusions: During head rotation in darkness, VOR gains are reduced during incyclotorsion, depression and abduction of the paretic eye, as anticipated from paresis of the superior oblique muscle. VOR gains during excyclotorsion, elevation and adduction of the paretic eye are also reduced, whereas VOR gains in the non-paretic eye remain normal, indicating a selective central adjustment of innervation to the paretic eye. In light, torsional VVOR gains in the paretic eye remained reduced. Visual input increases vertical and horizontal VVOR gains to normal in the paretic eye, without a conjugate increase in VVOR gains in the non-paretic eye, providing further evidence of selective adaptation in the paretic eye. Motions of the eyes after fourth nerve palsy exemplifies monocular adaptation of the VOR in three dimensions, in response to peripheral neuromuscular deficits in humans.
3.2 INTRODUCTION

Clinical testing of ocular motor nerve palsies emphasizes examination of static deviations of the eyes. The effects of fourth nerve palsy on the vestibulo-ocular reflex (VOR) have not been systematically investigated. The VOR stabilizes retinal images by generating compensatory smooth eye movements that are nearly equal in amplitude and opposite in direction to head rotations. Adaptive changes in the VOR occur in response to different visual stimuli.\(^1\)\(^-\)\(^5\) When normal subjects wear reversing prisms for two days, a large reduction of VOR gains is observed.\(^3\) After three to four weeks of vision reversal, VOR gains and phase actually reverse; head rotations cause eye movements in the same direction, so that retinal images are once again stabilized.\(^3\) Disconjugate VOR adaptation has also been elicited in response to anisometropic prisms\(^6\) and experimental weakening of the horizontal recti muscles in monkeys.\(^7\),\(^8\)

Since the primary action of the superior oblique is incyclotorsion\(^8\),\(^10\), one might predict a decreased gain during incyclotorsion of the paretic eye in fourth nerve palsy. Similarly, one might also anticipate decreased gains of the paretic eye during depression, its secondary action\(^8\),\(^10\), and during abduction, its tertiary action.\(^9\),\(^10\) In this study, we investigated patients with unilateral fourth nerve palsy to examine their VOR and its adaptation, if any, in three dimensions. We identified changes in VOR gains in the paretic eye that provide evidence of monocular neural adaptation to paralytic strabismus.

3.3 METHODS

Clinical assessment and imaging studies
Thirteen patients with unilateral fourth nerve palsy were recruited from the Neuro-ophthalmology Unit at the University Health Network. A complete history was taken, and detailed ophthalmic and neurologic examinations were performed. The age of onset, the presence or absence of risk factors for ischemia (diabetes mellitus and hypertension), and duration of diplopia were recorded. Superior oblique palsy was diagnosed using the following clinical criteria 11-13: Deficient depression of the hypertropic eye in adduction; incomitant hypertropia which increased with adduction of the hypertropic eye, and with head tilt towards the hypertropic eye; and presence of subjective excyclotorsion. Patients with a history of head tilt, diplopia or strabismus dating to infancy or early childhood, or prior strabismus surgery were excluded from this study.

The magnitude of strabismus was measured objectively using the prism and cover test, and subjectively using the Maddox rod and prism test (see Chapter 9 for details). The range of ductions was estimated independently by one of two examiners (AW and JAS), and the degree of duction defect was graded according to the estimated percentage of the normal duction in the fellow eye. When indicated, appropriate tests were performed to rule out myasthenia gravis, thyroid ophthalmopathy, other orbital diseases, or intracranial lesions.

In this investigation, magnetic resonance (MR) or computerized tomography (CT) imaging were performed on all patients with fourth nerve palsy, although imaging study is not our standard practice for all such patients. Serial axial and sagittal T1- and T2-weighted MR images with gadolinium enhancement were obtained (slice thickness = 5 mm) for all patients under 50 years of age. CT images of the head with contrast were
obtained in all patients with ischemic risk factors and for patients over 50 years of age. Those with an abnormal CT were further investigated with MR imaging.

**Eye movement recordings**

Please refer to METHODS section in Chapter 2 (section 2.3) for Experimental protocol, Recordings of eye movement and calibration, and Data analyses.

Mean peak velocities of nystagmus quick-phase during dynamic head roll in three axes of rotation were also quantified. Asymptotic velocities were derived by computer analysis of velocity-amplitude scatter plots using an exponential best fit curve: \( P = V (1 - e^{-A/C}) \), where \( P \) is peak velocity at any point on the curve, \( V \) is asymptotic velocity, \( A \) is saccade amplitude, and \( C \) is a constant.\(^{14}\)

The research protocol was approved by the University Health Network Ethics Committee and followed the tenets of the Declaration of Helsinki. Informed consent was obtained from all subjects.

### 3.4 RESULTS

**General characteristics of patients**

The characteristics of the 13 patients with fourth nerve palsy are shown in Table 3-1. The mean age was 54 ± 16 years (median age, 55; age range 23 - 81). There were 8 women. Mean age of symptoms onset was 51 ± 15 years (median age 54; age range 19 - 70). The duration of symptoms ranged from one week to 132 months, with a mean duration of 35 months. Mean follow-up duration was 49 months (range = 13 - 165 months). No
patients had any associated neurologic symptoms or signs. Nine patients had normal MR imaging and four had normal CT of the head.

Fifteen normal subjects served as controls (mean age 52 ± 15 years; median age 58; age range 19 to 69; 8 women).

**Dynamic Torsional VOR gain and phase**

In darkness, torsional VOR gains of the paretic eye were reduced symmetrically during both incyclotorsion and excyclotorsion in each (Figure 3-1) of the 13 patients ($p < 0.01$), whereas gains of the non-paretic eye were normal (Figure 3-2, top graph and Table 3-2). In light, during either paretic or non-paretic eye viewing (Figure 3-2, middle and bottom graphs), visually-enhanced torsional VOR (VVOR) gains of the paretic eye were also low in both directions ($p < 0.05$), while those of the non-paretic eye remained normal (Table 3-2). In light and in darkness, the mean phase differences between the eye and head positions approximated 180°, designated as zero phase shift.

Mean peak velocities of torsional nystagmus quick phase were asymmetric in the paretic eye, being reduced for incyclotorting and normal for excyclotorting quick phases. For a 2 deg torsional quick phase, mean peak velocity of the paretic eye during incyclotorsion was $27.2 \pm 12.7$ deg/sec, compared with $40.3 \pm 10.4$ deg/sec during excyclotorsion ($p < 0.05$), and $42.5 \pm 13.5$ deg/sec in normal controls ($p < 0.05$). Mean peak velocities of torsional quick phase were normal and symmetric in the non-paretic eye.

**Vertical VOR gain and phase**
In darkness (Figure 3-3, top graph), vertical VOR gains of the paretic eye were reduced during both depression and elevation \( (p < 0.05) \), whereas gains of the non-paretic eye were normal (Table 3-2); upward and downward gains did not differ. In light, during paretic eye and non-paretic eye viewing (Figure 3-3, middle and bottom graphs), vertical VOR gains of both the paretic and the non-paretic eyes were normal \( (p < 0.05) \) (Table 3-2). Neither eye showed any significant phase shift from zero in light or in darkness.

Mean peak velocities of vertical nystagmus quick phase were asymmetric in the paretic eye, being reduced for depression and normal for elevation. For a 5 deg vertical quick phase, mean peak velocity of the paretic eye during depression was \( 93.4 \pm 24.7 \) deg/sec, compared with \( 128.5 \pm 22.9 \) deg/sec during elevation \( (p < 0.05) \), and \( 139.1 \pm 23.0 \) deg/sec in normal controls\( (p < 0.05) \). Mean peak velocities of vertical quick phase were normal and symmetric in the non-paretic eye.

**Horizontal VOR gain and phase**

In darkness (Figure 3-4, top graph), horizontal VOR gains of the paretic eye were reduced during both abduction and adduction \( (p < 0.01) \), whereas gains of the non-paretic eye were normal (Table 3-2). Abducting and adducting gains were symmetric. In light, during paretic or non-paretic eye viewing (Figure 3-4, middle and bottom graphs), horizontal VOR gains of both the paretic and the non-paretic eyes were normal \( (p < 0.05) \) (Table 3-2). Neither eye showed any significant phase shift from zero in light or in darkness.

Mean peak velocities of horizontal nystagmus quick phase were asymmetric in the paretic eye, being reduced for abduction and normal for adduction. For a 5 deg horizontal
quick phase, mean peak velocity of the paretic eye during abduction was 123.3 ± 26.7 deg/sec, compared with 178.6 ± 27.9 deg/sec during adduction (p < 0.05), and 199.5 ± 41.5 deg/sec in normal controls (p < 0.05). Mean peak velocities of horizontal quick phase were normal and symmetric in the non-paretic eye.

**Static torsional VOR gain**

Static torsional VOR gains did not differ between viewing with the paretic eye or non-paretic eye, they were therefore reported as the pooled mean, under both viewing conditions, in light and in darkness (Table 3-3). Static torsional VOR and VVOR gains of the paretic eye were reduced during incyclotorsion (p < 0.05); they were normal during excyclotorsion of the paretic eye. In the non-paretic eye, static torsional VOR and VVOR gains were normal.

**3.5 DISCUSSION**

In this study, we investigated patients with unilateral fourth nerve palsy to examine their VOR. We found that torsional, vertical, and horizontal VOR gains in darkness are reduced during incyclotorsion, depression and abduction of the paretic eye, as anticipated from paresis of the superior oblique. However, VOR gains in darkness are also reduced during excyclotorsion, elevation and adduction of the paretic eye, while gains in the non-paretic eye remain normal in all directions.

Changes in the VOR in our patients, who were tested at one point in their courses, are expressed as changes from normal, rather than serial intra-subject changes. Recovery
toward normal values was not determined. Abnormalities are interpreted as deficits or adaptation to those deficits.

**VOR gains during active head rotation in normal subjects**

During passive whole-body rotation, horizontal VOR gains are less than unity, with typical values ranging from 0.7 at 0.5 Hz to 0.95 at 1 Hz.\(^{15,16}\) In agreement with previous studies\(^ {17-20}\), higher VOR gains were observed during active head rotation. Horizontal VOR gains during active head rotation in darkness were close to unity, while vertical VOR gains in darkness were about 0.9 in our normal subjects.

Higher VOR gains during active head motion could be explained by several influences. First, the cervico-ocular reflex might contribute. Vestibular and neck velocity signals are summed on neurons in the vestibular nuclei.\(^ {21,22}\) The response of ocular motor nerve fibers to vestibular stimulation is modulated by stimulation of neck proprioceptors.\(^ {23}\) However, the contribution of the cervico-ocular reflex in normal humans is negligible.\(^ {24,25}\)

Second, during voluntary head motion, the rotational axis of the head is displaced backward to the vertebral column, as opposed to a more head centered axis during passive whole body rotation.\(^ {26}\) VOR gain increases with larger radii of rotation, since the angular VOR then receives an increasing contribution from the translational VOR.\(^ {27}\)

Backward displacement of the rotational axis may contribute to the higher VOR gain recorded during active head rotation. Third, modulation by pre-programmed eye movements may also account for higher VOR gain during active head motion. When labyrinthine function is lost, gaze commands become important in generating compensating, stabilizing eye movements.\(^ {28}\)

An efference copy of head motor commands
during active head rotation could contribute to the higher gains of compensatory smooth eye movements.

**Overview of the vertical and torsional angular VOR pathway**

Primary afferents of the vertical and torsional VOR pathway originate from the anterior and posterior canals. When one anterior (or posterior) canal is stimulated, the posterior (or anterior) canal in the opposite labyrinth is inhibited. One anterior canal excites the ipsilateral superior rectus muscle and the contralateral inferior oblique muscle resulting in dysconjugate elevation and contralateral torsion of the upper poles of both eyes (Figure 3-5A); elevation of the ipsilateral eye is greater than that of the contralateral eye and torsion of the contralateral eye is greater than that of the ipsilateral eye. At the same time, the anterior canal sends reciprocal inhibitory signals to the antagonistic ipsilateral inferior rectus and contralateral superior oblique muscles (Figure 3-5B).

One posterior canal excites the ipsilateral superior oblique muscle and the contralateral inferior rectus muscle (Figure 3-5C). Thus, one posterior canal activates dysconjugate depression and contralateral torsion of the upper poles of both eyes; depression of the contralateral eye is greater than that of the ipsilateral eye and the torsion of the ipsilateral eye is greater than that of the contralateral eye. Reciprocal inhibition is conveyed from the posterior canal to the antagonistic ipsilateral inferior oblique and contralateral superior rectus muscles (Figure 3-5D).

Stimulation of both anterior canals by downward head acceleration activates the upward angular VOR, whereas stimulation of both posterior canals by upward head acceleration activates the downward angular VOR. Stimulation of the anterior and
posterior canals on one side during ipsilateral head roll activates the torsional angular VOR, so that the upper poles of the eyes roll toward the contralateral shoulder.

**VOR in darkness in unilateral fourth nerve palsy**

Torsional VOR in darkness. During head roll toward the left shoulder, the right eye incyclotorts, and the left eye excyclotorts. In right fourth nerve palsy, for example, weakness of the superior oblique muscle would decrease incyclotorting VOR gain of the paretic right eye during head roll to left shoulder. During head roll toward the right shoulder, the right eye excyclotorts, and the left eye incyclotorts. A right fourth nerve palsy might not be expected to affect excyclotorsion of the paretic right eye, so that excyclotorting VOR during head roll to right shoulder would be normal. We found that torsional VOR gains in darkness are reduced during incyclotorsion of the paretic eye in all patients, as anticipated from superior oblique palsy. However, VOR gains during excyclotorsion of the paretic eye are also reduced, while gains remain normal in the non-paretic eye in both directions (see Figure 3-2, top graph).

The unpredicted decreased VOR gains during excyclotorsion of the paretic eye, without any change in gains in the non-paretic eye, indicates a functional monocular adaptation to unilateral fourth nerve palsy. Without it, the VOR would be asymmetric in the paretic eye, weak in incyclotorsion but normal in excyclotorsion. The asymmetry would drive the paretic eye farther and farther into excyclotortion with each cycle of head rotation, resulting in increased torsional disparity between the two eyes and diplopia.

The brain might adopt any one of four strategies to prevent this torsional disparity. First, it might increase its innervation to the superior oblique to increase VOR gain of the
paretic eye, but this strategy is limited by the palsy itself. Second, the brain might generate incyclotorting saccades in the paretic eye to correct for the low incyclotorting VOR gains. Incyclotorting saccades could be generated either by activating the superior oblique or the superior rectus muscles of the paretic eye. However, during activation of the superior oblique muscle, if common premotor signals are sent to trochlear motoneurons and to motoneurons in the inferior rectus subdivision of the oculomotor nucleus, unwanted downward and excyclotorting (primary and secondary actions of inferior rectus) saccades would appear conjugately in the non-paretic eye. Similarly, during activation of the superior rectus muscle, if common premotor signals are sent to the superior rectus and inferior oblique subdivisions of the oculomotor nucleus, unwanted excyclotorting and upward (primary and secondary actions of inferior oblique) saccades would appear conjugately in the non-paretic eye.

Third, the brain might attempt to prevent asymmetry of the torsional VOR by decreasing excyclotorting gains in the paretic eye. This could be achieved by either inhibiting the ipsilateral inferior oblique, via the inhibitory posterior canal pathway (see Figure 3-5D), or by inhibiting the ipsilateral inferior rectus, via the inhibitory anterior canal pathway (see Figure 3-5B). However, for the inhibitory posterior canal pathway, if common premotor signals are sent to motoneurons in both the inferior oblique and superior rectus subdivisions of the oculomotor nucleus (see Figure 3-5D), the contralateral superior rectus would also be inhibited, decreasing the gains during elevation and incyclotorsion (primary and secondary actions of superior rectus), resulting in asymmetry of gains, and even upward and incyclotorting jerk nystagmus in the non-paretic eye. Similarly, for the inhibitory anterior canal pathway (see Figure 3-5B), the superior oblique muscle in the
non-paretic eye would also be inhibited conjugately, resulting in asymmetry of gains, and incyclotorting and downward jerk nystagmus in the non-paretic eye.

Fourth, the brain could selectively reduce VOR gains during excyclotorsion of the paretic eye by decreasing the innervation to the inferior oblique (but not to the contralateral superior rectus), or to the inferior rectus (but not to the contralateral superior oblique), or both. This is apparently the strategy that the brain uses in unilateral fourth nerve palsy to adapt to reduced gains of incyclotorsion.

**Vertical VOR in darkness.** During vertical head rotation about the interaural axis, an upward head acceleration stimulates depression of the eyes. In fourth nerve palsy, because the secondary action of superior oblique is depression, a decrease in VOR gain during depression of the paretic eye may occur. A downward head acceleration stimulates binocular elevation, and this might be expected to remain normal in fourth nerve palsy. As anticipated, we found that vertical VOR gains in darkness are reduced during depression of the paretic eye in all patients. However, VOR gains during elevation of the paretic eye are also reduced, while gains remain normal in the non-paretic eye in both directions (see Figure 3-3, top graph). The decrease in VOR gain during elevation of the paretic eye, without any change in gains in the non-paretic eye, again indicates monocular adaptation in the paretic eye. Using the same rationale discussed for the torsional VOR, this adaptation in the paretic eye could be achieved by decreasing the innervation to the ipsilateral inferior oblique (but not to the contralateral superior rectus), or to the ipsilateral superior rectus (but not to the contralateral inferior oblique), or both, of the paretic eye.

**Horizontal VOR in darkness.** The tertiary action of the superior oblique is abduction. We found that horizontal VOR gains in darkness are reduced during
abduction of the paretic eye in all patients, as expected from superior oblique palsy. However, VOR gains during adduction of the paretic eye are also reduced, while gains remain normal in the non-paretic eye in both directions (see Figure 3-4, top graph). The decrease in VOR gains during adduction of the paretic eye, without a conjugate decrease in VOR gains during abduction of the non-paretic eye, again indicates a central reduction of innervation selectively to the medial rectus, and possibly also to the vertical recti muscles of the paretic eye whose tertiary action is adduction.9,10

**Proprioception and VOR adaptation**

Proprioceptive signals from extraocular muscles might contribute to VOR adaptation. When, during sinusoidal head rotation, the movement of one eye is limited by a opaque suction contact lens (the artificial vestibulo-ocular reflex technique), such that the imposed eye velocity is slower than head velocity, VOR gains in the other eye increase immediately.35-37 Sectioning of the ophthalmic branch of the trigeminal nerve, which carries proprioceptive signals to the trigeminal nucleus, abolishes this velocity-dependent effect on VOR gains from imposed eye movements.38-40 In our patients, VOR gains of the paretic eye are reduced, while gains of the non-paretic eye remain normal. Why, then, did we not observe similar effects as in those observed in artificial VOR experiments? Proprioceptive signals may be defective after peripheral nerve palsy. Although proprioceptive signals are generally thought to project via the ophthalmic branch of the trigeminal nerve to the spinal trigeminal nucleus, a portion may also travel to the trigeminal nucleus via the ocular motor nerves.41 In addition, effects of muscle palsy differ from the effects of imposed movement of one eye; the paretic muscle is slack, whereas the muscle of an eye with imposed
movement is taut. Furthermore, artificial VOR elicited by passive eye motion confers no functional advantage; diplopia and oscillopsia would result from motion of the fellow eye. Visual signals play a more dominant role than proprioceptive signals in the control of VOR with or without peripheral nerve palsy.

**Orbital mechanics and VOR adaptation**

Changes in normal orbital plant mechanics might contribute to the decreased VOR gains of the paretic eye in fourth nerve palsy. The relative contribution of agonist contraction and antagonist relaxation varies with orbital position, and it may be altered when one muscle of an agonist-antagonist pair is palsied. In paralytic strabismus, "contracture" (shortening and increased stiffness) occurs in the non-paretic antagonist muscle, while the paretic muscle lengthens in response to a change in orbital position of the globe. Anatomical and histological study showed that shortening or contracture of the non-paretic antagonist is associated with a decrease in the number of sarcomeres, whereas lengthening of the paretic muscle is accompanied by an increase in sarcomeres. In superior oblique paresis, secondary changes such as "contracture" of the superior rectus muscle and "overaction" of the inferior oblique are observed. These changes may alter VOR gains in both directions.

If the reduction of VOR gains in both directions of the three axes of rotation was due to changes in extraocular muscle mechanics, one would predict VOR gains to remain the same during rotation in darkness or in light, and that the peak velocities of nystagmus quick phases would be reduced in each direction. However, our results indicate that while vertical and horizontal VOR gains were decreased, they increased to normal values in light
during the VVOR. In addition, although VOR gains were reduced in each direction, and although incyclotorting, depressing and abducting peak velocities in the paretic eye were reduced, excyclotorting, elevating and adducting peak velocities in the paretic eye were normal. Our results provide evidence that decrease VOR gains in fourth nerve palsy is not merely the result of changes in mechanical properties of the orbital plant, but due to a functional adaptation to the palsy.

**Visually enhanced VOR (VVOR) in unilateral fourth nerve palsy**

In darkness, the VOR functions poorly with a gain below one during passive head rotation at frequencies below 1 Hz. Vision enhances VOR gain to unity. VOR enhancement is a function of optokinetic system at very low frequencies. At frequencies below 1-2 Hz, smooth pursuit appears to be responsible for gain enhancement. The fixation system may also contribute to visual enhancement of VOR.

We found that during head rotation in light, vertical and horizontal VVOR gains increase to normal values in the paretic eye. This visual enhancement of the VOR can be the result of contributions from the smooth pursuit or fixation system at the frequencies tested. In addition, we found that visual input enhances the VOR of the paretic eye, without a conjugate increase in VVOR gains in the non-paretic eye, providing further evidence for monocular readjustment of innervation selectively to the paretic eye. This also suggests that the VOR and smooth pursuit systems may not operate in a conjugate fashion (see below).

In contrast to vertical and horizontal VVOR, during head roll in light, torsional VVOR gains of the paretic eye remain low during viewing with either eye. Vision does not
increase torsional VOR gains to normal in the paretic eye. The use of a small laser spot as a fixation target against a uniformly gray background in our experiments is adequate to elicit a strong VVOR response during vertical and horizontal head rotations, but not during head roll. The absence of a torsional pursuit system is another factor that explains the lack of visual enhancement of the torsional VOR.

**Monocular adaptation in unilateral fourth nerve palsy**

Hering suggested that the brain circuitry controlling gaze consists of two systems, one for conjugate movements, the other for vergence. Conjugate control operates in the vestibulo-ocular, saccade, smooth pursuit and optokinetic systems. Premotor neurons encode common signals to both abducens motoneurons and internuclear neurons in the abducens nucleus. The abducens motoneurons innervate the ipsilateral lateral rectus, while the internuclear neurons innervate the medial rectus motoneurons in the contralateral oculomotor nucleus. For upward and torsional eye movements, common premotor signals are sent to the oculomotor subnuclei that drive the contralateral superior rectus and ipsilateral inferior oblique muscles (see Figure 3-5A). For downward and torsional movements, common signals are relayed to the trochlear nucleus, which innervates the contralateral superior oblique muscle, and to the oculomotor subnucleus that innervates the ipsilateral inferior rectus muscle (see Figure 3-5C).

Because the neuronal connectivity is suitable for conjugate motion, it might be presumed that only conjugate plasticity is possible. However, experiments on primates have shown that the ocular motor systems are capable of selective, monocular adaptation. For example, in monkeys, surgical weakening of the horizontal recti muscles of one
eye causes an adaptation that selectively increases saccadic and VOR gains in the affected eye, while those of the unaffected eye remain normal.\textsuperscript{7, 8} Disconjugate ocular motor adaptation has also been demonstrated in normal humans\textsuperscript{64, 65} and monkeys\textsuperscript{6} in response to optical devices such as anisometropic spectacles and prisms. Disconjugate saccades and pursuit are generated to compensate for the disparate retinal errors produced by the optical device\textsuperscript{64, 65}.

To our knowledge, this study is the first to demonstrate monocular adaptation of the VOR in humans with fourth nerve palsy. We found that VOR gains are reduced in darkness during excyclotorsion, elevation and adduction of the paretic eye, as well as in the directions of pareticduction. Moreover, in light, vertical and horizontal VVOR gains are selectively increased in the paretic eye, without a conjugate increase in gains of the non-paretic eye. These results exemplify monocular adaptation in humans with peripheral neuromuscular deficits. Retinal slip differences between the two eyes is the stimulus that drives the monocular adaptation that we have identified.

One possible site where changes in neural drive to each eye could occur independently is at the level of motoneurons. Selective adaptation might be achieved by changing the sensitivity of each motoneurons pool to innervation from premotor neurons. The cerebellum, which mediates ocular motor adaptation, may have direct projections to ocular motoneurons.\textsuperscript{66} Using the Nauta method for tracing Wallerian degeneration, Carpenter and Strominger\textsuperscript{66} concluded that cerebello-oculomotor fibers from all part of the dentate nucleus project to the inferior rectus subdivision of the contralateral oculomotor nucleus, whereas fibers from ventral portions of the dentate nucleus project to the superior rectus subdivision of the contralateral oculomotor nucleus.\textsuperscript{66} However, using the more
modem retrograde tracer technique, afferents from the dentate nucleus to the oculomotor nucleus are not identified.\textsuperscript{57,68}

Supranuclear neural circuitry is another possible source of monocular drive to adaptation. For example, for saccades, different populations of burst neurons mediate a pulse of innervation to each eye. In monkeys\textsuperscript{69}, 79\% of premotor excitatory burst neurons in the caudal pontine paramedian reticular formation that were thought to encode conjugate velocity commands for saccades\textsuperscript{57-59}, actually encode monocular commands for either the ipsilateral or contralateral eye. Similarly, different populations of vestibular neurons provide innervation to the horizontal muscles of each eye.\textsuperscript{70} Neurons in the feline medial vestibular nucleus (MVN) are activated antidromically only by local stimulation of the contralateral abducens nucleus.\textsuperscript{70} Another group of MVN neurons are activated only by stimulation of the ipsilateral medial rectus motoneurons pool, but not by stimulation of contralateral abducens nucleus.\textsuperscript{70}

The cerebellum plays important roles in adaptive control of saccades\textsuperscript{71-74} and the VOR, including disconjugate control.\textsuperscript{72,75-78} Experimental inactivation of the deep cerebellar nuclei (including the fastigial nucleus) causes disconjugate saccadic dysmetria, such that both saccade magnitude and peak velocity differ in the two eyes.\textsuperscript{79} Patients with cerebellar dysfunction also show disconjugate dysmetria during and immediately after horizontal or vertical saccades.\textsuperscript{80} The flocculus regulates conjugate VOR responses, and unilateral lesions of the rabbit flocculus cause different VOR gain changes in the two eyes.\textsuperscript{81} Thus the cerebellum exerts selective, monocular control and may participate in the adaptation that we have identified.
3.6 TABLES AND FIGURES
Table 3-1. Characteristics of patients with fourth nerve palsy

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Side of hypertroplia</th>
<th>Duration (months)</th>
<th>Duction deficit*</th>
<th>Hypertroplia in primary position (PD)</th>
<th>Imaging</th>
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<td>39</td>
<td>F</td>
<td>Right</td>
<td>1 week</td>
<td>30%</td>
<td>3 RHT</td>
<td>Hypertension</td>
</tr>
<tr>
<td>5</td>
<td>SD</td>
<td>68</td>
<td>M</td>
<td>Right</td>
<td>3 weeks</td>
<td>50%</td>
<td>2 RHT</td>
<td>Normal MRI</td>
</tr>
<tr>
<td>6</td>
<td>GW</td>
<td>67</td>
<td>M</td>
<td>Left</td>
<td>39</td>
<td>50%</td>
<td>7 LHT</td>
<td>Trauma</td>
</tr>
<tr>
<td>7</td>
<td>SF</td>
<td>59</td>
<td>M</td>
<td>Left</td>
<td>24</td>
<td>50%</td>
<td>12 LHT</td>
<td>Trauma</td>
</tr>
<tr>
<td>8</td>
<td>JG</td>
<td>53</td>
<td>F</td>
<td>Left</td>
<td>24</td>
<td>50%</td>
<td>10 LHT</td>
<td>---</td>
</tr>
<tr>
<td>9</td>
<td>CG</td>
<td>59</td>
<td>M</td>
<td>Left</td>
<td>9</td>
<td>20%</td>
<td>2 LHT</td>
<td>Normal MRI</td>
</tr>
<tr>
<td>10</td>
<td>HL</td>
<td>41</td>
<td>F</td>
<td>Left</td>
<td>19</td>
<td>30%</td>
<td>3 LHT</td>
<td>Normal MRI</td>
</tr>
<tr>
<td>11</td>
<td>LA</td>
<td>55</td>
<td>F</td>
<td>Left</td>
<td>12</td>
<td>20%</td>
<td>6 LHT</td>
<td>Normal CT</td>
</tr>
<tr>
<td>12</td>
<td>EB</td>
<td>81</td>
<td>F</td>
<td>Left</td>
<td>132</td>
<td>20%</td>
<td>8 LHT</td>
<td>Normal MRI</td>
</tr>
<tr>
<td>13</td>
<td>SW</td>
<td>37</td>
<td>F</td>
<td>Left</td>
<td>40</td>
<td>10%</td>
<td>4 LHT</td>
<td>Normal MRI &amp; MRA</td>
</tr>
</tbody>
</table>

* percent of normal duction in adducted depression
PD, prism diopeter
RHT, right hypertroplia; LHT, left hypertroplia; MRA, MR angiogram
Table 3-2. Torsional, vertical and horizontal VOR and VVOR gains in patients with fourth nerve palsy

<table>
<thead>
<tr>
<th></th>
<th>VOR gain (SD)</th>
<th>Dark 0.5 Hz</th>
<th>Dark 1 Hz</th>
<th>Dark 2 Hz</th>
<th>Paretic eye viewing 0.5 Hz</th>
<th>Paretic eye viewing 1 Hz</th>
<th>Paretic eye viewing 2 Hz</th>
<th>Non-paretic eye viewing 0.5 Hz</th>
<th>Non-paretic eye viewing 1 Hz</th>
<th>Non-paretic eye viewing 2 Hz</th>
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</thead>
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<tr>
<td><strong>Torsional VOR</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Normal controls (n=15)</td>
<td>0.49 (0.09)</td>
<td>0.51 (0.10)</td>
<td>0.58 (0.08)</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>0.56 (0.10)</td>
<td>0.56 (0.08)</td>
<td>0.63 (0.08)</td>
</tr>
<tr>
<td>Paretic eye excycloptors</td>
<td>0.28 (0.12)*</td>
<td>0.30 (0.10)*</td>
<td>0.42 (0.12)*</td>
<td>0.36 (0.12)*</td>
<td>0.39 (0.14)$</td>
<td>0.49 (0.15)$</td>
<td>0.38 (0.15)*</td>
<td>0.41 (0.15)$</td>
<td>0.51 (0.14)$</td>
<td></td>
</tr>
<tr>
<td>Paretic eye incycloptors</td>
<td>0.31 (0.11)*</td>
<td>0.33 (0.09)*</td>
<td>0.42 (0.13)*</td>
<td>0.38 (0.11)*</td>
<td>0.36 (0.13)$</td>
<td>0.49 (0.15)$</td>
<td>0.37 (0.16)*</td>
<td>0.40 (0.17)$</td>
<td>0.51 (0.15)$</td>
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<tr>
<td>Non-paretic eye incycloptors</td>
<td>0.40 (0.15)</td>
<td>0.42 (0.14)</td>
<td>0.52 (0.15)</td>
<td>0.46 (0.13)</td>
<td>0.49 (0.16)</td>
<td>0.57 (0.17)</td>
<td>0.52 (0.18)</td>
<td>0.53 (0.15)</td>
<td>0.60 (0.15)</td>
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<tr>
<td>Non-paretic eye excycloptors</td>
<td>0.41 (0.17)</td>
<td>0.42 (0.13)</td>
<td>0.52 (0.16)</td>
<td>0.48 (0.15)</td>
<td>0.47 (0.17)</td>
<td>0.56 (0.18)</td>
<td>0.53 (0.17)</td>
<td>0.53 (0.16)</td>
<td>0.59 (0.17)</td>
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<tr>
<td><strong>Vertical VOR</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Normal controls (n=15)</td>
<td>0.90 (0.13)</td>
<td>---</td>
<td>0.91 (0.10)</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>1.07 (0.10)</td>
<td>---</td>
<td>0.99 (0.13)</td>
</tr>
<tr>
<td>Paretic eye elevates</td>
<td>0.71 (0.23)$</td>
<td>---</td>
<td>0.76 (0.17)$</td>
<td>1.00 (0.08)</td>
<td>---</td>
<td>0.93 (0.12)</td>
<td>0.96 (0.10)</td>
<td>---</td>
<td>0.93 (0.09)</td>
<td></td>
</tr>
<tr>
<td>Paretic eye depresses</td>
<td>0.73 (0.24)$</td>
<td>---</td>
<td>0.74 (0.18)$</td>
<td>1.03 (0.14)</td>
<td>---</td>
<td>0.95 (0.12)</td>
<td>1.00 (0.10)</td>
<td>---</td>
<td>0.94 (0.13)</td>
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<tr>
<td>Non-paretic eye elevates</td>
<td>0.85 (0.24)</td>
<td>---</td>
<td>0.85 (0.18)</td>
<td>1.13 (0.08)</td>
<td>---</td>
<td>1.05 (0.11)</td>
<td>1.07 (0.08)</td>
<td>---</td>
<td>1.04 (0.10)</td>
<td></td>
</tr>
<tr>
<td>Non-paretic eye depresses</td>
<td>0.84 (0.25)</td>
<td>---</td>
<td>0.86 (0.19)</td>
<td>1.15 (0.14)</td>
<td>---</td>
<td>1.06 (0.12)</td>
<td>1.11 (0.14)</td>
<td>---</td>
<td>1.05 (0.11)</td>
<td></td>
</tr>
<tr>
<td><strong>Horizontal VOR</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal controls (n=15)</td>
<td>0.96 (0.07)</td>
<td>---</td>
<td>0.92 (0.04)</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>1.01 (0.07)</td>
<td>---</td>
<td>0.97 (0.05)</td>
</tr>
<tr>
<td>Paretic eye adducts</td>
<td>0.65 (0.21)$</td>
<td>---</td>
<td>0.72 (0.14)$</td>
<td>1.02 (0.12)</td>
<td>---</td>
<td>0.97 (0.09)</td>
<td>1.03 (0.20)</td>
<td>---</td>
<td>0.96 (0.09)</td>
<td></td>
</tr>
<tr>
<td>Paretic eye abducts</td>
<td>0.67 (0.19)$</td>
<td>---</td>
<td>0.74 (0.15)$</td>
<td>1.01 (0.05)</td>
<td>---</td>
<td>0.97 (0.08)</td>
<td>1.02 (0.13)</td>
<td>---</td>
<td>0.98 (0.09)</td>
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<tr>
<td>Non-paretic eye adducts</td>
<td>0.96 (0.17)</td>
<td>---</td>
<td>0.93 (0.10)</td>
<td>0.99 (0.11)</td>
<td>---</td>
<td>0.98 (0.10)</td>
<td>1.01 (0.10)</td>
<td>---</td>
<td>0.93 (0.08)</td>
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<tr>
<td>Non-paretic eye abducts</td>
<td>0.98 (0.19)</td>
<td>---</td>
<td>0.95 (0.16)</td>
<td>0.98 (0.10)</td>
<td>---</td>
<td>0.98 (0.11)</td>
<td>1.01 (0.10)</td>
<td>---</td>
<td>0.95 (0.08)</td>
<td></td>
</tr>
</tbody>
</table>

* p < 0.001
† p < 0.01
‡ p < 0.05
Table 3-3. Static torsional VOR gain in patients with fourth nerve palsy

<table>
<thead>
<tr>
<th></th>
<th>Light</th>
<th></th>
<th></th>
<th>Dark</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Paretic eye</td>
<td>Non-paretic eye</td>
<td>Paretic eye</td>
<td>Non-paretic eye</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Inyclotort</td>
<td>Excyclotort</td>
<td>Inyclotort</td>
<td>Excyclotort</td>
<td>Inyclotort</td>
<td>Excyclotort</td>
</tr>
<tr>
<td>Normal (n=10)</td>
<td>0.21 (0.10)</td>
<td>0.20 (0.11)</td>
<td>0.22 (0.09)</td>
<td>0.21 (0.11)</td>
<td>0.20 (0.14)</td>
<td>0.19 (0.15)</td>
</tr>
<tr>
<td>Patients (n=13)</td>
<td>0.11 (0.07)*</td>
<td>0.17 (0.08)</td>
<td>0.22 (0.13)</td>
<td>0.19 (0.19)</td>
<td>0.12 (0.10)*</td>
<td>0.17 (0.10)</td>
</tr>
</tbody>
</table>

* $p < 0.01$

Values in parentheses are standard deviations
Figure 3-1. Recordings of a patient (KS) with right fourth nerve palsy during dynamic head roll at 0.5 Hz in darkness. VOR gains were symmetrically reduced in the paretic right eye in both directions, whereas gains were normal in the non-paretic left eye. RE, right eye; LE, left eye.
Figure 3-2. Mean dynamic torsional VOR and VVOR gains in patients fourth nerve palsy.

Error bars indicate one standard deviation.
Fourth Nerve Palsy (n=13)

Torsional VOR gain (dark)

![Graph showing torsional VOR gain in dark conditions.]

- Normal control
- Paretic eye excycloptors
- Paretic eye incycloptors
- Non-paretic eye incycloptors
- Non-paretic eye excycloptors

Torsional VOR gain (light) - Paretic eye viewing

![Graph showing torsional VOR gain for paretic eye viewing in light conditions.]

- Normal control
- Paretic eye excycloptors
- Paretic eye incycloptors
- Non-paretic eye incycloptors
- Non-paretic eye excycloptors

Torsional VOR gain (light) - Non-paretic eye viewing

![Graph showing torsional VOR gain for non-paretic eye viewing in light conditions.]

- Normal control
- Paretic eye excycloptors
- Paretic eye incycloptors
- Non-paretic eye incycloptors
- Non-paretic eye excycloptors
Figure 3-3. Mean vertical VOR and VVOR gains in patients fourth nerve palsy. Error bars indicate one standard deviation.
Fourth Nerve Palsy (n=13)

**Vertical VOR gain (dark)**

- Normal control
- Paretic eye elevates
- Paretic eye depresses
- Non-paretic eye elevates
- Non-paretic eye depresses

**Vertical VOR gain (light) - Paretic eye viewing**

**Vertical VOR gain (light) - Non-paretic eye viewing**

- Normal control
- Paretic eye elevates
- Paretic eye depresses
- Non-paretic eye elevates
- Non-paretic eye depresses
Figure 3-4. Mean horizontal VOR and VVOR gains in patients fourth nerve palsy. Error bars indicate one standard deviation.
Fourth Nerve Palsy (n=13)

**Horizontal VOR gain (dark)**

- Normal control
- Paretic eye abducts
- Paretic eye adducts
- Non-paretic eye abducts
- Non-paretic eye adducts

**Horizontal VOR gain (light) - Paretic eye viewing**

**Horizontal VOR gain (light) - Non-paretic eye viewing**
Figure 3-5. Direct vertical vestibulo-ocular projections from the vertical semicircular canals.

A. Excitatory afferents from the anterior semicircular canals (AC) synapse in the superior vestibular nucleus (SVN), and their signals are relayed via the brachium conjunctivum (BC) to the contralateral oculomotor subnuclei that drive the ipsilateral superior rectus (SR) and contralateral inferior oblique (IO) muscles. B. Inhibitory afferents from the anterior semicircular canals synapse in the SVN, and their signals are relayed via the medial longitudinal fasciculus (MLF) to the ipsilateral trochlear nucleus, which innervates the contralateral superior oblique (SO) muscle, and to the ipsilateral oculomotor subnucleus that innervates the ipsilateral inferior rectus (IR) muscle. C. Excitatory afferents from the posterior semicircular canals (PC) synapse in the medial vestibular nucleus (MVN), and their signals are relayed via the MLF to the contralateral trochlear nucleus, which innervates the ipsilateral superior oblique (SO) muscle, and to the contralateral oculomotor subnucleus that innervates the contralateral inferior rectus (IR) muscle. D. Inhibitory afferents from the posterior semicircular canals synapse in the SVN, and their signals are relayed via the MLF to the ipsilateral oculomotor subnuclei that drive the ipsilateral inferior oblique (IO) and contralateral superior rectus (SR) muscles.
3.7 REFERENCES


CHAPTER 4

ADAPTATIONS AND DEFICITS IN THE VESTIBULO-OCULAR REFLEX
AFTER THIRD NERVE PALSY
4.1 SUMMARY

PURPOSE: To analyze the vestibulo-ocular reflex (VOR) in patients with unilateral peripheral third nerve palsy.

METHODS: Ten patients and 15 normal subjects were studied using magnetic search coils. Subjects made sinusoidal ± 10° head on body rotations in yaw, pitch and roll in darkness and during monocular viewing in light.

RESULTS: Horizontal VOR (in darkness) and visually enhanced VOR (VOR) gains of the paretic eye were decreased during both abduction and adduction, whereas gains in the non-paretic eye were normal. Vertical VOR and VVOR gains of the paretic eye were decreased during both elevation and depression, consistent with palsy of the superior and inferior rectus muscles from third nerve palsy. Vertical gains were normal in the non-paretic eye. Dynamic and static torsional VOR and VVOR gains of the paretic eye were reduced during both excyclotorsion and incyclotorsion; they were normal in the non-paretic eye.

CONCLUSIONS: In the paretic eye, adducting VOR gains are reduced, as anticipated from medial rectus palsy. Abducting gains are also reduced, which are attributed to an adaptive decrease in innervation to the lateral rectus, to achieve symmetry of the horizontal VOR in the paretic eye. Torsional VOR gains are reduced during excyclotorsion from palsy of the inferior oblique muscle. Gains are also reduced during incyclotorsion, which can be explained by an adaptive decrease in innervation to the superior oblique, to restore symmetry of the torsional VOR in the paretic eye.
4.2 INTRODUCTION

The effects of third nerve palsy on the vestibulo-ocular reflex (VOR) have not been systematically investigated. Clinical testing of ocular motor nerve palsies emphasizes examination of static deviations of the eyes. The VOR stabilizes retinal images by generating compensatory smooth eye movements that are nearly equal in amplitude and opposite in direction to head rotations. Adaptive changes in the VOR occur in response to visual stimuli.\textsuperscript{1-5} When normal subjects wear reversing prisms for several days, VOR gains are substantially reduced.\textsuperscript{3} After three to four weeks of vision reversal, the phase of the VOR actually reverses; head rotations cause eye rotations in the same direction, so that retinal images are once again stabilized.\textsuperscript{3} Disconjugate VOR adaptation has been elicited in response to different prisms in each eye \textsuperscript{6} and experimental weakening of the horizontal rectus muscles of one eye in monkeys.\textsuperscript{7,8} Adaptive changes in the VOR might also improve defective visual stabilization of images caused by third nerve palsy.

In this study, we investigated patients with unilateral third nerve palsy to examine their VOR and its adaptation, if any, in three dimensions. The third (oculomotor) nerve innervates four extraocular muscles: the medial rectus, superior rectus, inferior rectus and inferior oblique. Since the primary action of the medial rectus is adduction, we hypothesized that weakness of the medial rectus in third nerve palsy causes a reduction in VOR gains during adduction. We also anticipated a decrease in vertical VOR gains during both elevation and depression in third nerve palsy, as these are the primary actions of the superior and inferior rectus muscles.\textsuperscript{9} Similarly, because the primary action of the inferior oblique is exocyclotorsion \textsuperscript{9}, we also predicted a decrease in VOR gains during
excyclotorsion in third nerve palsy. We identified changes in the VOR that signify monocular adaptation by the vestibulo-ocular system.

4.3 METHODS

Clinical assessment and imaging studies

We recruited 10 patients with unilateral peripheral third nerve palsy from the Neuro-ophthalmology Unit at the University Health Network. A complete history was taken, and detailed ophthalmic and neurologic examinations were performed, recording the duration and age of onset of diplopia, the presence or absence of risk factors for ischemia (diabetes mellitus and hypertension), and associated neurologic symptoms and signs. The magnitude of strabismus was measured objectively using the prism and cover test, and subjectively using the Maddox rod and prism test (see Chapter 9 for details). The range of ductions was estimated independently by two examiners (AW and JAS), and the degree of duction defect was graded according to the estimated percentage of the normal duction in the fellow eye. When indicated, appropriate tests were performed to rule out myasthenia gravis, thyroid ophthalmopathy, other orbital diseases, or intracranial lesions.

In this investigation, magnetic resonance (MR) or computerized tomography (CT) imaging were performed on all patients, although imaging is not our standard practice for all such patients. CT images of the head with contrast were obtained in all patients with ischemic risk factors and for patients over 50 years of age. Those with abnormal CT were further investigated with MR imaging. Serial axial and sagittal T1- and T2-weighted MR images with gadolinium enhancement were obtained (slice thickness = 5 mm) for all
patients under 50 years of age. MR imaging was also performed on all patients with pupillary involvement; if normal, cerebral angiography was performed.

**Eye movement recordings**

Please refer to METHODS section in Chapter 2 (section 2.3) for Experimental protocol, Recordings of eye movement and calibration, and Data analyses.

The research protocol was approved by the University Health Network Ethics Committee and followed the tenets of the Declaration of Helsinki. Informed consent was obtained from all subjects.

### 4.4 RESULTS

**General characteristics of patients**

The characteristics of the 10 patients are shown in Table 4-1. The mean age was 54 ± 13 years (median, 54; range, 38 - 70). There were 8 women. The duration of symptoms ranged from one week to 50 months, with a mean duration of 18 months. Mean follow-up duration was 38 months (range, 11 - 72 months). In all patients, the third nerve palsy affected both the superior and inferior divisions, with or without pupillary involvement. No patients had any clinical signs of misdirection involving the eyelid or pupil. Six patients had idiopathic, presumed ischemic, peripheral lesions; four of them had normal MR imaging and two had normal CT. Four of these six patients had ischemic factors, namely hypertension or diabetes, and had a complete resolution of their palsy within four to six months. Four other patients had intracranial lesions: head injury (1 patient), neurosarcoidosis with enhanced meninges at the cavernous sinus (1), posterior
communicating artery aneurysm (1), and pituitary tumor extending into the cavernous sinus (1). All four patients with intracranial lesions had neurologic symptoms and signs in addition to diplopia. None of them had signs or MR evidence of involvement of the third nerve nucleus or fascicle.

Fifteen normal subjects served as controls (mean age, 52 ± 15 years; median age, 58 years; age range, 19 to 69 years; 8 women).

**Horizontal VOR gain and phase**

In darkness (Figure 4-1, top graph), horizontal VOR gains of the paretic eye were reduced symmetrically (p < 0.05) during both abduction and adduction, whereas those of the non-paretic eye remained normal in both directions (Table 4-2). During viewing with either eye in light (Figure 4-1, middle and bottom graphs), horizontal visually enhanced VOR (VOR) gains of the paretic eye were low in both directions (p < 0.05), while VOR gains of the non-paretic eye were normal (Table 4-2). In light and in darkness, the mean phase differences between the eye and head positions approximated 180°, designated as zero phase shift.

**Vertical VOR gain and phase**

In darkness (Figure 4-2, top graph), vertical VOR gains of the paretic eye were reduced (p < 0.01) during both elevation and depression, whereas gains of the non-paretic eye were normal (Table 4-2); upward and downward gains did not differ. In light, during paretic eye or non-paretic eye viewing (Figure 4-2, middle and bottom graphs), vertical VVOR gains of the paretic eye remained reduced (p < 0.05), while gains in the non-paretic
eye were normal (Table 4-2). Neither eye showed any significant phase shift from zero in light or in darkness.

**Dynamic torsional VOR gain and phase**

In darkness (Figure 4-3, top graph), torsional VOR gains of the paretic eye were reduced during both incyclotorsion and excyclotorsion ($p < 0.01$), whereas gains of the non-paretic eye were normal (Table 4-2). In light, and during viewing with either eye (Figure 4-3, middle and bottom graphs), torsional VVOR gains of the paretic eye remained reduced ($p < 0.01$), while gains in the non-paretic eye were normal (Table 4-2). Neither eye showed any significant phase shift from zero in light or in darkness.

**Static torsional VOR gain**

Static torsional VOR gains did not differ between viewing with the paretic or non-paretic eye, they are therefore reported as the pooled mean for each eye with either eye fixating, in light and in darkness (Table 4-3). Static torsional VOR and VVOR gains of the paretic eye were reduced during incyclotorsion and excyclotorsion ($p < 0.05$); they were normal in the non-paretic eye.

**4.5 DISCUSSION**

In third nerve palsy, horizontal VOR and VVOR gains of the paretic eye are decreased during both abduction and adduction, whereas gains in the non-paretic eye are normal. Vertical VOR and VVOR gains of the paretic eye are decreased during both elevation and depression, consistent with palsy of the superior and inferior rectus muscles.
in third nerve palsy. In the non-paretic eye, vertical gains are normal. Dynamic and static torsional VOR and VVOR gains of the paretic eye are reduced during incyclotorsion and excyclotorsion. Torsional gains are normal in the non-paretic eye.

In light, horizontal, vertical and torsional VVOR gains in the paretic eye remain reduced, indicating that visual input does not enhance VVOR to normal in third nerve palsy.

Changes in the VOR in our patients, who were tested at one point in the course of their palsies, are expressed as changes from normal, rather than serial intra-subject changes. Any recovery toward normal values was not assessed. Abnormalities are interpreted as deficits, or adaptation to those deficits.

**Horizontal VOR in unilateral third nerve palsy**

During rotation in darkness, horizontal VOR gains are reduced during adduction of the paretic eye in all patients, as anticipated in palsy of the medial rectus muscle from third nerve palsy. VOR gains during abduction of the paretic eye are also reduced. In contrast, in the non-paretic eye, VOR gains are normal during both abduction and adduction (see Figure 4-1). Apparently the innervation to the lateral rectus of the paretic eye is reduced, along with the reduced innervation to the medial rectus resulting from the palsy, without changes in the innervation to the horizontal recti muscles of the non-paretic eye.

A functional adaptation to unilateral third nerve palsy can explain this adjustment in abducting VOR gain. Without it, the VOR would be asymmetric in the paretic eye, being reduced in adduction but normal in abduction. The asymmetry would drive the paretic eye farther and farther into abduction with each cycle of head rotation, soon ‘pinning’ it at its
temporal limits, and aggravating the patient's diplopia. There are several strategies that might seem to rectify this problem. The brain might increase its innervation to the paretic medial rectus to increase VOR gain during adduction, but this strategy is limited by the palsy itself. Or, the brain might generate adducting saccades in the paretic eye to correct for low VOR gains during adduction. However, adduction paresis would limit them. Moreover, if common premotor signals are sent to both the abducens motoneurons and internuclear neurons in the abducens nucleus (see below), the result might be unwanted abducting saccades in the non-paretic eye, taking it off its target. A better option would be to reduce the innervation just to the lateral rectus of the paretic eye, decreasing its abduction gain to make the VOR symmetrical in that eye, while leaving the VOR in the non-paretic eye intact. This is apparently the adaptive strategy that the brain adopts when challenged by retinal image disparity caused by paresis of the medial rectus muscle.

**Torsional VOR in unilateral third nerve palsy**

In third nerve palsy that affects both the superior and inferior divisions, three of the four cyclovertical extraocular muscles are involved, namely, the superior rectus, inferior rectus, and inferior oblique muscles. The cyclotorsional actions of the superior rectus and the inferior rectus are opposed; the superior rectus incyclotorts and the inferior rectus excyclotorts. If both vertical rectus muscles were equally palsied, the net effects of third nerve palsy on torsional VOR would be determined by weakness of the inferior oblique, whose primary action is excyclotorsion. As anticipated, dynamic and static torsional VOR gains are reduced during excyclotorsion. However, we found that torsional VOR gains are also reduced during incyclotorsion. Unequal involvement of the superior and inferior rectus
muscles, with the superior rectus being more severely affected than the inferior rectus, might make some contributions to reduction of incyclotorting gains. However, symmetry of upward and downward gains indicate that differential paresis of the vertical rectus muscles was not a factor.

The reduced VOR gains during incyclotorsion in the paretic eye, without any change in gains in the non-paretic eye, can be attributed to a functional adaptation in unilateral third nerve palsy. Without it, the VOR would be asymmetric in the paretic eye, weak in excyclotorsion but normal in incyclotorsion. The asymmetry would drive the paretic eye farther and farther into incyclotorsion with each cycle of head rotation, resulting in increased torsional disparity between the two eyes and diplopia. Using similar rationale discussed for the horizontal VOR, this adaptation in the paretic eye could be achieved by decreasing the innervation to the ipsilateral superior oblique (but not to the yolked contralateral inferior rectus) of the paretic eye.

**Proprioception and VOR adaptation**

Proprioceptive signals from extraocular muscles might contribute to VOR adaptation. When, during sinusoidal head rotation, the movement of one eye is limited by a opaque suction contact lens (the artificial vestibulo-ocular reflex technique), such that the imposed eye velocity is slower than head velocity, VOR gains in the other eye increase immediately.\textsuperscript{10-12} Sectioning of the ophthalmic branch of the trigeminal nerve, which carries proprioceptive signals to the trigeminal nucleus, abolishes this velocity-dependent effect on VOR gains from imposed eye movements.\textsuperscript{13-15} In our patients, horizontal VOR gains of the paretic eye are reduced in both directions, while gains of the non-paretic eye remain
normal. Why, then, did we not observe similar effects as in those observed in artificial VOR experiments? Proprioceptive signals may be defective after peripheral nerve palsy. Although proprioceptive signals are generally thought to project via the ophthalmic branch of the trigeminal nerve to the spinal trigeminal nucleus, a portion may also travel to the trigeminal nucleus via the ocular motor nerves. In addition, effects of muscle palsy differ from the effects of imposed movement of one eye; the paretic muscle is slack, whereas the muscles of an eye with imposed movement is taut. Furthermore, artificial VOR elicited by passive eye motion confers no functional advantage; diplopia and oscillopsia would result from motion of the fellow eye. Visual signals play a more dominant role than proprioceptive signals in the control of VOR with or without peripheral nerve palsy.

**Orbital mechanics and VOR adaptation**

Changes in normal orbital plant mechanics might contribute to the decreased VOR gains of the paretic eye in third nerve palsy. The relative contribution of agonist contraction and antagonist relaxation varies with orbital position, and it may be altered when one muscle of an agonist-antagonist pair is palsied. In paralytic strabismus, “contracture” (shortening and increased stiffness) occurs in the non-paretic antagonist muscle, while the paretic muscle lengthens in response to a change in orbital position of the globe. Anatomical and histological study showed that shortening or contracture of the non-paretic antagonist is associated with a decrease in the number of sarcomeres, whereas lengthening of the paretic muscle is accompanied by an increase in sarcomeres. In addition, denervation atrophy in the paretic muscle, and changes in orbital tissues have
also been documented in paralytic strabismus.\textsuperscript{23,24} These changes may alter VOR gains in both directions of the three axes of rotation.

**Monocular adaptation in unilateral third nerve palsy**

Hering suggested that the brain circuitry controlling gaze consists of two systems, one for conjugate movements, the other for vergence.\textsuperscript{25} Conjugate control operates in the vestibulo-ocular, saccade, smooth pursuit and optokinetic systems. Premotor neurons encode common signals to both abducens motoneurons and internuclear neurons in the abducens nucleus.\textsuperscript{26-28} The abducens motoneurons innervate the ipsilateral lateral rectus, while the internuclear neurons innervate the medial rectus motoneurons in the contralateral oculomotor nucleus.\textsuperscript{29-31}

Because the neuronal connectivity is suitable for conjugate motion, it might be presumed that only conjugate plasticity is possible. However, experiments on primates have shown that ocular motor systems are capable of selective, monocular adaptation.\textsuperscript{7,8,32} In monkeys, surgical weakening of the horizontal rectus muscles of one eye elicits an adaptation that selectively increases saccadic and VOR gains in the affected eye, while those of the unaffected eye remain normal.\textsuperscript{7,8} Disconjugate ocular motor adaptation has also been demonstrated in normal humans\textsuperscript{33,34} and monkeys\textsuperscript{6} in response to image disparity induced by anisometropic spectacles\textsuperscript{33} or prisms.\textsuperscript{6} Disconjugate saccades and pursuit are generated to compensate for the disparate retinal errors produced by the optical displacement of images.\textsuperscript{33,34}

This investigation is the first, to our knowledge, to demonstrate monocular adaptative change in the VOR in humans with third nerve palsy. We found that VOR gains
are selectively decreased during abduction and incyclotorsion of the paretic eye, without a conjugate decrease in gains of the non-paretic eye. These results exemplify monocular adaptation in humans with peripheral neuromuscular deficits. Differences in slippage of retinal images between the two eyes is a stimulus that can drive the monocular adaptation that we have recorded.

Changes in neural drive to each eye might occur independently at the level of motoneurons. Selective adaptation might be achieved by changing the sensitivity of each motoneuron pool to innervation from premotor neurons. The cerebellum, which mediates ocular motor adaptation, may have direct projections to ocular motoneurons. Using the Nauta method for tracing Wallerian degeneration, Carpenter and Strominger concluded that cerebello-oculomotor fibers from all part of the dentate nucleus project to the inferior rectus subdivision of the contralateral oculomotor nucleus, whereas fibers from ventral portions of the dentate nucleus project to the superior rectus subdivision of the contralateral oculomotor nucleus. However, using the more modern retrograde tracer technique, afferents from the dentate nucleus to the oculomotor nucleus are not identified.

Supranuclear neural circuitry is not exclusively conjugate. For example, for saccades, different populations of burst neurons mediate a pulse of innervation to each eye. In monkeys, 79% of premotor excitatory burst neurons in the caudal pontine paramedian reticular formation that were thought to encode conjugate velocity commands for saccades, actually encode monocular commands for either the ipsilateral or contralateral eye. Similarly, different populations of vestibular neurons provide innervation to the horizontal muscles of each eye. In addition to a major excitatory horizontal VOR
pathway which mediates conjugate eye movements via motoneurons and internuclear neurons in the abducens nucleus, a second direct excitatory horizontal VOR pathway exists. This second pathway originates from the ventral lateral vestibular nucleus, ascends through the ascending tract of Deiters to the ipsilateral medial rectus subdivision of the oculomotor nucleus.  

Furthermore, neurons in the feline medial vestibular nucleus (MVN) are activated antidromically only by local stimulation of the contralateral abducens nucleus, whereas another group of MVN neurons are activated only by stimulation of the ipsilateral medial rectus motoneurons pool, but not by stimulation of contralateral abducens nucleus.  

The cerebellum plays important roles in adaptive control of saccades and the VOR, including disconjugate control. Experimental inactivation of the deep cerebellar nuclei (including the fastigial nucleus) causes disconjugate saccadic dysmetria, such that both saccade magnitude and peak velocity differ in the two eyes. Patients with cerebellar degeneration or dysgenesis also show disconjugate dysmetria during and immediately after horizontal or vertical saccades, although brainstem circuits are typically not spared in spinocerebellar degenerations or malformations. The flocculus modulates VOR responses, and unilateral lesions of the rabbit flocculus cause different VOR gain changes in the two eyes. Thus the cerebellum exerts selective, dysconjugate control and may participate in the monocular adaptation of the horizontal and torsional VOR after third nerve palsy that we have identified.
<table>
<thead>
<tr>
<th>Patient</th>
<th>Age/Sex/ Duration</th>
<th>Side of lesion</th>
<th>% normal adduction*</th>
<th>% normal elevation*</th>
<th>% normal depression*</th>
<th>Deviations in primary position (PD)</th>
<th>Ptosis</th>
<th>Pupils</th>
<th>Misdirection</th>
<th>Imaging</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 AC</td>
<td>45 / F / 16 mo</td>
<td>Right</td>
<td>80%</td>
<td>0%</td>
<td>20%</td>
<td>14 XT, 6 LHT</td>
<td>Yes</td>
<td>Affected</td>
<td>No</td>
<td>MRI &amp; angiogram: PCA aneurysm</td>
<td>Surgical clipping</td>
</tr>
<tr>
<td>2 TA</td>
<td>39 / F / 2 wk</td>
<td>Right</td>
<td>10%</td>
<td>90%</td>
<td>10%</td>
<td>10 XT, 8 LHT</td>
<td>Yes</td>
<td>Spared</td>
<td>No</td>
<td>MRI: Enhanced meninges</td>
<td>Neurosarcodeosis</td>
</tr>
<tr>
<td>3 SF</td>
<td>44 / F / 23 mo</td>
<td>Right</td>
<td>60%</td>
<td>70%</td>
<td>90%</td>
<td>14 XT, 2 LHT</td>
<td>Yes</td>
<td>Spared</td>
<td>No</td>
<td>Normal MRI</td>
<td></td>
</tr>
<tr>
<td>4 DS</td>
<td>69 / F / 14 mo</td>
<td>Right</td>
<td>90%</td>
<td>50%</td>
<td>80%</td>
<td>16 XT, 6 LHT</td>
<td>Yes</td>
<td>Spared</td>
<td>No</td>
<td>Normal CT</td>
<td>Diabetes</td>
</tr>
<tr>
<td>5 MM</td>
<td>70 / F / 2 wk</td>
<td>Right</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>40 XT, 16 LHT</td>
<td>Yes</td>
<td>Spared</td>
<td>No</td>
<td>Normal CT</td>
<td>Diabetes, hypertension</td>
</tr>
<tr>
<td>6 GN</td>
<td>59 / M / 24 mo</td>
<td>Right</td>
<td>90%</td>
<td>20%</td>
<td>0%</td>
<td>30 XT, 16 LHT</td>
<td>Yes</td>
<td>Affected</td>
<td>No</td>
<td>Normal MRI &amp; angiogram</td>
<td></td>
</tr>
<tr>
<td>7 SC</td>
<td>66 / F / 1 wk</td>
<td>Right</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>16 XT, 6 LHT</td>
<td>Yes</td>
<td>Affected</td>
<td>No</td>
<td>Normal MRI &amp; angiogram</td>
<td>Diabetes, hypertension</td>
</tr>
<tr>
<td>8 WS</td>
<td>67 / M / 38 mo</td>
<td>Left</td>
<td>90%</td>
<td>80%</td>
<td>80%</td>
<td>4 XT, 4 RHT</td>
<td>Yes</td>
<td>Spared</td>
<td>No</td>
<td>Normal MRI</td>
<td>Diabetes, hypertension</td>
</tr>
<tr>
<td>9 VA</td>
<td>42 / F / 15 mo</td>
<td>Left</td>
<td>80%</td>
<td>0%</td>
<td>10%</td>
<td>6 XT, 8 RHT</td>
<td>Yes</td>
<td>Affected</td>
<td>No</td>
<td>MRI: Subarachnoid hemorrhage</td>
<td>Head trauma</td>
</tr>
<tr>
<td>10 AB</td>
<td>38 / F / 50 mo</td>
<td>Left</td>
<td>80%</td>
<td>80%</td>
<td>70%</td>
<td>6 XT, 4 RHT</td>
<td>Yes</td>
<td>Affected</td>
<td>No</td>
<td>MRI: Pituitary tumor extending to cavernous sinus</td>
<td>Surgical debulking</td>
</tr>
</tbody>
</table>

* Percent of normalduction
mo, month; wk, week; PD, prism dipters; XT, exotropia; RHT, right hypertropia; LHT, left hypertropia
PICA, posterior communicating artery
Table 4-2. Horizontal, vertical and torsional VOR and VVOR gains in patients with third nerve palsy

<table>
<thead>
<tr>
<th></th>
<th>VOR gain (SD)</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.5 Hz</td>
<td>Dark (VOR) 1 Hz</td>
<td>2 Hz</td>
<td>0.5 Hz</td>
<td>Paretic eye viewing (VVOR) 1 Hz</td>
<td>2 Hz</td>
</tr>
<tr>
<td></td>
<td>0.5 Hz</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Horizontal VOR</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal controls (n=15)</td>
<td>0.96 (0.07)</td>
<td>0.9 (0.04)</td>
<td>0.92 (0.04)</td>
<td>1.01 (0.07)</td>
<td>0.97 (0.05)</td>
<td>0.97 (0.05)</td>
</tr>
<tr>
<td>Paretic eye adducts</td>
<td>0.39 (0.21)*</td>
<td>0.51 (0.26)*</td>
<td>0.69 (0.33)**</td>
<td>0.59 (0.24)*</td>
<td>0.58 (0.31)*</td>
<td>0.62 (0.28)*</td>
</tr>
<tr>
<td>Paretic eye abducts</td>
<td>0.45 (0.19)*</td>
<td>0.55 (0.26)*</td>
<td>0.74 (0.31)**</td>
<td>0.59 (0.27)*</td>
<td>0.59 (0.30)*</td>
<td>0.62 (0.29)*</td>
</tr>
<tr>
<td>Non-paretic eye abducts</td>
<td>0.96 (0.20)</td>
<td>0.94 (0.17)</td>
<td>0.99 (0.32)</td>
<td>0.96 (0.17)</td>
<td>1.00 (0.04)</td>
<td>0.87 (0.14)</td>
</tr>
<tr>
<td>Non-paretic eye adducts</td>
<td>0.93 (0.31)</td>
<td>0.90 (0.21)</td>
<td>1.05 (0.38)</td>
<td>0.91 (0.15)</td>
<td>1.02 (0.07)</td>
<td>0.90 (0.10)</td>
</tr>
<tr>
<td><strong>Vertical VOR</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal controls (n=15)</td>
<td>0.90 (0.13)</td>
<td>0.91 (0.10)</td>
<td>0.91 (0.10)</td>
<td>1.07 (0.10)</td>
<td>0.99 (0.13)</td>
<td>0.99 (0.13)</td>
</tr>
<tr>
<td>Paretic eye elevates</td>
<td>0.37 (0.26)*</td>
<td>0.48 (0.27)*</td>
<td>0.67 (0.36)**</td>
<td>0.57 (0.35)*</td>
<td>0.52 (0.30)*</td>
<td>0.58 (0.30)*</td>
</tr>
<tr>
<td>Paretic eye depresses</td>
<td>0.45 (0.30)*</td>
<td>0.52 (0.31)*</td>
<td>0.67 (0.37)**</td>
<td>0.56 (0.35)*</td>
<td>0.51 (0.29)*</td>
<td>0.58 (0.29)*</td>
</tr>
<tr>
<td>Non-paretic eye elevates</td>
<td>0.73 (0.23)</td>
<td>1.02 (0.35)</td>
<td>1.07 (0.33)</td>
<td>1.06 (0.26)</td>
<td>1.10 (0.09)</td>
<td>1.05 (0.18)</td>
</tr>
<tr>
<td>Non-paretic eye depresses</td>
<td>0.75 (0.25)</td>
<td>1.02 (0.27)</td>
<td>1.06 (0.30)</td>
<td>1.07 (0.26)</td>
<td>1.09 (0.12)</td>
<td>1.05 (0.14)</td>
</tr>
<tr>
<td><strong>Torsional VOR</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal controls (n=15)</td>
<td>0.49 (0.08)</td>
<td>0.51 (0.10)</td>
<td>0.56 (0.08)</td>
<td>0.56 (0.10)</td>
<td>0.58 (0.08)</td>
<td>0.63 (0.08)</td>
</tr>
<tr>
<td>Paretic eye excurvator</td>
<td>0.16 (0.11)*</td>
<td>0.24 (0.12)*</td>
<td>0.33 (0.16)*</td>
<td>0.28 (0.10)*</td>
<td>0.28 (0.13)*</td>
<td>0.36 (0.20)*</td>
</tr>
<tr>
<td>Paretic eye incyclotors</td>
<td>0.18 (0.12)*</td>
<td>0.22 (0.12)*</td>
<td>0.32 (0.15)*</td>
<td>0.23 (0.16)*</td>
<td>0.24 (0.14)*</td>
<td>0.33 (0.22)*</td>
</tr>
<tr>
<td>Non-paretic eye Incyclotors</td>
<td>0.42 (0.16)</td>
<td>0.40 (0.14)</td>
<td>0.50 (0.13)</td>
<td>0.45 (0.20)</td>
<td>0.45 (0.15)</td>
<td>0.57 (0.14)</td>
</tr>
<tr>
<td>Non-paretic eye excurvator</td>
<td>0.46 (0.13)</td>
<td>0.41 (0.14)</td>
<td>0.51 (0.15)</td>
<td>0.46 (0.16)</td>
<td>0.46 (0.15)</td>
<td>0.59 (0.15)</td>
</tr>
</tbody>
</table>

* p < 0.001
* p < 0.01
Table 4-3. Static torsional VOR gain (ocular counterroll) in patients with third nerve palsy

<table>
<thead>
<tr>
<th></th>
<th>Light Non- Paretic Eye</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Incyclotort Excyclotort</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paretic eye</td>
<td>0.21 (0.10)</td>
<td>0.20 (0.11)</td>
<td>0.22 (0.09)</td>
<td>0.21 (0.11)</td>
<td>0.20 (0.14)</td>
<td>0.19 (0.15)</td>
<td>0.21 (0.13)</td>
</tr>
<tr>
<td>Normal (n=10)</td>
<td></td>
<td>0.11 (0.06)*</td>
<td>0.11 (0.09)**</td>
<td>0.23 (0.14)</td>
<td>0.23 (0.10)</td>
<td>0.08 (0.06)*</td>
<td>0.09 (0.10)**</td>
</tr>
</tbody>
</table>

* p < 0.01
** p < 0.05
Values in parentheses are standard deviations.
Figure 4-1. Mean horizontal VOR gains in patients with peripheral third nerve palsy. Adducting and abducting VOR and VVOR gains are reduced symmetrically in the paretic eye. Error bars indicate one standard deviation.
Third Nerve Palsy (n=10)

Horizontal VOR gain (dark)

Horizontal VOR gain (light) - Paretic eye viewing

Horizontal VOR gain (light) - Non-paretic eye viewing
Figure 4-2. Mean vertical VOR gains in patients with peripheral third nerve palsy. Upward and downward VOR and VVOR gains are reduced symmetrically in the paretic eye, so that their VVOR plots are overlapped in the middle and lower graphs. Error bars indicate one standard deviation.
Third Nerve Palsy (n=10)

Vertical VOR gain (dark)

Vertical VOR gain (light) - Paretic eye viewing

Vertical VOR gain (light) - Non-paretic eye viewing
Figure 4-3. Mean dynamic torsional VOR gains in patients with peripheral third nerve palsy. Excyclotorting and incyclotorting VOR and VVOR gains are reduced symmetrically in the paretic eye. Error bars indicate one standard deviation.
Third Nerve Palsy (n=10)

Torsional VOR gain (dark)

Torsional VOR gain (light) - Paretic eye viewing

Torsional VOR gain (light) - Non-paretic eye viewing
4.7 REFERENCES


SECTION II

THE SACCADIC SYSTEM IN THREE DIMENSIONS
CHAPTER 5

DYNAMICS OF SACCADES IN SIXTH NERVE PALSY
5.1 SUMMARY

Purpose: To analyze the effects of unilateral peripheral sixth nerve palsy on the dynamics of saccades in three axes of rotation.

Methods: Twenty-one patients (6 severe, 7 moderate, 8 mild) and 26 normal subjects were studied. Magnetic scleral search coils recorded movements of each eye during monocular viewing. Saccade amplitudes and peak velocities were computed.

Results: In severe palsy, the viewing paretic eye made a series of hypometric and slow abducting saccades, while the adducting non-paretic occluded eye made a series of saccades of decreasing amplitude and normal velocity. When the target stepped from the paretic hemi-range of duction to the center, the paretic eye made a normal initial saccade, followed by “backward” abducting drifts. Meanwhile, the non-paretic occluded eye made a normal saccade followed by “forward” abducting drifts. In moderate and mild palsy, horizontal saccade amplitudes and peak velocities were normal within the range of their excursion in both eyes. Vertical saccades and torsional nystagmus quick phases were normal in all patients.

Conclusions: The backward drifts that occur when the paretic eye adducts can be attributed to the relative contributions of the medial and lateral rectus muscles in different orbital positions, or to glissadic overshoot from a pulse-width error. The forward abducting drifts that occur when the non-paretic eye abducts are consistent with pulse-step mismatch in which the pulse is too small, indicating a neural adaptation to reduce the pulse that causes the backward drifts in the paretic eye.
Normal abducting peak velocities in the paretic eye in *moderate and mild* abduction palsy, without a conjugate increase in adducting peak velocities above normal in the non-paretic eye, indicates a selective neural adaptation in the paretic eye.
5.2 INTRODUCTION

Clinical testing of paralytic strabismus emphasizes examination of static deviations of the eyes. Information on saccade performance after sixth nerve palsy is sparse.\textsuperscript{1-4} Abduction palsy would be expected to lower saccades amplitude and velocity in the direction of palsy in the paretic eye. In this study, we investigated patients with unilateral peripheral sixth nerve palsy to assess the saccades of both the paretic and non-paretic eyes during monocular viewing with each eye. We describe here how horizontal saccades made by the paretic and non-paretic eyes vary with the eye used for fixation, the direction of movement, eye position in the orbit, and severity of palsy.

5.3 METHODS

Clinical assessment and imaging studies

Twenty-one patients with unilateral peripheral sixth nerve palsy were recruited from the Neuro-ophthalmology Unit at the University Health Network. Complete histories, and detailed ophthalmic and neurologic examinations were performed, recording the duration and age of onset of diplopia, the presence or absence of risk factors for ischemia (diabetes mellitus and hypertension), and associated neurologic symptoms and signs. The magnitude of strabismus was measured objectively using the prism and cover test, and subjectively using the Maddox rod and prism test (see Chapter 9 for details). Appropriate tests were performed, when indicated, to rule out myasthenia gravis, thyroid ophthalmopathy, other orbital diseases, and to detect intracranial lesions.

Ranges of duction was estimated independently by two examiners (AW and JAS) who graded the abduction defect as the estimated percentage of the normal abduction in
the other eye. Based on the abduction defect, patients were classified into three groups: mild (81-95% of normal range of abduction), moderate (51-80%), and severe (≤50%). Serial axial and sagittal T1- and T2-weighted magnetic resonance (MR) images with gadolinium enhancement were obtained (slice thickness = 5 mm) for all patients under 50 years of age and those with other neurologic signs. In this investigation, CT images of the head with contrast were obtained in all patients with ischemic risk factors and for patients over 50 years of age, although CT imaging is not our standard practice for such patients. If CT imaging was normal, patients were followed up after about 3 months. Those without improvement of their sixth nerve palsy at 3 months and those with an abnormal CT scan were further investigated with MR imaging.

**Eye movement recordings**

Visual stimuli and experimental protocol. To measure horizontal and vertical saccades, patients fixated a red laser spot of 0.25° in diameter, rear-projected onto a vertical flat screen 1 m away from the nasion. The laser was programmed to appear in five different target positions: center (at eye level in patient's midsagittal plane), 10° right, 10° left, 10° up and 10° down. Head position was stabilized with an occipital support and monitored by a search coil taped to the forehead. With one eye covered, patients were instructed to follow the laser spot as it stepped among positions. At each position the laser halted for 3 sec. In the horizontal target sequence, the laser started in the center, then stepped to 10° right, then back to center, then 10° left, cycling through this pattern 20 times. The vertical sequence was the same but with the laser stepping center-up-center-down. The horizontal and vertical target sequences were then repeated
with the other eye covered. To avoid fatigue, breaks for 1-3 min were provided approximately every 2 min.

Because torsional saccades cannot be elicited, torsional saccades data were obtained by analyzing quick phases during dynamic roll of the head about its naso-occipital axis (torsional vestibulo-ocular reflex, VOR). While viewing the laser target in the center position, subjects made active sinusoidal head-on body rotations in roll at frequencies of about 0.5, 1 and 2 Hz and amplitudes of about ± 10°, as monitored by a dual search coil taped to the forehead. Frequency of head roll was paced to a periodic "beep" tone.

**Recordings of eye movement and calibration.** Eye positions were measured by a 3-dimensional magnetic search coil technique, using 6 ft (183 cm) diameter coils field arranged in a cube (CNC Engineering, Seattle, Washington). In each eye, the patient wore a dual-lead scleral coil annulus designed to detect horizontal, vertical, and torsional gaze positions (Skalar Instrumentation, Delft, Netherlands). Horizontal and vertical eye movements were calibrated with saccades to steps of the laser target. Torsional movements were calibrated by attaching the scleral coil to a rotating protractor. Phase detectors employing amplitude modulation as described by Robinson provided signals of torsional gaze position within the linear recording range. Torsional precision was about ± 0.2°. There was minimal crosstalk; large horizontal and vertical movements produced deflections in the torsional channel of less than 4% of the amplitude of the horizontal and vertical movement. Any coil slippage was assessed by monitoring offsets in torsional eye position signal during testing. Consistency of calibrated positions after each eye movement provided evidence that the coil did not slip on the eye. Eye position data were filtered with
a bandwidth of 0 to 90 Hz and digitized at 200 Hz. They were recorded on disc for off-line analysis. Analog data were also displayed in real time by a rectilinear thermal array recorder (Model TA 2000, Gould Inc., Ohio).

Quick phases of vestibular nystagmus were identified by inspecting the eye position and velocity tracings. Eye position signal was digitally differentiated to yield eye velocity using 50 msec central difference differentiation. For each eye movement with a velocity greater than 10 deg/sec, peak velocity was marked. For each selected peak velocity, the time when eye velocity surpassed or dropped below 5% of maximum velocity was taken as the beginning and the end of a saccade. Cursors then marked the beginning and end of saccades in the corresponding eye position channel.

Data analyses. Asymptotic peak velocities of horizontal, vertical and torsional saccades were derived by computer analysis of velocity-amplitude scatter plots using an exponential best fit curve $^7$:

$$ P = V (1 - e^{-A/C}) $$

where $P$ is peak velocity at any point on the curve, $V$ is asymptotic peak velocity, $A$ is saccade amplitude, and $C$ is a constant (Figure 5-1).

For horizontal and vertical saccades, we used data from 26 normal subjects $^9,10$ (16 women; mean age, 61 ± 7 years; median age, 62 years; age range, 37 to 84 years). For torsional quick phases, we recruited ten other normal volunteers to serve as controls (5 women; mean age, 49 years; median age, 55 years; age range, 19 to 69 years).

Main sequence saccades in patients were compared to those in normals using the analysis of variance (ANOVA). Normometric saccades were defined as initial saccades (for a 10° target step) with amplitudes no different from those found in normal subjects, while
hypermetric and hypometric saccades were those with amplitudes of the initial saccade that differed significantly from normal controls. Because patients performed saccades to a 10° target step, asymptotic peak velocity in this range was also used for control subjects data. We used the initial slope (V/C ratio) of the best fit exponential curves (representing main sequences) to compare saccade velocities between patients and normal controls (see appendix). The steeper the initial slope, the higher the peak velocity for a given saccade amplitude.

To compare saccade durations between patients and normal controls, we calculated the mean saccade durations for saccades in amplitude bins of two degrees' width, and performed analysis of variance for each bin.

The research protocol followed the tenets of the Declaration of Helsinki and informed consent was obtained from all subjects.

5.4 RESULTS

General characteristics of patients

The characteristics of the 21 patients are shown in Table 5-1. The mean age was 59 ± 17 years (range, 19 - 77 years; median age, 64 years). There were 12 men. The duration of symptoms ranged from two weeks to 96 months, with a mean duration of 16 months. Mean follow-up duration was 16 months (range, 9 - 26 months). Six patients had severe sixth nerve palsy, seven had moderate and eight had mild palsy. Nineteen patients had idiopathic, presumed ischemic, peripheral lesions, and two had cavernous sinus lesions on MR imaging. Of the 19 patients with idiopathic palsy, 13 had normal MR imaging and 6 had normal CT scanning of the brain (Table 5-1). Five out of the six patients with
normal CT scans had ischemic factors, namely hypertension and diabetes, and had a complete resolution of their palsy within four to six months.

**Horizontal saccades**

**Severe sixth nerve palsy.** To illustrate saccades after severe palsy, Figure 5-2 shows recordings of horizontal saccades made by a patient (PL) with a right-sided palsy. With the *paretic right eye viewing*, the right eye made a series of hypometric rightward (abducting) saccades such that it reached a final position of 10° right (Figure 5-2A, top panel). At the same time, the occluded left eye made a series of rightward (adducting) saccades, with an initial amplitude of 10°, that progressively decreased with each successive saccade, until the eye reached a final position of 26° right (Figure 5-2A, bottom panel). During refixation from 10° in the right orbital hemi-range ofduction back to center position, the right eye made an initial leftward (adducting) saccade with an initial amplitude of 8°, followed by small backward drifts and corrective saccades until the eye reached center position (Figure 5-2A, top panel and inset). At the same time, the occluded left eye made a series of leftward (abducting) saccades, with an initial amplitude of 11°, that progressively decreased with each successive saccade. Forward drifts occurred between each successive abducting saccade (Figure 5-2A, bottom panel and inset).

When the target stepped from center to the 10° left position, both eyes made normometric leftward saccades (Figure 5-2A, top and bottom panels). During refixation from 10° left position back to the center, the abducting paretic right eye again made a series of hypometric rightward saccades until it reached center position (Figure 5-2A, top
panel). At the same time, the occluded non-paretic left eye made a series of rightward adducting saccades of decreasing amplitude (Figure 5-2A, bottom panel).

With the non-paretic left eye viewing, the paretic right eye made a hypometric (3°) rightward abducting saccade, which was followed by a small saccade to reach a final position of 4° right (Figure 5-2B, top panel). At the same time, the left eye made a normal rightward saccade and reached a final position of 10° in the right orbital hemi-range of duction (Figure 5-2B, bottom panel). During refixation from 10° right back to center, and from center to 10° in the left orbital hemi-range of duction, both eyes made leftward saccades that were normometric (Figure 5-2B, top and bottom panels). When the target stepped from the 10° left position back to center, abducting (rightward) saccades of the right eye were hypometric (Figure 5-2B, top panel), whereas those of the left eye were normometric (Figure 5-2B, bottom panel).

Similar patterns of duction were observed in the other five patients with severe sixth nerve palsy. Figure 5-3 shows the mean final eye position reached for 10° target steps in each eye for the group of six patients. During saccades from center to the paretic orbital hemi-range of duction (i.e. paretic eye abducts and non-paretic eye adducts) and with the paretic eye viewing, the mean final position reached was 6.7° for the paretic eye and 20.3° for the non-paretic eye (Figure 5-3A). The mean deviation between the eyes was 13.6°, being the secondary deviation (the angle between the visual axes when the paretic eye fixates) at 6.7° in the paretic hemi-range of motion. With non-paretic eye viewing, the mean final position reached was 2.3° for the paretic eye and 10.3° for the non-paretic eye (Figure 5-3B). The mean deviation between the eyes was 8.0°, being the primary deviation
(the angle between the visual axes when the non-paretic eye fixates) at 10.3° in the paretic hemi-range of motion in the orbit.

We plotted retinal error after each saccadic step in the viewing paretic eye versus saccade amplitude of the non-paretic occluded eye (Figure 5-4). Retinal error is defined as the difference between the retinal target position in space and the actual position of the paretic eye in the orbit after each saccade. Retinal error in the paretic fixating eye correlated highly with amplitude of the next saccade in the non-paretic occluded eye (Pearson correlation, \( r = 0.81 \)), consistent with retinal error signals from the paretic viewing eye driving both eyes.

Plots of amplitude versus peak velocity of initial saccades in patients with severe sixth nerve palsy are shown in Figure 5-5. In the paretic eye, abducting saccades were hypometric (Table 5-2; \( p < 0.001 \)), slow (Table 5-3; \( p < 0.01 \)), and of longer duration for their amplitudes (Table 5-4; \( p < 0.05 \)) during viewing with either eye. Adducting saccades in the paretic eye were within normal velocity range and durations, but were slightly slower than normal saccades (\( p < 0.1 \)). Saccade amplitudes, velocities, and durations in the non-paretic eye were normal.

**Moderate and mild sixth nerve palsy.** During viewing with either eye, saccades to 10° target steps had normal amplitudes (Table 5-2), velocities (Table 5-3), and durations (Table 5-4) in patients with moderate and mild sixth nerve palsy (Figures 5-6 to 5-8).

**Vertical saccades and torsional quick phases**
The amplitudes and peak velocities of vertical saccades, and torsional quick phases during dynamic head roll were normal in all patients (Figures 5-9 and 5-10). Durations of vertical saccades were normal.

5.5 DISCUSSION

The effects of sixth nerve palsy on saccades had not been systematically examined. We found that, in unilateral abduction palsy, horizontal saccades made by the paretic and non-paretic eyes vary with the eye used for fixation, the direction of movement, eye position in the orbit, and the severity of palsy. Abducting saccades are hypometric and slow in the paretic eye in severe palsy, as expected from weakness of the lateral rectus muscle.\(^{14,11}\) In moderate and mild palsy, horizontal saccade velocity and accuracy are normal within the range of their ductions.

Vertical and torsional saccades are normal, irrespective of the severity of palsy. In the straight ahead position, the lateral rectus acts as a pure abductor, with no vertical or torsional actions.\(^{12,13}\) When the eye is in an elevated position, the lateral rectus may have a secondary component of elevation. Similarly, when the eye is depressed, it may have a secondary component of depression.\(^{13-15}\) Whether the eye is in an adducted or abducted position, no additional vertical or torsional components of lateral rectus actions have been observed. Normal vertical saccades and torsional quick phases in our patients with sixth nerve palsy provide further evidence that the lateral rectus functions mainly as an abductor.

Changes in the dynamics of saccades in our patients, who were tested at one point in their courses, were expressed as changes from normal, rather than serial intra-subject
changes. Recovery toward normal values was not determined. Abnormalities were interpreted as deficits or adaptation to those deficits. In addition, the eye that patients habitually used for fixation was not determined. Each eye was alternately occluded and its immediate effects on saccade dynamics were assessed.

Centrifugal saccades to the paretic hemi-range of motion in severe abduction palsy

With the paretic eye viewing in severe sixth nerve palsy, when the target steps from center to 10° in the paretic hemi-range, an initial retinal error of 10° is used to drive both eyes, as evident by the initial 10° saccade made by the non-paretic occluded eye. The paretic eye, however, makes a hypometric saccade and falls short of the target. After the initial saccade, a residual retinal error signal, corresponding to the difference between the target position and orbital position of the paretic eye, generates a corrective saccadic command to both eyes. Thus, the non-paretic occluded eye makes a series of normometric saccades, in response to each successive retinal error signal from the paretic fixating eye, while the paretic eye makes a series of hypometric saccades until the target is placed on its fovea. When this is achieved, the final position of the non-paretic occluded eye overshoots the target, representing the secondary deviation.

With the non-paretic eye viewing when an initial retinal error signal of 10° is used to drive each eye, the non-paretic fixating eye makes a normometric saccade, while the paretic occluded eye makes a hypometric saccade. At the end of the initial saccade, the non-paretic eye reaches the target and retinal error becomes zero, such that no further saccades are generated. Thus, the final position of the paretic occluded eye undershoots the target, representing the primary deviation.
Retinal error in the paretic viewing eye correlated with saccade amplitude in the normal occluded eye, consistent with retinal error signals from the paretic eye driving both eyes.

**Centripetal saccades from the paretic hemi-range of motion to center in severe abduction palsy**

When the target steps from 10° in the paretic hemi-range back to the center, the viewing paretic eye in severe palsy makes a normometric initial adducting saccade. This is followed by "backward" abducting drifts of the paretic eye, which are corrected by small adducting saccades (see Figure 5-2A and insets). Meanwhile, the non-paretic occluded eye makes a normometric abducting saccade followed by a series of "forward" drifts and smaller abducting saccades.

The innervational changes during saccades consist of two components. A *pulse of innervation* 16, 17 consisting of a high frequency burst of phasic activity in agonist motoneurons. Phasic contraction of the agonist muscle overcomes viscous drag in the orbit, and is responsible for the rapid eye movement. Once the eye has been brought to a new position, agonist motoneurons assume a new, higher than resting level of tonic innervation, constituting saccadic step of innervation, which holds the eye in its new position against orbital elastic recoiling forces. The saccadic step, an eye position command, is created from the pulse (an eye velocity command) by a neural network that integrates, in the mathematical sense, eye-velocity commands into the appropriate position-coded information for the ocular motoneurons. For horizontal movements, this neural integrator is located in the medial vestibular nucleus and adjacent nucleus
prepositus hypoglossi \(^{18-20}\), and for vertical and torsional movements, it resides in the interstitial nucleus of Cajal and vestibular nucleus.\(^ {21-24}\)

For each position of the eye, there is a specific step discharge rate of agonist motor units and a reciprocally lower step discharge rate of their antagonist motor units. Thus, the ocular motor control signal for saccadic eye movement is a pulse and a step of innervation.\(^ {16, 25}\) Both the pulse and the step must be of the correct amplitude and appropriately matched for the eyes to be moved rapidly from one position to another and held steady at the end of the movement. The pulse does not actually have an abrupt offset before the step change in activity of eye muscles. Instead, there is a gradual decline (called a slide) in muscle torque after the saccade lands the eye at the position specified by the step in the orbit.\(^ {16, 26, 27}\) This slide may result from a gradual transition from the high frequency discharge of motoneurons during the pulse to a lower frequency discharge for the step. The innervation for a saccade then consists of a pulse-slide-step.

Backward abducting drifts of the paretic eye when it adducts were observed in previous studies \(^ {1, 2, 11}\), and can be attributed to the relative contribution of the agonist medial rectus and antagonist lateral rectus when the eye is in different orbital positions. By measuring \textit{in-situ} tendon forces and using electromyography, Collins \(^ {28}\) found that the medial rectus is important for phasic acceleration (created by the pulse) of the globe in both the adducting and abducting hemi-range of motion. However, for tonic position change (the step), the medial rectus contributes in the adducting field, and very little in the abducting hemi-range.\(^ {28}\) Thus, when the eye moves from an abducted position to the center, the adducting phasic acceleration comes mainly from contraction of the medial rectus, while the tonic eye position is maintained, in part, by relaxation of the lateral rectus.
In sixth nerve palsy, however, the paretic lateral rectus cannot be further relaxed, leading to a loss of the decrement in antagonist forces for the step of innervation. This results in a pulse-step mismatch in which the step is too small and accounts for the backward abducting drifts of the paretic eye.

The *forward drifts* that occur simultaneously in the *occluded non-paretic* eye may be explained if the brain detects the backward drifts in the paretic eye as pulse-step mismatch and attempts to compensate for the mismatch by increasing the size of the step command. This results in an inappropriately large step, and thus forward drifts, observed in the non-paretic eye.

A second central mechanism might also contribute to the backward abducting drift observed in the adducting paretic eye. For a typical normal saccade, the eye accelerates rapidly, reaching its peak velocity between 1/3 and 1/2 of the way through the movement.\(^{27}\) The eye then gently decelerates but usually stops relatively abruptly. Occasionally, in normal persons, the eye drifts for a few hundred milliseconds after the initial portion of the horizontal saccade is finished. Such postsaccadic drifts are called *glissades*.\(^{29}\) They are considered to represent a mismatch between the sizes of the pulse and step innervations that produce saccades. If the pulse portion is too large for a given step, glissadic overshoot occurs; if the pulse is small relative to the step, glissadic undershoot occurs.\(^{30}\)

The size of saccadic pulse is determined by *pulse width*, which corresponds to the duration of motoneurons firing, and by *pulse height*, which corresponds to the frequency of motoneurons firing and the number of motoneurons recruited.\(^{31}\) Using computer simulation and eye movement data from normal subjects, Bahill et al.\(^{31}\) demonstrated that normal saccades with glissadic overshoot have lowered peak velocities, and concluded
that glissadic overshoot is caused by pulse-width errors and not by pulse-height errors \(^{31}\); the pulse is too wide for its height in glissadic overshoot.

In our patients with severe sixth nerve palsy, adducting saccades in the paretic eye has lower peak velocities than most normal saccades \((p<0.1)\), and the backward abducting drifts that occur between saccades show decreasing velocity waveforms (see Figure 5-2A, top panel)—both being characteristics of glissadic overshoots. A pulse-step mismatch, resulting from pulse width errors, can explain the backward abducting drifts found in the paretic eye when it adducts.

The backward abducting drift in the viewing paretic eye delays the time for the eye to acquire a retinal target. As discussed, movements of the occluded non-paretic eye reflect the central signal that is used to drive both eyes. The forward drift that occurs simultaneously in the occluded non-paretic eye (see Figure 5-2A, bottom panel, upper inset) is consistent with a pulse-step mismatch in which the pulse is too small. This forward drift in the non-paretic eye may represent a central adaptation to decrease the pulse of innervation that is sent to both eyes, in order to reduce the pulse-step mismatch which created the backward abducting drifts in the paretic eye when it adducts. However, because the paretic lateral rectus cannot further relax, the step of innervation in the paretic eye remains small relative to the reduced pulse of innervation. Therefore, a pulse-step mismatch and backward abducting drifts persist in the paretic eye, despite this apparent neural adaptation.

**Proprioception and saccadic control**
Afferents from extraocular muscles proprioceptors project via the ophthalmic branch of the trigeminal nerve and the Gasserian ganglion to the spinal trigeminal nucleus. A portion of the afferent innervation may also travel to the trigeminal nucleus via the ocular motor nerves. The role of proprioception in the control of saccadic eye movements is uncertain. In monkeys, after bilateral sectioning of the ophthalmic branch of the trigeminal nerve, saccades made to remembered visual targets are accurate, even after the eyes are driven to a new position by electrical stimulation of the superior colliculus just before the saccade. Gauthier and Vercher measured the amplitudes of human horizontal saccades in the viewing eye, while the occluded eye was either allowed to move freely or held immobile in an eccentric position. No differences were found in saccade amplitudes in the viewing eye, whether the occluded eye was free or immobilized. In contrast, using a similar method but with movement of the occluded eye impeded near the straight ahead position, Knox et al. found a consistent decrease in saccade amplitudes in the viewing eye, which they interpreted as an attempt by the saccadic system to maintain conjugacy.

In our patients, saccade amplitudes in the non-paretic eye remain normal, despite decreased range of duction and the esotropic position of the paretic eye, suggesting that proprioception has little effect on saccadic control in paralytic strabismus. Effects of muscle palsy differ from the effects of experimental immobilization of one eye; the paretic muscle is slack, whereas the muscle of an immobilized eye is taut. No effect of defective proprioceptive signals from the paretic eye was detected after peripheral nerve palsy. Visual signals play a more dominant role than proprioceptive signals in the control of saccades with or without peripheral nerve palsy.
Saccade amplitudes and velocities in sixth nerve palsy

The size of the saccadic pulse is determined by pulse width, which corresponds to the duration of motoneurons firing, and by pulse height, which corresponds to the frequency of motoneurons firing and the number of motoneurons recruited. In ocular motor nerve palsies, the frequency of motoneuron firing transmitted to the muscle, and the number of axons innervating the muscle can be reduced. Since saccade amplitude is determined by pulse width multiplied by pulse height, one would anticipate a decrease in saccade amplitude in ocular motor nerve palsy. In addition, since saccade velocity is determined by the frequency of axon firing distal to the site of nerve damage, one would also anticipate a reduction in saccade velocity. This is indeed the case in our patients with severe palsy; their abducting saccades are hypometric, slow and of longer duration.

In contrast, in patients with moderate and mild palsy, abducting saccades have normal amplitudes, peak velocities and durations, despite the presence of palsy as indicated by limited abduction and esotropia. Abducting saccade amplitudes are normal because saccades are made to targets within the range of their limited duction. However, one might anticipate that the peak velocities would be reduced. Why are saccade velocities normal in our patients with moderate and mild palsy? One possibility is that saccade dynamics are unaffected unless a certain threshold number of axons are damaged. However, the pathophysiology of ocular motor nerve palsy is not known. A second possibility is that an ocular motor nerve lesion, such as after ischemic damage, may act as a high pass filter, allowing transient, high frequency firing but not sustained, low frequency firing. In this situation, the burst of activity may be normal, resulting in
normal saccade peak velocities, while the step of innervation is abnormal, resulting in abnormal eye positions.

Alternatively, the normal peak velocities in moderate and mild palsy may be due an adaptive neural mechanism. Patients with Guillain-Barré syndrome are capable of making saccades that have decreasing velocity waveforms and normal initial velocities.\textsuperscript{37} Using computer simulation, these saccades are attributed to intermittent block of peripheral conduction and an adaptive increase in saccadic burst duration.\textsuperscript{37} However, such increase in saccadic burst duration is not consistent with the normal peak velocities in our patients; their saccade durations are also normal. A likely explanation for the normal peak velocities that we found in moderate and mild palsy is an adaptive increase in the discharge frequency of motoneurons, so that the eyes can rapidly reach their target.

**Monocular adaptation in unilateral sixth nerve palsy**

This adaptation is apparently selectively monocular; the firing frequency increases only in motoneurons innervating the lateral rectus of the paretic eye. If the adaptation were binocular, arising from common premotor signals that are sent to both the abducens motoneurons and internuclear neurons in the abducens nucleus (see below), one would predict a conjugate increase in motoneuron firing to the medial rectus of the non-paretic eye, and hence an increase in adducting peak velocities above normal in the non-paretic eye. However, this would be disadvantageous - the non-paretic eye would reach the target before the paretic eye does. Indeed, we found that the peak velocities are normal in the non-paretic eyes, providing evidence that the adaptation is monocular. This selective
adaptation allows both eyes to reach a target in the paretic hemifield of motion rapidly and simultaneously.

Hering suggested that the brain circuitry controlling gaze consists of two systems, one for conjugate movements, the other for vergence. Conjugate control operates in the vestibulo-ocular, saccade, smooth pursuit and optokinetic systems. Premotor neurons encode common signals to both abducens motoneurons and internuclear neurons in the abducens nucleus. The abducens motoneurons innervate the ipsilateral lateral rectus, while the internuclear neurons innervate the medial rectus motoneurons in the contralateral oculomotor nucleus.

Because the neuronal connectivity is suitable for conjugate motion, it might be presumed that only conjugate plasticity is possible. However, experiments on primates have shown that ocular motor systems are capable of selective, monocular adaptation. In monkeys, surgical weakening of the horizontal rectus muscles of one eye elicits an adaptation that increases saccadic and VOR gains in the affected eye, while those of the unaffected eye remain normal. Disconjugate ocular motor adaptation has also been demonstrated in normal humans and monkeys in response to image disparity induced by anisometropic spectacles or prisms. Disconjugate saccades and pursuit are generated to compensate for the disparate retinal errors produced by the optical displacement of images.

Monocular adaptation might occur at the level of motoneurons, though they receive only sparse direct projections from the cerebellum, which is thought to mediate such adaptive changes. Supranuclear neural circuitry is not exclusively conjugate. Indeed, for saccades, different populations of burst neurons are found to mediate a pulse of
innervation to each eye. In monkeys, 79% of premotor excitatory burst neurons in the caudal pontine paramedian reticular formation that were thought to encode conjugate velocity commands for saccades, actually encode monocular commands for either the ipsilateral or contralateral eye.

The cerebellum plays important roles in adaptive control of saccades, including disconjugate control. Experimental inactivation of the deep cerebellar nuclei (including the fastigial nucleus) causes disconjugate saccadic dysmetria, such that both saccade magnitude and peak velocity differ in the two eyes. Patients with cerebellar degeneration or dysgenesis also show disconjugate dysmetria during and immediately after horizontal or vertical saccades, although brainstem circuits are typically not spared in spinocerebellar degenerations or developmental malformations. The cerebellum appears to exert selective, monocular control and may participate in the adaptation that we have identified in the saccadic system in response to peripheral nerve damage.
APPENDIX

The main sequence relationship of saccades is:

\[ P = V(1 - e^{-A/C}) \]

where \( P \) is peak velocity, \( V \) is asymptotic velocity, \( A \) is saccade amplitude and \( C \) is a constant.

The slope of the main sequence curve at any point is:

\[
\text{slope} = \frac{dP}{dA} = \frac{d}{dA}(V - Ve^{-A/C})
\]
\[
= \frac{d}{dA}(-Ve^{-A/C})
\]
\[
= -Ve \frac{d}{dA}(e^{-A/C})
\]
\[
= -V(-\frac{1}{C}e^{-A/C})
\]
\[
= \frac{V}{C}e^{-A/C}
\]

To calculate the initial slope of the main sequence, set \( A = 0 \)

then, \( e^{-A/C} = e^{-0} = 1 \)

then, initial slope = \( V/C \)
Table 5-1. Characteristics of patients with 6th nerve palsy

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age / Sex</th>
<th>Side of lesion</th>
<th>Duration (months)</th>
<th>Abduction deficit (% normal)</th>
<th>Imaging</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (PL)</td>
<td>21 / M</td>
<td>Right</td>
<td>2 weeks</td>
<td>0% (severe)</td>
<td>Normal MRI</td>
<td>Improved after 4 mons</td>
</tr>
<tr>
<td>2 (JM)</td>
<td>46 / M</td>
<td>Right</td>
<td>2 weeks</td>
<td>0% (severe)</td>
<td>Normal MRI</td>
<td>Resolved after 3 mons</td>
</tr>
<tr>
<td>3 (KE)</td>
<td>75 / F</td>
<td>Right</td>
<td>2</td>
<td>10% (severe)</td>
<td>Normal CT</td>
<td>Resolved after 4 mons (HTN, DM)</td>
</tr>
<tr>
<td>4 (AM)</td>
<td>75 / F</td>
<td>Right</td>
<td>2</td>
<td>50% (severe)</td>
<td>Normal CT</td>
<td>Resolved after 6 mons (HTN)</td>
</tr>
<tr>
<td>5 (VI)</td>
<td>65 / F</td>
<td>Left</td>
<td>36</td>
<td>50% (severe)</td>
<td>Normal MRI</td>
<td>Idiopathic</td>
</tr>
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<td>6 (MB)</td>
<td>19 / F</td>
<td>Left</td>
<td>3 weeks</td>
<td>0% (severe)</td>
<td>MRI: Left cavernous sinus hemangioma</td>
<td>Diplopia</td>
</tr>
<tr>
<td>7 (SC)</td>
<td>65 / M</td>
<td>Right</td>
<td>3 weeks</td>
<td>80% (moderate)</td>
<td>Normal CT</td>
<td>Resolved after 4 mons (DM)</td>
</tr>
<tr>
<td>8 (JC)</td>
<td>40 / M</td>
<td>Right</td>
<td>9</td>
<td>80% (moderate)</td>
<td>MRI: Sphenoid wing meningioma with invasion of right cavernous sinus</td>
<td>Diplopia, right facial paraesthesia</td>
</tr>
<tr>
<td>9 (TH)</td>
<td>77 / M</td>
<td>Right</td>
<td>30</td>
<td>60% (moderate)</td>
<td>Normal MRI</td>
<td>Idiopathic</td>
</tr>
<tr>
<td>10 (DW)</td>
<td>65 / M</td>
<td>Left</td>
<td>96</td>
<td>70% (moderate)</td>
<td>Normal MRI</td>
<td>Idiopathic</td>
</tr>
<tr>
<td>11 (SCH)</td>
<td>50 / F</td>
<td>Left</td>
<td>24</td>
<td>80% (moderate)</td>
<td>Normal MRI</td>
<td>Idiopathic</td>
</tr>
<tr>
<td>12 (JM2)</td>
<td>46 / M</td>
<td>Left</td>
<td>3 weeks</td>
<td>80% (moderate)</td>
<td>Normal MRI</td>
<td>Resolved after 6 mons (HTN)</td>
</tr>
<tr>
<td>13 (EM)</td>
<td>64 / M</td>
<td>Left</td>
<td>3 weeks</td>
<td>80% (moderate)</td>
<td>Normal CT</td>
<td>Resolved after 5 mons (HTN)</td>
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<tr>
<td>14 (NR)</td>
<td>75 / F</td>
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<td>4</td>
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<td>Idiopathic</td>
</tr>
<tr>
<td>Patient</td>
<td>Age / Sex</td>
<td>Side of lesion</td>
<td>Duration (months)</td>
<td>Abduction deficit (% normal)</td>
<td>Imaging</td>
<td>Comments</td>
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<tr>
<td>15</td>
<td>RL</td>
<td>Right</td>
<td>10</td>
<td>95% (mild)</td>
<td>Normal MRI</td>
<td>Idiopathic</td>
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<tr>
<td>16</td>
<td>EF</td>
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<td>95% (mild)</td>
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<td>17</td>
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<td>Resolved after 4 months (HTN, DM)</td>
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<td>19</td>
<td>GC</td>
<td>Left</td>
<td>34</td>
<td>90% (mild)</td>
<td>Normal MRI</td>
<td>Idiopathic</td>
</tr>
<tr>
<td>20</td>
<td>IW</td>
<td>Left</td>
<td>12</td>
<td>90% (mild)</td>
<td>Normal MRI</td>
<td>Idiopathic</td>
</tr>
<tr>
<td>21</td>
<td>LC</td>
<td>Left</td>
<td>60</td>
<td>80% (mild)</td>
<td>Normal MRI</td>
<td>Idiopathic</td>
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HTN, hypertension; DM, diabetes mellitus
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</tr>
<tr>
<td>Abduction</td>
<td>3.15 (2.13)*</td>
<td>8.59 (1.82)</td>
</tr>
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<td>Adduction</td>
<td>8.35 (1.38)</td>
<td>8.33 (1.94)</td>
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<td>MODERATE (n=7)</td>
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<td>Abduction</td>
<td>8.51 (1.93)</td>
<td>8.61 (2.22)</td>
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<td>Adduction</td>
<td>8.29 (2.46)</td>
<td>8.43 (2.12)</td>
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<tr>
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<tr>
<td>Abduction</td>
<td>8.32 (2.31)</td>
<td>8.60 (1.96)</td>
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<tr>
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<td>8.25 (1.84)</td>
<td>8.43 (1.81)</td>
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<td>NORMAL CONTROLS (n=26)</td>
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<tr>
<td>Abduction</td>
<td>--</td>
<td>8.44 (1.32)</td>
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<tr>
<td>Adduction</td>
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<td>8.28 (1.42)</td>
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* p < 0.001
Table 5-3. Saccadic peak velocities: Mean initial slope (V/C ratio)

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<tr>
<td>Abduction</td>
<td>27.9 (4.9)</td>
<td>28.5 (4.5)</td>
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<td>Adduction</td>
<td>30.4 (3.3)</td>
<td>29.6 (3.9)</td>
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<td>NORMAL CONTROLS  (n=26)</td>
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<tr>
<td>Abduction</td>
<td>--</td>
<td>31.6 (2.7)</td>
</tr>
<tr>
<td>Adduction</td>
<td>--</td>
<td>30.7 (2.8)</td>
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* p < 0.01
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<tr>
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<th>0 - 2 deg saccades</th>
<th>2.01 - 4 deg saccades</th>
<th>4.01 - 8 deg saccades</th>
<th>6.01 - 8 deg saccades</th>
<th>8.01 - 10 deg saccades</th>
<th>10.1 - 12 deg saccades</th>
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<td>Paretic eye abducts</td>
<td>59.3 (6.5)*</td>
<td>91.0 (14.3)†</td>
<td>91.0 (5.3)†</td>
<td>114.0 (1.4)*</td>
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<td>---</td>
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<td>40.2 (4.3)</td>
<td>63.7 (7.2)</td>
<td>78.2 (5.3)</td>
<td>83.2 (5.4)</td>
<td>84.2 (3.7)</td>
<td>98.2 (4.8)</td>
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<td>61.4 (4.7)</td>
<td>74.5 (4.9)</td>
<td>82.4 (5.7)</td>
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<td>65.9 (6.2)</td>
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<td><strong>Moderate (n=7)</strong></td>
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<td>44.5 (6.5)</td>
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<td>77.4 (5.8)</td>
<td>78.1 (4.7)</td>
<td>91.2 (4.2)</td>
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<td><strong>Mild (n=8)</strong></td>
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<td>44.9 (3.9)</td>
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<td>70.0 (7.1)</td>
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<td>100.6 (19.9)</td>
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<td>63.3 (5.0)</td>
<td>74.3 (4.2)</td>
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<td>81.7 (4.9)</td>
<td>91.0 (7.1)</td>
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<td>71.8 (7.4)</td>
<td>75.4 (6.1)</td>
<td>82.1 (5.3)</td>
<td>90.5 (6.7)</td>
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<td><strong>Normal controls (n=26)</strong></td>
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<tr>
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<td>42.0 (5.6)</td>
<td>65.3 (8.0)</td>
<td>75.0 (8.1)</td>
<td>79.4 (6.3)</td>
<td>82.9 (2.5)</td>
<td>93.0 (5.7)</td>
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</table>

* p < 0.01
† p < 0.05

Values in brackets are 1 standard deviations
Figure 5-1. Plot of saccade amplitudes versus peak velocities in a normal subject during horizontal saccades. Solid line is the exponential best fit curve using the equation: \( P = V \left(1 - e^{-A/C}\right) \), where \( P \) is peak velocity at any point on the curve, \( V \) is asymptotic peak velocity, \( A \) is saccade amplitude, and \( C \) is a constant.
Figure 5-2. Magnetic scleral search coil recordings of horizontal saccades to 10° target steps of a patient (PL) with severe right sixth nerve palsy during (A) paretic right eye viewing, and (B) non-paretic left eye viewing. Insets in (A) show that during refixation from 10° right to center position, the paretic right eye made an initial leftward (adducting) saccade, followed by small backward drifts and corrective saccades. At the same time, the occluded left eye made a series of leftward (abducting) saccades, followed by forward drifts between each successive saccade. R, right; L, left.
(B) Left (non-paretic) eye viewing

Right (paretic) eye

Left (non-paretic) eye
Figure 5-3. Mean final eye position reached for $10^\circ$ target steps from center to paretic hemi-range of duction, and from paretic hemi-range of duction to center, in each eye for the group of six patients with severe sixth nerve palsy during (A) paretic eye viewing, and (B) non-paretic eye viewing. Error bars indicate one standard deviation.
A. Paretic eye viewing

![Graph A: Paretic eye viewing](image)

B. Non-paretic eye viewing

![Graph B: Non-paretic eye viewing](image)
Figure 5-4. Plot of retinal error after each saccade in the viewing paretic eye versus saccade amplitude of the non-paretic occluded eye in 21 patients with unilateral sixth nerve palsy, during 10° target steps from center to paretic hemi-range of duction. Pearson correlation coefficient (r) is 0.81. Retinal error signals from the paretic eye determine the saccadic amplitude of the non-paretic eye.
Figure 5-5. Plots of amplitude versus peak velocity of initial horizontal saccades in patients with severe sixth nerve palsy during (A) paretic eye viewing, and (B) non-paretic eye viewing. Solid lines represent one standard deviation above and below the mean peak velocity of 26 normal subjects. Scattered symbols represent saccades from the six patients with severe palsy. Abducting saccades are hypometric and slow for their amplitude in the paretic eye during viewing with either eye. Adducting saccades are slightly slowed (p<0.1) in the paretic eye. Both abducting and adducting saccades in the non-paretic eye have normal velocities.
Severe 6th Nerve Palsy (n = 6)

(A) Paretic eye viewing - Horizontal saccades

(B) Non-paretic eye viewing - Horizontal saccades
Figure 5-6. Magnetic scleral search coil recordings of horizontal saccades to 10° target steps of a patient (RL) with mild right sixth nerve palsy during (A) paretic right eye viewing, and (B) non-paretic left eye viewing. During either eye viewing, both the paretic and non-paretic eyes made normometric saccades on abduction and adduction. R, right; L, left.
Figure 5-7. Plots of amplitude versus peak velocity of initial horizontal saccades in patients with moderate sixth nerve palsy during (A) paretic eye viewing, and (B) non-paretic eye viewing. Solid lines represent one standard deviation above and below the mean peak velocity of 26 normal subjects. Scattered symbols represent saccades from the seven patients with moderate palsy. Both abducting and adducting saccades in the paretic and non-paretic eyes have normal velocities.
Moderate 6th Nerve Palsy (n = 7)

Paretic eye viewing - Horizontal saccades

Non-paretic eye viewing - Horizontal saccades
Figure 5-8. Plots of amplitude versus peak velocity of initial horizontal saccades in patients with mild sixth nerve palsy during (A) paretic eye viewing, and (B) non-paretic eye viewing. Solid lines represent one standard deviation above and below the mean peak velocity of 26 normal subjects. Scattered symbols represent saccades from the eight patients with moderate palsy. Both abducting and adducting saccades in the paretic and non-paretic eyes have normal velocities.
Mild 6th Nerve Palsy (n = 8)

**Paretic eye viewing - Horizontal saccades**

**Non-paretic eye viewing - Horizontal saccades**
Figure 5-9. Plots of amplitude versus peak velocity of vertical saccades in patients with severe, moderate, and mild sixth nerve palsy during paretic and non-paretic eye viewing. Solid lines represent one standard deviation above and below the mean peak velocity of 26 normal subjects. Scattered symbols represent saccades from patients. Vertical saccades in the paretic and non-paretic eyes have normal velocities and amplitudes.
Vertical saccades

Paretic eye viewing

Severe (n=6)

Moderate (n=7)

Mild (n=8)

Non-paretic eye viewing

- Paretic eye elevates
- Paretic eye depresses
- Non-paretic eye elevates
- Non-paretic eye depresses
**Figure 5-10.** Plots of amplitude versus peak velocity of torsional quick phases in patients with severe, moderate, and mild sixth nerve palsy during paretic and non-paretic eye viewing. Solid lines represent one standard deviation above and below the mean peak velocity of 10 normal subjects. Scattered symbols represent quick phases from patients. Torsional quick phases in the paretic and non-paretic eyes have normal velocities and amplitudes.
Torsional saccades

Paretic eye viewing

Severe (n=6)

Moderate (n=7)

Mild (n=8)

Non-paretic eye viewing

- Paretic eye excyclo-torts
- Paretic eye incyclo-torts
- Non-paretic eye excyclo-torts
- Non-paretic eye incyclo-torts
REFERENCES


34. Guthrie BL, Porter JD, Sparks DL. Corollary discharge provides accurate eye position information to the oculomotor system. Science 1983;221:1193-1195.


SECTION III

LISTING'S AND DONDER'S LAWS DURING SACCADIES AND FIXATION
CHAPTER 6

ADAPTIVE NEURAL MECHANISM FOR LISTING'S LAW

REVEALED BY SIXTH NERVE PARALYSIS
6.1 SUMMARY

Purpose: During fixation and saccades, human eye movements obey Listing's law, which specifies the torsional eye position for each combination of horizontal and vertical eye positions. To study the brain regions that implement Listing's law, we measured whether it was violated in peripheral and central unilateral sixth nerve palsy.

Methods: Twenty patients with peripheral sixth nerve palsy (13 chronic i.e. ≥ 4 weeks duration; and 7 acute, i.e. < 4 weeks duration), seven patients with central sixth nerve palsy caused by brainstem lesions, and ten normal subjects were studied using scleral search coils. With head immobile, subjects made saccades to a target that moved between straight ahead and 8 eccentric positions. At each target position, fixation was maintained for 3 seconds before the next saccade. To quantify violations of Listing's law, we measured ocular torsion during fixation and during saccades, and compared it to the torsion predicted by the law; the standard deviation of the differences between the predicted and measured torsion was called Listing deviation.

Results: Patients with central sixth nerve palsy had abnormal ocular torsion in both the paretic and non-paretic eyes, violating Listing's law. During fixation, Listing deviation averaged 2.4° in the paretic eye, and 1.7° in the non-paretic eye, compared to 0.8° in normal controls (p<0.05). During saccades, Listing deviation averaged 2.7° in the paretic eye, and 1.6° in the non-paretic eye, compared to 0.8° in normal controls (p<0.05). Donders' law was also violated in both eyes of patients with central sixth nerve palsy; they showed an abnormally wide range of ocular torsion in any given gaze direction. In contrast, patients with acute peripheral palsy had abnormal ocular torsion only in the paretic eye, but not the non-paretic eye. Listing deviation of the paretic eye averaged 2.3° during
fixation and 3.2° during saccades (p<0.05). Donders' law was obeyed in acute peripheral palsy. Patients with chronic peripheral sixth nerve palsy obeyed Listing's and Donders' laws during both fixation and saccades.

**Conclusions:** Patients with central unilateral sixth nerve palsy have abnormal ocular torsion in both eyes, demonstrating that brainstem circuits normally participate in the maintenance of Listing's law. Patients with acute peripheral sixth nerve palsy violate Listing's law, whereas patients with chronic palsy obey it, indicating that neural adaptation can restore Listing's law even when the eye muscles remain abnormal.
6.2 INTRODUCTION

During fixation, saccades and smooth pursuit, the eyes rotate freely in the horizontal and vertical dimensions, with torsion being constrained.\textsuperscript{1-3} This constrain on torsion has been described by Donders' and Listing's laws.\textsuperscript{4} Donders' law states that there is only one torsional eye position for each combination of horizontal and vertical eye positions.\textsuperscript{2,4} Listing's law is a special case of Donders' law and quantitatively specifies the torsional angle for each gaze direction. It states that, with the head fixed, there is an eye position called primary position, with the property that all other eye orientations that the eye actually assumes can be reached by a single rotation about an axis in a plane called Listing's plane.\textsuperscript{4}

Listing's law has been studied systematically in monkeys\textsuperscript{5-9} and normal humans\textsuperscript{1,2,10,11}, but not in any subjects with paralytic strabismus. Here we investigated patients with unilateral sixth nerve palsy to determine whether Listing's law is obeyed during fixation and saccades. We found that patients with central sixth nerve palsy have abnormal ocular torsion in both eyes, suggesting that brainstem circuits normally help maintain Listing's law. Patients with acute peripheral sixth nerve palsy violate Listing's law, whereas patients with chronic palsy obey it, suggesting that neural adaptation can restore Listing's law even when the eye muscles remain abnormal.

6.3 METHODS

We recruited 27 patients with unilateral sixth nerve palsy from the Neuro-ophthalmology Unit at the University Health Network. A complete history was taken, and detailed ophthalmic and neurologic examinations were performed. The age of onset,
the presence or absence of risk factors for ischemia (diabetes mellitus and hypertension), duration of diplopia, and associated neurologic symptoms and signs were recorded. Patients with diplopia of less than 4 weeks' duration were classified as having acute palsy; all others were designated here as chronic. Strabismus was measured using the prism and cover test, and the Maddox rod (see Chapter 9 for details). When indicated, appropriate tests were performed to rule out myasthenia gravis, thyroid ophthalmopathy, other orbital diseases, or intracranial lesions.

Ranges of duction was estimated independently by two examiners (AW and JAS) who graded the abduction defect as the estimated percentage of the normal abduction in the other eye. Based on the abduction defect, patients were classified into three groups: mild (81-95% of normal range of abduction), moderate (51-80%), and severe (≤50%).

Serial axial and sagittal T1- and T2-weighted magnetic resonance (MR) images with gadolinium enhancement were obtained (slice thickness = 5 mm) for all patients under 50 years of age and those with other neurologic signs. In this investigation, CT images of the head with contrast were obtained in all patients with ischemic risk factors and for patients over 50 years of age, although CT imaging is not our standard practice for such patients. If CT imaging was normal, patients were followed at about 3 months. Those without improvement of their sixth nerve palsy at 3 months and those with an abnormal CT scan were further investigated with MR imaging.

**Eye movement recordings**

**Visual stimuli and experimental protocol.** Eye position was measured with search coils while patients fixated a red laser spot of 0.25° in diameter, rear-projected onto a
vertical flat screen 1 m away from the nasion. The laser was programmed to appear in nine different target positions, arranged in a 3 x 3 square. The middle row of this array was at eye level, the other two 10° above and below. In each row, the center target lay in the patient's midsagittal plane, the other two 10° right and left of it.

With one eye covered, patients were instructed to follow the laser spot as it stepped among positions. At each position the laser halted for 3 s. In the horizontal target sequence, the laser started in the center, then stepped to the 10° right position, then back to center, then 10° left, cycling through this pattern 10 times for each eye. The vertical sequence was the same but with the laser stepping center-up-center-down; the two diagonal sequences stepped along oblique lines, between opposite corners of the target array. Recordings were then made with the other eye fixating and the fellow eye occluded. To avoid fatigue, breaks for 1-3 min were provided approximately every 2 min.

**Recordings of eye movement and calibration.** Eye positions were measured by a 3-dimensional magnetic search coil technique, using a 6 ft (183 cm) diameter coil field arranged in a cube (CNC Engineering, Seattle, Washington). In each eye, the patient wore a dual-lead scleral coil annulus designed to detect horizontal, vertical, and torsional gaze positions (Skalar Instrumentation, Delft, Netherlands). Horizontal and vertical eye movements were calibrated with saccades to steps of the laser target. Torsional movements were calibrated by attaching the scleral coil to a rotating protractor. Phase detectors employing amplitude modulation as described by Robinson\textsuperscript{12} provided signals of torsional gaze position within the linear range. Torsional precision was about ± 0.2°. There was minimal crosstalk; large horizontal and vertical movements produced deflections in the torsional channel of less than 4% of the amplitude of the horizontal and
vertical movement. Any coil slippage was assessed by monitoring offsets in torsional eye position signal during testing. Consistency of calibrated positions after each eye movement provided evidence that the coil did not slip on the eye. Eye position data were filtered with a bandwidth of 0 to 90 Hz and digitized at 200 Hz. They were recorded on disc for off-line analysis. Analog data were also displayed in real time by a rectilinear thermal array recorder (Model TA 2000, Gould Inc., Ohio).

**Coordinate system**

Listing's law can be expressed using different coordinate systems.\(^1\text{,}^2\text{,}^3\text{,}^10\text{,}^{11}\text{,}^{13\text{,}15}\) In this paper, we used Helmholtz's coordinate, which is particularly useful in presenting binocular data.\(^15\) In this system, an eye position is decomposed into a series of three sub-rotations. Starting from primary position: first a torsional rotation through angle T about the line of sight, then a horizontal rotation through angle H about a head-fixed vertical axis, and finally a vertical rotation through angle V about the interaural axis. Expressed in Helmholtz coordinates, Listing's law says that:

\[
T = -\frac{HV}{2} \quad (1)
\]

where all angles are given in radians (not degrees). Positive directions for angles T, H and V are clockwise, right and up, respectively, all from the subject's point of view. Equation (1) is actually not precisely equivalent to Listing's law, but it is a very close approximation; within 30° of primary position, the discrepancy is less than 0.1°.\(^16\)

We defined the direction of torsion from the subject's point of view. Rotation of the upper pole of the iris towards the subject's right shoulder was designated as clockwise
(CW), whereas rotation of the upper pole of the iris towards the subject's left shoulder was designated as counter-clockwise (CCW).

As equation (1) makes clear, Listing's law requires that the Helmholtz-torsional angle of the eye varies as a function of horizontal and vertical eye position. Figure 6-1 depicts the torsional positions of the eye, represented by thin black lines with respect to the vertical meridian, in different combination of horizontal and vertical eye positions, as viewed by the examiner. If the eye is 30° down and 30° left (bottom right panel), then the eye (thin black line) rotates 7.9° (0.14 rad) counterclockwise, with respect to the vertical meridian (dashed line). In other words, Listing's law specifies quantitatively the degree of ocular torsion for any given horizontal and vertical eye position. Any torsion that differs from that specified by equation (1) means that Listing's law is violated.

Data analysis and statistical methods

Eye position and angular velocity were computed from coil signals. Eye positions were expressed using Helmholtz angles in degrees. For analysis, fixations were defined as periods when eye velocity was less than 30°/s, and saccades when eye velocity exceeded 50°/s. For each subject, we computed a set of best-fit functions, expressing each eye's torsion as a function of its horizontal and vertical angles, and expressing the horizontal and vertical angles of the non-viewing eye as a function of the horizontal and vertical angles of the viewing eye. Using these fitted functions, we then computed the typical torsion of both eyes, and the typical horizontal and vertical positions of the non-viewing eye, when the viewing eye fixated the 9 targets in our array. For example, Figure 6-2A shows the eye movement recordings of patient CS while the non-paretic left
eye viewed a target that stepped from center – 10° up – center – 10° down. Figure 6-2B shows the horizontal, vertical and torsional angles of the non-viewing, paretic right eye of this patient while the left eye looked at the 9 target positions—the 9 corners of the inside grid in the figure. The center of each small cross marks the gaze direction of the right eye; the tilt of the cross depicts the eye's torsion. We fitted functions to these data to find the typical torsion of the paretic right eye for each position of the fixating left eye. The large crosses in Figure 6-2C plot these fitted torsional positions. For comparison, the regions with a grid patterns in this figure mark the range one standard deviation above and below the mean torsion in normal subjects. For example, when this patient looked 10° up with the left eye, the paretic right eye was typically oriented 6.1° clockwise, well outside the range of normal torsion, indicating that Listing's law was violated in this position.

To quantify violations of Listing's law, we compared the ocular torsion in each recorded eye position to the torsion predicted by the law; the standard deviation of the differences between the predicted and measured torsion was called the Listing deviation. To quantify violations of Donders' law, we computed the second-order function of best fit (see Appendix). The ocular torsion in each recorded eye position was compared to the torsion predicted by this second-order function; the standard deviation of the differences between the predicted and measured torsion was called the Donders deviation.

In all 27 patients, Listing's and Donders' deviations in both the paretic and non-paretic eyes did not differ during paretic or non-paretic eye viewing. In what follows, we report only Listing's and Donders' deviations during non-paretic eye viewing; deviations during paretic eye viewing were similar. Statistical analysis was performed using analysis of variance. Values were defined as significant when p < 0.05.
The research protocol was approved by the University Health Network Ethics Committee and followed the tenets of the Declaration of Helsinki. Informed consent was obtained from all subjects.

6.4 RESULTS

General characteristics of patients

The characteristics of the 27 patients are shown in Tables 6-1 and 6-2. The mean age was 60 years (range, 21 - 79 years; median age, 64 years); 14 of them were men. The duration of symptoms ranged from one week to 240 months, with a mean duration of 31 months. Mean follow-up duration was 13 months (range, 8 - 24 months). All patients had an inconstant esotropia, which increased in the field of action of the paretic muscle. Twenty patients had sixth nerve palsy caused by idiopathic, presumed ischemic, peripheral lesions (Table 6-1). Thirteen of them had chronic peripheral palsy, while 7 had acute peripheral palsy. Fourteen patients had normal MR imaging and 6 had normal CT scanning of the brain. Five out of the six patients with normal CT scan had ischemic factors, such as hypertension and diabetes, and had a complete resolution of their palsy within four to six months. Seven patients had central sixth nerve palsy caused by brainstem lesions, as shown by MR imaging (Table 6-2). Lesions included demyelination (3 patients), cavernous hemangioma (2), meningioma (1), and infarct (1). All seven patients had neurologic symptoms and signs in addition to diplopia.

Ten normal subjects served as controls (5 women; mean age, 49 years; median age, 55 years; age range, 19 to 69 years).
Listings and Donders deviations in peripheral sixth nerve palsy

**Chronic peripheral palsy.** Figure 6-3 shows the mean torsion in 9 target positions in patients with *chronic* peripheral sixth nerve palsy, as compared with the range one standard deviation above and below the mean torsion in normal subjects. All 13 patients had normal torsion in all 9 target positions in both the paretic and non-paretic eyes, regardless of whether they had mild, moderate or severe palsy. Listing deviation of the paretic eye averaged $0.8 \pm 0.2^\circ$ during fixation and $0.9 \pm 0.2^\circ$ during saccades, compared to $0.8 \pm 0.3^\circ$ in controls during both tasks (Figure 6-4). Chronic peripheral sixth nerve palsy obeyed Listing’s law.

**Acute peripheral palsy.** Patients with *acute* peripheral sixth nerve palsy had abnormal torsion in the *paretic* eye, but normal torsion in the *non-paretic* eye, regardless of the severity of their palsy (Figure 6-5). Listing deviation of the paretic eye averaged $2.3 \pm 1.3^\circ$ during fixation and $3.2 \pm 2.0^\circ$ during saccades ($p<0.05$) (Figure 6-4). Listing's law failed idiosyncratically in any of the 9 target positions, with no pattern across patients.

However, all patients with *acute* peripheral palsy obeyed Donders’ law. Donders deviation of the paretic eye averaged $0.9 \pm 0.6^\circ$ during fixation, compared with $0.5 \pm 0.3^\circ$ in normal subjects (Figure 6-6). During saccades, Donders deviation averaged $0.9 \pm 0.4^\circ$ in the paretic eye, compared with $0.6 \pm 0.2^\circ$ in normal controls (Figure 6-6).

Listings and Donders deviations in central sixth nerve palsy

While patients with acute peripheral palsy had abnormal torsion only in their paretic eye, all patients with *central* palsy caused by brainstem lesions had abnormal ocular torsion in *both* eyes, regardless of the duration and severity of their palsy (Figure 6-7).
During fixation, Listing deviation averaged 2.4 \( \pm \) 1.2° in the paretic eye, and 1.7 \( \pm \) 0.3° in the non-paretic eye (p<0.05) (Figure 6-4). During saccades, Listing deviation averaged 2.7 \( \pm \) 1.4° in the paretic eye, and 1.6 \( \pm \) 0.4° in the non-paretic eye (p<0.05) (Figure 6-4).

Patients with central palsy also violated Donders' law; that is, they showed not one consistent angle of torsion for any given gaze direction, but rather an abnormally wide range of torsional angles. During fixation, Donders deviation averaged 1.4 \( \pm \) 0.7° in the paretic eye and 1.2 \( \pm \) 0.3° in the non-paretic eye (p<0.05) (Figure 6-6). During saccades, Donders deviation averaged 1.5 \( \pm \) 0.6° and 1.2 \( \pm \) 0.6° in the non-paretic eye (p<0.05) (Figure 6-6). Listing's and Donders' laws failed not only when the target is in the paretic hemifield, but also in any one of nine target positions.

6.5 DISCUSSION

Listing’s law holds during fixation, saccades and smooth pursuit, but fails during sleep \(^7\) and vestibulo-ocular reflex (VOR).\(^9\) Its failure shows that the eye muscles are capable of violating Listing’s law, so it is not the muscles but the neural commands driving fixation, saccades and pursuit that constrain the eye to obey the law.\(^17\), \(^20\) The muscles may, however, be arranged in a way that simplifies the brain’s work in implementing Listing’s law \(^21\) as in the “active-pulley hypothesis” \(^26\), where contraction of the *global* layer of the rectus muscle rotates the globe, while contraction of the *orbital* layer displaces the connective-tissue sleeves, or ‘pulleys’, which direct the paths of the muscles.

*Active Neural Implementation of Listing’s law*
In our patients with acute peripheral sixth nerve palsy, Listing's law was violated in the paretic eye, presumably because the lateral rectus muscle was paretic and perhaps also because its pulley was abnormally positioned. In patients with chronic peripheral palsy, both eyes obeyed Listing's law, even though the lateral rectus was still markedly weak. This recovery shows that the neural circuitry underlying Listing's law is adaptive, restoring the law despite a palsied muscle and possibly a disrupted pulley system. Neural adaptation must work by readjusting the innervations to the remaining extraocular muscles; it may also adjust their pulleys, though theoretically Listing's law could be restored with or without a new pattern of pulley placement and motion. All patients with central palsy caused by brainstem lesions had abnormal ocular torsion in both the paretic and non-paretic eyes, regardless of the duration and severity of their palsy. Evidently the neural adaptive mechanisms underlying Listing's law cannot restore it after certain brainstem lesions.

**Neural Pathway for the implementation of Listing’s law**

Our results indicate that an adaptive neural mechanism is responsible for the implementation of Listing's law. However, the brain circuits responsible for Listing's law have not been located. A major neural pathway underlying saccadic eye movements involves the superior colliculus \(^{28-30}\), which sends saccadic signals to the medium-lead burst neurons in the pontine paramedian reticular formation (PPRF) and the rostral interstitial nucleus of the medial longitudinal fasciculus (riMLF).\(^{31,32}\) These burst neurons, in turn, project to the extraocular motoneurons, the final common pathway for all eye movements.\(^{31,32}\) Electrical stimulation and three-dimensional recordings in alert monkeys
have shown that the superior colliculus generates saccades that fit Listing's law.\textsuperscript{33} Stimulation of the medium-lead burst neurons in the caudal PPRF and riMLF evokes abnormal saccades that violate Listing's law.\textsuperscript{34} These findings suggest that the circuitry implementing Listing's law is downstream from the superior colliculus and upstream from the medium-lead burst neurons.

The caudal nucleus reticularis tegmenti pontis (cNRTP), which lies ventral to the rostral PPRF, receives inputs from the superior colliculus and projects to the dorsal vermis and caudal fastigial nucleus.\textsuperscript{35, 36} Inactivation of the cNRTP caused torsional errors, indicating that the cNRTP contributes to stabilization of Listing's plane against torsional errors of the saccadic system.\textsuperscript{37} Torsional pulsion of vertical and horizontal saccades is observed in patients with lateral medullary infarction, suggesting that the lateral medulla participates in torsional control. Another center for 3D eye control may be in the cerebellum;\textsuperscript{33} the influence of NRTP on the 3D control of eye movements may depend on its cerebellar projections.\textsuperscript{38} In this study, we found that patients with sixth nerve palsy caused by pontomedullary lesions violate Listing's law. This provides evidence that this region is an element of the neural pathway that enforces Listing's law.
APPENDIX

To quantify how well subjects obeyed Listing's law, we computed the best-fit function relating the eye's torsion, t, to its horizontal and vertical angles, h and v, in a three-parameter equation:

\[ t = \text{hv}/2 + a_1 + a_2 h \cdot a_3 v \]

We computed the parameters \( a_1 \) through \( a_3 \) that yielded the best fit to the data. Here \( a_1 \) quantifies any torsional shift of primary position, \( a_2 \) and \( a_3 \) quantify its vertical and horizontal rotation. This equation defined a surface of best fit to the eye-position data. The standard deviation of the separation of the data points from the surface was the Listing deviation.

To quantify adherence to Donders' law, we fitted a very flexible, curved surface to the same eye-position data using a 15-parameter equation:

\[ t = a_1 + a_2 h + a_3 v + a_4 d_h + a_5 d_v + a_6 h^2 + a_7 h v + a_8 h d_h + a_9 h d_v + a_{10} v^2 + a_{11} v d_h + a_{12} v d_v + a_{13} d_h^2 + a_{14} d_h d_v + a_{15} d_v^2 \]

where \( d_h \) is disconjugate horizontal eye position (i.e. the difference between the Helmholtz horizontal angles of the two eyes) and \( d_v \) is disconjugate vertical eye position. The standard deviation of the data points' separation from this surface we called the Donders' deviation, reasoning that, if the data could not be well fitted using a highly flexible surface with 15 parameters, they were likely not confined to any surface at all.
6.6 TABLES AND FIGURES
Table 6-1. Characteristics of patients with 6th nerve palsy caused by a presumed peripheral lesion

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age / Sex</th>
<th>Side of lesion</th>
<th>Duration (months)</th>
<th>Abduction deficit (% normal)</th>
<th>Imaging</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (TM)</td>
<td>50 / F</td>
<td>Right</td>
<td>68</td>
<td>30%</td>
<td>Normal MRI</td>
<td>Idiopathic</td>
</tr>
<tr>
<td>2 (TH)</td>
<td>77 / M</td>
<td>Right</td>
<td>30</td>
<td>60%</td>
<td>Normal MRI</td>
<td>Idiopathic</td>
</tr>
<tr>
<td>3 (PL)</td>
<td>21 / M</td>
<td>Right</td>
<td>2 weeks</td>
<td>0%</td>
<td>Normal MRI</td>
<td>Improved after 4 mons</td>
</tr>
<tr>
<td>4 (JM)</td>
<td>46 / M</td>
<td>Right</td>
<td>2 weeks</td>
<td>0%</td>
<td>Normal MRI</td>
<td>Resolved after 3 mons</td>
</tr>
<tr>
<td>5 (NR)</td>
<td>75 / F</td>
<td>Right</td>
<td>4</td>
<td>90%</td>
<td>Normal MRI</td>
<td>Idiopathic</td>
</tr>
<tr>
<td>6 (RL)</td>
<td>77 / F</td>
<td>Right</td>
<td>10</td>
<td>95%</td>
<td>Normal MRI</td>
<td>Idiopathic</td>
</tr>
<tr>
<td>7 (EF)</td>
<td>52 / M</td>
<td>Right</td>
<td>3 weeks</td>
<td>95%</td>
<td>Normal MRI</td>
<td>Idiopathic</td>
</tr>
<tr>
<td>8 (AM)</td>
<td>75 / F</td>
<td>Right</td>
<td>2</td>
<td>70%</td>
<td>Normal CT</td>
<td>Resolved after 6 mons (HTN)</td>
</tr>
<tr>
<td>9 (GD)</td>
<td>64 / M</td>
<td>Right</td>
<td>15</td>
<td>90%</td>
<td>Normal CT</td>
<td>Claustrophobia</td>
</tr>
<tr>
<td>10 (KE)</td>
<td>75 / F</td>
<td>Right</td>
<td>2</td>
<td>10%</td>
<td>Normal CT</td>
<td>Resolved after 4 mons (HTN, DM)</td>
</tr>
<tr>
<td>11 (THA)</td>
<td>57 / M</td>
<td>Right</td>
<td>2</td>
<td>90%</td>
<td>Normal CT</td>
<td>Resolved after 4 mons (HTN, DM)</td>
</tr>
<tr>
<td>12 (SC)</td>
<td>66 / M</td>
<td>Right</td>
<td>3 weeks</td>
<td>80%</td>
<td>Normal CT</td>
<td>Resolved after 4 mons (DM)</td>
</tr>
<tr>
<td>13 (DW)</td>
<td>65 / M</td>
<td>Left</td>
<td>96</td>
<td>70%</td>
<td>Normal MRI</td>
<td>Idiopathic</td>
</tr>
<tr>
<td>14 (GC)</td>
<td>57 / M</td>
<td>Left</td>
<td>34</td>
<td>90%</td>
<td>Normal MRI</td>
<td>Idiopathic</td>
</tr>
</tbody>
</table>
Table 6-1 (Continued). Characteristics of patients with 6th nerve palsy caused by a presumed peripheral lesion

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age / Sex</th>
<th>Side of lesion</th>
<th>Duration (months)</th>
<th>Abduction deficit (% normal)</th>
<th>Imaging</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 (VI)</td>
<td>65 / F</td>
<td>Left</td>
<td>36</td>
<td>50%</td>
<td>Normal MRI</td>
<td>Idiopathic</td>
</tr>
<tr>
<td>18 (SCH)</td>
<td>50 / F</td>
<td>Left</td>
<td>24</td>
<td>80%</td>
<td>Normal MRI</td>
<td>Idiopathic</td>
</tr>
<tr>
<td>17 (JM2)</td>
<td>46 / M</td>
<td>Left</td>
<td>3 weeks</td>
<td>80%</td>
<td>Normal MRI</td>
<td>Resolved after 6 mons (HTN)</td>
</tr>
<tr>
<td>18 (IV)</td>
<td>75 / F</td>
<td>Left</td>
<td>2 weeks</td>
<td>90%</td>
<td>Normal MRI</td>
<td>Idiopathic</td>
</tr>
<tr>
<td>19 (EM)</td>
<td>64 / M</td>
<td>Left</td>
<td>3 weeks</td>
<td>80%</td>
<td>Normal CT</td>
<td>Resolved after 5 mons (HTN)</td>
</tr>
<tr>
<td>20 (LC)</td>
<td>54 / F</td>
<td>Left</td>
<td>60</td>
<td>80%</td>
<td>Normal MRI</td>
<td>Idiopathic</td>
</tr>
</tbody>
</table>

mons, months
HTN, hypertension
DM, diabetes mellitus
<table>
<thead>
<tr>
<th>Patient</th>
<th>Age / Sex</th>
<th>Side of lesion</th>
<th>Duration (months)</th>
<th>Abduction deficit (% normal)</th>
<th>Imaging</th>
<th>Presenting symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>21 (CS)</td>
<td>79 / F</td>
<td>Right</td>
<td>19</td>
<td>0%</td>
<td>MRI: Right pontine meningioma</td>
<td>Diplopia, right facial paraesthesia</td>
</tr>
<tr>
<td>22 (AK)</td>
<td>75 / M</td>
<td>Right</td>
<td>1 week</td>
<td>70%</td>
<td>MRI: Right pontine demyelinating lesion</td>
<td>Diplopia, ataxia (MS for 27 years)</td>
</tr>
<tr>
<td>23 (MD)</td>
<td>75 / M</td>
<td>Left</td>
<td>240</td>
<td>40%</td>
<td>MRI: Left caudal pontine infarct</td>
<td>Dysarthria, tinnitus, limb weakness</td>
</tr>
<tr>
<td>24 (WS)</td>
<td>59 / M</td>
<td>Left</td>
<td>52</td>
<td>90%</td>
<td>MRI: Left pontomedullary cavernoma &amp; hematoma</td>
<td>Headache, right paraesthesia, ataxia</td>
</tr>
<tr>
<td>25 (RC)</td>
<td>56 / F</td>
<td>Left</td>
<td>132</td>
<td>70%</td>
<td>MRI: Left pontomedullary cavernoma &amp; hematoma</td>
<td>Left facial palsy and paraesthesia</td>
</tr>
<tr>
<td>26 (JP)</td>
<td>36 / F</td>
<td>Left</td>
<td>3</td>
<td>80%</td>
<td>MRI: Left pontomedullary and middle cerebellar peduncle demyelinating lesions</td>
<td>Diplopia, right leg paraesthesia, ataxia</td>
</tr>
<tr>
<td>27 (WR)</td>
<td>30 / F</td>
<td>Left</td>
<td>2 weeks</td>
<td>70%</td>
<td>MRI: Left pontomedullary demyelinating lesion</td>
<td>Diplopia, ataxia</td>
</tr>
</tbody>
</table>

MS, multiple sclerosis
Figure 6-1. Torsional positions of the eye, as represented by thin black lines with respect to the vertical meridian, in different combination of horizontal and vertical eye positions, as viewed by the examiner. If the eye is 30° down and 30° left (bottom right panel), then the eye (thin black line) rotates 7.9° (0.14 rad) counterclockwise, with respect to the vertical meridian (dashed line). CW, clockwise from the subject’s reference; CCW, counterclockwise from the subject’s reference.
30° Up & Right

7.9° CCW

30° Up

7.9° CW

30° Up & Left

30° Right

Center

30° Left

30° Down & Right

7.9° CW

30° Down

7.9° CCW

30° Down & Left
Figure 6-2. (A) Eye movement recordings of patient CS while the non-paretic left eye viewed a target that stepped from center – 10° up – center – 10° down. (B) Horizontal, vertical and torsional eye positions of the paretic non-viewing right eye of this patient, from the patient's viewpoint, while the left eye looked at the 9 target positions—the 9 corners of the inside grid in the figure. The center of each small cross marks the gaze direction of the right eye; the tilt of the cross depicts the eye's torsion. We fitted functions to these data to find the typical torsion of the right eye for each position of the left. (C) The typical torsion of the patient's right eye in different combination of horizontal and vertical positions, shown from the examiner's viewpoint, are represented by large crosses as computed using fitted functions. For comparison, the regions with a grid pattern in this figure mark the range one standard deviation above and below the mean torsion in normal subjects. For example, when this patient looked 10° up with the left eye, the paretic right eye was typically oriented 6.1° clockwise (from the patient's reference), well outside the range of normal torsion, indicating that Listing's law was violated in this position. CW, clockwise from the subject's reference; CCW, counterclockwise from the subject's reference.
Patient CS - Right central sixth nerve palsy

Right eye

10 deg right
Horizontal
10 deg left

10 deg up
Vertical
10 deg down

10 deg CW
Torsional
10 deg CCW

3 sec

Left eye

10 deg right
Horizontal
10 deg left

10 deg up
Vertical
10 deg down

10 deg CW
Torsional
10 deg CCW

3 sec
(B) Fixation Saccades

(C) Fixation Saccades

- Left 10°
- Center
- Right 10°
- Up 10°
- Center
- Down 10°

Up 10° 6.1° CW

Right 10° Center Left 10° Right 10° Center Left 10°
Figure 6-3. Mean torsional position of the paretic eye in the nine target positions during fixation and saccades in 13 patients with peripheral sixth nerve palsy, as compared with the range one standard deviation above and below the mean torsion in normal subjects (regions with grid pattern). Torsional angles depicted in the figure are the actual torsional angles multiplied by five to facilitate easier viewing.
Chronic peripheral sixth nerve palsy (n=13)

Right-sided palsy (n=7)

**Fixation**

- Right 10°
- Center
- Left 10°

**Saccades**

- Right 10°
- Center
- Left 10°

Left-sided palsy (n=6)

**Fixation**

- Right 10°
- Center
- Left 10°

**Saccades**

- Right 10°
- Center
- Left 10°
Figure 6-4. Listing deviations during (A) fixation and (B) saccades in normal controls and patients with peripheral (chronic and acute) and central sixth nerve palsy caused by brainstem lesions.
Listing deviation during fixation and saccades in 6th nerve palsy

**Fixation**

![Graph showing fixation deviation with bars for normal, chronic peripheral 6th, acute peripheral 6th, and central 6th palsy. The graph includes two conditions: paretic eye and non-paretic eye. Stars indicate statistical significance (* p < 0.05).]

**Saccades**

![Graph showing saccade deviation with bars for normal, chronic peripheral 6th, acute peripheral 6th, and central 6th palsy. The graph includes two conditions: paretic eye and non-paretic eye. Stars indicate statistical significance (* p < 0.05).]
Figure 6-5. Mean torsional position of the paretic eye during fixation and saccades in 7 patients with acute peripheral sixth nerve palsy, as compared with the range one standard deviation above and below the mean torsion in normal subjects (regions with grid pattern). Torsional angles depicted in the figure are the actual torsional angles multiplied by five to facilitate easier viewing.
Acute peripheral sixth nerve palsy (n=7)

Right-sided palsy (n=4)

Fixation
Right 10°  Center  Left 10°
Up 10°
Center
Down 10°

Saccades
Right 10°  Center  Left 10°
Up 10°
Center
Down 10°

Left-sided palsy (n=3)

Fixation
Right 10°  Center  Left 10°
Up 10°
Center
Down 10°

Saccades
Right 10°  Center  Left 10°
Up 10°
Center
Down 10°
Figure 6-6. Donders deviations during (A) fixation and (B) saccades in normal controls and patients with peripheral (chronic and acute) and central sixth nerve palsy caused by brainstem lesions.
Donders deviation during fixation and saccades in 6th nerve palsy

**Fixation**

![Fixation Graph](image)

**Saccade**

![Saccade Graph](image)

* p < 0.05
Figure 6-7. Mean torsional position of the paretic eye during fixation and saccades in 7 patients with central sixth nerve palsy caused by brainstem lesions, as compared with the range one standard deviation above and below the mean torsion in normal subjects (regions with grid pattern). Torsional angles depicted in the figure are the actual torsional angles multiplied by five to facilitate easier viewing.
Central sixth nerve palsy (n=7)

Right-sided palsy (n=2)

Fixation

Right 10°  Center  Left 10°
Up 10°
Center
Down 10°

Saccades
Right 10°  Center  Left 10°
Up 10°
Center
Down 10°

Left-sided palsy (n=5)

Fixation

Right 10°  Center  Left 10°
Up 10°
Center
Down 10°

Saccades
Right 10°  Center  Left 10°
Up 10°
Center
Down 10°
6.7 REFERENCES


CHAPTER 7
EFFECTS OF BRAINSTEM AND CEREBELLAR LESIONS ON LISTING'S LAW
REVEALED BY SKEW DEVIATION
7.1 SUMMARY

**Purpose:** During fixation and saccades, human eye movements obey Listing's law, which specifies the torsional eye position for each combination of horizontal and vertical eye position. Brain circuits responsible for Listing's law have not been identified. To investigate the mechanisms that implement Listing's law, we studied the effects of brainstem and cerebellar lesions on Listing's law in patients with skew deviation.

**Methods:** Eleven patients with skew deviation caused by brainstem or cerebellar lesions were studied using scleral search coils. Ten normal subjects served as controls. With head immobile, subjects made saccades to a target that moved between straight ahead and 8 eccentric positions. At each target position, fixation was maintained for 3 seconds before the next saccade. To quantify violations of Listing's law, we measured ocular torsion during fixation and during saccades, and compared it to the torsion predicted by the law; the standard deviation of the differences between the predicted and measured torsion was called Listing deviation.

**Results:** All patients had abnormal ocular torsion in both eyes, violating Listing's law. Listing deviation averaged 3.1 degree during fixation and 6.3 degree during saccades, compared to 0.8 degree in controls during both tasks. They also violated Donders' law; that is, they did not show one consistent angle of torsion for any given gaze direction, but rather an abnormally wide range of torsional angles.

**Conclusions:** Patients with skew deviation caused by brainstem or cerebellar lesions have abnormal ocular torsion in both eyes during fixation and during saccades. This provides evidence that brainstem and cerebellum circuits that maintain vertical alignment.
of the eyes are also elements of the neural pathway that participates in the maintenance of Listing's law.
7.2 INTRODUCTION

During fixation, saccades and smooth pursuit, the eyes rotate freely in the horizontal and vertical dimensions, with torsion being constrained.\textsuperscript{1-3} Helmholtz described this restriction on ocular torsion and expressed it as Donders' and Listing's laws.\textsuperscript{4} Donders' law states that there is only one torsional eye position for each combination of horizontal and vertical eye positions.\textsuperscript{2,4} Listing's law is a special case of Donders' law and quantitatively specifies the torsional angle for each gaze direction. It states that, with the head fixed, there is an eye position called primary position, with the property that all other eye orientations that the eye actually assumes can be reached from primary position by a single rotation about an axis in a plane called Listing's plane.\textsuperscript{4}

We have recently demonstrated that Listing's law is violated in patients with central sixth nerve palsy caused by pontomedullary lesions, whereas those with chronic peripheral palsy obeys it, indicating that an adaptive neural mechanism is responsible for the implementation of Listing's law.\textsuperscript{5} However, the brain circuits responsible for Listing's law have not been identified.

Skew deviation is a vertical strabismus caused by supranuclear lesions, and has been attributed to asymmetric disruption of projections from otolithic receptors to the oculomotor and trochlear nuclei.\textsuperscript{6,7} Magendie \textsuperscript{8} and Hertwig \textsuperscript{9} produced skew deviation in cats by lesioning the middle cerebellar peduncle, but adjacent tegmental structures may have been damaged. Subsequently, others \textsuperscript{6,10,11} have also attributed skew deviation to cerebellar damage after surgery \textsuperscript{10} or cerebellar diseases based on clinical findings.\textsuperscript{6,11} However, imaging or pathological correlation is lacking. Patients with cerebellar degeneration or dysgenesis may exhibit vertical phoria or small vertical tropia \textsuperscript{12}, but
involvement of brainstem circuits might contribute to the vertical strabismus. Skew deviation is typically caused by damage to the brainstem tegmentum.\textsuperscript{6,10,11,13,14}

Here we investigated patients with skew deviation associated with brainstem or cerebellar lesions to determine whether Listing's law is obeyed. We found that these patients have abnormal ocular torsion in both eyes during fixation and during saccades, and that cerebellar lesion can cause skew deviation. Elements of the neural pathway that enforce Listing's law traverse the regions of the brainstem and cerebellum that are damaged in skew deviation.

### 7.3 METHODS

We recruited patients with skew deviation caused by brainstem or cerebellar lesions from the Neuro-ophthalmology Unit at the University Health Network. A complete history was taken, and detailed neurologic and ophthalmic examinations were performed. The age of onset, duration of diplopia, and associated neurologic symptoms and signs were recorded. Strabismus was measured using the prism and cover test, and the Maddox rod (see Chapter 9 for details). Ocular motility was assessed independently by two examiners (AW and JAS). Patients with limitation of ductions in any directions, vertical or horizontal gaze palsy were excluded from the study.

Appropriate tests were performed to rule out myasthenia gravis, thyroid ophthalmopathy, or other orbital diseases. Serial axial and sagittal T1- and T2-weighted magnetic resonance (MR) images with gadolinium enhancement were obtained (slice thickness = 5 mm) for all patients.
Please refer to METHODS section in Chapter 6 (section 6.3) for Eye movement recordings, Coordinate system, Data analysis and statistical methods.

The research protocol was approved by the University Health Network Ethics Committee and followed the tenets of the Declaration of Helsinki. Informed consent was obtained from all subjects.

7.4 RESULTS

General characteristics of patients

The characteristics of 11 patients are shown in Table 7-1. The mean age was 48.5 ± 17 years (median 57 years; range 19 - 69 years). There were seven men. Duration of symptoms ranged from 1 week to 336 months, with a mean duration of 78 months. Mean follow-up duration was 56 months (range 5 - 326 months). Eight patients had brainstem lesions (4 infarcts, 2 demyelination, 1 germinoma, 1 astrocytoma) and three had cerebellar lesions (1 cavernous hemangioma, 1 astrocytoma, 1 hemangioblastoma) (Figure 7-2). All had skew deviation at presentation; six were comitant, four were incomitant and one had alternating skew deviation, with right hypertropia on right gaze and left hypertropia on left gaze. No patients had limitation of duction or gaze in any direction.

Ten normal subjects served as controls (5 women; mean age 49 ± 12 years; median age 55 years; age range 19 to 69 years).

Listings deviations in the straight ahead position during fixation

In the straight ahead gaze position, Listing deviation averaged 4.0 ± 5.2 deg, compared with 0.1 ± 1.3 deg in normal subjects (p<0.05), indicating that all patients with
skew deviation had abnormal ocular torsion in both eyes. In each of the 11 patients, the hypertropic eye was incyclotorted, relative to the hypotropic eye (Table 7-1).

**Listings and Donders deviations across nine target positions**

Each (Figure 7-3) of 13 patients had abnormal ocular torsion in both eyes during fixation and saccades, violating Listing's law (Figure 7-4). Listing deviation, averaged across 9 target positions, was $3.1 \pm 2.2$ deg during fixation and $6.3 \pm 5.4$ deg during saccades ($p<0.01$) (Figure 7-5). All patients with brainstem or cerebellar lesions also violated Donders' law; they did not show one, consistent angle of torsion for any given gaze direction, but rather an abnormally wide range of torsional angles. Donders deviation, averaged across 9 target positions, was $2.0 \pm 1.7$ deg during fixation and $3.0 \pm 2.3$ deg during saccades, compared with $0.5 \pm 0.3$ deg during fixation and $0.6 \pm 0.2$ during saccades in normal controls ($p<0.05$) (Figure 7-5). Listing's and Donders' laws failed idiosyncratically in any of the 9 target positions, with no pattern of torsional deviations across patients.

**7.5 DISCUSSION**

**Skew deviation and ocular torsion in brainstem lesions**

In humans, static lateral head tilt causes sustained conjugate counterroll of the eyes and a small vertical misalignment. Brainstem or acute peripheral vestibular lesions that disrupt the otolith inputs cause the ocular tilt reaction, a triad of dysjunctive vertical deviation (skew deviation), ocular torsion and head tilt. Among 56 patients with skew deviation from unilateral brainstem infarction, Brandt and Dieterich reported a mean
vertical strabismus of 4° (ranging from 1° to 20°). Rostral pontomesencephalic lesions were associated with ipsi-lesional hypertropia, and caudal pontomedullary lesions with contra-lesional hypertropia. Abnormal ocular torsion was also present in the straight ahead position. The mean ocular torsion was 8° (ranging from 2° to 28°), with the hypertropic eye incyclotorted, and the hypotropic eye excyclotorted.

We investigated eight patients with skew deviation caused by brainstem lesions. Each of them had associated neurologic symptoms and signs in addition to diplopia. The skew deviation was comitant in four patients, and incomitant in three, with one mimicked an isolated inferior rectus palsy and two showed no specific pattern of hypertropia (see Table). Another patient had an alternating skew deviation, with right hypertropia on right gaze and left hypertropia on left gaze. Three patients with caudal pontomedullary lesions had contra-lesional hypertropia, whereas two with rostral pontomesencephalic lesions had ipsi-lesional hypertropia. Three patients had bilateral brainstem lesions. We identified the presence of abnormal static ocular torsion in different positions of gaze, with the hypertropic eye incyclotorted, relative to the hypotropic eye. In addition, we identified abnormal torsion during saccades.

**Skew deviation and ocular torsion in cerebellar lesions**

Damage to the cerebellum has been implicated as a cause of skew deviation. Magendie and Hertwig first produced skew deviation in cats by lesioning the middle cerebellar peduncle, but adjacent tegmental structures may have been damaged. Others have attributed skew deviation to cerebellar damage from surgery or cerebellar diseases based on clinical findings. In those cases, however, brainstem
involvement had not been excluded by either imaging or pathological correlation. One reported patient with cerebellar infarct had abnormal ocular torsion and tilt of subjective visual horizontal, but not skew deviation.¹⁷ Patients with cerebellar degeneration or dysgenesis may exhibit vertical phoria or small tropia¹²; however, brainstem circuits are seldom spared in spinocerebellar degenerations or developmental malformations.

We provide evidence of skew deviation caused by cerebellar lesions in three patients. One of them (JF) had a cavernous hemangioma in the left cerebellar hemisphere. In this patient, the only clinical finding was a comitant right hypertropia, without any other neurological symptoms or signs. Another patient (EM) had a cerebellar astrocytoma which was resected as a child, and presented with a comitant left hypertropia, gaze-evoked nystagmus and ataxia. A third patient (CH) had a hemangioblastoma in the right cerebellar hemisphere, and presented with a persistent incomitant left hypertropia, which mimicked an isolated left inferior rectus palsy, before and after resection.

We found that patients with skew deviation caused by cerebellar lesions have abnormal ocular torsion during fixation and during saccades to different target positions, just as our patients with skew deviation caused by brainstem lesions.

Although precise anatomic connections between the otoliths and cerebellum are not known, there are potential anatomic and physiologic substrates for cerebellar skew deviation. The vestibulocerebellum (flocculus, paraflocculus, nodulus and uvula) receives otolith projections both directly from the labyrinth, and indirectly via the vestibular nuclei.¹⁸ ¹⁹ Vermis Purkinje cells monosynaptically inhibit neurons in the vestibular nucleus, the site of second order otolithic-ocular neurons.²⁰ Lesions of the nodulus alone, or of the nodulus and uvula together, impair otolith-ocular reflexes and otolithic modulation of semicircular
canal vestibulo-ocular reflexes. In monkeys, lesions of the nodulus and / or uvula cause an inability to reorient vertical semicircular canal signals on the basis of gravitoinertial signals, and a loss of steady-state nystagmus response to off-axis rotation.

**Active Neural Implementation of Listing's law**

Listing's law holds during fixation, saccades and smooth pursuit, but fails during sleep and during the vestibulo-ocular reflex (VOR). This physiological failure shows that neural commands are important for the implementation of the law. The extraocular muscles may, however, be arranged in a way that simplifies the brain's work in implementing Listing's law, as in the "active-pulley hypothesis".

In this study, we included only patients with skew deviation that had full range of ductions, and exclude those who had other ocular motility dysfunctions, such as internuclear ophthalmoplegia, horizontal or vertical gaze palsy, or torsional nystagmus. We found that all our patients have abnormal torsion and violate Listing's law, providing further evidence that a central neural mechanism is essential for the implementation of Listing's law.

**Neural Pathways for the implementation of Listing's law**

A major neural pathway underlying saccadic eye movements involves the superior colliculus, which sends saccadic signals to the medium-lead burst neurons in the pontine paramedian reticular formation (PPRF) and the rostral interstitial nucleus of the medial longitudinal fasciculus (riMLF). These burst neurons, in turn, project to the...
extraocular motoneurons, the final common pathway for all eye movements.\textsuperscript{37,38} Electrical stimulation and three-dimensional recordings in alert monkeys have shown that the superior colliculus generates saccades that fit Listing's law.\textsuperscript{39} Stimulation of the medium-lead burst neurons in the caudal PPRF and riMLF evokes abnormal saccades that violate Listing's law.\textsuperscript{40} These findings suggest that the circuitry implementing Listing's law during saccades is downstream from the superior colliculus and upstream from the medium-lead burst neurons.

The caudal nucleus reticularis tegmenti pontis (cNRTP), which lies ventral to the rostral PPRF, receives inputs from the superior colliculus and projects to the dorsal vermis and caudal fastigial nucleus.\textsuperscript{41,42} Electrical stimulation of the cNRTP elicits ipsiversive saccades with a small torsional displacement, which brings the eye out of Listing's plane, and a torsional saccadic reset in the opposite direction which brings the eye back to Listing's plane.\textsuperscript{43} Inactivation of the cNRTP results in an absence of torsional saccadic reset, such that the eye remains out of Listing's plane.\textsuperscript{43} This indicates that the cNRTP participates in stabilization of Listing's plane against torsional errors of the saccadic system.\textsuperscript{43} Torsional pulsion of saccades (torsipulsion), consisting of torsional fast eye movements away from the side of lesion (from examiner's viewpoint) induced during saccades downward or away from the side of lesion, has been recorded in patients with lateral medullary infarction.\textsuperscript{13} Torsional blips, consisting of torsional fast eye movements followed by slow exponential drifts towards the initial torsional eye position during horizontal and vertical saccades, were reported in a patient with an infarct involving the dorsolateral medulla and the cerebellum.\textsuperscript{44} These findings indicate that neurons in the lateral medulla participate in torsional control that implements Listing's law.
The cerebellum may also implement three dimensional control of eye motions. In addition to receiving inhibitory inputs from Purkinje cells of the dorsal vermis, the fastigial nucleus of the cerebellum receives projections from the frontal eye fields and superior colliculus, via the NRTP. Projections from the caudal part of the fastigial nucleus ascend in the brainstem to innervate the medium-lead burst neurons, which generate horizontal, vertical and torsional saccades. The caudal part of the fastigial nucleus also projects to the dorsolateral pontine nuclei and participates in the control of smooth pursuit. The influence of NRTP on three dimensional control of eye movements may depend on its cerebellar projections. The torsional pulsion of saccades seen in lateral medullary syndrome may be caused by interruption of olivocerebellar climbing fibers, leading to increased activity of vermis Purkinje cells and inhibition of the underlying fastigial nucleus.

We found that patients with brainstem or cerebellar lesions have abnormal ocular torsion during fixation in different orbital positions and during saccades. In addition, in each of our patients, Listing's and Donders' laws failed idiosyncratically, with no pattern of torsional deviations across patients. Torsional pulsion or torsional blips during saccades were not detected. Our data provide evidence that brainstem and cerebellum circuits that maintain vertical alignment of the eyes are also elements of the neural pathway that participate in the maintenance of Listing's law.
7.6 TABLES AND FIGURES
<table>
<thead>
<tr>
<th>Patient</th>
<th>Age / Sex</th>
<th>Duration (months)</th>
<th>Pattern of hypertropia</th>
<th>Ocular torsion (deg) in the hypertropic eye in straight ahead position*</th>
<th>Magnetic resonance imaging findings</th>
<th>Clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (JF)</td>
<td>61 / M</td>
<td>14</td>
<td>Comitant RHT</td>
<td>17.1 CCW</td>
<td>Left cerebellar cavernous hemangioma</td>
<td>Skew deviation</td>
</tr>
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<td>2 (FP)</td>
<td>59 / M</td>
<td>24</td>
<td>Comitant RHT</td>
<td>1.5 CCW</td>
<td>Left caudal pontine infarct</td>
<td>Skew deviation, left hemiplegia, right facial paresis</td>
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<td>3 (DV)</td>
<td>29 / M</td>
<td>1</td>
<td>Comitant RHT</td>
<td>4.8 CCW</td>
<td>Left pontomedullary infarct</td>
<td>Skew deviation, vertigo, dysphagia, ataxia</td>
</tr>
<tr>
<td>4 (JV)</td>
<td>19 / M</td>
<td>30</td>
<td>Alternating skew*</td>
<td>4.0 CCW (right eye)</td>
<td>Suprasellar &amp; pineal region germinoma</td>
<td>Skew deviation, pretectal syndrome</td>
</tr>
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<td>5 (MF)</td>
<td>69 / M</td>
<td>120</td>
<td>Comitant LHT</td>
<td>2.2 CW</td>
<td>Left midbrain infarct</td>
<td>Skew deviation, right hemiparesis</td>
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<td>6 (RP)</td>
<td>60 / F</td>
<td>23</td>
<td>Incomitant LHT; no pattern</td>
<td>2.7 CW</td>
<td>Left cerebellar hemorrhage from arteriovenous malformation</td>
<td>Skew deviation, gaze-evoked nystagmus, ataxia</td>
</tr>
<tr>
<td>7 (EM)</td>
<td>33 / F</td>
<td>336</td>
<td>Comitant LHT</td>
<td>5.9 CW</td>
<td>Right cerebellar astrocytoma with marked dilatation of the fourth ventricle</td>
<td>Skew deviation, gaze-evoked nystagmus, ataxia</td>
</tr>
<tr>
<td>8 (JB)</td>
<td>36 / M</td>
<td>36</td>
<td>Incomitant LHT; mimic left IR palsy</td>
<td>2.4 CW</td>
<td>Left rostral pontine demyelinating lesions</td>
<td>Skew deviation, ataxia</td>
</tr>
<tr>
<td>9 (JV)</td>
<td>53 / M</td>
<td>1 week</td>
<td>Comitant LHT</td>
<td>3.4 CW</td>
<td>Bilateral pontine infarct</td>
<td>Skew deviation, dysarthria, left hemiparesis, ataxia</td>
</tr>
<tr>
<td>10 (KT)</td>
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<td>2.7 CW</td>
<td>Bilateral pontomedullary demyelinating lesions</td>
<td>Skew deviation</td>
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<tr>
<td>11 (CH)</td>
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<td>278</td>
<td>Incomitant LHT; mimic left IR palsy</td>
<td>3.4 CW</td>
<td>Right cerebellar hemangioblastoma</td>
<td>Skew deviation, ataxia</td>
</tr>
</tbody>
</table>

* relative to the hypertropic eye
* right hypertropia on right gaze and left hypertropia on left gaze
RHT, right hypertropia; LHT, left hypertropia; SO, superior oblique; IR, inferior rectus
CW, upper pole of the eye rotates toward subject's right shoulder; CCW, upper pole of the eye rotates toward subject's left shoulder
Figure 7-1. Torsional positions of the normal eye, as predicted by Listing's law, are represented by thin black lines with respect to the vertical meridian, in different combination of horizontal and vertical eye positions, as viewed by the examiner. If the eye is 30° down and 30° left (bottom right panel), then the eye (thin black lines) rotates 7.9° (0.14 rad) counterclockwise, with respect to the vertical meridian (dashed lines). CW, clockwise from the subject’s reference; CCW, counterclockwise from the subject’s reference.
Figure 7-2. (A) Axial T2 - weighted magnetic resonance image of patient JF showing a cavernous hemangioma in the left cerebellar hemisphere. The mixed signal intensity within the lesion, which is surrounded by a dark rim on T2, is characteristic for a cavernous hemangioma. (B) Axial T1 - weighted magnetic resonance image with gadolinium enhancement in patient EM showing a residual cystic astrocytoma in the cerebellum, and surrounding area of encephalomalacia in the vermis and both cerebellar hemispheres. (C) Axial T1 - weighted magnetic resonance image of patient CH showing postsurgical changes in the inferior right cerebellar hemisphere, following resection of a hemangioblastoma.
Figure 7-3. (A) Recordings of patient JF while the left eye viewed a target that stepped from center – 10° up – center – 10° down. (B) Horizontal, vertical and torsional eye positions of the non-viewing right eye of this patient, from the patient’s viewpoint, while the left eye looked at the 9 target positions—the 9 corners of the inside grid in the figure. The center of each small cross marks the gaze direction of the right eye; the tilt of the cross depicts the eye’s torsion. We fitted functions to these data to find the typical torsion of the right eye for each position of the left. (C) The typical torsion of the patient’s occluded right eye in different combination of horizontal and vertical positions while the patient viewed with the left eye, shown from the examiner’s viewpoint, are represented by large black crosses as computed using fitted functions. For comparison, the regions with a grid pattern in this figure mark the range one standard deviation above and below the mean torsion in normal subjects. For example, when this patient looked 10° up with the left eye, the right eye was typically oriented 4.2° clockwise (from the patient’s reference), well outside the range of normal torsion, indicating that Listing’s law was violated in this position. Torsional angles depicted in the figure are the actual torsional angles multiplied by five to facilitate viewing. CW, clockwise from the subject’s reference; CCW, counterclockwise from the subject’s reference.
Patient JF - Left cerebellar cavernous hemangioma

(A)

Right eye

Horizontal
- 10 deg right
- 10 deg left

Vertical
- 10 deg up
- 10 deg down

Torsional
- 10 deg CW
- 10 deg CCW

3 sec

Left eye

Horizontal
- 10 deg right
- 10 deg left

Vertical
- 10 deg up
- 10 deg down

Torsional
- 10 deg CW
- 10 deg CCW

3 sec
Figure 7-4. Pooled mean torsional position of the occluded eye in nine target positions (black crosses) during fixation and saccades in 11 patients with skew deviation, as compared with the range one standard deviation above and below the mean torsion of the occluded eye in 10 normal subjects (regions with grid pattern) during monocular viewing. Group mean data for patients and normal subjects are from the occluded eyes while each was occluded during monocular viewing with the other eye. Torsional angles depicted in the figure are the actual torsional angles multiplied by five to facilitate viewing.
Brainstem or cerebellar lesions (n=11)

**Fixation**
- Right 10°
- Center
- Left 10°

**Saccades**
- Right 10°
- Center
- Left 10°

- Up 10°
- Center
- Down 10°
Figure 7-5. Listing deviations during (A) fixation and (B) saccades, and Donders deviations during (C) fixation and (D) saccades, in normal controls and patients with skew deviation caused by brainstem or cerebellar lesions. * p<0.05.
**Listing Deviations**

(A)

Fixation

- Normal
- Brainstem / Cerebellar lesion

(B)

Saccades

- Normal
- Brainstem / Cerebellar lesion

**Donders Deviations**

(C)

Fixation

- Normal
- Brainstem / Cerebellar lesion

(D)

Saccades

- Normal
- Brainstem / Cerebellar lesion

*p < 0.05
REFERENCES


CHAPTER 8
ADAPTIVE NEURAL MECHANISM FOR LISTING'S LAW REVEALED BY
FOURTH NERVE PALSY
8.1 SUMMARY

Purpose: During fixation and saccades, human eye movements obey Listing's law, which specifies the eye's torsional angle as a function of its horizontal and vertical position. Torsion of the eye is in part controlled by the trochlear nerve. The central nervous system may adapt to defective torsional control caused by trochlear nerve palsy. This study investigates this adaptation.

Methods: Thirteen patients with fourth nerve palsy (11 chronic, 2 acute), and ten normal subjects were studied using scleral search coils. With head immobile, subjects made saccades to a target that moved between straight ahead and 8 eccentric positions. At each target position, fixation was maintained for 3 seconds before the next saccade. From the eye position data, we computed a plane of best fit, called Listing's plane. Violations of Listing's law were quantified by computing the 'thickness' of this plane, defined as the standard deviation of the distances to the plane from the data points.

Results: Patients with chronic fourth nerve palsy obeyed Listing's law. During fixation and saccades, thickness of Listing's plane averaged 0.7° in the paretic eye and 0.6° in the non-paretic eye, compared to 0.8° in normal controls for both tasks. But Listing's planes of both eyes were rotated temporally, compared with controls. In contrast, acute fourth nerve palsy violated Listing's law during saccades. During downward saccades, transient torsional deviations moved the paretic eye out of Listing's plane. Torsional drifts returned the eye to Listing's plane during subsequent fixation. Conclusions: Listing's law is violated during saccades in acute but not in chronic fourth nerve palsy. This indicates that neural adaptation can restore Listing's law by adjusting the innervations to the remaining extraocular muscles, even when one eye muscle remains paretic. Although Listing's law
is obeyed in chronic palsy, Listing's plane has an abnormal orientation, being tilted temporally. In acute palsy, rapid torsional deviations and slow torsional drifts occur during downward saccades. These saccadic intrusions are attributed to pulse-step mismatch, as a result of changes in muscle or orbital plant dynamics, which lead to an imbalance of phasic and tonic signals reaching the muscles. The corrective slow torsional drifts bring the eye back to Listing's plane after each saccade.
8.2 INTRODUCTION

During fixation, saccades and smooth pursuit, the eye rotate freely in the horizontal and vertical dimensions, but torsion is constrained.\textsuperscript{1-3} This restriction on ocular torsion is described by Donders' and Listing's laws.\textsuperscript{4} Donders' law states that horizontal and vertical positions of the eye determine the torsional angle.\textsuperscript{2,4} Donders' law does not specify what torsional angle the eye assumes, but only that there is a unique torsional angle for each gaze direction. Listing's law is a special case of Donders' law which quantitatively specifies the torsional angle for each gaze direction. It states that, when the head is fixed, there is an eye position called primary position, and that the eye assumes only those orientations that can be reached from primary position by a single rotation about an axis in a plane called Listing's plane\textsuperscript{4}; this plane, furthermore, is orthogonal to the gaze line when the eye is in primary position.

Listing's law is illustrated in Figure 8-1. The eye at the center is in primary position and the plane of the paper is Listing's plane. All the eye orientations drawn with solid lines accord with Listing's law, because they can be reached from the primary position by rotating about axes (straight black lines extending from the globes) in Listing's plane. But the position drawn with dashed lines at the top center violates Listing's law, because the rotation to that orientation from primary position has its axis (white line) tilted out of Listing's plane.

We have recently demonstrated that acute peripheral sixth nerve palsy violates Listing's law, whereas chronic palsy obeys it, indicating that the neural mechanism that enforces Listing's law is adaptive.\textsuperscript{5} Here we investigated patients with unilateral fourth nerve palsy to determine whether Listing's law is obeyed during fixation and saccades. We
found that the neural mechanism underlying Listing’s law is adaptive even when one eye muscle is abnormal.

8.3 METHODS

We recruited 13 patients with unilateral fourth nerve palsy from the Neuro-ophthalmology Unit at the University Health Network. A complete history was taken, and detailed ophthalmic and neurologic examinations were performed. The age of onset, the presence or absence of risk factors for ischemia (diabetes mellitus and hypertension), duration of diplopia, and associated neurologic symptoms and signs were recorded. Patients with diplopia of less than 4 weeks’ duration were classified as having acute palsy; all others were designated here as chronic. Superior oblique palsy was diagnosed using the following clinical criteria 64: Deficient depression of the hypertropic eye in adduction; incomitant hypertropia which increased with adduction of the hypertropic eye, and with head tilt towards the hypertropic eye; and presence of subjective exocycloversion. Patients with a history of head tilt, diplopia or strabismus dating to infancy or early childhood, or prior strabismus surgery were excluded from this study.

The magnitude of strabismus was measured objectively using the prism and cover test, and subjectively using the Maddox rod and prism test (see Chapter 9 for details). The range of ductions was estimated independently by one of two examiners (AW and JAS), and the degree of duction defect was graded according to the estimated percentage of the normal duction in the fellow eye. When indicated, appropriate tests were performed to rule out myasthenia gravis, thyroid ophthalmopathy, other orbital diseases, or intracranial lesions.
In this investigation, magnetic resonance (MR) or computerized tomography (CT) imaging were performed on all patients, although imaging is not our standard practice for all such patients. CT images of the head with contrast were obtained in all patients with ischemic risk factors and for patients over 50 years of age. Those with abnormal CT were further investigated with MR imaging. Serial axial and sagittal T1- and T2-weighted MR images with gadolinium enhancement were obtained (slice thickness = 5 mm) for all patients under 50 years of age.

**Eye movement recordings**

Visual stimuli and experimental protocol. Eye position was measured with search coils while patients fixated a red laser spot of 0.25° in diameter, rear-projected onto a vertical flat screen 1 m away from the nasion. The laser was programmed to appear in nine different target positions, arranged in a 3 x 3 square. The middle row of this array was at eye level, the other two 10° above and below. In each row, the center target lay in the patient's midsagittal plane, the other two 10° right and left of it.

With one eye covered, patients were instructed to follow the laser spot as it stepped among positions. At each position the laser halted for 3 s. In the horizontal target sequence, the laser started in the center, then stepped to the 10° right position, then back to center, then 10° left, cycling through this pattern 20 times for each eye. The vertical sequence was the same but with the laser stepping center—up—center—down; the two diagonal sequences stepped along oblique lines, between opposite corners of the target array. Recordings were then made with the other eye fixating and the fellow eye occluded. To avoid fatigue, breaks for 1-3 min were provided approximately every 2 min.
Recordings of eye movement and calibration. Eye positions were measured by a 3-dimensional magnetic search coil technique, using a 6 ft (183 cm) diameter coil field arranged in a cube (CNC Engineering, Seattle, Washington). In each eye, the patient wore a dual-lead scleral coil annulus designed to detect horizontal, vertical, and torsional gaze positions (Skalar Instrumentation, Delft, Netherlands). Horizontal and vertical eye movements were calibrated with saccades to steps of the laser target. Torsional movements were calibrated by attaching the scleral coil to a rotating protractor. Phase detectors employing amplitude modulation as described by Robinson⁹ provided signals of torsional gaze position within the linear range. Torsional precision was about ± 0.2°. There was minimal crosstalk; large horizontal and vertical movements produced deflections in the torsional channel of less than 4% of the amplitude of the horizontal and vertical movement. Any coil slippage was assessed by monitoring offsets in torsional eye position signal during testing. Consistency of calibrated positions after each eye movement provided evidence that the coil did not slip on the eye. Eye position data were filtered with a bandwidth of 0 to 90 Hz and digitized at 200 Hz. They were recorded on disc for off-line analysis. Analog data were also displayed in real time by a rectilinear thermal array recorder (Model TA 2000, Gould Inc., Ohio).

Data analyses and statistical methods

Eye position and angular velocity were computed from coil signals.¹⁰,¹¹ For analysis, fixations were defined as periods when eye velocity was less than 20°/s, and saccades when eye velocity exceeded 50°/s. Coil signals were converted into eye-position quaternions using a method described previously.¹¹ Quaternions represent each eye
position as a fixed-axis rotation from a reference position. This reference position was recorded when subjects looked straight ahead at the center target. Listing's law predicts that during fixation and saccades, the quaternions vectors of eye positions lie in a plane. This plane is not necessarily Listing's plane, unless the reference position happens to be the primary position, but by computing the orientation of the plane with respect to the gaze direction at reference position, one can determine the primary position and the orientation of Listing's plane. Listing's primary position is not the primary position commonly used clinically, which refers to the straight ahead gaze position and roughly corresponds to the center of the oculomotor range. In this paper, all plots of eye position are set up so that the origin of the coordinate system (the zero position) is Listing's primary position.

Figure 8-2 shows the three-dimensional (3D) eye position data of a normal subject fixating nine target positions. Listing's plane is the best-fit plane through the data cloud of eye positions. To assess the scatter in the data, we measured the distance of each eye position from the plane of best fit; the standard deviation of these distances we call the 'thickness' of the plane. The smaller the thickness, the better the data fit Listing's law.

For a distant target, Listing's plane is approximately parallel to the frontal plane of the head. During near viewing, however, the Listing's planes of the two eyes rotate temporally. This is also illustrated in Figure 8-2, when a normal subject viewed a target 1 m away from the nasion. This temporal rotation of Listing's plane means that both eyes undergo excyclotorsion during downgaze and incyclotorsion during upgaze. Thus, during vergence, eye positions still remain restricted to a plane, and therefore obey Listing's law, though the planes are turned.
We defined the direction of torsion from the subject's point of view. Rotation of the upper pole of the iris towards the subject's right shoulder was designated as clockwise (CW), whereas rotation of the upper pole of the iris towards the subject's left shoulder was designated as counter-clockwise (CCW).

Oculography was performed at one point in each patient's course (Table 8-1). Thus, changes from normal, rather than serial intra-subject changes, were available for analyses. We compared the thickness of Listing's plane between patients and normal subjects. Because thickness of Listing's plane did not differ between viewing with the paretic or non-paretic eye, the values reported were the pooled mean under both viewing conditions. As Donders' law implies merely that the eye position data will lie in some two-dimensional surface, not necessarily in a plane, we also computed the second-order and third-order surfaces of best fit to assess whether Donders' law was obeyed when Listing's law was violated. The thickness (one standard deviation) of the fitted curved surface was compared in patients and normal subjects.

In all 13 patients, Listing's and Donders' deviations in both the paretic and non-paretic eyes did not differ during paretic or non-paretic eye viewing. In what follows, we report only Listing's and Donders' deviations during non-paretic eye viewing; deviations during paretic eye viewing were similar. Statistical analysis was performed using analysis of variance. Values were defined as significant when p < 0.05.

The research protocol was approved by the University Health Network Ethics Committee and followed the tenets of the Declaration of Helsinki. Informed consent was obtained from all subjects.
8.4 RESULTS

General characteristics of patients

The characteristics of the 13 patients with fourth nerve palsy are shown in the Table 8-1. The mean age was 54 ± 16 years (median age, 55; range, 23 - 81). There were 8 women. The duration of symptoms ranged from one week to 132 months, with a mean duration of 35 months. Mean follow-up duration was 49 months (range, 13 - 165 months). No patients had any associated neurologic symptoms or signs. Eleven patients had chronic palsy, while 2 had acute palsy. All had a hypertropia on the same side of the muscle palsy, and the hypertropia increased on gaze opposite to the paretic eye and on head tilt toward the ipsilateral shoulder (positive Bielschowsky head tilt test). All patients had normal neuro-imaging: nine had normal MR imaging and four had normal CT of the head.

Ten normal subjects served as controls (5 women; mean age, 49 ± 12 years; median age, 55; age range, 19 to 69).

Chronic fourth nerve palsy

Figure 8-3 shows the 3D eye positions data and the fitted Listing’s plane of a patient (SF) with chronic left fourth nerve palsy, during fixation with the paretic right eye. The thickness of Listing’s plane was 1.0° in both the right and left eye. Listing’s planes rotated temporally 15.4° in the right eye and 9.1° in the left eye. In this patient, Listing’s law was obeyed with temporal rotation of Listing’s planes in both eyes.

The same was observed in each of 11 patients with chronic fourth nerve palsy, regardless of the severity of their palsy. Thickness of Listing’s plane, averaged across all
patients, was 0.7 ± 0.3° for the paretic eye, and 0.6 ± 0.4° for the non-paretic eye, compared to 0.8 ± 0.3° in controls during both fixation and saccades. During fixation, rotation of Listing's plane, averaged across the 11 patients, was 21.0 ± 2.3° temporally in the paretic eye and 12.8 ± 3.1° temporally in the non-paretic eye, compared to 0.8 ± 0.4° temporally in control subjects (p<0.05). During saccades, rotation of Listing's plane was 20.4 ± 1.9° temporally in the paretic eye and 13.7 ± 2.0° temporally in the non-paretic eye, compared to 0.8 ± 0.3° temporally in control subjects (p<0.05). Listing's law held in chronic fourth nerve palsy, but with abnormally rotated planes.

**Acute fourth nerve palsy**

During saccades, thickness of Listing's plane of the paretic eye, averaged across the two patients with acute palsy, was 8.3 ± 0.4° (p < 0.05), which was 10 times the thickness seen in normal controls. The plane of the non-paretic eye was of normal thickness. When we fit the data from the paretic eye with curved surfaces rather than planes, the thickness scarcely diminished—it averaged 8.0 ± 1.2° when the surface was second-order, and 7.7 ± 1.2° when it was third-order, compared to 0.7 ± 0.3° and 0.6 ± 0.3° in normal controls (p<0.05). Thus, during saccades in acute fourth nerve palsy, not only was Listing's law violated, but also Donders' law; that is, the paretic eye did not show one consistent angle of torsion for any given gaze direction, but rather an abnormally wide range of torsional angles.

During fixation, the thickness of Listing's plane of the paretic eye averaged 10.0 ± 1.1° (p<0.05), while that of the non-paretic eye was again normal. But when we fit a Listing's plane to positions of the paretic eye that followed saccades by no less than 1.5
s, the thickness returned to normal, with a mean of $1.1 \pm 0.9^\circ$. The orientation of this newly fitted Listing's plane was also normal, with a mean temporal rotation of $1.2 \pm 0.9^\circ$. Thus, during saccades and immediately after, the paretic eye showed abnormal torsion, but 1.5 s after saccades were over, normal torsion was restored. In patients with acute fourth nerve palsy, the eye made abnormal torsional excursions during saccades and then it drifted back to Listing's plane.

Figure 8-4 shows the eye movements made by one of these patients (KS), while the paretic right eye viewed a target that stepped center – $10^\circ$ up – center – $10^\circ$ down. When the target stepped downward (that is, from $10^\circ$ up to center, and from center to $10^\circ$ down), the paretic right eye made hypermetric downward and leftward saccades, each followed without interval by corrective upward and rightward saccades (Figure 8-4, top panel, vertical and horizontal traces). At the same time, it made rapid clockwise movements, defined as rotation of the upper pole of the iris towards the subject's right shoulder, which were followed by slow counterclockwise drifts (Figure 8-4, top panel, torsional trace). In the non-paretic left eye, vertical saccades were of normal amplitude, and were not associated with horizontal saccades or transient torsion (Figure 8-4, bottom panel). The same pattern was also observed in our other patient with acute right fourth nerve palsy.

8.5 DISCUSSION

The diagnosis of fourth nerve palsy is generally made on the basis of incomitant hypertropia, which increases on head tilt to the ipsilateral shoulder (positive Bielschowsky head tilt test). Because the primary action of the superior oblique is incyclotorsion, abnormal excyclotorsion is also associated with fourth nerve palsy, as demonstrated by
double Maddox rods and fundus photography. One would predict that in fourth nerve palsy, the paretic eye might adopt abnormal eye positions and violate Listing's law. This was indeed the case in acute fourth nerve palsy during saccades. But in chronic fourth nerve palsy, although Listing's plane is rotated temporally, meaning that the eye undergoes excyclotorsion during downgaze and incyclotorsion during upgaze, nevertheless the eye positions remain restricted to planes and therefore obey Listing's law. Thus, in chronic fourth nerve palsy, the abnormality is not that Listing’s law fails but that Listing’s plane has an abnormal orientation.

Neural Implementation of Listing’s law

Listing's law holds during fixation, saccades and smooth pursuit, but fails during sleep and during vestibuloocular reflex (VOR). Its failure shows that the eye muscles are capable of violating Listing’s law, so it is not the muscles but the neural commands driving fixation, saccades and pursuit that constrain the eye to obey the law. The muscles may, however, be arranged in a way that simplifies the brain’s work in implementing Listing’s law, as in the "active-pulley hypothesis", where contraction of the global layer of the extraocular muscle rotates the globe, while contraction of the orbital layer displaces the connective-tissue sleeves, or ‘puleys’, which direct the paths of the muscles.

In our patients with acute fourth nerve palsy, Listing’s law is violated in the paretic eye during saccades. In patients with chronic fourth nerve palsy, both eyes obey Listing’s law, even though the superior oblique in the paretic eye is still markedly weak, as indicated by restricted duction and hypertropia. This recovery shows that the neural circuitry
underlying Listing's law is adaptive, restoring the law despite a palsied muscle. Neural adaptation must work by readjusting the innervations to the remaining extraocular muscles; it may also adjust their pulleys 27, though theoretically Listing's law could be restored with or without a new pattern of pulley placement and motion.

**Functional significance of Listing's law**

Chronic fourth nerve palsy has abnormal torsion, as indicated in the temporal shift of Listing's plane, but nonetheless obeys Listing's law. That these patients re-establish Listing's law without restoring normal torsion suggests that there is some advantage to Listing's law that goes beyond any specific set of torsional angles. That is, there is some advantage to keeping the axes of eye rotations in a plane, and it may not matter so much what the orientation of the plane is.

The functional significance of Listing's law is uncertain. Herring 28 and Helmholtz 4 proposed that it optimizes certain aspects of image flow across the retina, thereby simplifying the neural processing of visual information. As optical flow depends on the eye's motion relative to space, both theories tacitly assume that the eyes rotates relative to space in the way dictated by Listing's law. But, in fact, it is eye rotation relative to head that follows Listing's law, whereas, owing to head movement, eye rotation relative to space does not. 29-31 Thus, theories based on optical flow likely cannot explain Listing's law.

Fick and Wundt proposed that Listing's law enhances motor efficiency by minimizing eccentricity during motion of the eye. 4 Minimizing eccentricity during movement may reduce the elastic recoiling force acting on the eye, and therefore reduce the work load on the eye muscles. Or, it may bring the eye the same advantage that staying near
the center court brings a squash player, namely swift and flexible responses to incoming stimuli. By ensuring that all gaze shifts toward and away from primary position are made along the shortest path, Listing's law permits quick responses to unpredictable targets that may appear from any direction.

These motor advantages may be regained when patients with chronic fourth nerve palsy reestablish Listing's law. After adaptation, the only difference from normals is that primary position, and therefore Listing's plane, is further temporal. Each of our 11 patients with chronic palsy showed temporal rotation of Listing's plane in both eyes, in contrast to one reported patient with nasal rotation in the non-paretic eye.32 This temporal rotation may serve some functional purpose, or it may be an unavoidable consequence of the palsy: the inferior rectus attempts to compensate for the deficits of the palsied superior oblique, causing abnormal excyclotorsion on downgaze, and so rotating Listing's plane in the paretic eye. The temporal rotation of Listing's plane of the non-paretic eye can be explained by a conjugate increase in activity of the inferior rectus of the non-paretic eye.

*Transient torsional deviations in acute fourth nerve palsy*

Abnormal torsional deviations have been reported in patients with medullary and cerebellar lesions. Torsional pulsion of saccades (torsipulsion), consisting of torsional fast eye movements away from the side of lesion (from examiner's viewpoint) induced during saccades downward or away from the side of lesion, has been recorded in patients with lateral medullary infarction.33 Torsional blips, consisting of torsional fast eye movements followed by slow exponential drifts in the opposite direction during horizontal and vertical saccades, were observed in a patient with infarction of the dorsolateral medulla and
Damage to the medulla and the cerebellum may disturb the neural commands that normally prevent or correct torsional deviations during saccades.

We found that in acute fourth nerve palsy, both Listing's and Donders' laws fail during saccades, but the eye then drifts back into Listing's plane. The likely mechanism is pulse-step mismatch. In normal saccades, a pulse of innervation, consisting of a high frequency burst of phasic activity in the agonist motoneurons, drives the eye rapidly to its target. Once the eye has reached its target, agonist motoneurons assume a new, higher than resting level of tonic innervation, constituting saccadic step of innervation, which holds the eye in its new position. If the pulse drives the eye to some position that cannot be held by the step command, a pulse-step mismatch occurs, so that the eye drifts, after every saccade, to a position dictated by the step command.

Our findings are explained if, in patients with acute fourth nerve palsy, the pulse drives the eye into abnormal torsional angles, but the step command specifies a torsional position in Listing's plane. Presumably the pulse misdirects the eye because the normal torsional action of the superior oblique has been lost, or because other aspects of the normal orbital plant dynamics have been altered. This results in a loss of the precise control of torsional eye velocity and explains why Donders' law fails during saccades. Despite the peripheral lesion, the brain should still generate identical step commands every time it directs the eye to fixate in any one particular direction, so that after the eye makes abnormal torsional excursions during a saccade, it should drift to the same torsional position for any one gaze direction as specified by the normal step command. This explains why, in acute palsy patients, Donders' law is restored by the post-saccadic drift.
8.6 TABLE AND FIGURES
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<th>Duration (months)</th>
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* percent of normal duction in adducted depression
PD, prism diopter
RHT, right hypertropia; LHT, left hypertropia; MRA, MR angiogram
Figure 8-1. The nine orientations drawn in solid lines accord with Listing's law, because they are attainable by rotating from primary position (center) about axes lying in Listing's plane (the plane of the paper). The position drawn in dashed lines at top center does not fit Listing's law because the rotation to this position from primary position occurs about an axis that is tilted out of primary position. (Adapted from Tweed D, Vilis T. Geometric relations of eye position and velocity vectors during saccades. Vision Research 1990; 30:111-127.)
Figure 8-2. Plots of eye positions relative to primary position, in coil coordinates, of a normal subject during fixation at nine target positions, 1 m away from the nasion. (A) Behind view and (B) Top view. Listing’s plane is the best-fit plane through the data cloud of eye positions. A small temporal rotation of Listing’s plane is also demonstrated in (B). The central cloud among the nine little clouds of eye positions represents Listing’s primary position and is shifted away from the zero position of the coordinate system (intersection of left-right and up-down axes), which is the straight ahead gaze position. Note that Listing’s primary position and straight ahead gaze position are different.
Normal subject (KQ)

(A) Behind View

(B) Top View
Figure 8-3. Plots of eye positions relative to primary position, in coil coordinates, of a patient (SF) with a chronic left fourth nerve palsy during fixation of nine target positions. (A) Behind view and (B) Top view. Note that Listing's planes are of normal thickness, but are rotated temporally in each eye.
Chronic left fourth nerve palsy (SF)

(A) Behind View

Left eye

Right eye

(B) Top View

Left eye

Right eye
Figure 8-4. Eye positions plotted against time for a patient (KS) with acute fourth sixth nerve palsy, while the paretic right eye viewed a target that stepped from center to 10° up to center to 10° down. When the target stepped downward, the paretic right eye made hypermetric downward and leftward saccades followed by corrective upward and rightward saccades. A fast clockwise eye rotation movements occurred in the paretic right eye, which were followed by slow counterclockwise drifts back to initial torsional eye positions. In the non-paretic left eye, vertical saccades were normal in amplitude and direction. Rotation of the upper pole of the iris towards the subject's right shoulder was designated as clockwise (CW), whereas rotation of the upper pole of the iris towards the subject's left shoulder was designated as counter-clockwise (CCW).
Patient KS - Right acute fourth nerve palsy

**Right eye**

**Horizontal**
- 10 deg right
- 10 deg left

**Vertical**
- 10 deg up
- 10 deg down
- 10 deg CW

**Torsional**
- 10 deg CCW

---

**Left eye**

**Horizontal**
- 10 deg right
- 10 deg left

**Vertical**
- 10 deg up
- 10 deg down
- 10 deg CW

**Torsional**
- 10 deg CCW

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3 sec
8.7 REFERENCES


SECTION IV: VERTICAL MISALIGNMENT IN SIXTH NERVE PALSY
CHAPTER 9

VERTICAL MISALIGNMENT IN SIXTH NERVE PALSY

AND ITS CLINICAL IMPLICATIONS
9.1 SUMMARY

**Purpose:** To detect and determine the magnitude of vertical deviation in patients with unilateral sixth nerve palsy.

**Methods:** Twenty patients with unilateral peripheral sixth nerve palsy, seven patients with central palsy caused by brainstem lesions, and ten normal subjects were studied. The magnitudes of horizontal and vertical deviations were measured using the prism and cover test, Maddox rod and prism test, and magnetic search coil recordings in nine diagnostic eye positions, and during static lateral head tilt.

**Results:** All patients had an abduction deficit and incomitant esodeviation that increased in the field of action of the paretic muscle, indicating sixth nerve palsy. Mean vertical deviations, for all positions of gaze, in peripheral palsy were: $0.3 \pm 0.8$ prism diopters (PD) by prism-cover test, $1.3 \pm 1.6$ PD by Maddox test, and $2.0 \pm 1.4$ PD by coil recordings. Mean vertical deviations in normal subjects were: $0.0 \pm 0.0$ PD by prism-cover test, $1.0 \pm 0.9$ PD by Maddox test, and $1.9 \pm 2.1$ PD by coil recordings. Therefore, peripheral palsy did not cause abnormal vertical deviation. In central palsy, mean vertical deviations were: $0.9 \pm 1.3$ PD by prism-cover test, $1.4 \pm 1.6$ PD by Maddox test, and $2.5 \pm 1.6$ PD by coil recordings; they were not different from normal values. During static head roll, patients with peripheral palsy had a right hyperdeviation on right head tilt, and a left hyperdeviation on left head tilt, regardless of the side of the palsy. In contrast, in central palsy, head tilt caused vertical strabismus that remained on the same side on head tilt to either side.

**Conclusions:** Small vertical deviations in sixth nerve palsy are consistent with normal hyperphorias that become manifest in the presence of esotropia. In peripheral sixth nerve palsy, static head roll to either side induces hyperdeviation in the eye on the side of the
head tilt. Hyperdeviation of the same eye induced by head tilt to either shoulder implicates a brainstem lesion as the cause of paretic abduction. Quantitative study of sixth nerve palsy demonstrates that if a vertical deviation falls within the normal range of hyperphoria, multiple cranial nerves palsy or skew deviation is not responsible. Conversely, vertical deviation over 5 PD indicates skew deviation or peripheral nerve palsy in addition to abduction palsy.
9.2 INTRODUCTION

Sixth nerve palsy is the most common ocular motor nerve palsy. It is characterized by incomitant esotropia with or without a visible limitation of abduction. When a vertical strabismus accompanies defective abduction, multiple cranial nerves palsy or skew deviation from a brainstem lesion should be considered in the differential diagnosis.

Although the abducens nerve and lateral rectus muscle function to abduct the eye, effects of palsy suggest that they play a role in vertical alignment of the eyes.\textsuperscript{1-3} Evidence for this has been sparse, based on subjective testing, and not quantified. Our preliminary clinical observations suggested that patients with isolated sixth nerve palsy could have a small vertical strabismus, the magnitude of which changed with lateral head tilt. Roll of the head about its naso-occipital axis activates the torsional vestibulo-ocular reflex (VOR), causing the eyes to rotate around their visual axes. The torsional VOR has a dynamic counterroll component \textsuperscript{4-7} during head roll, and a static counterroll component after the head comes to rest in a position of lateral tilt.\textsuperscript{8} Using objective and subjective techniques, and magnetic search coil oculography, we investigated patients with unilateral sixth nerve palsy from a peripheral cause to determine the vertical alignment of their eyes and their responses to static change in head roll. They were compared to normal subjects and to patients with central sixth nerve palsy caused by brainstem lesions.

9.3 METHODS

Twenty-seven consecutive patients with unilateral sixth nerve palsy were recruited from the Neuro-ophthalmology Unit at the University Health Network. A complete history was taken, and detailed ophthalmic and neurologic examinations were performed. The age
of onset, the presence or absence of risk factors for ischemia (diabetes mellitus and hypertension), duration of diplopia, range of duction, horizontal and vertical deviations (see Orthoptic assessment below), and associated neurologic symptoms and signs were recorded. When indicated, appropriate tests were performed to rule out myasthenia gravis, thyroid ophthalmopathy, other orbital diseases, or intracranial lesions. Informed consent was obtained from each subject.

**Orthoptic assessment**

The range of ductions was examined and the degree of abduction defect was graded according to the estimated percentage of the normal abduction in the fellow eye. Vertical ductions were also recorded.

The amount of horizontal and vertical deviations were measured in nine diagnostic positions. This was achieved by turning the patient's head in the appropriate direction to put the eyes into the desired positions. The nine diagnostic positions were: (1) the straight ahead position; (2) four secondary positions i.e. about 10° to the right and left (by turning the face to the left and right), and about 10° up and down (by depressing and elevating the chin); and (3) four tertiary positions i.e. 10° up and right, up and left, down and right, and down and left (by a combination of face turn and chin depression / elevation). The amount of vertical deviations were also measured by tilting patient's head 30° toward each shoulder. Both primary deviation (non-paretic eye fixating) and secondary deviation (paretic eye fixating) were measured.

To standardize the amount of head turn and gaze positions, patient wore a cervical range of motion (CROM) instrument (Performance Attainment Associates, Roseville, MN),
which measures the amount of cervical rotation (face turn), extension and flexion (chin elevation and depression) and lateral flexion (head tilts) in degrees.\textsuperscript{10, 11} The CROM instrument consists of inclinometers which are attached to a frame similar to that for glasses: one in the sagittal plane for chin up and down position, a second in the frontal plane for head tilt, and a third in the horizontal plane for face turn.\textsuperscript{10, 11} Two of these inclinometers have gravity-dependent needles (in the sagittal and frontal planes). The other has a magnetic needle (in the horizontal plane) directed to a trunk-fixed magnet placed in midline of the upper chest and back.\textsuperscript{10-12}

The CROM instrument has been demonstrated to have a high reliability and validity.\textsuperscript{10-14} In a study of 337 subjects, Youdas et al\textsuperscript{10} found that the CROM device has a good intra-tester and inter-tester reliability, with intra-class correlation coefficients greater than 0.80.\textsuperscript{10} Tousignant \textsuperscript{11} assessed the validity of CROM by comparing the measurements obtained from the CROM device with those from a "gold standard" radiographic technique. He \textsuperscript{11} found that there was a high correlation between the two techniques in measuring cervical spine movement ($r=0.98$, Pearson's $r$ correlation test), and concluded that the CROM device has a high validity. Kushner \textsuperscript{12} examined 39 patients and demonstrated that CROM is a reliable device for ocular motility examination, including abnormal head postures, limitations of ductions, and the range of single binocular vision.\textsuperscript{12}

The amounts of horizontal and vertical deviations were measured in each of the nine diagnostic positions with the head erect, and in the straight ahead position during static lateral head tilt, both objectively using the prism and cover test, and subjectively using the Maddox rod and prism test.\textsuperscript{8} For the prism and cover test (prism-cover test), which measured the magnitude of tropia (i.e. manifest deviation), patients fixated at a
20/30 Snellen symbol at a distance of 6 meter. A cover was placed in front of one eye several times while the patient maintained fixation with the other eye. This cover-uncover technique was repeated with the other eye. To achieve maximum deviation, care was taken to ensure that fusion was not regained while the cover was being placed. The amount of deviation was grossly estimated, and a loose glass prism of a strength less than the estimated deviation was placed in the Prentice position (i.e. placing the posterior face of the prism perpendicular to the line of sight) in the appropriate direction in front of one eye. The prism strength was increased until refixation movement ceased. The increase in prism strength was tailored to each patient and was not performed in uniform steps. Horizontal deviation was first neutralized, followed by measurement of vertical deviation. To ensure full dissociation and to obtain the full amount of deviation, prism strength was increased not only until refixation movement has stopped, but also until a reversal of the direction of movement was noted. The highest prism strength used immediately before the reversal of direction of refixation movement was recorded as the amount of deviation in each position of gaze. The test was performed with either eye fixating to measure both the primary deviation (non-paretic eye fixating) and secondary deviation (paretic eye fixating).

The amounts of horizontal and vertical deviations were also measured subjectively using the Maddox rod and prism test (Maddox test). The Maddox rod is a device that consists of a series of parallel cylinders. It converts a point source of light into a streak. The optical properties of the cylinders cause the streak of light to be 90° to the orientation of the parallel cylinders. To measure horizontal deviations, a red Maddox rod was placed over the right eye with the small glass rods arranged horizontally. The patient fixated a
small white light at 6 meter, and stated whether the white light was to the right or to the left of the vertical red streak. Glass prisms of increasing strength were placed in front of one eye in the appropriate direction until the red streak was reported to go through the white spotlight to measure the horizontal deviation at each diagnostic position. The same procedure was then repeated with the small glass rods of the Maddox rod arranged vertically to measure vertical deviation in nine diagnostic positions and during head tilt. Ten normal subjects served as controls.

Eye positions and alignment from eye movement recordings

Visual stimuli and experimental protocol. In addition to using clinical techniques, we also measured eye deviations with magnetic search coils while patients fixated a red laser spot of 0.25° in diameter, rear-projected onto a vertical flat screen 1 m away from the nasion. The laser was programmed to appear in nine different target positions, arranged in a 3 x 3 square. The middle row of this array was at eye level, the other two 10° above and below. In each row, the center target lay in the patient's midsagittal plane, the other two 10° right and left of it.

With one eye covered, patients were instructed to follow the laser spot as it stepped among positions. At each position the laser halted for 3 sec. In the horizontal target sequence, the laser started in the center, then stepped to the 10° right position, then back to center, then 10° left, cycling through this pattern 20 times for each eye. The vertical sequence was the same but with the laser stepping center–up–center–down; the two diagonal sequences stepped along oblique lines, between opposite corners of the target array. Recordings were then made with the other eye fixating and the fellow eye occluded.
Recordings of eye movement and calibration. Position of each eye was simultaneously measured in the nine diagnostic positions by a 3-dimensional magnetic search coil technique, using a 6 ft (183 cm) diameter coil field arranged in a cube (CNC Engineering, Seattle, Washington). Eye positions were not measured during static lateral head tilt with magnetic search coils. Phase detectors employing amplitude modulation as described by Robinson provided signals of torsional gaze position within the linear range. In each eye, the patient wore a dual-lead scleral coil annulus designed to detect horizontal, vertical, and torsional gaze positions (Skalar Instrumentation, Delft, Netherlands). Head position was detected by another coil taped to the patient’s forehead. The patient’s head was immobilized and centered in the field coils. Horizontal and vertical eye movements were calibrated with saccades to steps of the laser target. Head and torsional eye movements were calibrated by attaching the scleral coil to a rotating protractor. Torsional precision was about ± 0.2°. There was minimal crosstalk; large horizontal and vertical movements produced deflections in the torsional channel of less than 4% of the amplitude of the horizontal and vertical movement. Any coil slippage was assessed by monitoring offsets in torsional eye position signal during testing. Consistency of calibrated positions after each eye movement provided evidence that the coil did not slip on the eye. Eye position data were filtered with a bandwidth of 0 to 90 Hz and digitized at 200 Hz. They were recorded on disc for off-line analysis. Analog recordings were also displayed in real time by a thermal array recorder (Model TA 2000, Gould Inc., Ohio).

Data analyses. Eye position and angular velocity were computed from coil signals. Eye positions were expressed using Helmholtz angles in degrees. To exclude saccades, we analyzed only data in which both eyes were turning at less than 30
For each subject we computed a set of best-fit functions, expressing each eye's torsion as a function of its horizontal and vertical angles, and expressing the horizontal and vertical angles of the non-viewing eye as a function of the horizontal and vertical angles of the viewing eye. Using these fitted functions we then computed the typical torsions of both eyes, and the typical horizontal and vertical positions of the non-viewing eye, when the viewing eye fixated the nine targets in our array. To quantify ocular alignment in these nine positions, we calculated the difference (right minus left) between the two eyes' horizontal, vertical and torsional angles. Exodeviation, right hyperdeviation and excyclotorsion (of the non-viewing eye) were positive; esodeviation, left hyperdeviation, and incyclotorsion (of the non-viewing eye) were negative. The horizontal, vertical and torsional deviations between the two eyes were then converted from degrees to prism diopters using the formula:

\[ \Delta = 100 \tan \theta \]

where \( \Delta \) is angle in prism diopters, and \( \theta \) is angle in degrees.\(^{19}\)

This relationship between the angle in prism diopters and angle in degrees is non-linear. However, it approximates linearity for deviations up to 30°.\(^{17}\) In this study, only one of 27 patients had horizontal deviations of more than 20°. No patients had vertical deviations of more than 4°. Relative to the precision of clinical measurement, the relation between prism diopters and degrees is linear within this range.

*Imaging studies and follow-up*

Serial axial and sagittal T1- and T2-weighted magnetic resonance (MR) images with gadolinium enhancement were obtained (slice thickness = 5 mm) for all patients under 50
years of age and those with other neurologic signs. In this investigation, CT images of the head with contrast were obtained in all patients with ischemic risk factors and for patients over 50 years of age, although CT imaging is not our standard practice for such patients. If CT imaging was normal, patients were followed at about 3 months. Those without improvement at 3 months and those with an abnormal CT scan were further investigated with MR imaging.

Data analyses and statistical methods

In all 27 patients and by all three measuring techniques—prism-cover test, Maddox test, coils recordings—the secondary deviations (with the paretic eye fixating) were always larger than the primary deviations (with the non-paretic eye fixating). In what follows, we report only the primary deviations; the results for secondary deviations were similar. Analyses of variance (ANOVA) were used to compare mean deviations between patients with peripheral palsy and normal controls, as well as between central palsy and normal controls. Correlations between the degree of abduction defect and the magnitude of hyperdeviation were assessed using linear regressions. Fisher exact tests were used to examine the relationship between the side of palsy and the side of hyperdeviation. To assess whether the vertical deviations were comitant, the mean differences of vertical deviations between upgaze and downgaze were calculated and compared using ANOVA. The difference in vertical deviations on right and left head tilt between patients and normal subjects were assessed using ANOVA.

9.4 RESULTS
General characteristics of patients

Twenty patients had peripheral palsy caused by idiopathic, presumed ischemic, peripheral lesion (Table 9-1). The mean age was 61 ± 14 years (age range 21 - 77; median age 64); 11 of them were men. The duration of symptoms ranged from two weeks to 96 months, with a mean duration of 20 ± 17 months. Mean follow-up duration was 10 months (range 8 - 22 months). Fourteen had normal MR imaging and 6 had normal CT scanning of the brain. Five out of the six patients with normal CT scan had ischemic risk factors, such as hypertension or diabetes, and had a complete resolution of their palsy within four to six months.

Seven patients had sixth nerve palsy caused by central brainstem lesion, as shown by MR imaging (Table 9-2). The mean age was 59 ± 20 years (age range 30 - 79; median age 59); 3 of them were men. The duration of symptoms ranged from one week to 240 months, with a mean duration of 64 ± 91 months. Mean follow-up duration was 16 months (range 10 - 24 months). Lesions included demyelination (3 patients), pontomedullary cavernous hemangioma (2), meningioma compressing the pons (1), and infarct (1). All seven patients had neurologic symptoms and signs in addition to abduction paresis, but no other ocular motor signs.

Ten normal subjects served as controls (5 men; mean age 49 ± 12 years; median age 55; age range 19 to 69).

Horizontal deviations in the nine diagnostic positions

Figure 9-1 shows the horizontal and vertical deviations (primary deviations; non-paretic eye fixating), in prisms diopters (PD), in all 27 patients. The mean horizontal
deviations in all 27 patients in the nine diagnostic positions are shown in Figure 9-2. Consistent with a paralytic strabismus, all patients had an incomitant esodeviation, which increased in the field of action of the paretic muscle. In general, the magnitudes of esodeviation measured by the prism-cover test were slightly smaller than those measured by the Maddox test or coil recordings; however, these differences were not statistically significant (NS) (ANOVA).

**Vertical deviations in nine diagnostic positions**

The prism-cover test revealed hyperdeviation in at least one eye position in 4 (20%) patients with peripheral palsy and 2 (29%) patients with central palsy. The Maddox test revealed hyperdeviation in 15 (75%) patients with peripheral and 5 (71%) patients with central palsy. Coils recordings identified hyperdeviation in all 27 (100%) patients. No vertical duction deficits were found in any patient.

**Peripheral palsy.** Mean vertical deviations in nine diagnostic positions are shown in Figure 9-3. Mean vertical deviations, averaged across the 20 patients and nine eye positions, were: 0.3 ± 0.8 prism diopters (PD) by prism-cover test, 1.3 ± 1.6 PD by Maddox test, and 2.0 ± 1.4 PD by coil recordings (Figure 9-4A). Mean vertical deviations in normal subjects were: 0.0 ± 0.0 PD by prism-cover test, 1.0 ± 0.9 PD by Maddox test, and 1.9 ± 2.1 PD by coil recordings (Figure 9-4A). Thus, peripheral palsy did not cause abnormal vertical deviation (ANOVA, NS). There was no correlation between the degree of abduction defect and the magnitude of hyperdeviation in any diagnostic position (linear regression, NS). No correlation was found between the side of palsy and the side of hyperdeviation (Fisher exact test, NS). No patients exhibited any pattern of vertical
deviation consistent with an associated vertical rectus or oblique muscle paresis. The vertical deviations were comitant in individual patients and in normal subjects, as were the group means (Figure 9-3) (ANOVA, NS). The maximum difference between hyperdeviation on upgaze and downgaze in any individual patients was 3 PD.

Central palsy. Mean vertical deviations in the nine diagnostic positions are shown in Figure 9-5. Mean vertical deviations, averaged across the 7 patients and nine eye positions, were 0.9 ± 1.3 PD by prism-cover test, 1.4 ± 1.6 PD by Maddox test, and 2.5 ± 1.6 PD by coil recordings (Figure 9-4A). They were not statistically different than normal values (ANOVA). No patient had features of an associated vertical rectus or oblique muscle paresis. Two patients with a right rostral pontomesencephalic lesion had a right (ipsilateral) hyperdeviation (when tested with coil recordings), while 5 patients with a left caudal pontomedullary lesion had a right (contralateral) hyperdeviation. The vertical deviations were comitant in individual patients, as were the group means (Figure 9-5) (ANOVA, NS). The maximum difference between hyperdeviation on upgaze and downgaze in any individual patients was 2 PD.

Vertical deviations during static head roll

Peripheral palsy. During static lateral head roll, 18 of the 20 patients with peripheral palsy exhibited a right hyperdeviation on lateral head tilt to the right shoulder (right head tilt), and a left hyperdeviation on lateral tilt toward the left shoulder (left head tilt) on testing with the Maddox test, regardless of the side of palsy (Figure 9-3). Two other patients had hyperdeviation on head roll to one side only. The Maddox test detected a mean of 4.28 PD right hyperdeviation (range: 1 to 14 PD) on right head tilt, and 2.86 PD
left hyperdeviation (range: 0 to 8 PD) on left head tilt. The difference in vertical deviations between right and left static head roll was statistically significant (ANOVA, p < 0.001). Among 10 normal subjects, 5 had a small hyperphoria (maximum = 1 PD) on lateral head tilt. The side of hyperphoria did not correlate with the side of head tilt (Fisher exact test, NS). The mean vertical deviations in normal subjects were 0.30 right hyperphoria (range: 0 to 1 PD) on both right and left head tilt, using the Maddox test. The difference in vertical deviations on head tilt between patients with peripheral palsy and normal subjects was statistically significant (ANOVA, p < 0.001).

Central palsy. In contrast to patients with peripheral palsy, 4 of the 7 patients with central palsy had hyperdeviation that remained on the same side during static lateral head tilt to either side on testing with the Maddox test (Figure 9-5). Two other patients had hyperdeviation on head tilt to one side only. One patient had no vertical deviation during head tilt. The Maddox test detected a mean of 2.10 PD right hyperdeviation (range: 0 to 4 PD) on right head tilt, and 1.25 PD right hyperdeviation (range: 0 to 4 PD) on left head tilt. The difference in vertical deviations between right and left head tilt was not statistically significant (ANOVA). However, the difference in vertical deviations during head tilt between patients with central palsy and normal subjects was significant (ANOVA, p < 0.01).

9.5 DISCUSSION

Information about vertical strabismus in sixth nerve palsy is sparse. Kestenbaum stated that "in abducens paresis a vertical component is sometimes found" and this slight vertical component can be up to 3 diopters before one can conclude that a vertical muscle
is involved pathologically. Smith cited Dr. F. Walsh, stating that "one could accept up to 2-3 prism diopters of vertical deviation with a VI nerve palsy alone, but any amount more than that was significant." They did not present data or clinical documentation.

Slavin examined 61 normal subjects subjectively with the Maddox test, and found that up to 77% showed a vertical misalignment of 2-10 PD in any field of gaze. In another study, Slavin examined 16 patients with isolated unilateral sixth nerve palsy using the same method. He concluded, in contrast to Kestenbaum and Walsh, that a large amount of hyperdeviation, up to 16 PD, could be detected in these patients in different gazes, as well as during head tilt.

The Maddox test prevents fusional vergence by creating dissimilar images between the eyes, and reveals the magnitude of heterophoria (i.e. latent deviation) or heterotropia. In this investigation, we also used the prism-cover test which measures the magnitude of heterotropia (i.e. manifest deviation). However, when a horizontal heterotropia exists (as in our patients with sixth nerve palsy), any vertical heterophoria becomes manifest, and is measured as if it were a heterotropia. Since about 80% of our normal subjects have a vertical heterophoria, any vertical heterotropia, as measured by the prism-cover test, in patients with sixth nerve palsy cannot be considered a genuine vertical heterotropia, unless it exceeds the magnitude of the range of vertical heterophoria in normal subjects.

**Vertical misalignment in peripheral sixth nerve palsy**

In our study, most normal subjects (80%) were found to have a vertical heterophoria in at least one of the 9 diagnostic positions. Three of them had a vertical deviation in the straight ahead position. The vertical phoria ranged from 0 to 5 PD, as measured by the
Maddox test. Our findings were comparable to those from a previous study 20, although we found a smaller maximum deviation (5 PD versus 10 PD 20).

In isolated peripheral sixth nerve palsy, the Maddox test showed that 75% of our 20 patients had a vertical deviation in at least one eye position. This is in contrast to a prior study 3, which found that all 16 patients had a vertical deviation. In addition, we found that the maximum magnitude of hyperdeviation was smaller (6 PD versus 16 PD 3). These discrepancies may be due to methodological differences 3: fixation target distance was 14 inches; only 5 of 16 patients had CT scan or MR imaging to exclude brainstem involvement of vertically acting muscles; and the duration of follow-up was not specified. 3

With the prism-cover test, the maximum hypertropia measured in any of our patients with peripheral sixth nerve palsy was 4 PD (Figure 9-4B). The estimates by Kestenbaum and Walsh 1,2 of the magnitude of vertical strabismus associated with sixth nerve palsy are consistent with the results of our quantitative investigation. Hypertropia in our patients varied idiosyncratically with gaze direction and always fell within the range of hyperphoria seen in our normal subjects (maximum = 5 PD) (Figure 9-4B). Normal hyperphoria that becomes manifest in paralytic strabismus explains these findings.

Comparison of the prism-cover test, Maddox test and magnetic search coil methods

Deviations estimated by the prism-cover test were usually slightly smaller than those estimated by the Maddox test and by coil recordings. This discrepancy can be explained by several factors. As mentioned, whereas the prism-cover test measured the amount of heterotropia, the Maddox test and coil recordings measured heterophoria, plus heterotropia if present.
In addition, a small deviation may not be detected by the prism-cover test. The smallest refixation movement detectable with the prism-cover test has been estimated to be from 1 to 4 PD. Ludvigh and Romano and von Noorden reported that 2 PD (about 1.1°) should be considered the smallest deviation detectable by the prism-cover test with the unaided eye. The absence of detectable refixation movement means that a deviation, if present, is probably less than 2 PD, but does not exclude strabismus. In agreement with early studies, we found that the prism-cover test detected vertical deviation in fewer normal subjects than the other two techniques, and measurements obtained by the prism-cover test were 1-2 PD lower.

Furthermore, the testing conditions and the underlying physiologic basis for the 3 techniques are different. In the prism-cover test, the refixation movement is a visually guided saccade that occurs in both eyes when one eye refixates, bringing the image of the target to the fovea. Prisms of increasing power in front of the eye bring the image of the target closer and closer to the fovea, decreasing the refixation movement, and allowing for objective measurement of the angle of deviation. In the Maddox test, the measurement is based on the diplopia principle. One determines the subjective localization of a single object point imaged on the fovea of the fixating eye, and an extrafoveal retinal area in the other eye. The distance of the double images is then a subjective measure of the deviation that can be quantified by using prisms until a single image is seen.

While the prism-cover and the Maddox tests are commonly used clinically, the scleral search coil technique is available in few laboratories. Dual search coils allow one to measure simultaneously the three-dimensional positions of both eyes; from these data the three-dimensional misalignment of the two eyes can be computed. The coil method
allows measurements with high temporal and spatial resolution\textsuperscript{24}, detecting eye movements as small as 30 seconds of arc.\textsuperscript{25} The present study, to our knowledge, is the first to systematically compare two standard clinical methods of measuring ocular deviation with the scleral search coil technique. Although deviations measured by the prism-cover test tend to be smaller than those measured by the Maddox test and by coil recordings, the differences were not statistically significant, indicating that all 3 methods were concordant in clinical utility. The search coil technique provides objective, high resolution determination of changes in eye position.

The difference in viewing distance between the three techniques might contribute to the discrepancy of measured deviations. The fixation distance was 6 meters for the prism-cover and the Maddox tests, compared with one meter for the search coils technique. Differences in horizontal eye positions could affect the amounts of vertical deviations. However, in normal subjects, vertical misalignment of the eyes is small and varies idiosyncratically with viewing distance.\textsuperscript{26} In addition, both the prism-cover and the Maddox tests were performed using a fixation target at 6 meters, the discrepancy of measured vertical deviations between these two techniques cannot be explained by fixation distance.

**Vertical misalignment in central sixth nerve palsy**

Brainstem or acute peripheral vestibular lesions that disrupt the otolith-ocular pathway cause large amounts of vertical (skew) deviation and ocular torsion. Brandt and Dieterich\textsuperscript{27} reported a mean skew deviation of 4° (ranging from 1° to 20°) in 56 patients with unilateral brainstem infarction. Rostral pontomesencephalic lesions were associated
with ipsi-lesional hypertropia, and caudal pontomedullary lesions with contra-lesional hypertropia. Abnormal ocular torsion was also present. The mean ocular torsion was 8° (ranging from 2° to 28°), with the hypertropic eye incyclotorted, and the hypotropic eye excyclotorted.

We investigated 7 patients with central sixth nerve palsy caused by brainstem lesions. All patients had associated neurologic symptoms and signs in addition to abduction paresis, but no other ocular motor signs. Magnetic resonance imaging showed unilateral lesions in the brainstem tegmentum. Caudal pontomedullary lesions were associated with contralateral hyperdeviation, whereas rostral pontomesencephalic lesions were associated with ipsilateral hyperdeviation. The hyperdeviation did not exhibit any pattern that could localize a palsy to one of the vertical rectus or oblique muscles, using the three-step test. In addition, the hyperdeviation was comitant, with the maximum difference between upgaze and downgaze never exceeding 2 PD in any of our patients. Their vertical strabismus might represent a small skew deviation caused by disruption of the otolith-ocular pathway. However, because the magnitude of hyperdeviation in individual patients (maximum = 4 PD) did not differ from normal subjects (maximum = 5 PD) (Figure 9-4B), their vertical strabismus was consistent with normal vertical heterophoria that become manifest in the presence of esotropia.

**Vertical misalignment during static ocular counterroll in peripheral and central sixth nerve palsy**

Sustained head roll evokes compensatory changes in torsional eye position, called "static ocular counterroll", that are mediated mainly by the otolith-ocular reflex from inputs
of the utricles. In humans, static head tilt causes sustained conjugate counterroll of the eyes and a small vertical misalignment, with static counterroll (OCR) gain ranging from 0.10 to 0.24, depending on target distance.

One study quantified the change in vertical alignment of the eyes during static head roll while subjects fixated binocularly. In normal subjects, the hypertropia was small (up to 3.6° for a 20° head roll), and varied idiosyncratically with viewing distance. In general, during viewing of a distant target (7.2 m), a right head tilt is associated with a left hyperdeviation, and a left head tilt with a right hyperdeviation. The reverse was observed during viewing of a near target (20 cm): a right head tilt was associated with a right hyperdeviation, and a left head tilt with a left hyperdeviation. This vertical misalignment was not accompanied by subjective diplopia in normal subjects. In the same study, four patients with skew deviation were investigated and their vertical deviation did not change with head tilt.

In our normal subjects, prism-cover testing did not identify a vertical hypertropia in static head roll, with a detection threshold of about 2 PD (about 1.1°). Maddox rod testing detected a vertical heterophoria in five normal subjects during static head roll, with a detection threshold of about 1 PD (about 0.6°). However, the magnitude was small (maximum = 1 PD) and no specific pattern was detected. In contrast to a prior study, we did not record vertical strabismus after static head roll with coil recordings.

In sixth nerve palsy, we observed a distinct pattern of vertical misalignment using the Maddox test (Figure 9-6). In peripheral palsy, right head tilt was associated with right hyperdeviation, and left head tilt with left hyperdeviation. In contrast, in central palsy, the side of hyperdeviation did not change on head tilt to either side. This pattern of
hyperdeviation during static head tilt in peripheral palsy cannot be attributed to a concurrent bilateral fourth nerve palsy; in fourth nerve palsy, the hypertropia typically increases during adduction and depression, but this was not the case in our patients.

Using magnetic search coils, Averbuch-Heller et al \(^{26}\) reported that during near viewing, normal subjects exhibited a small right hyperdeviation on right head tilt, and a small left hyperdeviation on left head tilt. We did not detect any pattern of vertical misalignment during head tilt in our normal subjects using the Maddox test, which is less sensitive than coil recordings. However, in our patients with peripheral palsy, we detected a pattern of right hyperdeviation on right head tilt, and left hyperdeviation on left head tilt, similar to that reported in their normal subjects in a previous study.\(^{26}\) This pattern of vertical misalignment in peripheral palsy may represent an exaggerated response to static head roll.

Static head tilt stimulates otolith receptors in the maculae, leading to ocular counterroll and a small change in vertical alignment in normal subjects.\(^{26,30}\) However, when the otolith-ocular reflex pathway is disrupted, ocular torsion and skew deviation is observed.\(^{27}\) This indicates that under normal circumstances, the otolith-ocular reflex is symmetrical and balanced; it is also suppressed during static head roll. This suppression is probably mediated, in part, by visual mechanisms. Disruption of binocular vision may remove the suppression on the otolith-ocular reflex, and lead to the pattern of right hyperdeviation on right head tilt and left hyperdeviation on left head tilt observed in patients with peripheral palsy. In contrast, in patients with central sixth nerve palsy, unilateral lesions that disrupt the balance of the otolith-ocular reflex may lead to the
pattern of vertical deviation that we recorded, with hyperdeviation remains on the same side regardless of the direction of head roll.

**Clinical implications**

Sixth nerve palsy in patients over 50 years of age is usually caused by ischemia, occurring with greater frequency in patients with diabetes mellitus or hypertension. Since most patients recover within 3 months, they require little investigation at the time of initial presentation, if they have no other neurologic symptoms or signs. However, if vertical misalignment is found in a patient with an abduction defect, the physician should consider involvement of vertically acting muscles or additional cranial nerves, or skew deviation indicating brainstem dysfunction. In this situation, imaging studies, and possibly cerebral angiography and lumbar puncture, are indicated.

Our results indicate that a small hypertropia can be detected in patients with peripheral and central sixth nerve palsy. This hypertropia falls within the normal range of hyperphoria seen in healthy subjects, indicating that it is a normal hyperphoria that becomes manifest in the presence of esotropia. In normal subjects, the mean vertical deviation in the straight ahead position is $1.5 \pm 1.5$ PD. Thus, in patients with sixth nerve palsy, if a hypertropia is detected in the straight ahead position, which is less than or equal to 5 PD (normal mean $\pm$ 2 SD), multiple cranial nerves palsy or skew deviation is not responsible. Conversely, vertical deviations over 5 PD indicate skew deviation or peripheral nerve or muscle damage in addition to abduction palsy. In addition, a distinct pattern of hyperdeviation is observed in over 90% of patients during static head roll. In peripheral palsy, right head tilt is associated with a right hyperdeviation, and left head tilt
is associated with a left hyperdeviation. This contrasts with central palsy, in which the same eye hyperdeviates during head tilt to either side. This second pattern of hyperdeviation induced by lateral head tilt may warrant investigation for a brainstem lesion as the cause of paretic abduction.
9.6 TABLES AND FIGURES
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<td>9 (GD)</td>
<td>64 / M</td>
<td>Right</td>
<td>15</td>
<td>90%</td>
<td>Normal CT</td>
<td>Claustrophobia</td>
</tr>
<tr>
<td>10 (KE)</td>
<td>75 / F</td>
<td>Right</td>
<td>2</td>
<td>10%</td>
<td>Normal CT</td>
<td>Resolved after 4 mons (HTN, DM)</td>
</tr>
<tr>
<td>11 (THA)</td>
<td>57 / M</td>
<td>Right</td>
<td>2</td>
<td>90%</td>
<td>Normal CT</td>
<td>Resolved after 4 mons (HTN, DM)</td>
</tr>
<tr>
<td>12 (SC)</td>
<td>66 / M</td>
<td>Right</td>
<td>3 weeks</td>
<td>80%</td>
<td>Normal CT</td>
<td>Resolved after 4 mons (DM)</td>
</tr>
<tr>
<td>13 (DW)</td>
<td>65 / M</td>
<td>Left</td>
<td>34</td>
<td>90%</td>
<td>Normal MRI</td>
<td>Idiopathic</td>
</tr>
<tr>
<td>14 (GC)</td>
<td>57 / M</td>
<td>Left</td>
<td>34</td>
<td>90%</td>
<td>Normal MRI</td>
<td>Idiopathic</td>
</tr>
</tbody>
</table>
Table 9-1 (Continued). Characteristics of patients with 6th nerve palsy caused by a presumed peripheral lesion

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age / Sex</th>
<th>Side of lesion</th>
<th>Duration (months)</th>
<th>Abduction deficit (% normal)</th>
<th>Imaging</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 (VI)</td>
<td>65 / F</td>
<td>Left</td>
<td>36</td>
<td>50%</td>
<td>Normal MRI</td>
<td>Idiopathic</td>
</tr>
<tr>
<td>16 (SCH)</td>
<td>50 / F</td>
<td>Left</td>
<td>24</td>
<td>80%</td>
<td>Normal MRI</td>
<td>Idiopathic</td>
</tr>
<tr>
<td>17 (JM2)</td>
<td>46 / M</td>
<td>Left</td>
<td>3 weeks</td>
<td>80%</td>
<td>Normal MRI</td>
<td>Resolved after 6 mons (HTN)</td>
</tr>
<tr>
<td>18 (IW)</td>
<td>75 / F</td>
<td>Left</td>
<td>12</td>
<td>90%</td>
<td>Normal MRI</td>
<td>Idiopathic</td>
</tr>
<tr>
<td>19 (EM)</td>
<td>64 / M</td>
<td>Left</td>
<td>3 weeks</td>
<td>80%</td>
<td>Normal CT</td>
<td>Resolved after 5 mons (HTN)</td>
</tr>
<tr>
<td>20 (LC)</td>
<td>54 / F</td>
<td>Left</td>
<td>60</td>
<td>80%</td>
<td>Normal MRI</td>
<td>Idiopathic</td>
</tr>
</tbody>
</table>

mons, months
HTN, hypertension
DM, diabetes mellitus
Table 9-2. Characteristics of patients with 6th nerve palsy caused by a central lesion in the brainstem

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age / Sex</th>
<th>Side of lesion</th>
<th>Duration (months)</th>
<th>Abduction deficit (% normal)</th>
<th>Imaging</th>
<th>Presenting symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>21 (CS)</td>
<td>79 / F</td>
<td>Right</td>
<td>19</td>
<td>0%</td>
<td>MRI: Right pontine meningioma</td>
<td>Diplopia, right facial paraesthesia</td>
</tr>
<tr>
<td>22 (AK)</td>
<td>75 / M</td>
<td>Right</td>
<td>1 week</td>
<td>70%</td>
<td>MRI: Right pontine demyelinating lesion</td>
<td>Diplopia, ataxia (MS for 27 years)</td>
</tr>
<tr>
<td>23 (MD)</td>
<td>75 / M</td>
<td>Left</td>
<td>240</td>
<td>40%</td>
<td>MRI: Left caudal pontine infarct</td>
<td>Dysarthria, tinnitus, limb weakness</td>
</tr>
<tr>
<td>24 (WS)</td>
<td>59 / M</td>
<td>Left</td>
<td>52</td>
<td>90%</td>
<td>MRI: Left pontomedullary cavemoma &amp; hematoma</td>
<td>Headache, right paraesthesia, ataxia</td>
</tr>
<tr>
<td>25 (RC)</td>
<td>56 / F</td>
<td>Left</td>
<td>132</td>
<td>70%</td>
<td>MRI: Left pontomedullary cavemoma &amp; hematoma</td>
<td>Left facial palsy and paraesthesia</td>
</tr>
<tr>
<td>26 (JP)</td>
<td>38 / F</td>
<td>Left</td>
<td>3</td>
<td>80%</td>
<td>MRI: Left pontomedullary and middle cerebellar peduncle demyelinating lesions</td>
<td>Diplopia, right leg paraesthesia, ataxia</td>
</tr>
<tr>
<td>27 (WR)</td>
<td>30 / F</td>
<td>Left</td>
<td>2 weeks</td>
<td>70%</td>
<td>MRI: Left pontomedullary demyelinating lesion</td>
<td>Diplopia, ataxia</td>
</tr>
</tbody>
</table>

MS, multiple sclerosis
Figure 9-1. Horizontal and vertical deviations (in prism diopters), measured by prism and cover test, Maddox rod and prism test, and magnetic search coil recordings, in 27 patients with sixth nerve palsy, as viewed by the examiner. Cases 1-20 are peripheral palsies, whereas cases 21-27 are central palsies. ET, esotropia; Eso, esodeviation; RHT, right hypertropia; RHD, right hyperdeviation; LHT, left hypertropia; LHD, left hyperdeviation. Arrows on left (counterclockwise arrows) denote deviation during right head tilt, arrows on right (clockwise arrows) denote deviation during left head tilt.
### Prism cover test

**Patient 1 (TM)**  
(Right 6th)

<table>
<thead>
<tr>
<th>30 ET</th>
<th>No ET</th>
<th>No ET</th>
</tr>
</thead>
<tbody>
<tr>
<td>No HT</td>
<td>No HT</td>
<td>No HT</td>
</tr>
<tr>
<td>30 ET</td>
<td>No ET</td>
<td>No ET</td>
</tr>
<tr>
<td>No HT</td>
<td>No HT</td>
<td>No HT</td>
</tr>
</tbody>
</table>

**Patient 2 (THO)**  
(Right 6th)

<table>
<thead>
<tr>
<th>14 ET</th>
<th>4 ET</th>
<th>2 ET</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 LHT</td>
<td>2 LHT</td>
<td>2 LHT</td>
</tr>
<tr>
<td>14 ET</td>
<td>4 ET</td>
<td>4 ET</td>
</tr>
<tr>
<td>2 LHT</td>
<td>2 LHT</td>
<td>3 LHT</td>
</tr>
<tr>
<td>16 ET</td>
<td>4 ET</td>
<td>2 ET</td>
</tr>
<tr>
<td>2 LHT</td>
<td>2 LHT</td>
<td>2 LHT</td>
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</tbody>
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**Patient 3 (PL)**  
(Right 6th)

<table>
<thead>
<tr>
<th>35 ET</th>
<th>25 ET</th>
<th>4 ET</th>
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</thead>
<tbody>
<tr>
<td>2 RHT</td>
<td>2 RHT</td>
<td>No HT</td>
</tr>
<tr>
<td>35 ET</td>
<td>25 ET</td>
<td>6 ET</td>
</tr>
<tr>
<td>2 RHT</td>
<td>2 RHT</td>
<td>No HT</td>
</tr>
</tbody>
</table>

### Maddox rod and prism test

**Patient 1 (TM)**  
(Right 6th)

<table>
<thead>
<tr>
<th>30 Eso</th>
<th>No Eso</th>
<th>No Eso</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 LHD</td>
<td>1 LHD</td>
<td>1 LHD</td>
</tr>
<tr>
<td>30 Eso</td>
<td>No Eso</td>
<td>No Eso</td>
</tr>
<tr>
<td>3 LHD</td>
<td>1 LHD</td>
<td>No HD</td>
</tr>
</tbody>
</table>

**Patient 2 (THO)**  
(Right 6th)

<table>
<thead>
<tr>
<th>14 Eso</th>
<th>4 Eso</th>
<th>4 Eso</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 LHD</td>
<td>3 LHD</td>
<td>4 LHD</td>
</tr>
<tr>
<td>14 Eso</td>
<td>6 Eso</td>
<td>4 Eso</td>
</tr>
<tr>
<td>3 LHD</td>
<td>3 LHD</td>
<td>4 LHD</td>
</tr>
<tr>
<td>14 Eso</td>
<td>4 Eso</td>
<td>4 Eso</td>
</tr>
<tr>
<td>3 LHD</td>
<td>3 LHD</td>
<td>4 LHD</td>
</tr>
</tbody>
</table>

### Coil recordings

**Patient 1 (TM)**  
(Right 6th)

<table>
<thead>
<tr>
<th>32.48 Eso</th>
<th>2.62 Eso</th>
<th>2.42 Eso</th>
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</thead>
<tbody>
<tr>
<td>3.67 LHD</td>
<td>1.33 LHD</td>
<td>1.39 LHD</td>
</tr>
<tr>
<td>32.8 Eso</td>
<td>2.17 Eso</td>
<td>1.02 Eso</td>
</tr>
<tr>
<td>3.33 LHD</td>
<td>1.54 LHD</td>
<td>0.98 LHD</td>
</tr>
<tr>
<td>32.98 Eso</td>
<td>1.71 Eso</td>
<td>2.57 Eso</td>
</tr>
<tr>
<td>4.73 LHD</td>
<td>0.95 LHD</td>
<td>1.04 LHD</td>
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</table>

**Patient 2 (THO)**  
(Right 6th)

<table>
<thead>
<tr>
<th>18.84 Eso</th>
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<th>2.02 Eso</th>
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<tbody>
<tr>
<td>1.96 LHD</td>
<td>1.57 LHD</td>
<td>1.17 LHD</td>
</tr>
<tr>
<td>18.01 Eso</td>
<td>6.17 Eso</td>
<td>2.57 Eso</td>
</tr>
<tr>
<td>1.54 LHD</td>
<td>1.13 LHD</td>
<td>1.74 LHD</td>
</tr>
<tr>
<td>17.17 Eso</td>
<td>6.71 Eso</td>
<td>2.25 Eso</td>
</tr>
<tr>
<td>1.11 LHD</td>
<td>1.71 LHD</td>
<td>1.34 LHD</td>
</tr>
</tbody>
</table>

**Patient 3 (PL)**  
(Right 6th)

<table>
<thead>
<tr>
<th>40 Eso</th>
<th>25 Eso</th>
<th>6 Eso</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 RHD</td>
<td>4 RHD</td>
<td>No HD</td>
</tr>
<tr>
<td>40 Eso</td>
<td>25 Eso</td>
<td>8 Eso</td>
</tr>
<tr>
<td>4 RHD</td>
<td>6 RHD</td>
<td>No HD</td>
</tr>
<tr>
<td>40 Eso</td>
<td>25 Eso</td>
<td>10 Eso</td>
</tr>
<tr>
<td>4 RHD</td>
<td>6 RHD</td>
<td>1 RHD</td>
</tr>
<tr>
<td>12 RHD</td>
<td>6 RHD</td>
<td>6 LHD</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>31.70 Eso</th>
<th>21.68 Eso</th>
<th>5.83 Eso</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.72 RHD</td>
<td>1.43 RHD</td>
<td>0.16 RHD</td>
</tr>
<tr>
<td>34.32 Eso</td>
<td>24.14 Eso</td>
<td>7.95 Eso</td>
</tr>
<tr>
<td>3.69 RHD</td>
<td>2.41 RHD</td>
<td>1.12 RHD</td>
</tr>
<tr>
<td>36.65 Eso</td>
<td>26.60 Eso</td>
<td>9.23 Eso</td>
</tr>
<tr>
<td>4.67 RHD</td>
<td>3.40 RHD</td>
<td>3.07 RHD</td>
</tr>
</tbody>
</table>
### Prism cover test

<table>
<thead>
<tr>
<th>Patient 4 (JM)</th>
<th>40 ET</th>
<th>14 ET</th>
<th>No ET</th>
<th>No ET</th>
<th>6 RHD</th>
<th>8 LHD</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Right 6th)</td>
<td>40 ET</td>
<td>16 ET</td>
<td>No ET</td>
<td>No ET</td>
<td>6 RHD</td>
<td>8 LHD</td>
</tr>
<tr>
<td></td>
<td>No HT</td>
<td>No HT</td>
<td>No HT</td>
<td>No HT</td>
<td>6 RHD</td>
<td>8 LHD</td>
</tr>
<tr>
<td></td>
<td>40 ET</td>
<td>14 ET</td>
<td>No ET</td>
<td>No ET</td>
<td>6 RHD</td>
<td>8 LHD</td>
</tr>
<tr>
<td></td>
<td>No HT</td>
<td>No HT</td>
<td>No HT</td>
<td>No HT</td>
<td>6 RHD</td>
<td>8 LHD</td>
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</table>

### Maddox rod and prism test

<table>
<thead>
<tr>
<th>Patient 4 (JM)</th>
<th>40 Eso</th>
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<th>4 Eso</th>
<th>36.98 Eso</th>
<th>11.12 Eso</th>
<th>3.41 Eso</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Right 6th)</td>
<td>2 LHD</td>
<td>No HD</td>
<td>3 LHD</td>
<td>4.59 LHD</td>
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<tr>
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<td>16 Eso</td>
<td>4 Eso</td>
<td>38.52 Eso</td>
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<td>4.58 Eso</td>
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<td>4.55 LHD</td>
<td>4.69 LHD</td>
<td>4.83 LHD</td>
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<tr>
<td></td>
<td>40 Eso</td>
<td>14 Eso</td>
<td>3 Eso</td>
<td>30.06 Eso</td>
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<tr>
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<td>5.75 LHD</td>
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### Coil recordings

<table>
<thead>
<tr>
<th>Patient 5 (NR)</th>
<th>10 Eso</th>
<th>1 Eso</th>
<th>No Eso</th>
<th>10.51 Eso</th>
<th>1.30 Eso</th>
<th>0.00 Eso</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Right 6th)</td>
<td>2 RHD</td>
<td>No HD</td>
<td>1 RHD</td>
<td>2.30 RHD</td>
<td>2.45 RHD</td>
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</tr>
<tr>
<td></td>
<td>8 Eso</td>
<td>1 Eso</td>
<td>No Eso</td>
<td>10.26 Eso</td>
<td>0.77 Eso</td>
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<tr>
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### Patient 6 (RL)

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<th>No ET</th>
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<th>No Eso</th>
<th>No Eso</th>
<th>4.64 Eso</th>
<th>2.06 Eso</th>
<th>2.36 Eso</th>
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<tbody>
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<td>0.69 LHD</td>
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### Patient 7 (EF)
(Right 6th)

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### Patient 8 (AM)
(Right 6th)

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### Prism cover test

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**Coil recordings**

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<th>18.29 Eso</th>
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<td>18.02 Eso</td>
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<td>1.62 RHD</td>
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<tr>
<td>Prism cover test</td>
<td>Maddox rod and prism test</td>
<td>Coil recordings</td>
<td></td>
</tr>
<tr>
<td>------------------</td>
<td>---------------------------</td>
<td>----------------</td>
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<tr>
<td><strong>Patient 16 (SCH)</strong> (Left 6th)</td>
<td></td>
<td></td>
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</tr>
<tr>
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<td>6 ET</td>
<td>16 ET</td>
<td>6 Eso</td>
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<td>6 Eso</td>
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<td>No HT</td>
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<td>8 ET</td>
<td>16 ET</td>
<td>6 Eso</td>
</tr>
<tr>
<td>No HT</td>
<td>No HT</td>
<td>No HT</td>
<td>2 LHD</td>
</tr>
</tbody>
</table>

| **Patient 17 (JM2)** (Left 6th) | | |
| 12 ET | 12 ET | 30 ET | 12 Eso | 14 Eso | 30 Eso | 9.76 Eso | 10.30 Eso | 25.68 Eso |
| No HT | No HT | No HT | No HD | No HD | 2 RHD | 1.05 RHD | 1.45 RHD | 1.85 RHD |
| 12 ET | 14 ET | 30 ET | 12 Eso | 14 Eso | 30 Eso | 11.00 Eso | 12.40 Eso | 27.87 Eso |
| No HT | No HT | No HT | No HD | 3 RHD | 2 RHD | 1.75 RHD | 1.35 RHD | 0.94 RHD |
| 12 ET | 20 ET | 30 ET | 12 Eso | 14 Eso | 30 Eso | 13.12 Eso | 14.52 Eso | 25.07 Eso |
| No HT | 2 RTH | No HT | 1 RHD | 3 RHD | 2 RHD | 4.55 RHD | 4.14 RHD | 2.77 RHD |
| 14 RHD | | | 5 LHD | | |

| **Patient 18 (IW)** (Left 6th) | | |
| 2 ET | 2 ET | 8 ET | 4 Eso | 4 Eso | 8 Eso | 0.80 Eso | 4.12 Eso | 5.72 Eso |
| No HT | No HT | No HT | 1 RHD | No HD | No HD | 0.09 RHD | 0.31 RHD | 0.53 RHD |
| 2 ET | 4 ET | 8 ET | 4 Eso | 4 Eso | 8 Eso | 0.05 Eso | 3.26 Eso | 6.57 Eso |
| No HT | No HT | No HT | 2 RHD | 2 RHD | No HD | 0.50 RHD | 0.28 RHD | 0.06 RHD |
| 2 ET | 2 ET | 8 ET | 4 Eso | 2 Eso | 8 Eso | 0.06 Eso | 2.41 Eso | 6.58 Eso |
| No HT | No HT | No HT | 1 RHD | 2 RHD | 1 RHD | 1.08 RHD | 0.87 RHD | 1.62 RHD |
| 2 RHD | | | 2 LHD | | |
| Patient 19 (EM) |  
| Left 6th |  
| Prism cover test |  
| 2 ET | 4 ET | 8 ET | 2 Eso | 6 Eso | 8 Eso | 0.94 Eso | 5.34 Eso | 6.43 Eso |
| No HT | No HT | No HT | No HD | No HD | No HD | 1.48 RHD | 1.96 RHD | 2.54 RHD |
| No HT | No HT | No HT | No HD | No HD | No HD | 1.41 Eso | 6.82 Eso | 7.38 Eso |
| No HT | No HT | No HT | No HD | No HD | No HD | 1.51 RHD | 1.15 RHD | 2.81 RHD |
| No HT | No HT | No HT | No HD | No HD | No HD | 2.07 Eso | 6.22 Eso | 7.95 Eso |
| No HT | No HT | No HT | No HD | No HD | No HD | 2.27 RHD | 1.26 RHD | 1.47 RHD |

| Patient 20 (LC) |  
| Left 6th |  
| Prism cover test |  
| No ET | 10 ET | 12 ET | 6 Eso | 12 Eso | 16 Eso | 9.52 Eso | 12.01 Eso | 15.37 Eso |
| No HT | No HT | No HT | No HD | No HD | No HD | 2.55 RHD | 3.66 RHD | 4.77 RHD |
| No ET | 10 ET | 12 ET | 6 Eso | 12 Eso | 16 Eso | 8.69 Eso | 13.04 Eso | 16.42 Eso |
| No HT | No HT | No HT | No HD | No HD | No HD | 2.37 RHD | 3.48 RHD | 4.59 RHD |
| No ET | 10 ET | 12 ET | 6 Eso | 12 Eso | 16 Eso | 10.72 Eso | 14.09 Eso | 16.62 Eso |
| No HT | No HT | No HT | No HD | No HD | No HD | 2.20 RHD | 3.30 RHD | 3.44 RHD |

| Patient 21 (CS) |  
| Right 6th |  
| Prism cover test |  
| 15 ET | 10 ET | 6 ET | 15 Eso | 12 Eso | 4 Eso | 12.14 Eso | 12.75 Eso | 2.37 Eso |
| No HT | No HT | No HT | No HD | No HD | No HD | 0.53 RHD | 0.53 RHD | 1.58 RHD |
| 15 ET | 10 ET | 8 ET | 15 Eso | 10 Eso | 6 Eso | 16.95 Eso | 10.62 Eso | 4.47 Eso |
| No HT | No HT | No HT | No HD | No HD | No HD | 0.96 LHD | 0.10 RHD | 1.15 RHD |
| 15 ET | 10 ET | 8 ET | 15 Eso | 10 Eso | 6 Eso | 12.74 Eso | 15.64 Eso | 8.51 Eso |
| No HT | No HT | No HT | No HD | No HD | No HD | 1.38 RHD | 0.34 LHD | 0.25 RHD |
**Prism cover test**

*Patient 22 (AK)*
(Right 6th)

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<th>No HT</th>
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*Patient 23 (MD)*
(Left 6th)

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*Patient 24 (WS)*
(Left 6th)

<table>
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<th>3 RHT</th>
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**Maddox rod and prism test**

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(Right 6th)

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*Patient 23 (MD)*
(Left 6th)

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*Patient 24 (WS)*
(Left 6th)

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**Coil recordings**

*Patient 22 (AK)*
(Right 6th)

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*Patient 23 (MD)*
(Left 6th)

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*Patient 24 (WS)*
(Left 6th)

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<th>3 RHT</th>
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<td>2.12 RHD</td>
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<td>1.76 RHD</td>
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<td>2.58 RHD</td>
<td>2.26 RHD</td>
<td>7.13 RHD</td>
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<tbody>
<tr>
<td>1.26 RHD</td>
<td>6.13 RHD</td>
<td>6.44 RHD</td>
</tr>
</tbody>
</table>
## Patient 25 (RC)
*(Left 6th)*

- **Prism cover test**
  - 40 ET | 40 ET | 45 ET
  - No HT | No HT | 2 RHT
  - 40 ET | 40 ET | 45 ET
  - No HT | No HT | 3 RHT
  - 40 ET | 40 ET | 45 ET
  - No HT | No HT | 4 RHT

- **Maddox rod and prism test**
  - 40 Eso | 40 Eso | 45 Eso
  - 4 RHD | No HD | 3 RHD

- **Coil recordings**
  - 45.71 Eso | 38.91 Eso | 48.33 Eso

## Patient 26 (JP)
*(Left 6th)*

- **Prism cover test**
  - 8 ET | 14 ET | 30 ET
  - 2 RHT | 2 RHT | 2 RHT
  - 8 ET | 16 ET | 30 ET
  - 2 RHT | 2 RHT | 2 RHT

- **Maddox rod and prism test**
  - 12 Eso | 16 Eso | 30 Eso
  - 3 RHD | 2 RHD | 4 RHD
  - 10 Eso | 16 Eso | 30 Eso
  - 3 RHD | 4 RHD | 5 RHD

- **Coil recordings**
  - 14.31 Eso | 16.11 Eso | 24.36 Eso
  - 4.06 RHD | 4.10 RHD | 4.13 RHD
  - 12.85 Eso | 15.49 Eso | 27.99 Eso
  - 1.42 RHD | 1.45 RHD | 1.49 RHD

## Patient 27 (WR)
*(Left 6th)*

- **Prism cover test**
  - No ET | No ET | 8 ET
  - No HT | 2 RHT | 2 RHT
  - No ET | No ET | 8 ET
  - No HT | 2 RHT | 2 RHT

- **Maddox rod and prism test**
  - No Eso | 2 Eso | 8 Eso
  - No HD | 1 RHD | 2 RHD

- **Coil recordings**
  - 4.56 Eso | 1.43 Eso | 8.33 Eso
  - 3.21 RHD | 4.09 RHD | 4.97 RHD
  - 2.99 Eso | 1.86 Eso | 8.77 Eso
  - 4.03 RHD | 3.17 RHD | 2.31 RHD
  - 4.56 Eso | 2.29 Eso | 8.36 Eso
  - 1.48 RHD | 4.56 RHD | 3.69 RHD
Figure 9-2. Mean horizontal esodeviations ± 1 SD (in prism diopters) in nine diagnostic positions of 27 patients with sixth nerve palsy, as viewed by the examiner. (* indicates p < 0.05)
<table>
<thead>
<tr>
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<th>Maddox rod and prism test</th>
<th>Coil recordings</th>
</tr>
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<tbody>
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<td><strong>Right 6th nerve palsy (n = 14)</strong></td>
<td></td>
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<tr>
<td>16.93*</td>
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</tr>
<tr>
<td>(± 13.38)</td>
<td>(± 9.22)</td>
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<td>(± 12.68)</td>
</tr>
<tr>
<td>16.93*</td>
<td>6.71*</td>
<td>18.36*</td>
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<td>(± 13.38)</td>
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<td>6.21*</td>
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<td>(± 13.27)</td>
<td>(± 8.52)</td>
<td>(± 13.81)</td>
<td>(± 12.29)</td>
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<tr>
<td><strong>Left 6th nerve palsy (n = 13)</strong></td>
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Figure 9-3. Mean vertical deviations ± 1 SD (in prism diopters) in nine diagnostic positions and during static lateral head tilt in 20 patients with peripheral sixth nerve palsy, as viewed by the examiner. Negative values indicate left hyperdeviation, unsigned values indicate right hyperdeviation. LH, left hyperdeviation; RH, right hyperdeviation. Arrows on left (counterclockwise arrows) denote deviation during right head tilt, arrows on right (clockwise arrows) denote deviation during left head tilt. The mean deviations being a right hypertropia in both right and left sixth nerve palsy is simply a group result, whereas individual patients had either right or left hyperdeviation with either right or left sixth nerve palsy.
### Prism Cover Test

**Peripheral Right 6th Nerve Palsy**  
(n = 12)

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**Maddox Rod and Prism Test**

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Figure 9-4. (A) Mean vertical deviations (in prism diopters) of all nine diagnostic positions in normal subjects and patients with peripheral and central sixth nerve palsy. Error bars indicate 1 SD. (B) Maximum vertical deviations (in prism diopters) measured in any diagnostic position in normal subject and in any single patient with peripheral or central sixth nerve palsy.
Figure 9-5. Mean vertical deviations ± 1 SD (in prism diopters) in nine diagnostic positions and during static lateral head tilt in 7 patients with central sixth nerve palsy, as viewed by the examiner. LH, left hyperdeviation; RH, right hyperdeviation. Arrows on left (counterclockwise arrows) denote deviation during right head tilt, arrows on right (clockwise arrows) denote deviation during left head tilt.
### Prism cover test

#### Central right 6th nerve palsy

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**Figure 9-6.** Diagrammatic summary of changes in vertical deviation during lateral head roll. (A) In peripheral sixth nerve palsy, right head tilt is associated with right hyperdeviation, and left head tilt with left hyperdeviation. (B) In central palsy, the side of hyperdeviation does not change on head tilt to either side.
(A) Peripheral sixth nerve palsy

Right head tilt
Right hyperdeviation

Left head tilt
Left hyperdeviation

(B) Central sixth nerve palsy

Right head tilt
Right hyperdeviation

Left head tilt
Right hyperdeviation
9.7 REFERENCES


SECTION V

FINAL DISCUSSION
CHAPTER 10

FINAL DISCUSSION AND FUTURE DIRECTIONS
10.1 Summary

This thesis examined the effects of paralytic strabismus and neural lesions on three dimensional eye movements in humans. In Section I, we investigated deficits and adaptations of the vestibulo-ocular reflex after sixth, fourth and third nerve palsy. We demonstrated monocular adaptative changes in the VOR; in sixth nerve palsy, horizontal VOR gains are not only decreased during abduction, but also during adduction of the paretic eye, without a conjugate decrease in gains of the non-parietic eye. Similarly, in fourth nerve palsy, VOR gains are not only reduced during incyclotorsion, depression and abduction, but also during excyclotorsion, elevation and adduction of the paretic eye, while VOR gains in the non-parietic eye remain normal. In third nerve palsy, VOR gains are not only decreased during adduction and excyclotorsion, but also during abduction and incyclotorsion of the paretic eye, without a conjugate decrease in gains of the non-parietic eye.

In light, horizontal visually enhanced VOR (VVOR) gains are selectively increased in the paretic eye in mild and moderate sixth nerve palsy, without a conjugate increase in VVOR gains of the non-parietic eye. In fourth nerve palsy, vertical and horizontal VVOR gains are selectively increased in the paretic eye, while VOR gains in the non-parietic eye remain unchanged. These results exemplify monocular adaptation in humans with peripheral neuromuscular deficits. The monocular adaptation that we have identified is attributed to retinal slip differences between the two eyes.

In Section II, we examined the dynamics of saccades after sixth nerve palsy and demonstrated monocular adaption in the saccadic system. In mild and moderate palsy, saccade peak velocities in the paretic field of motion are normal in the paretic eye, without
a conjugate increase in peak velocities in the non-paretic eye. This selective adaptation is also visually driven; it allows both eyes to reach a target in the paretic hemifield of motion rapidly and simultaneously.

In Section III, we investigated the three dimensional kinematics of the eyes in patients with sixth and fourth nerve palsy, as well as brainstem and cerebellar lesions, to determine whether Listing's and Donders' laws are obeyed. We found that acute peripheral sixth and fourth nerve palsy violate Listing's law, whereas chronic palsy obeys it, indicating that neural adaptation can restore Listing's law even when the eye muscle remains abnormal, as indicated by restricted duction and heterotropia. In addition, we found that patients with brainstem or cerebellar lesions have abnormal ocular torsion in both eyes, providing evidence that the brainstem and cerebellum are elements of the neural pathway that normally participate in the maintenance of Listing's law.

In Section IV, we detected and quantified the magnitude of vertical misalignment in sixth nerve palsy. We found that small vertical deviations in peripheral and central sixth nerve palsy are consistent with normal hyperphorias that become manifest in the presence of esotropia. We concluded that if a vertical deviation falls within the range of normal hyperphoria, aggressive investigation for vertical muscle palsies or skew deviation is not required. In addition, we detected that in peripheral sixth nerve palsy, static head roll to either side induces hyperdeviation in the eye on the side of the head tilt. This contrasts with central palsy, in which the same eye hyperdeviates during head tilt to either side. We concluded that this pattern of hyperdeviation induced by lateral head tilt may warrant investigation for a brainstem lesion as the cause of paretic abduction.
10.2 Functional Need for Monocular Adaptation

A major observation arising from this thesis is that the VOR and the saccadic system are capable of monocular adaptation in humans with peripheral neuromuscular deficits. The functional need for a selective adjustment of innervation to each eye clearly exists. For example, in anisometropia, the VOR gains must be adjusted differentially in the two eyes, because the differences in rotational magnification of the two lenses would produce retinal slip differences between the two eyes during head rotation, unless a selective mechanism exists. In addition, conjugate adaptation could not correct for changes that occur only in one eye, such as those that may develop during aging or disease processes. To correct for such differences, selective recalibration of commands to each eye muscle must occur. Our data provide evidence that ocular motor systems in humans are capable of selective adaptation of innervation to muscles of each eye independently, when challenged by a peripheral neuromuscular deficit.

10.3 Three Dimensional Kinematics of the Eyes in Paralytic Strabismus and After Neural Lesions

Another major observation arising from this thesis is that an adaptive neural mechanism exists for the implementation of Listing's law. Although the functional significance of Listing's law is not known for certain, re-establishment of the law after ocular motor nerve palsy provides evidence that there are advantages in maintaining it. One plausible advantage is that by ensuring all gaze shifts toward and away from primary position are made along the shortest path, Listing's law permits quick responses to unpredictable targets that may appear from any direction. Our data also provide evidence
that this adaptive mechanism is neural, since lesions in the brainstem or cerebellum prevent restoration of the law.

10.4 Future Directions

In our investigations, the eye that the patients habitually used for fixation was not determined. Since secondary deviation (when the paretic eye fixates) is always greater than primary deviation (when the non-paretic eye fixates), most patients prefer to fixate with their non-paretic eye to minimize diplopia. However, some patients may prefer to use their paretic eye for fixation if it has better visual acuity, or because the secondary deviation becomes so large that it facilitates ignoring the second image.

The pattern of adaptation of the ocular motor systems may depend on the eye that is habitually used for fixation.1–4 Optican et al.4 examined the saccades made by the non-paretic eye of three patients with unilateral sixth nerve palsy and one with combined unilateral sixth and third nerve palsy. They found that when patients were forced to view monocularly with their paretic eye for several days, the non-paretic eye overshot its target. They did not, however, record the movements of the paretic eye. In another report,2 a patient with third nerve palsy was forced to use the paretic eye for monocular viewing. After six days, the amplitudes of adducting saccades in the paretic eye increased.2 When the patch was switched to occlude the paretic eye, the amplitudes of adducting saccades decreased.2

In our protocol, the eye that patients habitually used for fixation was not controlled. After patients had used a preferred eye for fixation for days, weeks or months, each eye was alternately occluded and the immediate effects on ocular motor systems were
assessed. A systematic study that controls for the eye that is habitually used for fixation may provide additional information on how different ocular motor systems adapt in response to peripheral neuromuscular deficits. This could be achieved only by experimentally patching one eye for a period of time before each recording.

Another interesting question is the behavior of the ocular motor systems over time. In our studies, patients were tested at one point in their course. Changes were expressed as changes from normal, rather than serial intra-subject changes. Recovery toward normal values was not determined, and abnormalities were interpreted as either deficits or adaptation to those deficits. A longitudinal approach, by performing periodic orthoptics assessment and oculography, may provide further insight into the behavior of the ocular motor systems in response to recovery, and its adaptative properties in the face of persistent deficits.

In our studies, the VOR and the saccadic system were investigated, but not the smooth pursuit system. In patients with unilateral sixth nerve palsy, excessively high pursuit gains and pendular oscillations during smooth pursuits were reported. Further studies are required to systematically investigate the deficits and adaptation, if any, of the smooth pursuit system, in patients with peripheral neuromuscular deficits.

Perhaps the most interesting question is the effects of strabismus surgery on eye movement dynamics. The goal of strabismus surgery is to reestablish ocular alignment, so that fusion and single binocular vision can be restored. The mechanical changes evoked by surgery that function to optimize static alignment would not necessarily optimize the dynamic properties of eye movements. New anatomic, mechanical and sensory factors resulting from surgical realignment of the eyes, however, may stimulate innervational
changes to the eye muscles, so that different patterns of adaptation may occur. Lewis et al \(^5\) studied seven patients with fourth nerve palsy, before and after strabismus surgery. Prior to surgery, a position-dependent vertical ocular misalignment was present, and downward saccades of the paretic eye were hypometric.\(^5\) Strabismus surgery not only reduced the magnitude of the static misalignment, but also resulted in a disconjugate increase in saccade amplitude in the paretic eye, such that the alignment of the eyes improved during saccades.\(^5\) Future studies will be performed to investigate the effects of surgery on different ocular motor systems in patients with strabismus caused by ocular motor nerve palsy and brainstem lesions.
10.5 REFERENCES


