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MAJOR REVIEW

Listing's Law: Clinical Significance and Implications for Neural Control

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Abstract. Listing's law governs the three-dimensional orientation of the eye and its axes of rotation. It states that, when the head is fixed, there is an eye position called *primary position*, such 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. Listing's law can also be expressed in terms of any initial eye position, not just primary position (Listing's half-angle rule). The binocular extension of Listing's law is equivalent to Listing's law when the vergence angle is zero, and adjusts the eyes' torsion when they converge. Listing's law holds during fixation, saccades, smooth pursuit, and vergence, but not during sleep and vestibulo-ocular reflex, suggesting that it is actively implemented by a neural mechanism. Orbital constraints, such as "pulleys," may also play a role. Adherence to Listing's law and its extension may serve the purpose of optimizing motor efficiency, or simplifying neural processing for binocular vision, or both. The study of Listing's law not only allows us to understand the organization of neural and mechanical factors in the control of three-dimensional eye movements, it also has important clinical implications for strabismus and the optimal management of this disorder. (**Surv Ophthalmol 49**:563–575, 2004. © 2004 Elsevier Inc. All rights reserved.)

Key words. Listing's law • torsion • three dimension • eye movements • kinematics • saccades • smooth pursuit • vestibulo-ocular reflex • vergence • pulleys

I. Introduction

How the eye rotates during eye movement has been a fascinating subject for centuries. From 1846 to 1868, Ruete, Donders, Listings, Fick, Helmholtz and many others published seminal works on this topic that still exert influence today. The great 19th-century physiologist Hermann von Helmholtz[73] devoted over 50 pages in his book *Treatise on Physiological Optics* to what he called *Listing's law*, a principle that governs three-dimensional (horizontal, vertical, and torsional) eye movements. However, despite the attention that Helmholtz gave to Listing's law, 20th century physiologists have mostly ignored it, largely because understanding three-dimensional eye movements requires a strong knowledge of kinematics (the study of motion) and of the mathematical language used to describe rotary motions. The lack of understanding of subtle kinematic concepts and mathematical language has perpetuated a general sense of confusion about Listing's law among ophthalmologists.

The last 10 years have brought a resurgence of interest in Listing's law. Although confusion abounds because of the advanced mathematical language used in the literature, a fundamental understanding of

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Listing's law is of great importance to clinicians. Here, I attempt to explain Listing's law using a non-mathematical approach. I will discuss what Listing's law is, how it is implemented, what its functional significance is, and whether it is adaptive. I will also discuss its implications for ocular motor control, as well as its clinical significance. In the appendix, I have included a discussion on some commonly asked questions. This is not meant to be comprehensive review, but rather, a concise practical review of key concepts that pertain to Listing's law.

II. Who was Listing?

Johannes Benedict Listing (1808–1882) was a German mathematician who taught engineering in Hannover before he was appointed professor of physics at Göttingen University. He apparently formulated his law based on pure geometrical aesthetics. He never produced any formal publication about this law, and it was unclear whether he did any measurements at all. In 1855, Ruete first mentioned this law in his textbook on ophthalmology, but its significance was not fully appreciated until Helmholtz verified it using careful measurements of afterimages and attributed it to Listing.[73]

III. What is Listing's Law?

The eye rotates with three degrees of freedom. This means that the eye can rotate about the following axes: 1) a vertical axis to generate horizontal eye movements (abduction and adduction), 2) a horizontal axis to generate vertical eye movements (elevation and depression), and 3) the line of sight to generate torsional eye movements (excyclotorsion and incyclotorsion). In theory, the eye could assume an infinite number of torsional positions for any gaze direction (Fig. 1). Fig. 1A is a schematic of an eye directed straight ahead at the reader, and the thick black vertical (solid) line represents its superior pole, which is at 12 o'clock. Figs. 1B, 1C, and 1D show that there are many different torsional positions that the eye can adopt when it looks straight ahead: at 1 o'clock, 2 o'clock, 3 o'clock, and so on. In other words, the eye can theoretically rotate $x°$ about the line of sight, where x is any number, without displacing the line of sight away from its target. Thus, there are infinitely many ways to fixate any given target.

If there is an infinite number of possible torsional positions for each gaze direction, does the eye adopt one or multiple torsional position(s) for a particular gaze direction? The answer to this question was provided by Donders, who observed the rotation of his own eye about the visual axis using afterimages.[11] In his experiments, Donders produced a monocular

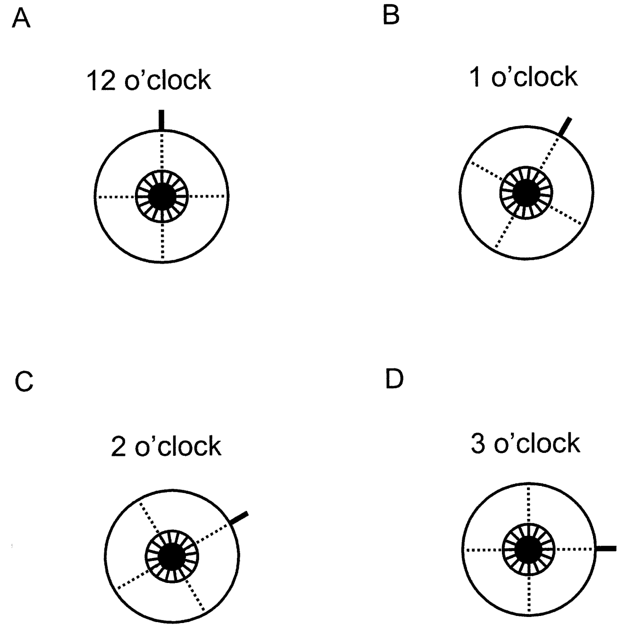

Fig. 1. The eye can theoretically assume an infinite number of torsional positions for any position of gaze. (*A*) A schematic of an eye directed straight ahead at the reader, with the thick black vertical (solid) line represents its superior pole, which is at 12 o'clock. There are many different torsional positions that the eye can adopt when it looks straight ahead: (*B*) at 1 o'clock, (*C*) 2 o'clock, (*D*) 3 o'clock, and so on.

green afterimage by looking at a red target in the form of a cross for a long period of time. He then looked at a screen in front of him to see whether the afterimage cross remained vertical when he looked in different directions. He found that the afterimage cross remained vertical when he looked right, left, up, or down. However, when he looked in tertiary positions of gaze (i.e., right-up, right-down, left-up, or left-down), the afterimage cross tilted. Furthermore, the amount of the tilt depended upon the eccentricity of the eye position. In this way, he observed that there is only one torsional eye position for each combination of horizontal and vertical eye position,[11,66,73] and postulated that the torsional position of the eye is always the same, independent of how the eye reaches a particular gaze direction. This principle has been referred to as *Donders' law.* Note that the afterimage cross is tilted because the eye tilts when it is in different tertiary positions of gaze. This phenomenon is observed independent of whether the afterimage is projected onto a flat screen or a cylindrical surface.

Although Donders' law states that there is only one torsional eye position for each gaze direction, it does not specify what the torsional angle is. It is Listing's law that *quantitatively* defines a specific torsional angle for each gaze direction. Listing's law states that, when the head is fixed, there is an eye position called primary position, such 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.[73] This plane is orthogonal to the line of sight when the eye is in primary position. In other words, one can visualize any given eye movement as caused by rotation about an axis. The collection of these axes for all rotations that start from primary position constitutes Listing's plane.

Listing's law is illustrated in Fig. 2. The eye at the center is in primary position and the plane of the paper is Listing's plane, which is orthogonal to the line of sight. All the eye orientations drawn with solid lines accord with Listing's law, because they can be reached from primary position by rotating about axes (thick black solid 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 (thick dotted line) tilted out of Listing's plane. Fig. 2 also shows that Listing's law implies Donders' law, that is, for any gaze direction, there is only one unique orientation assumed by the eye.

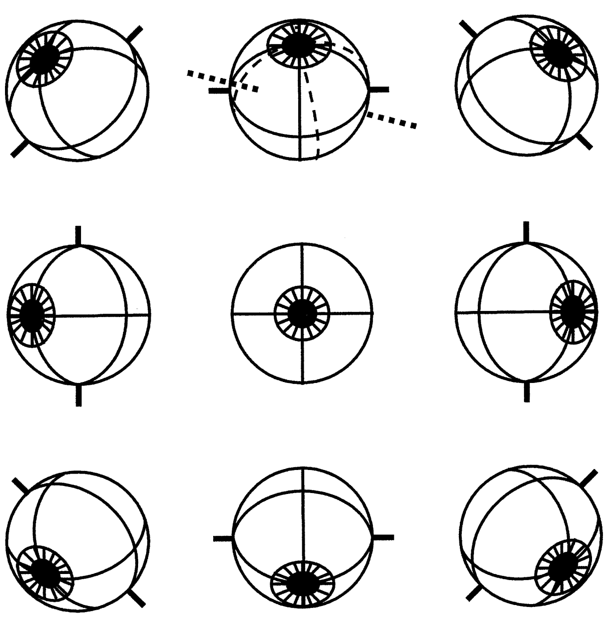

Fig. 2. Listing's law states that, when the head is fixed, there is an eye position called *primary position*, such that the eye assumes only those orientations that can be reached from primary position by a single rotation about an axis in a plane called Listing's plane. The nine orientations drawn in solid lines accord with Listing's law, because they are attainable by rotating from primary position (*center*) about axes (thick black solid lines) 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 (thick dotted line) that is tilted out of primary position. (Redrawn from Wong et al.[77])

The "primary position" defined in Listing's law (Listing's primary position) is not synonymous with the primary position used clinically. Listing's primary position is defined as the reference eye position from which all other eye positions can be reached by a single rotation about an axis that lies in Listing's plane, whereas the primary position used clinically refers to the straight ahead gaze position and roughly corresponds to the center of the ocular motor range. For the rest of this review, primary position will refer to Listing's primary position.

IV. Which Coordinate System to Use?

There are many different coordinate systems that mathematicians use to describe rotary motion. The most commonly used ones include Fick coordinates, Helmholtz coordinates, rotation vectors, and quaternions. All have relative strengths and weaknesses, so which coordinate system to use depends on the problem at hand (for an excellent review of different coordinate systems, see Haslwanter[17]). The Helmholtz coordinate system is perhaps the most intuitively appealing to clinicians, and it is especially useful in presenting binocular data.[52] In Helmholtz's system, an eye position is described by a series of three rotations in a fixed sequential order. Starting from primary position, the eye first undergoes 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 mathematically in Helmholtz coordinates, Listing's law says:

$$T = -HV/2 \qquad (1)$$

where T represents torsional, H horizontal and V vertical angles in radians (not degrees). Positive directions for angles T, H, and V are defined as clockwise, right, and up, respectively, all from the subject's point of view.

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. Fig. 3 depicts the torsional positions of the eye, represented by thin black lines with respect to the vertical meridian, in different combinations 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 from the subject's point of view (and clockwise from the examiner's point of view), 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

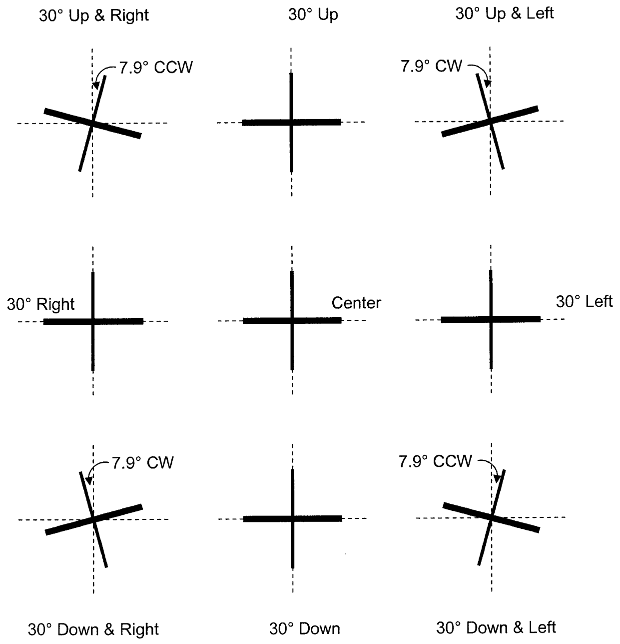

Fig. 3. Torsional positions of the eye, as represented by thin black lines with respect to the vertical meridian, in different combination of horizontal and vertical eye positions, as viewed by the examiner. If the eye is 30°down and 30°left (*bottom right*), then the eye (thin black line) rotates 7.9°(0.14 rad) counterclockwise from the subject's point of view (and clockwise from the examiner's point of view), with respect to the vertical meridian (dashed line). CW = clockwise from the subject's reference; CCW = counterclockwise from the subject's reference. Note that the crosses represent the torsional positions of the subject's eye, not afterimages viewed by the subject. (Redrawn from Wong et al.[77])

that specified by equation (1) means that Listing's law is violated. Note that Fig. 3 represents the torsional positions of the subject's eye, not afterimages viewed by the subject (for interested readers, the tilt of the afterimages is opposite to the tilt of the torsional positions of the eye for any given horizontal and vertical eye position).

So far, we have expressed Listing's law using primary position as reference position. We shall see in the next section that there is a second way of stating Listing's law that does not rely on choosing Listing's primary position as reference position; that is, Listing's law can be expressed using any eccentric eye position as reference position (Listing's half-angle rule).

V. What is Listing's Half-Angle Rule?

Listing's law holds during fixation, saccades, and smooth pursuit.[34,62,66] It defines Listing's plane as orthogonal to the line of sight when the eye is in primary position, but what if the eye starts its rotation from an eccentric eye position? In this situation, the orientation of the eye is still determined by rotation about axes that lie in a plane (irrespective of the direction of movement), but this plane is no longer orthogonal to the line of sight; instead it is tilted in the same direction as the line of sight but only half as much.[62,66] This relationship between rotational axes and gaze angle is called Listing's half-angle rule.

Fig. 4 illustrates Listing's half-angle rule. The dashed horizontal line represents the line of sight, and the dashed vertical line represents Listing's plane, which is orthogonal to the line of sight when the eye is in Listing's primary position. When the eye is not in primary position (i.e., in an eccentric position), say when it is looking up at angle α (solid arrow), then the new plane is rotated in the same direction, but only half as much as the line of sight, that is $\alpha/2$. For example, if the eye makes a horizontal saccade in the upper half of the visual field when looking 30° up (α), then the new plane is rotated 15° up ($\alpha/2$), such that the angle between the new plane and the line of sight is now 75° (instead of 90°). Note that this new plane is now called the *velocity plane*, and that Listing's plane is a special name given to a unique velocity plane that is orthogonal to the line of sight when the eye is in primary position.

To summarize, Listing's law can be expressed in terms of any initial eye position, not just primary position. In this form the law states that for any eye position, there is an associated velocity plane such

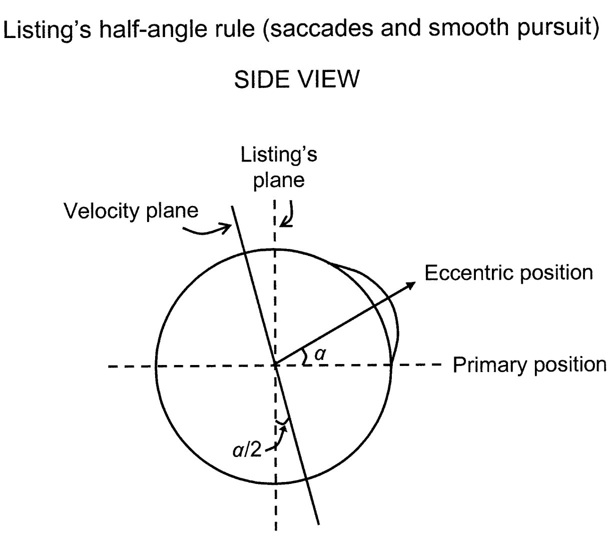

Fig. 4. Listing's half-angle rule for saccades and smooth pursuit. The dashed horizontal line represents the line of sight when the eye is in primary position, and the dashed vertical line represents Listing's plane, which is orthogonal to the line of sight. When the eye starts from an eccentric position (angle α, solid arrow), the orientation of the eye is determined by rotation about axes that lie in a plane. This plane is rotated in the same direction, but only half as much as the line of sight, that is $\alpha/2$.

that any position can be reached from that position by rotating about an axis that is confined to this particular plane. The orientation of velocity planes (and hence rotational axes of the eye) depends on initial eye position: when the eye is in primary position, the velocity plane is called Listing's plane, which is orthogonal to the gaze line. For any other eye position, the corresponding velocity plane is rotated half as far as the gaze line (half-angle rule). An in-depth derivation of these facts can be found elsewhere.[61,73]

VI. What is Binocular Extension of Listing's Law?

Listing's law applies when the eye fixates a target at optical infinity. However, the torsional position of the eye changes when the eyes converge on near object. During convergence, the orientation of each eye is still determined by rotation about axes that lie in a plane; however, this velocity plane is rotated temporally and roughly symmetrically in each eye,[33,38,42,72] through about a quarter of the vergence angle (Fig. 5). [68] These convergence-dependent changes of torsional position (i.e., orientation of Listing's plane) have been referred to as the binocular extension of Listing's law or L2.[52,60,72] Note that L2 is a generalization of Listing's original, monocular law, and reduces to it when the vergence angle is zero, as when the eye fixates a distant object. In other words, as long as the vergence angle is fixed, there is still one and only one torsional position that the eye adopts for any one gaze direction, but the torsion can change when vergence changes. The more the convergence, the more the temporal rotation of the plane, meaning that during convergence, there is a relative excyclotorsion on upgaze, and a relative incyclotorsion on downgaze, when one expresses torsion in Helmholtz coordinates.

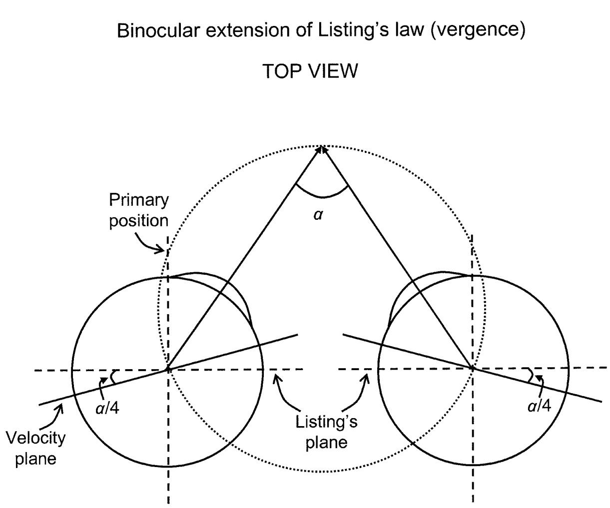

Fig. 5. Binocular extension of Listing's law for vergence. During convergence, the orientation of each eye is determined by rotation about axes that lie in a plane. This plane is rotated temporally and symmetrically in each eye and about a quarter (α/4) as much as the vergence angle (α).

VII. What is Half-Listing's Law Strategy for the Vestibulo-Ocular Reflex (VOR)?

One eye movement system that does not obey Listing's law is the vestibulo-ocular reflex (VOR). Listing's law only applies to eye rotation when the head is fixed, whereas the VOR generates compensatory eye movements when the head moves. By counter-rotating the eye at about the same speed as the head but in opposite direction, the VOR stabilizes retinal image during head rotation. An ideal VOR that stabilizes the entire retinal image therefore requires the eye to rotate about the head's rotation axis, independent of the direction of the gaze line. However, empirical human data showed that when the head turns, the VOR does not counter-rotate the eye about exactly the same axis as the head, as one might expect for optimal retinal image stabilization. Nor does it tilt the eye's velocity plane by half as much as the gaze line, as required for full compliance to Listing's half-angle rule. Rather, during horizontal (about an earth-vertical axis) and vertical (about an earth-horizontal axis) head rotation, the eye's rotation axes tilt in the same direction but only about a quarter to a third as much as the gaze line,[35–37,41,51] whereas during head roll, they tilt as far as the gaze line but in the opposite direction.[35–37] This characteristic behavior of the human VOR reflects a compromise strategy halfway between optimal retinal image stabilization (no tilting of eye's rotation axes with gaze line) and perfect compliance with Listing's law to maximize motor efficiency (tilting of eye's rotation axes half as much as the gaze line, i.e., half-angle rule). It is therefore referred to as half-Listing's law strategy (Fig. 6). Some authors have used the term "quarter-angle rule" to describe this VOR behavior. This term is confusing and should be avoided because it implies that the behavior of VOR represents another consequence of Listing's law, when, in fact, it does not.

To illustrate how the VOR breaks Listing's law, let us consider the torsional VOR when the head rolls between the right and left shoulders while looking straight ahead. In humans, the normal dynamic torsional VOR gain, defined as the ratio of the speed of eye rotation to the speed of head rotation, is about 0.7.[6] For example, with the eye looking straight ahead, when the head rolls at 10°/sec, the eye counterrolls at about 7°/sec; when the head rolls at

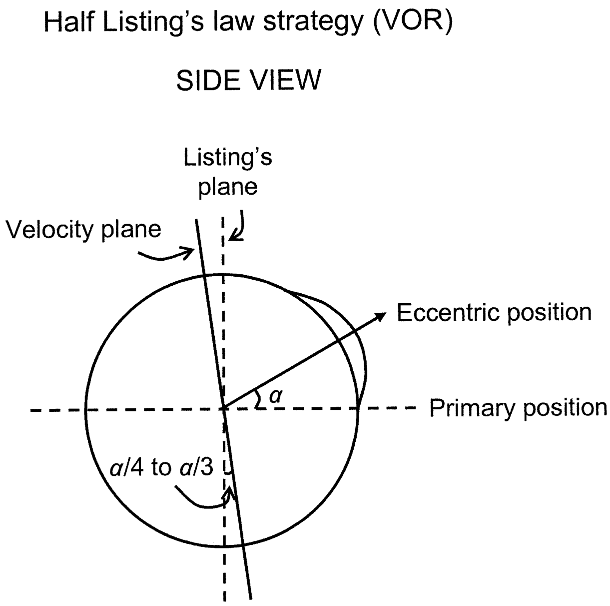

Fig. 6. Half Listing's law strategy for VOR. The dashed horizontal line represents the line of sight when the eye is in primary position, and the dashed vertical line represents Listing's plane, which is orthogonal to the line of sight. During horizontal and vertical head rotations, when the eye starts from an eccentric position (angle α, solid arrow), the eye's rotation axes tilt in the same direction but only about a quarter to a third (α/4 to α/3) as much as the line of sight.

20°/sec, it counterrolls at about 14°/sec; when the head rolls at 30°/sec, it counterrolls at about 21°/sec, and so on. Thus without changing the gaze direction, the eye can roll into many different torsional positions, depending on the amplitude of the head roll, and so VOR does not follow Listing's law.

We will discuss the functional significance and visual consequence of half-Listing's law strategy for the VOR in section IX below.

VIII. How is Listing's Law Implemented?

Listing's law holds during fixation, saccades and smooth pursuit, but fails during sleep[39,58] and VOR.[63] This failure shows that the eye muscles are capable of violating Listing's law, so it is not the orbital plant but neural commands driving fixation, saccades and pursuit that constrain the eye to obey the law.[7,56,66] The muscles may, however, be arranged in a way that simplifies the brain's work in implementing Listing's law,[8,9,43,45,47,57,59] as in the "active-pulley hypothesis,"[9] where contraction of the global layer of the rectus muscle rotates the globe, whereas contraction of the orbital layer displaces the connective-tissue sleeves, or "pulleys", which direct the paths of the muscles.

The brain circuitry responsible for implementing Listing's law has not been identified. A major neural pathway underlying saccadic eye movements involves the superior colliculus,[29,74,75] which sends saccadic signals to the medium-lead burst neurons in the paramedian pontine reticular formation (PPRF) and the rostral interstitial nucleus of the medial longitudinal fasciculus (riMLF).[13,22,30] These burst neurons, in turn, project to the extraocular motoneurons, the final common pathway for all eye movements.[13,22] Electrical stimulation and three-dimensional recordings in alert monkeys have shown that the superior colliculus generates saccades that conform to Listing's law.[24] Stimulation of the short-lead burst neurons in the caudal PPRF and riMLF evokes abnormal saccades that violate Listing's law.[23] 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 of the cerebellum.[14,40] 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.[71] Inactivation of the cNRTP results in an absence of torsional saccadic reset, such that the eye remains out of Listing's plane.[71] This evidence indicates that the cNRTP participates in stabilization of Listing's plane against torsional errors of the saccadic system.[71] In addition, the cerebellum may play a role in minimizing torsional drifts, and in maintaining ocular torsion in compliance with Listing's law.[55,80]

IX. What is the Functional Significance of Listing's Law?

Why does the brain go through the trouble of maintaining Listing's law, and why do different ocular motor systems implement the law differently?

A. DOES LISTING'S LAW OPTIMIZE VISUAL INFORMATION PROCESSING?

Both Helmholtz[73] and Hering[25] felt that the purpose of Listing's law was to optimize visual processing. Hering[25] proposed that Listing's law optimizes certain aspects of image flow across the retina, thereby simplifying the neural processing of visual information. Assume, for example, that the eye begins in primary position and looks at the center of a pattern of radiating lines. As the eye follows any of the lines outward, the retinal image of the line will continue to fall along the same set of receptors as long as the eye follows Listing's law. This steady retinal image flow may simplify the brain's work in identifying and locating lines in space. Helmholtz's theory[21,73] was more complex, but it too essentially proposed that Listing's law optimizes certain aspects of retinal image flow.

As retinal image flow depends on the eye's motion relative to space, both Hering and Helmholtz assumed that the eye rotates relative to space in the way dictated by Listing's law. However, it is only eye rotation relative to head that follows Listing's law. Owing to head movement, eye rotation relative to space does not.[15,44,64] This reference frame problem undermines any "visual" explanations of Listing's law that are based on retinal image flow.

B. LISTING'S LAW—AN OPTIMIZATION STRATEGY FOR MOTOR EFFICIENCY

Fick and Wundt proposed that Listing's law enhances motor efficiency by minimizing the rotational eccentricity of the eye.[20,73] Minimizing eccentricity may reduce the elastic recoiling force, and thereby minimize the work load on the eye muscles to maintain the globe in an eccentric position. It may also allow the eye to respond to incoming stimuli swiftly and flexibly. Just as a squash player tries to stay near center court so that no corner is unguarded, Listing's law keeps the eye near the center of its torsional range so it can quickly respond to unpredictable targets that may appear from any direction.

We discussed in section VII that the VOR follows half-Listing's law strategy. What is its functional significance and visual consequence? Listing's law optimizes motor efficiency by minimizing the rotational eccentricity of the eye. However, a perfect VOR that stabilizes the entire retinal image requires the eye to rotate about the head rotational axis, independent of the direction of the gaze line, and thus it cannot obey Listing's law. Faced with these two competing but equally important demands, the brain utilizes half-Listing's law strategy, which represents a compromised strategy that strikes a balance between the motor advantage of Listing's law and the visual advantage of optimal image stabilization. The visual consequence of this strategy is that, instead of stabilizing retinal image over the entire retina, retinal image is stabilized over a small portion of the retina, the fovea, a region that has the highest visual acuity.[35]

C. L2—AN OPTIMIZATION STRATEGY FOR BOTH MOTOR EFFICIENCY AND BINOCULAR VISUAL FUNCTION

When the eyes converge, Listing's plane for each eye rotates temporally depending on the vergence angle. This motor program has been called the binocular extension of Listing's law, or L2. What is the functional advantage of L2?

Recent evidence suggests that L2 may represent an optimization strategy that combines motor efficiency with stereo vision.[26,48,49] To achieve stereoscopic vision, the brain must search for corresponding image features on the two retinas. Stereo matching is a very complex task. For example, in a random-dot stereogram that presents 5,000 dots to each eye, there are $5{,}000^2$ (i.e., 2.5×10^7) possible pairings between the right and left images, with only 5,000 of them being correct. Yet, the brain can solve this type of random-dot stereogram within a few hundred milliseconds. How can the brain perform such a complex task within such a short time? The answer lies in the fact that, instead of searching the entire retina of each eye for matching features, the brain narrows its search by searching retina-fixed zones that are large enough to cover all the usual locations of the features in question.[49]

The smaller the search zone, the more efficient the stereo matching and the lighter the computational load on the brain. As discussed above, during monocular viewing of a distant object, Listing's law enhances motor efficiency by minimizing the rotational eccentricity of the eye. Unfortunately, optimizing motor efficiency does not also minimize the area of the search zone. Schreiber et al[49] proposed that L2 represents a compromise strategy between the motor program that minimizes the rotational eccentricity of the eye (i.e., Listing's law), and the motor program that would minimize the size of the retinal search zones for stereo matching. In other words, the brain utilizes a strategy that strikes a balance between the motor, monocular advantage of Listing's law and the optimization of stereoscopic search.

X. Is Listing's Law Adaptive?

Recent studies in normal subjects[26,32,48,53] and in patients with paralytic strabismus[77–79] have shown that Listing's law is adaptive, suggesting that an active neural mechanism implements the law. Plasticity has been demonstrated in the orientation of Listing's plane during binocular viewing (i.e., L2) using different stimuli, including prism-induced vertical vergence,[32,53] cyclodisparity,[48] and a combination of disparity vergence with depth perception.[26] Tweed[60] proposed that by equalizing the torsional orientation of both eyes in the visual plane, this adaptive behavior of Listing's law minimizes the changes in cyclodisparity between the two eyes, thereby simplifying the neural processing of visual information.

The effects of strabismus and ocular motor nerve palsy on the implementation of Listing's law have also been investigated.[31,67,77–79] We studied patients with unilateral sixth nerve palsy and divided them into three groups: those with 1) acute peripheral palsy caused by a presumed ischemic lesion; 2) chronic peripheral palsy caused by a presumed ischemic lesion; and 3) central fascicular palsy caused by brainstem lesions.[78] We found that, during fixation and saccades, Listing's law was violated in the paretic eye in patients with acute peripheral palsy, presumably because the lateral rectus muscle was paretic. In contrast, both the paretic and non-paretic eyes obeyed Listing's law in patients with chronic peripheral palsy, even though the lateral rectus was still markedly weak, as evidenced by limited abduction and persistent esotropia. 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. In addition, we found that patients with central fascicular palsy had abnormal ocular torsion in both the paretic and non-paretic eyes, regardless of the duration and severity of their palsy.[78] This finding indicates that the neural adaptive mechanisms underlying Listing's law cannot restore it after certain brainstem lesions.

In another study, we investigated patients with acute versus chronic unilateral fourth nerve palsy.[77] We found that patients with acute palsy violated Listing's law, whereas those with chronic palsy obeyed it, providing further evidence that Listing's law is adaptive.

What is the functional advantage of reestablishing Listing's law after neural injury? As discussed, Listing's law permits quick responses to unpredictable targets that may appear from any direction by ensuring that the eye stays near the center of its torsional range. This motor advantage may be regained when patients with chronic ocular motor nerve palsy reestablish Listing's law.

XI. What are the Implications of Listing's Law for Ocular Motor Control?

To appreciate the significance of Listing's law for ocular motor control, it is important to recognize that rotations are non-commutative. Non-commutativity means that the order of rotations affects the final orientation. Rigid bodies undergo two types of motion: translation and rotation. A change in position is called translation, whereas a change in orientation is called rotation. Motions are said to combine commutatively if the order is irrelevant. Ordinary addition of numbers is commutative because the order of the numbers makes no difference, for example, $3+5 = 5+3$. Translations combine commutatively: whether one first steps 1 meter forward and then 2 meters left, or first 2 meters left and then 1 meter forward, one would still reach the same final location. In contrast, rotations are non-commutative. This is illustrated in Fig. 7. Starting from the same orientation, the schematic heads undergo identical rotations in different orders. In Fig. 7A, the head first rotates 90° right and then 90° up, whereas in Fig. 7B, it rotates first 90° up and then 90° right. As shown, the final orientations of the heads clearly differ.

Because rotations are non-commutative, traditional ocular motor concepts that were well established for the horizontal (one dimensional [1D]) system needed to be re-evaluated. Let us take the velocity-to-position neural integrator as an example. During conjugate eye movements, the command that *moves* the eye to a new position is a velocity signal that is encoded by premotor neurons. During the motion, the neural integrator uses the velocity signal to compute a position signal. Once the eye reaches its desired position, the signal from the neural integrator holds the eye in its new position. In one dimension, a linear velocity-to-position neural integrator could simply mathematically integrate the eye velocity into an eye position signal. In three dimensions (3D), however, because of non-commutativity, angular velocity is not the derivative of 3D eye position. Thus, in order to extend the neural integration concept from 1D to 3D, one hypothesis suggests

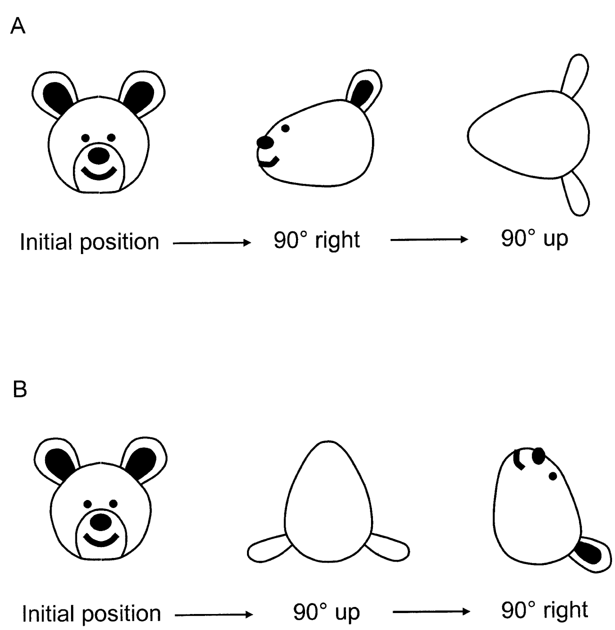

Fig. 7. Rotations are non-commutative. In (*A*) and (*B*), the schematic heads, starting from the same position, undergo identical rotations in different order. In (*A*), the head first rotates 90°right and then 90°up, whereas in (*B*), it rotates first 90°up and then 90°right. As shown, the final orientations of the heads clearly differ.

that premotor neurons encode 3D angular velocity and that a nonlinear (multiplicative) neural integrator transforms the 3D angular velocity into 3D eye position signal.[65,66] The computation is therefore more complex in 3D than in 1D.

However, this hypothesis has been challenged. Attempts to identify a clear neural representation of 3D angular velocity in the premotor pathway for saccades have been unsuccessful.[24,46,69–71] This has prompted an alternate hypothesis which proposes that kinematically appropriate eye movements could be generated from the ocular motor plant itself. According to this hypothesis,[9,28,59] the rectus extraocular muscles run through adjustable connective tissue sheaths or "pulleys", which shift position on different gaze. With mobile pulleys, a two-dimensional (2D) derivative of eye orientation (instead of 3D angular velocity) could be encoded by premotor neurons, and the neural integrator could then be linear, thereby simplifying the brain's work. A theoretical study has shown that appropriately placed pulleys can generate physiologically realistic saccades and implement the half-angle rule without a need for a nonlinear neural integrator.[43]

This latter hypothesis is viable in theory for saccades and pursuit but not for the VOR.[1,10,16] In the VOR, semicircular canal afferents are known to encode 3D angular velocity rather than 2D derivative of eye orientation.[10,16] In the pursuit system, recent evidence indicates that premotor pathways encode 3D angular velocity.[2] Thus, nonlinear mathematical operations, in addition to appropriately placed pulleys, are likely required for pursuit and the VOR.[35,50] Even in the saccadic system, nonlinear, non-commutative operations are mathematically required somewhere in the processing stream in order to generate the 2D derivative of eye orientation signals that make it possible to compute eye position commands using simple integration.

The rediscovery of extraocular muscle pulleys[27] and their role in changing the pulling direction of the extraocular muscles as a function of gaze has sometimes been interpreted to suggest that 3D ocular kinematics merely reflect mechanical constraints imposed by orbital mechanics. The fact that different eye movement systems with different functional goals use different 3D strategies would argue against this idea. Nevertheless, the continuing debate on how 3D eye control is implemented shows that the study of Listing's law is not only relevant to our understanding of torsional control, but it also provides important insights into the fundamental neural and mechanical organization of the ocular motor system.

XII. What are the Clinical Implications of Listing's Law?

Because rotations in different orders produce different 3D orientation (non-commutativity), there is no a priori reason why a specific torsional orientation should be defined for each position of gaze, as required by Listing's law. If the brain and the ocular motor plant orchestrate to control torsional eye position with such precision, there must be strong benefits in doing so. Traditionally, the clinical evaluations of strabismus and strabismus surgery have mainly focused on horizontal and vertical alignment; little is known about the relationship between torsion, motor efficiency and stereo vision. To date, a few studies[3–5,18,31,54] have used a three-dimensional approach to investigate the effects of strabismus and strabismus surgery. However, because these studies examined a heterogeneous group of patients who had different form of strabismus and different type of operations, it is difficult to draw any conclusion at the present time. Several questions remained unanswered. For example, what are the effects of strabismus and strabismus surgery on 3D orientation of the eye? What are the consequences of surgery for torsion despite good eye realignment? How do neural commands and orbital mechanical factors (including pulleys) interact to control 3D eye movements during normal and diseased states? What type of surgery would best optimize ocular alignment, motor efficiency and stereo vision? The answers to these questions will have important clinical implications for the optimal management of strabismus.

XIII. Summary and Conclusion

Listing's law governs the 3D orientation of the eye and its axes of rotation. It can be expressed in terms of any initial eye position (half-angle rule). The binocular extension of Listing's law, or L2, is equivalent to Listing's law when the vergence angle is zero, and adjusts the eyes' torsion when they converge. Listing's law holds during fixation, saccades, smooth pursuit, and vergence, but not during sleep and vestibulo-ocular reflex, suggesting that it is actively implemented by a neural mechanism. Orbital mechanics, such as "pulleys", may also play a role in the implementation of the law. At present, the neural circuitry that implements the law is unknown; it is probably located somewhere downstream from the superior colliculus and upstream from the medium-lead burst neurons. Adherence to Listing's law and its extensions may serve the purpose of optimizing motor efficiency, or simplifying neural processing for binocular vision, or both. Finally, Listing's law is plastic, as demonstrated in patients with strabismus and ocular motor nerve palsy. This adaptability may allow the eye to regain motor efficiency, or preserve optimal visual function, although the central and peripheral mechanisms that underlie the adaptability of the law remain to be elucidated.

The study of Listing's law is of basic importance because it allows us to understand the organization of neural and mechanical factors in the control of 3D eye movements. It is also of importance to clinicians because it has important implications for the optimal management of strabismus.

XIV. Appendix

COMMONLY ASKED QUESTIONS

What are the differences between coordinate systems?

As mentioned previously, there are many different coordinate systems that can be used to describe rotary motions. The most commonly used ones include Fick coordinates, Helmholtz coordinates, rotation vectors, and quaternions. Because rotations are non-commutative, one has to specify the order in which the angles of rotation are measured, and the coordinate system used. All coordinate systems require the definition of a reference position, which is defined as the eye position where the values for all three dimensions (horizontal, vertical, and torsional) are zero. Fick[12] and Helmholtz[73] used different variants of the idea of Euler angles to represent eye position. In both systems, the orientation of the eye is defined by three subrotations. In Fick coordinates, the eye, starting from straight ahead position, first rotates torsionally about the line of sight, then vertically about the interaural axis, and finally horizontally about a head-fixed vertical axis. In Helmholtz's coordinate, the eye also first undergoes a torsional rotation, but the horizontal rotation then precedes the vertical rotation. In most natural eye movements, however, the eye does not reach another position by rotating sequentially about three different axes; rather, it rotates about a single axis. Coordinate systems such as rotation vectors[19] or quaternions[65,76] describe the orientation of the eye by rotation about a single axis from a reference position. The rotation vector assigns a numerical value to the orientation of the rotation axis, and the length of the vector represents the rotation angle.

A more detailed description of coordinate systems, which involves advanced mathematics, is beyond the scope of this review. Interested readers can refer to Van Opstal,[70] Hepp,[20] and Haslwanter[17] for a more in-depth discussion.

In the literature, some papers say that if the eye obeys Listing's law, torsion is always zero for any gaze direction. However, in this review, Listing's law is expressed as $T = -HV/2$, which indicates that torsion is variable, depending on the horizontal and vertical eye positions. Why is there a discrepancy?

The apparent discrepancy results from the different coordinate systems used. If one uses Helmholtz coordinates, the torsional position of the eye required by Listing's law is given by the formula $T = -HV/2$, whereas if one uses quaternions, then the torsional position of the eye is always zero, irrespective of the horizontal and vertical eye positions.

We can explain this apparent discrepancy by using an analogy. Suppose that a man is inside an elevator and it ascends from the ground to the third floor. Further, let us denote any floor above the reference position with a plus sign (+) and below with a minus sign (−). If we use the ground floor (which we will regard as the zeroth floor) as our reference position, then we would say that the new position of the man relative to the ground floor is +3. However, if we use the floor of the elevator as the reference position, then the new position of the man relative to the floor of the elevator remains zero. Now if we imagine that the elevator ascends from the ground floor to *x* floor, where *x* is any number, then the new position of the man relative to the ground floor is variable (that is, $+x$); in contrast, the new position of the man remains zero relative to the floor of the elevator, irrespective of the value of *x*. Thus, a description of the relative position of the man depends on the reference position used. Similarly, when one deals with the torsional position of the eye, the coordinate system used has to be specified.

What is "false torsion" (or "pseudotorsion")?

As discussed above, torsion is always zero if one uses a quaternion or rotation vector coordinate system (when the eye obeys Listing's law). In contrast, if one uses Helmholtz or Fick coordinates, which define eye orientation by three subrotations, the torsional position of the eye varies with its horizontal and vertical position. These non-zero values for torsion have been called "false torsion" or "pseudotorsion" by Helmholtz because they are dependent on the sequence of rotations. An advantage of using quaternions or rotation vector coordinate system is that the problem of false torsion does not arise. More generally, "false torsion" is torsion that is measured in a coordinate system other than the one you are using. The best way to clarify the situation (rather than disparaging some torsion as "false") is simply to specify the coordinate system being used, for instance, "Helmholtz torsion," or "quaternion torsion."

A patient starts out looking straight ahead during clinical examination, and suppose in one case, the patient rotates the eye first 90° rightward then 90° upward, and in the second case, the patient rotates the eye first 90° upward then 90° rightward (although 90° is outside the normal range of eye rotation in human, we will use it as an example). If eye rotations are non-commutative, does it mean that the torsional position of the eye will be different in these two instances? However, if the eye obeys Listing's law, because the horizontal and vertical positions of the eye in both *situations are the same, should the torsional position of the eye be the same in these two instances given that $T = -HV/2$?*

This apparent contradiction occurs because the final gaze direction is different in the two situations. Listing's law states that, for a given gaze direction, the torsional position of the eye is always the same. However, because the final gaze direction in the two situations is different, Listing's law does not apply, therefore the final torsional position of the eye differs.

To illustrate why the final gaze direction in the two situations is different, let us look at Fig. 7 again. In Figs. 7A and 7B, the initial position of the schematic heads and their anteroposterior (AP) axes both point straight ahead toward the reader. In the first set of rotation (Fig. 7A), the final orientation of the head has the AP axis pointing to the right, whereas in the second set (Fig. 7B) the AP axis points up, thus the final torsional positions of the schematic heads also differ. Similarly, we can use the AP axis of the schematic head as analogous to the gaze direction of the eye. If a patient's eye undergoes two set of rotations that have the same numerical values but are in different order, then the final gaze direction and thus the torsional position will be different.

L2 states that, during convergence, Listing's plane rotates temporally. According to this review, this temporal rotation means that there is a relative excyclotorsion on upgaze, and a relative incyclotorsion on downgaze. However, other papers say that it is the opposite, that is, temporal rotation means that there is a relative incyclotorsion on upgaze, and a relative excyclotorsion on down gaze. Why would some say there is excyclotorsion, and others say there is incyclotorsion, on upgaze?

Again, the apparent discrepancy results from the coordinate system used. If one uses Helmholtz coordinates, as in this review, then temporal rotation of Listing's plane means that there is a relative excyclotorsion on upgaze, and a relative incyclotorsion on downgaze, whereas if one uses quaternions, then it means that there is a relative incyclotorsion on upgaze, and a relative excyclotorsion on downgaze.

We can illustrate this apparent discrepancy using the same analogy as above, that is, suppose a man is inside an elevator and it ascends from the ground to the third floor. If we use the ground floor as the reference position, then the new position of the man relative to the ground floor is +3. However, if we use the fourth floor as the reference position, then the new position of the man relative to the fourth floor is −1. Note that in both reference systems, the *direction and amount of change* in position of the man is the same, that is the addition of 3 floors in the "more plus" direction: with ground floor as reference position, the change in position is from zero to +3, whereas with fourth floor as reference position, the change is from −4 to −1. However, because of the use of different reference position, the same change in the direction and amount of the man's position result in a "plus" representation in one system, and a "minus" in another. Just as the elevator rider is at −1 in one system and at +3 in another, so the same binocular configuration can be incyclorotated in one coordinate system and excyclorotated in another.

METHOD OF LITERATURE SEARCH

A search of the MEDLINE database (1970–2004) was conducted. The following key words were used: *Listing's law, torsion, three dimensional, eye movement, kinematics, saccades, smooth pursuit, vestibulo-ocular reflex, vergence, and pulleys.* Additional sources included publications cited in other articles. Relevant articles were reviewed and included.

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Outline