A decade of magnetic vestibular stimulation (MVS): from serendipity to physics to the clinic.

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Abstract:

For many years, people working near strong static magnetic fields of magnetic resonance imaging (MRI) machines have reported dizziness and sensations of vertigo. The discovery a decade ago that a sustained nystagmus can be observed in all humans with an intact labyrinth inside MRI machines led to a possible mechanism: a Lorentz force occurring in the labyrinth from the interactions of normal inner ear ionic currents and the strong static magnetic fields of the MRI machine. Inside an MRI, the Lorentz force acts to induce a constant deflection of the semicircular canal cupula of the superior and lateral semicircular canals. This inner ear stimulation creates a sensation of rotation, and a constant horizontal/torsional nystagmus that can only be observed when visual fixation is removed. Over time, the brain adapts to both the perception of rotation and the nystagmus, with the perception usually diminishing over a few minutes, and the nystagmus persisting at a reduced level for hours. This observation has led to discoveries about how the central vestibular mechanisms adapt to a constant vestibular asymmetry and is a useful model of set-point adaptation or how homeostasis is maintained in response to changes in the internal milieu or the external environment. We review what is known about the effects of stimulation of the vestibular system with high strength-magnetic fields and how the mechanism has been refined since it was first proposed. We suggest future ways that MVS might be used to understand vestibular disease and how it might be treated.

Ten years ago, Vincenzo Marcelli and colleagues (Marcelli et al. 2009) noted a peculiar phenomenon while using functional imaging (fMRI,1.5 Tesla) to explore patterns of activation in the brain by vestibular stimuli. Using a cold-water caloric stimulus as the probe, and *before* any images were taken, he reported *"the existence of spontaneous nystagmus activity preceding the injection"* and presciently speculated, "*which could be related to the spontaneous vestibular stimulation recently described because of the exposure to strong magnetic fields in the MRI environment*". He then cited the work of Glover et al (Glover et al. 2007) who had written about the possible influences of magnetic fields on the inner ear. Indeed, dizziness and vertigo around high-strength magnetic fields had been reported by human subjects for decades, and a possible labyrinthine origin had been suggested more than 25 years ago by Schenck (Schenck 1992). And there was evidence from animal experiments, for example, by Houpt et al (Cason et al. 2009; Houpt et al. 2003, 2005, 2007; Snyder et al. 2000; Weiss et al. 1992), who reported that rats without a functioning labyrinth entered a high strength magnetic field willingly while those with intact labyrinths did not. But Marcelli's observation of an induced nystagmus in the MRI machine, which would not have been possible had he not followed a fundamental clinical dictum – to best observe a peripheral vestibular nystagmus one must eliminate the suppression effect of visual fixation on an unwanted nystagmus – first explicitly tied effects of magnetic fields to the function of the vestibulo-ocular reflex (VOR).

I. What caused the nystagmus: The Lorentz force hypothesis

We learned of Marcelli's observation during a casual conversation with him at a conference in Siena, Italy, which stimulated us to investigate this phenomenon at our newly installed 7T magnet at the Kennedy-Krieger Institute at Johns Hopkins University in Baltimore. First, we confirmed that the origin of the MRI induced nystagmus required a functioning labyrinth by recording patients with no labyrinthine function who showed no nystagmus in the 7T MRI machine.

One of us, Dale Roberts (Roberts et al. 2011), then developed the hypothesis that static magnetic-hydrodynamic forces (Lorentz forces) within the endolymph were the source of the labyrinthine stimulation in the magnetic field. The idea was that the ionic currents normally generated in the endolymph fluid above the hair cells of the utricle interacted with the magnetic field to produce a sustained Lorentz force (Figure 1). This force pushed the fluid into the adjacent opening of the lateral semicircular canal, pushing on and bending the cupula and, in turn, the processes of the hair cells that extend into the gelatinous matrix of the cupula, sending a (mistaken) signal to the brain that the head was rotating. The force was acting as a constant *acceleration* of the head, which with a natural rotation would cause a sustained displacement of the cupula in the same way. Consequently, a sustained nystagmus was produced to compensate for a head rotation that did not actually happen. The sustained displacement of the cupula, which leads to a persistent nystagmus in the MRI machine, differs from the more commonly used

rotational stimulus – a constant *velocity* rotation of the body – which initially displaces the cupula, but as the rotation continues the cupula gradually returns toward its initial position over a period of a minute or so, and the nystagmus fades away. The advantage of the constant-acceleration vestibular stimulus induced in the magnet is that it produces a vestibular nystagmus (and imbalance in central vestibular tone) that can last for minutes or hours, ideal for study of vestibular adaptation and potentially for therapy to promote an adaptive response for rehabilitation.

It should be noted that this pattern of labyrinthine stimulation in an MRI machine is artificial in the sense that with a normal pair of functioning labyrinths there is no natural way to rotate the head and produce the same pattern of stimulation of the semicircular canals as when they are activated in the MRI machine. Furthermore, when the head is earth-horizontal, any stimulation of the lateral semicircular canals should be accompanied by changing activity of the utricle due to its revolution around the gravity vector. Likewise, with stimulation in the magnetic bore when the subject is supine the otoliths do not signal rotation, but the semicircular canals do. The unusual pattern of stimulation, of course, does not allow for a perfect mimic of naturally-occurring central responses to a prolonged nystagmus. However, it also may have advantages in studying the motor and perceptual responses to vestibular stimuli that are discordant and produce an intralabyrinthine conflict between what the semicircular canals and what the otolith organs are sensing.

The robust and easily observed nystagmus resulting from exposure to the MRI magnetic field provided a clear, quantifiable signal for testing the various ways that magnetic fields might affect human tissues – diamagnetic and paramagnetic properties of tissues, electromagnetic induction (Faraday) forces related to movement in a magnetic field, magneto-hydrodynamics, and static Lorentz forces. By manipulating the speed of entry of the subject into the magnetic field, the subject's orientation relative to the magnetic field, the subject's direction of motion, and the magnetic field strength (using 3T and 7T magnets), we were able to tease apart both the *time course* of the stimulation (dynamic and transient vs. static and continuous), and the *polarity dependence* of the stimulation (field polarity-dependent vs. not polarity-dependent). The observation of a *continuous* and *polarity-dependent* response allowed us to eliminate dynamic Faraday forces, dynamic magneto-hydrodynamic forces, and polarity-insensitive diamagnetic and paramagnetic forces, and focus on the possibility of a continuous and polarity-dependent Lorentz force. The Hall Effect is another continuous and polarity-dependent mechanism, but it has been dismissed as a possibility due to the negligible effect that might be produced within a volume of conductive fluid (Schenck 1992). Fortunately, to aid in the estimation of a possible Lorentz force, there were already models regarding the magnitude of forces needed to deflect the cupula and produce nystagmus, and data indicating the strength of the ion currents available

within the inner ear fluids to interact with the magnetic field (Oman and Young 1972). We could then estimate the size of the induced Lorentz force due to natural ionic currents, and whether it could produce nystagmus. These considerations and the experimental results made the Lorentz force hypothesis plausible(Antunes et al. 2012; Glover 2015; Glover et al. 2014; Roberts et al. 2011).

We further tested these ideas with a geometric model of the relations betweeen the openings of the semicircular canals and the position of the utricle in the vestibule. By changing the static orientation of the head of normal subjects in the magnet, by comparing the response when they entered the magnet head first versus feet first, and by recording the response of patients with only one functioning labyrinth we developed further evidence for the Lorentz force hypothesis. In intact human subjects the usual pattern of response with the subject lying supine in our MRI machine (magnetic field vector points head to toe with the subject entering the front of the MRI machine head first) was a conjugate, primarily mixed horizontal-torsional nystagmus with the slow phases of the horizontal components directed toward the left ear and the slow phases of the torsional components such that the top poles of the eyes rotated toward the right ear (Otero-Millan et al. 2017; Roberts et al. 2011). However, with the chin pitched far up the horizontal component of the slow phases were still to the left (but with higher slow-phase velocities), and with the chin tucked far down, the horizontal component of slow phases usually reversed, now being directed to the right. Consequently, there was one pitch orientation where there was a "null" with no nystagmus. When subjects were placed into the bore feet first instead of head first, which reversed the relative orientation of the utricular current and the magnetic field vectors, the directions of the horizontal and torsional components of the nystagmus also reversed.

These patterns of nystagmus are explained by the fundamental rules of labyrinthine excitation based on the work from the nineteenth century masters: the response of the eye (or head) to excitation of an individual semicircular canal (Breur, Ewald, Flourens) (Wiest 2015). Stimulation of a lateral canal elicits horizontal slow phases and stimulation of a vertical canal elicits a mixed vertical-torsional nystagmus with the slow phases upward (superior canal) or downward (posterior canal) but with the torsional component from each vertical canal always such that the top pole rotates toward the opposite ear. Furthermore, Ewald's second and third laws define ampullopetal movement of the cupula in the lateral canals as excitatory and ampullopetal movement of the cupula in the vertical canals as inhibitory.

Thus, the nystagmus with the head supine and with the chin pitched far up was explained by excitation of the right lateral semicircular canal and inhibition of the left (to produce the horizontal component, as during natural stimulation with rotation of the head around its yaw axis) and by excitation of the left superior canal (contralateral to the excited lateral canal) and inhibition of the right superior canal (ipsilateral to the excited lateral canal) to produce the torsional component (the opposing effects on torsion from the two superior canals adding)

without a vertical component (the similar effects on vertical eye movements from the two anterior canals subtracting and cancelling, figure 2).

Further support for this scheme came from the nystagmus induced in the MRI machine in patients with unilateral labyrinthine hypofunction (Ward et al. 2014a). In addition to a horizontal component they also had a vertical component with slow phases upward from *excitation* of the remaining left superior semicircular canal with right-sided loss of function, or slow phases downward from *inhibition* of the remaining right superior semicircular canal with left-sided loss of function. Taken together these patterns of nystagmus in intact human subjects and in patients with unilateral loss of function in one labyrinth strongly supported the Lorentz force hypothesis. More recently (Ward et al. 2018a) studies of mice with genetic defects in the development of the utricle further support this idea. Like human beings, mice with an intact labyrinth have similar patterns of nystagmus in an MRI machine; however, mice without a functioning utricle, but intact semicircular canals do not have nystagmus in an MRI. This suggests that ionic currents from a normal utricle are necessary to generate the nystagmus observed in an MRI machine and that semicircular canals are insufficient. The utricle is believed to be the predominant source of the ionic currents that, when in a strong static magnetic field, generate the Lorentz force in the endolymph that displaces the cupulae of the lateral and superior semicircular canals. We emphasize that the macula of utricle itself is not displaced by the Lorentz force in the endolymph; the utricle only supplies the ionic currents that interact with the magnetic field (Figure 3).

II. MVS and vestibular adaptation: A tool to study set-point adaptation (Zee et al. 2017)

MVS has many advantages over other forms of vestibular stimulation in that it imposes, a precise, sustained signal comparable to a constant angular acceleration, that can last hours but without having to rotate the head. One caveat as discussed above, is that MVS does not stimulate the semicircular canals with a pattern that can be produced with a natural head rotation. Such prolonged stimulation would be impossible with any natural rotation of the body, and impractical and less exact when using other artificial forms of vestibular stimulation such as caloric or galvanic excitation of the labyrinth and vestibular nerve. In our original studies of MVS we noted that the induced nystagmus did not remain at a constant level but partially dissipated slowly over time. Furthermore, when subjects were removed from the magnet after being inside for a while, a transient after effect, lasting minutes, appeared with nystagmus directed oppositely to the nystagmus when in the magnet. The initial slow-phase velocity of the aftereffect slowly increased the longer the subject was in the magnet and the aftereffect slowly faded away over minutes when outside the magnet.

It is likely that adaptation is occurring in the vestibular periphery at the hair cells or peripheral vestibular afferents, but the contribution of peripheral adaptation to the observed nystagmus is uncertain. The adaptation rates of hair cells are short (on the order of milliseconds (Eatock 2000)), however, some peripheral afferents do adapt over seconds to minutes in response to constant acceleration in primates and could account for a portion of the early components of adaptation (Goldberg and Fernandez 1971). We interpreted this pattern of behavior as the natural "adaptive" response of the brain to any sustained unidirectional nystagmus which is always inferred as being "pathological". The imbalance induced by MVS between the tonic levels of activity in the vestibular nuclei on either side of the brainstem serves as an "error signal" that drives central adaptive mechanisms to nullify the unwanted behavior (the sustained spontaneous nystagmus). The adaptive mechanism creates an opposing bias that restores balanced vestibular tone, and in turn, ocular stability and clear vision. This process of adaptation is an example of wide-spread, homeostatic mechanisms in the body in which "set-points" of equilibrium are maintained to optimize biological functions (Zee et al. 2017).

50 years ago, Young and Oman, and Malcomb and Melvill jones (Malcolm and Jones 1970; Young and Oman 1969) identified, quantified and mathematically modelled this form of short-term vestibular adaptation in normal human subjects based on recording nystagmus in response to relatively brief, for a few minutes, constant velocity or constant accelerations of the body. Using an approach based on control system engineering principles they identified "an adaptation operator", which could be implemented with an integrator and feedforward or feedback signals, to null any unwanted, spontaneous nystagmus. While this work was seminal, its scope was limited by the relatively short time – a few minutes – during which they could comfortably and safely challenge the brain to make an adaptive correction. With MVS, however, we can extend the stimulation time to hours, and so we were able to identify multiple adaptation mechanisms with different time courses and different degrees of fragility, as reflected in the different durations of their after effects (Jareonsettasin et al. 2016). Adaptation that was acquired more slowly was more enduring, with a longer-lasting after effect. This type of behavior can be interpreted using various conceptual approaches to learning – Bayesian, Skinnerian, or bioengineering control systems – but they have in common a perspective based on when, by how much, and for how long we must change our behavior in a new environment.

Recently we studied the effects of vision (fixation to suppress the spontaneous nystagmus), and of continuous head motion during MVS, on the early phases of set-point adaptation (Ward et al. 2018b). Fixation of either a small or a large visible target, or sustained head shaking either in the dark or with visual fixation inside a strong static magnetic field had little effect on short-term, VOR set-point adaptation. The relative independence of set-point adaptation from superimposed activity contrasts with the critical and necessary influence of vision and motion of images on the retina during head rotation that drives the dynamic (gain and direction) components of VOR

adaptation. The brain relies on internal signals to assure a stable platform and on external feedback to optimize its movements. And in a more general sense, we note these characteristics of vestibular, set-point adaptation are in accord with the biological imperative of quiet and stillness for survival. In this way the body is optimally poised to make the next important move, be it for defense, food, or procreation.

The studies of the multiple mechanisms and time courses underlying "set-point" adaptation in the vestibulo-ocular system using MVS may have wider implications to motor control of other types, including normal and abnormal control of the limbs, and the posture of the body during standing and walking. Perception and its disorders, too, require similar adaptive strategies to revise mental constructs of our relationship to a changing internal or external environment (Mian et al. 2013, 2015, 2016). Homeostatic mechanisms are pervasive for all types of control systems in the body, and MVS can give us clues to the general principles that underlie them.

MVS gives us a tool to investigate the many possible mechanisms underlying motor learning and how we adapt to disease and trauma. As an example, pharmacological manipulation of adaptive processes can be easily studied using MVS and might encourage novel therapeutic approaches to disease. The study of adaptive responses to MVS might help us understand how different peripheral lesions affect adaptive responses, e.g., recurrent attacks of Meniere's syndrome or vestibular migraine versus a single attack of vestibular neuritis, and how patients with central lesions, for example in the cerebellum, adapt to vestibular imbalance. Producing a new, sustained vestibular bias directed oppositely to an imbalance already imposed by disease might encourage more robust or faster restoration of normal vestibular balance. Extension of MVS to study of vestibulospinal and control of posture might be possible by studying after effects on balance outside the magnet. And the dissociation between perception, which is transient, and nystagmus, which is sustained, seen with MVS may provide clues to similar dissociations between what the subject feels and what the eyes show, that often occur in patients with vestibular disorders, such as benign paroxysmal positional vertigo (BPPV).

III. Implications for fMRI

One of our first thoughts about the implications for MVS was that it could be a potential confound in functional imaging studies. Whether the eyes are open or closed, except when the orientation of the head of the subject happens to be in the null position, every part of the brain to which the vestibular system projects is activated by the central imbalance induced by MVS. These structures include much of the cerebral cortex, and many areas in the thalamus, cerebellum and brainstem(Kirsch et al. 2016). Furthermore, if the eyes are open, visual areas are also activated by motion of images on the retina, and ocular motor areas are activated as they issue or monitor the ensuing motor commands that attempt to suppress the unwanted spontaneous nystagmus and keep the eyes still. Since adaptation occurs over multiple time courses, the

amount of nystagmus will vary over time and lead to activity that fluctuates in different parts of the brain over time. Recent studies confirmed that MVS can affect resting-state activity in functional MRI(Boegle et al. 2016, 2017). Of course, one could find a null position in each subject before doing a functional imaging study, or design paradigms that consider the changing patterns of central activation by MVS over time, but these confounds have not been considered in fMRI studies. Given the many behavioral confounds and caveats already known for fMRI, the widespread nature of vestibular projections to the cerebral hemispheres, cerebellum brainstem, more detailed analysis of the potential for MVS to produce artifacts are needed.

IV. The Future of MVS

Looking at the history of how previous ways to stimulate the vestibular system have been applied to both science and disease, we can predict where MVS may take us. Because MVS is a reliable, nonvarying and easy to manipulate vestibular stimulus (e.g., strength of the induced response, orientation of the labyrinth relative to the magnetic field vector), the induced nystagmus provides a consistent, quantitative readout of brain function that can be tied to many aspects of behavior and activity in the brain. One can imagine applications to the results of functional and other forms of imaging (e.g., movement of fluids in the labyrinth during vestibular stimulation), to perception, attention, neglect and other cognitive measures during vestibular stimulation, and to motor behaviors apart from nystagmus (e.g., postural tone, movements of the limbs, vestibulo-spinal and vestibulocollic reflexes). As shown above MVS is an ideal model for studying the multiple time courses of set-point adaptation which may have implications for many types of learning including optimizing programs of rehabilitation. MVS can be relatively easily studied in experimental animals (Houpt et al. 2011; Ward et al. 2014b), measuring not only vestibulo-ocular but vestibulospinal and vestibulocollic function, and recall that early studies in rats pointed to the critical role of the labyrinth in producing symptoms in human subjects who worked around high-strength magnetic fields. Knowledge of MVS is critical for assessing the safety and potential side effects of vestibular stimulation, as the use of stronger magnetic fields spreads for both basic science and clinical use.

The effects and implications of discordant labyrinthine stimulation is another area for further study since MVS does not stimulate the labyrinth in a way that can occur naturally with motion of the head. This includes the selective stimulation of the superior and lateral semicircular canals with MVS which is not possible when human beings with intact labyrinths rotate their heads. Likewise, MVS with the subject supine and stationary induces a sense of rotation from stimulation of the semicircular canals but this is not corroborated by a fluctuating pattern of otolith stimulation, as happens during “natural” barbeque rotation (rotation around an earth horizontal axis). Because of this unnatural, inherent conflict between signals from the semicircular canals and the otolith organs, motion sickness and perceptual illusions are potential

side effects of MVS. These can serve for study of activation of the labyrinth and of vestibular perception (Mian et al. 2013, 2015, 2016) but also can have important clinical implications as they may induce motion sickness and vomiting which can be deleterious to a patient whose wounds are fragile because of recent surgery (Ward et al. 2015).

Finally, scientists have speculated for over 150 years that migratory species can use the magnetic field of the earth for navigation, yet the receptor that detects this signal is unknown (Nordmann et al. 2017, Wiltschko and Wiltschko 1996). While there is some evidence that a neural response for magnetoreception can be recorded in the vestibular nucleus of pigeons (Wu and Dickman 2012), we emphasize that that the strength of the magnetic field used in our studies to stimulate the labyrinth is *orders of magnitude larger* than that of the magnetic field of the Earth, making the stimulation of the labyrinth by strong magnetic fields in an MRI machine unrelated to any possible use of the Earth's magnetic field for navigation.

V. Summary

It has been about a century since a new tool to stimulate the vestibular system has emerged. Rotation of the head or the body, caloric stimulation and galvanic stimulation have been reliable mainstays of vestibular stimulation. Sound, too, has been used to stimulate the vestibular system since Tullio described his phenomenon and sound is now used to elicit vestibular-evoked myogenic potentials. But MVS adds many advantages to all these methods because of its consistency, ease of quantification, comfort over long periods of stimulation, and the relative ease by which its effects can be manipulated. Many behaviors controlled by the brain can be studied with MVS including perception and cognition, motor performance, learning and adaptation, both to understand the function of the brain and for diagnosis and treatment of disease. As the strength of magnetic fields of MRI machines increases for both scientific and clinical use it becomes increasingly important to understand the mechanisms and safety issues related to its use.

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References

Antunes A, **Glover PM**, **Li Y**, **Mian OS**, **Day BL**. Magnetic field effects on the vestibular system: calculation of the pressure on the cupula due to ionic current-induced Lorentz force. *Phys Med Biol* 57: 4477–4487, 2012.

Boegle R, **Ertl M**, **Stephan T**, **Dieterich M**. Magnetic vestibular stimulation influences resting-state fluctuations and induces visual-vestibular biases. *J Neurol* 264: 999–1001, 2017.

Boegle R, **Stephan T**, **Ertl M**, **Glasauer S**, **Dieterich M**. Magnetic vestibular stimulation modulates default mode network fluctuations. *Neuroimage* 127: 409–421, 2016.

Cason AM, **Kwon B**, **Smith JC**, **Houpt TA**. Labyrinthectomy abolishes the behavioral and neural response of rats to a high-strength static magnetic field. *Physiol Behav* 97: 36–43, 2009.

Eatock RA. Adaptation in hair cells. *Annu Rev Neurosci* 23: 285–314, 2000.

Glover P. Magnetic Field-Induced Vertigo in the MRI Environment. *Curr Radiol Rep* 3: 29, 2015.

Glover PM, **Cavin I**, **Qian W**, **Bowtell R**, **Gowland PA**. Magnetic-field-induced vertigo: a theoretical and experimental investigation. *Bioelectromagnetics* 28: 349–361, 2007.

Glover PM, **Li Y**, **Antunes A**, **Mian OS**, **Day BL**. A dynamic model of the eye nystagmus response to high magnetic fields. *Phys Med Biol* 59: 631–645, 2014.

Goldberg JM, **Fernandez C**. Physiology of peripheral neurons innervating semicircular canals of the squirrel monkey. I. Resting discharge and response to constant angular accelerations. *J Neurophysiol* 34: 635–660, 1971.

Houpt TA, **Carella L**, **Gonzalez D**, **Janowitz I**, **Mueller A**, **Mueller K**, **Neth B**, **Smith JC**. Behavioral effects on rats of motion within a high static magnetic field. *Physiol Behav* 102: 338–346, 2011.

Houpt TA, **Cassell JA**, **Riccardi C**, **DenBleyker MD**, **Hood A**, **Smith JC**. Rats avoid high magnetic fields: dependence on an intact vestibular system. *Physiol Behav* 92: 741–747, 2007.

Houpt TA, **Pittman DW**, **Barranco JM**, **Brooks EH**, **Smith JC**. Behavioral Effects of High-Strength Static Magnetic Fields on Rats. *J Neurosci* 23: 1498–1505, 2003.

Houpt TA, **Pittman DW**, **Riccardi C**, **Cassell JA**, **Lockwood DR**, **Barranco JM**, **Kwon B**, **Smith JC**. Behavioral effects on rats of high strength magnetic fields generated by a resistive electromagnet. *Physiol Behav* 86: 379–389, 2005.

Jareonsettasin P, **Otero-Millan J**, **Ward BK**, **Roberts DC**, **Schubert MC**, **Zee DS**. Multiple Time Courses of Vestibular Set-Point Adaptation Revealed by Sustained Magnetic Field Stimulation of the Labyrinth. *Curr Biol* 26: 1359–1366, 2016.

Kirsch V, **Keeser D**, **Hergenroeder T**, **Erat O**, **Ertl-Wagner B**, **Brandt T**, **Dieterich M**. Structural and functional connectivity mapping of the vestibular circuitry from human brainstem to cortex. *Brain Struct Funct* 221: 1291–1308, 2016.

Malcolm R, **Jones GM**. A quantitative study of vestibular adaptation in humans. *Acta Otolaryngol* 70: 126–135, 1970.

Marcelli V, **Esposito F**, **Aragri A**, **Furia T**, **Riccardi P**, **Tosetti M**, **Biagi L**, **Marciano E**, **Di**

Salle F. Spatio-temporal pattern of vestibular information processing after brief caloric stimulation. *Eur J Radiol* 70: 312–316, 2009.

Mian OS, **Glover PM**, **Day BL**. Reconciling Magnetically Induced Vertigo and Nystagmus. *Front Neurol* 6: 201, 2015.

Mian OS, **Li Y**, **Antunes A**, **Glover PM**, **Day BL**. On the vertigo due to static magnetic fields. *PLoS One* 8: e78748, 2013.

Mian OS, **Li Y**, **Antunes A**, **Glover PM**, **Day BL**. Effect of head pitch and roll orientations on magnetically induced vertigo. *J Physiol* 594: 1051–1067, 2016.

Nordmann GC, **Hochstoeger T**, **Keays DA**. Magnetoreception—A sense without a receptor. *PLoS Biol* 15: e2003234, 2017.

Oman CM, **Young LR**. The physiological range of pressure difference and cupula deflections in the human semicircular canal. Theoretical considerations. *Acta Otolaryngol* 74: 324–331, 1972.

Otero-Millan J, **Zee DS**, **Schubert MC**, **Roberts DC**, **Ward BK**. Three-dimensional eye movement recordings during magnetic vestibular stimulation. *J Neurol* 264: 7–12, 2017.

Roberts DC, **Marcelli V**, **Gillen JS**, **Carey JP**, **Della Santina CC**, **Zee DS**. MRI magnetic field stimulates rotational sensors of the brain. *Curr Biol* 21: 1635–1640, 2011.

Schenck JF. Health and physiological effects of human exposure to whole-body four-tesla magnetic fields during MRI. *Ann N Y Acad Sci* 649: 285–301, 1992.

Snyder DJ, **Jahng JW**, **Smith JC**, **Houpt TA**. c-Fos induction in visceral and vestibular nuclei of the rat brain stem by a 9.4 T magnetic field. *Neuroreport* 11: 2681–2685, 2000.

Ward BK, **Lee YH**, **Roberts DC**, **Naylor E**, **Migliaccio AA**, **Della Santina CC**. Mouse Magnetic-field Nystagmus in Strong Static Magnetic Fields Is Dependent on the Presence of Nox3. *Otol Neurotol* 39: e1150–e1159, 2018a.

Ward BK, **Roberts DC**, **Della Santina CC**, **Carey JP**, **Zee DS**. Magnetic vestibular stimulation in subjects with unilateral labyrinthine disorders. *Front Neurol* 5: 28, 2014a.

Ward BK, **Tan GX-J**, **Roberts DC**, **Della Santina CC**, **Zee DS**, **Carey JP**. Strong static magnetic fields elicit swimming behaviors consistent with direct vestibular stimulation in adult zebrafish. *PLoS One* 9: e92109, 2014b.

Ward BK, **Zee DS**, **Roberts DC**, **Schubert MC**, **Perez-Fernandez N**, **Otero-Millan J**. Visual Fixation and Continuous Head Rotations have Minimal Effect on Set-Point Adaptation to Magnetic Vestibular Stimulation. *Front Neurol* 9: 1197, 2018b.

Ward BK, **Zee DS**, **Solomon D**, **Gallia GL**, **Reh DD**. CSF leak: A complication from vomiting after magnetic vestibular stimulation. *Neurology* 85: 551–552, 2015.

Weiss J, **Herrick RC**, **Taber KH**, **Contant C**, **Plishker GA**. Bio-effects of high magnetic fields: A study using a simple animal model. *Magn Reson Imaging* 10: 689–694, 1992.

Wiest G. The origins of vestibular science. *Ann N Y Acad Sci* 1343: 1–9, 2015.

Wiltschko W, **Wiltschko R**. Magnetic orientation in birds. *J Exp Biol* 199: 29–38, 1996.

Wu L-Q, **Dickman JD**. Neural correlates of a magnetic sense. *Science* 336: 1054–1057, 2012.

Young LR, **Oman CM**. Model for vestibular adaptation to horizontal rotation. *Aerosp Med* 40: 1076–1080, 1969.

Zee DS, **Jareonsettasin P**, **Leigh RJ**. Ocular stability and set-point adaptation. *Philos Trans R Soc Lond B Biol Sci* 372, 2017.

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Legends

Figure 1 - The Lorentz hypothesis proposes that the interaction of the MRI magnetic field (yellow arrows) with naturally-occurring ionic currents flowing into the hair cells in the utricule (green arrows) in the inner ear endolymph fluid (inside blue volume) creates a persistent Lorentz force within the fluid. This fluid force then pushes on the cupulae (the head rotation sensors, orange areas), which creates the observed nystagmus via the vestibulo-ocular reflex. Although the precise nature of endolymph ion current flow and direction is unknown, the utricle is believed to be the predominant destination of the ion currents that generate the Lorentz force.

Figure 2 - In magnetic vestibular stimulation a Lorentz force is hypothesized to induce a mixed horizontal and torsional nystagmus due to the stimulation of the horizontal and superior semicircular canal cupulae. A) The nystagmus generated is a mixture primarily of horizontal and torsional components as shown in the traces of eye position over time in one subject. B) After entering the magnetic field (at time 2 min), a subject develops a predominantly horizontal and torsional nystagmus. The slow-phase velocity of nystagmus shows a partial, but incomplete adaptation over time for both the horizontal and torsional components, and an aftereffect occurs upon exiting the magnetic field (at time 7 min). C) Whenever the vectors of the static magnetic field and the net utricular current are not parallel, a Lorentz force is generated (its direction determined by the right-hand rule, see inset) that displaces the cupulae of the horizontal and superior semicircular canals. The equation for the Lorentz force ($\boldsymbol{F}$) is represented by $\boldsymbol{F} = L\boldsymbol{j} \times \boldsymbol{B}$, where $\boldsymbol{j}$ represents the current vector giving the direction of positive charge movement, $\boldsymbol{B}$ the static magnetic field vector, and L the distance over which the current flows.

Figure 3 - A) At rest, potassium ions (K+) enter the apical ends of vestibular hair cells, leading to Ca2+ influx and hair cell depolarization. B) Potassium ions are secreted into endolymph by dark cells. We hypothesize that the potassium ions are concentrated in the endolymph above the utricle and enter the utricular macula with relative uniform direction. C) In a strong static magnetic field, a Lorentz force is generated when there are differences in the orientation of the utricle current and the magnetic field vectors. This Lorentz force creates endolymph fluid

movement near the cupula of the superior and lateral semicircular canals, that in a strong magnetic field is enough to displace the cupula and generate nystagmus.