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Potential solutions to several vestibular challenges facing clinicians

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Abstract

Among other problems, patients with vestibular problems suffer imbalance, spatial disorientation, and blurred vision. These problems lead to varying degrees of disability and can be debilitating. Unfortunately, a large number of patients with vestibular complaints cannot be diagnosed with the clinical tests available today. Nor do we have treatments for all patients that we can diagnose. These clinical problems provide challenges to and opportunities for the field of vestibular research. In this paper, we discuss some new diagnostic and treatment options that could become available for tomorrow's patients. As a new diagnostic, we have begun measuring patient's perceptual direction-detection thresholds. Preliminary results appear encouraging; patients diagnosed with bilateral loss have yaw rotation thresholds almost ten times greater than normals, while patients diagnosed with migraine associated vertigo have roll tilt thresholds well below normal at 0.1 Hz. As a new treatment, we have performed animal studies looking at responses evoked by electrical stimulation provided by a vestibular prosthesis. Results measuring the VOR demonstrate promise and preliminary studies of balance and perception are also encouraging. While electrical stimulation is a standard means of stimulation, optical stimulation is also being investigated as a way to improve prosthetic stimulation specificity.

Keywords

Perception; prosthesis; psychophysics; threshold; clinical; spatial disorientation; imbalance

1. Introduction

The vestibular labyrinth senses angular and linear head motion and head orientation with respect to gravity. This information contributes to postural control (e.g. [1]), percepts of head orientation and motion (e.g. [2]), and the vestibulo-ocular reflex (VOR) that stabilizes images on the retina (e.g. [3]). (For a brief overview of vestibular function, see [4]). When the vestibular periphery is damaged or when there are central vestibular lesions, these normal processes are impaired. Patients with vestibular deficits experience dysequilibrium and ataxia (e.g. [5]), abnormal percepts of head orientation and motion (e.g, vertigo and spatial disorientation) (e.g. [6]), and visual difficulties (e.g., blurriness and oscillopsia) (e.g. [7]).

In these difficulties faced by patients, we see challenges that lead to opportunities. [1] From a diagnostic perspective, about one third of patients reporting dizziness or imbalance have

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normal vestibular test results [8]. This poses an obvious challenge, which will, in our opinion, in part, be addressed by developing quantitative clinical tests of vestibular perception. A synopsis of our logic follows: A) Patients complain of perceptual symptoms whose basis cannot be determined with available clinical tests. B) We know much less about vestibular perception than we know about vestibular reflexes like the vestibulo-ocular reflex (VOR). C) Recent studies [9,10] show that vestibular perception utilizes qualitatively different sensory processing mechanisms than the VOR. D) Standard clinical tests do not assess vestibular perception. E) Due to high sensitivity and high specificity, perceptual thresholds provide the most common way to assay sensory function in the clinic (e.g., audiogram). F) Perceptual thresholds may prove particularly relevant as a vestibular diagnostic because it is reasonable to hypothesize that patients will not easily adapt to deficits caused by threshold-level stimuli. G) Therefore, we have begun to measure vestibular thresholds as a function of frequency – the vestibular equivalent to the standard audiogram that we call a "vestibulogram" – in both normals and patients. The section entitled "Diagnostics" discusses this in more detail.

Furthermore, many patients – even those who are diagnosed correctly – cannot be adequately treated today. Since both the underlying peripheral vestibular deficits and the resultant symptoms are often poorly responsive to available modes of therapy, the development of vestibular prostheses has become an area of considerable interest (e.g. [11,12]), which is discussed in the section entitled "Vestibular Implants."

2. Diagnostics

2.1. Vestibulo-ocular reflexes (VOR)

Vestibular disorders may result in deficient VOR function resulting in increased retinal image motion and symptoms such as blurring of vision or oscillopsia. Clinicians rely heavily on the VOR to diagnose vestibular disorders [13–15]. Peripheral vestibular nystagmus is a manifestation of vestibular tone imbalance and inappropriate activation of the VOR. Clinical tests such as dynamic visual acuity testing, the head impulse test, the Dix-Hallpike maneuver, and examination for post headshake nystagmus involve the VOR. Standard vestibular laboratory testing (caloric ENG and rotary chair testing) involves quantitative assessment of (usually horizontal canal) VOR function. While the utility of these diagnostic tests has been well established, particularly for diagnosing peripheral vestibular hypofunction, limitations arise from the heavy reliance on ocular motor measures. In about one third of patients with vestibular symptoms, no abnormality is found to explain their symptoms using traditional clinical methods and vestibular laboratory testing [8], which suggests that the standard vestibular evaluation is inadequate. Specifically, 1) the vestibular disorder may not involve the VOR, 2) the vestibular disorder may selectively involve otolith function or canal-otolith interaction which are not readily evaluated using standard vestibular diagnostic methods, and 3) a co-existing disorder of ocular motility (ophthalmoplegia or constant nystagmus) may obscure measures of VOR function.

2.2. Perceptual

Vestibular perceptual testing provides a method for assessing vestibular function independent of ocular motor responses. Such an approach has been used to assess vestibular function in patients with congenital nystagmus [16] and in patients with acquired ophthalmoplegia [17] where the ocular motility abnormality obscures or limits the ocular motor response of the VOR. The method used by this group involves the subjects turning a tachometer wheel according to the perceived velocity of rotation during or following horizontal velocity steps. The method

[1]As part of a strategic planning activity hosted by the Man-Vehicle Laboratory at MIT, we were invited to contribute what we see as some of the most significant clinical challenges – both diagnostic and treatment – related to vestibular function.

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measures a dynamic perceptual response from which the duration and time constant are determined.

Another approach mimics the success of other clinical tests that measure perceptual thresholds to assay sensory function by measuring vestibular perceptual direction detection thresholds. For example, perceptual yaw-rotation direction-detection thresholds have been measured and plotted as a function of rotation frequency [18] to form a “vestibulogram” – analogous to an audiogram. Preliminary data from our laboratory measuring yaw rotation direction detection thresholds in patients with severe bilateral peripheral vestibular hypofunction show thresholds that are elevated by nearly a factor of ten compared to age-matched controls. Such threshold measures may be preferable to measures of rotation velocity perception in detecting peripheral vestibular hypofunction since patients with congenital nystagmus [16] or acquired ophthalmoplegia [17] may also have shortened vestibular responses as a compensatory mechanism to suppress spatial disorientation and motion-induced sickness.

Different aspects of vestibular function can be measured by changing the motion characteristics and subject orientation; for example, rotational, translational or tilt thresholds might be measured. Rotational thresholds associated with horizontal semicircular canal stimulation can be studied by yaw rotation about an earth-vertical axis. Perhaps more importantly, because vertical canal function is more difficult to assay, rotational thresholds evoked by vertical canal stimulation can be studied by applying roll rotation with the subject in the supine position, pitch rotations with the subject ear down, or right-anterior left-posterior (RALP) and left-anterior right posterior (LARP) rotations all about an earth-vertical axis.

A similar approach can be used to assess translation thresholds related to dynamic otolith stimulation. For example, it is reasonable to envision that an inter-aural translation direction-detection threshold could provide a test of utricular function; such a quantitative test of utricular function is presently absent from the clinical test battery. Furthermore, dynamic tilt motion stimuli could be used to measure tilt thresholds related to simultaneous otolith and vertical canal stimulation. The frequency of the roll-tilt motion stimulus used can be varied to test predominantly canal related responses at high frequencies and otolith mediated responses at low frequencies [19,20].

Vestibular perceptual studies may also provide a novel approach for studying central vestibular disorders such as migraine associated vertigo (MAV). Vestibular symptoms are common in migraine with over half of migraineurs developing vestibular symptoms at some point during the course of the illness [21]. Peripheral vestibular dysfunction has been described in cases of MAV, which may be more common in a subset of patients with basilar migraine [22]. Oculographic studies may show evidence of central-vestibular dysfunction with acute migrainous vertigo [23]. No specific neurootologic abnormality has been linked to MAV although patients with MAV were 4 times more likely to develop nausea with caloric stimulation [24]. In the absence of a confirmatory diagnostic test, the diagnosis of MAV is based on clinical criteria [25]. Central nervous system sensitization to vestibular signals from the inner ear may be responsible for vestibular symptoms in MAV; this would be similar to the sensitization that occurs to other sensory modalities resulting in photophobia, phonophobia, and osmophobia that are characteristic features of migraine [26]. The vestibular dysfunction in MAV may be downstream or parallel to vestibular ocular motor pathways, which may explain why assays of VOR function are often normal in these patients. Since MAV symptoms are perceptual in nature, perceptual studies provide a way to assess vestibular function at this higher level.

Preliminary data from our study of roll-tilt perceptual thresholds in patients with MAV shows significantly reduced thresholds compared to age-matched controls at 0.1 Hz but not at the

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lower (DC) or higher (1.0) frequencies tested. Semicircular canal signals appear to dominate thresholds at 1.0 Hz and otolith signals appear predominant for static tilts (DC) [27]. At 0.1 Hz, both semicircular canal and otolith signals appear important. A possible explanation for the selective reduction of perceptual thresholds at 0.1 Hz is that canal-otolith interaction may be abnormal in patients with MAV. Another possible explanation is that vertical canal signals associated with lower perceptual thresholds may dominate at 0.1 Hz roll-tilt in patients with MAV. By studying perceptual thresholds in these patients we may be able to determine the relative contribution of the vertical canals and otoliths to the lowered perceptual thresholds.

3. Vestibular implants

3.1. Sensory replacement implant

To replace absent vestibular function for a patient suffering severe bilateral vestibular hypofunction, a vestibular prosthesis requires a sensor to transduce the physical parameters normally sensed by the damaged periphery, and a method to provide this information to the brain through some form of stimulation. Two general approaches have been developed to provide sensory information about head motion and orientation to the brain – direct stimulation of vestibular nerve afferents and non-vestibular (or sensory substitution) stimulation using tactile or auditory feedback. While sensory substitution has demonstrated promise [28–30], we focus on direct stimulation of vestibular afferents in this paper. We discuss three different direct stimulation approaches – electrical stimulation and two forms of optical stimulation.

3.1.1. Electrical stimulation—We have developed a “canal prosthesis” that senses angular head velocity and provides this information to the brain by stimulating canal ampullary nerves electrically with implanted electrodes [31,32]. Since the polarities of all hair cells in each canal cristae are aligned, afferent activity in each associated nerve fiber modulates in a similar manner during head rotation, and we can approximate this effect by modulating the frequency of stimulation provided by the electrode. Direct vestibular nerve stimulation therefore allows one to encode head angular velocity in the afferent nerve in a reasonably physiologic manner. Conversely, in the maculae of the otolith organs the polarities of the hair cells are not aligned [15] and hence electrical stimulation of otolith afferents [33] would not approximate the complex modulation in macular afferent activity that occurs in response to shifts in gravito-inertial force. For these reasons, we, like others [34], are concentrating on a three-dimensional canal prosthesis that senses head rotation about all three cardinal axes and stimulates all three semicircular canals in one ear. To date, we have used a prosthetic device that senses angular head rotation in yaw and stimulates one lateral canal afferent nerve, and with this approach we have generated compensatory VOR responses in squirrel monkeys with bilateral horizontal canal plugs [35,36]. We choose to begin our prosthesis investigations by measuring the VOR because eye movements are easily quantified and because their dependence on vestibular inputs is relatively straightforward. The symptoms described by patients with vestibular dysfunction, however, are principally postural and perceptual. To evaluate the potential clinical utility of a vestibular prosthesis in an animal model, we have begun to extend our measurements beyond eye movements and are now also investigating the more complex, integrative behaviors of postural control and spatial orientation.

We are currently testing a three-dimensional canal prosthesis in rhesus monkeys with bilateral vestibular hypofunction to determine if the prosthesis can improve balance, tilt perception, and vestibular eye movements in these animals. First, we characterize postural stability [37], roll tilt psychophysics [37,38], and VOR responses in normal rhesus monkeys, and then introduce a static bilateral vestibular deficit by damaging the hair cells in the vestibular labyrinth with IT gentamicin [7]. The deficits associated with the bilateral vestibular damage are defined, and then three-dimensional rotational information is re-introduced with the prosthesis. The animals are studied chronically to determine if the rotational information supplied by the prosthesis has

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a long-term beneficial effect on postural, perceptual, and oculomotor behaviors. Preliminary results in a rhesus monkey with a one-dimensional (posterior canal) prosthesis demonstrated improvement in the amplitude of the VOR response during head rotation, and suggested that percepts of head orientation relative to gravity and postural stability during head turns may also improve with chronic prosthetic stimulation [37,39].

3.1.2. Optical stimulation of neurons: An alternative to electrically based vestibular prostheses—One shortcoming associated with existing experimental vestibular implants is the nonspecific spread of electrical current to surrounding nerves. Ideally, a single electrode would stimulate vestibular nerve afferents to only one of the vestibular organs. The optimal placement of the electrode would be at the nerve endings innervating the hair cells of a specific endorgan, before the nerve fibers aggregate with the fibers innervating other regions of the vestibular periphery. However, direct access to neurons may not be feasible due to intervening bone, epithelium, and other tissue. Consequently, increasing the current level high enough to stimulate vestibular afferents often causes the current to spread to surrounding regions, allowing more distant (non-targeted) nerve fibers to be stimulated. An analogous situation occurs with cochlear implants, and is the likely cause of perceptual interaction between two or more channels of stimulation [40,41]. In addition, placing two (or three) wires in a bipolar (or tripolar) configuration may restrict the current spread to some degree compared to a single wire. However, one drawback of this approach is that each electrode must be connected to a separate current source. Also, the higher currents required to reach response threshold may limit the working intensity range due to voltage compliance, as seen with current cochlear implant technology [42]. Other potentially viable approaches include optical stimulation.

3.1.2.1. Infrared neural stimulation (INS): Low-power infrared neural stimulation (INS) is an exciting new alternative to electrical stimulation to activate neurons selectively [43–45]. In the auditory periphery, INS has been used to optically stimulate spiral ganglion cells. Stable, optically-evoked auditory brainstem responses (oABRs) have been observed during 6 hours of continuous exposure of spiral ganglion cells in gerbil with pulsed mid-wavelength infrared laser energy [45]. Optical radiation of cochlear spiral ganglion cells evoked cochlear compound action potentials (CAP's) that increased over a laser energy range of 30–40 dB. Additional tone-on-light-masking experiments showed that restricted populations of cochlear spiral ganglion cells were stimulated [45]. This pioneering work suggests that INS stimulation can achieve a high resolution of cochlear nerve activation to potentially minimize undesirable channel interactions.

A second advantage of optical stimulation is the potential to activate neurons in a stable fashion while maintaining selectivity. Electrical stimulation involves a complicated conductive interface between the electrode and excitable tissue, including bone, fluid, and any fibrous sheath covering the implanted array. Studies have demonstrated that electrode impedance can change over time as the result of various tissue reactions [46,47]. Although certain electrode materials can minimize reactions due to dissolved metals and electrolytic processes [48], neurons close to an implanted electrode array can be vulnerable to injury following chronic stimulation [49]. An optically based electrode, on the other hand, might be better tolerated as a chronic implant because of its relatively inert surface materials. Additionally, INS may not require close contact in order to selectively stimulate nerve tissue. For example, previous application of INS demonstrated that activation of the auditory nerve could be achieved even with a layer of bone separating the laser from the spiral ganglion [45].

3.1.2.2. Laser-tissue interactions: The biophysical mechanism responsible for optical stimulation of neural tissue has been attributed to a photothermal effect [44]. Specifically, the mechanism requires a time and space dependent thermal gradient established across the axonal

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membrane. Photothermal effects result from the absorption and transformation of optical energy to heat. Optical parameters can be selected to obtain the clinically desired endpoint. At a wavelength of 2.12 or 1.86 μm, there is little light scattering in tissue and the primary method of light-tissue interaction is light absorption by water in the tissue. The tissue absorption at a given wavelength dictates the optical penetration depth, and in the case of nerve stimulation the volume of excitable tissue. By using a diode that is tunable in wavelength, the laser penetration depth can be controlled for maximum efficiency of stimulation based on the geometry of the target tissue [50]. Upon absorption, this optical energy is transferred to thermal energy and results in heating of the target area. Because of the potential for thermal tissue damage, the heat transfer into the tissue must be balanced by heat transfer away from the target volume. Heat transfer in tissue is primarily achieved by conduction, although in some tissues convective heat transfer via flowing blood can be significant. As high repetition rates of optical stimulation are required for vestibular implants, it is important that heat accumulation be limited to minimize subsequent tissue damage. Stimulation rates up to 400 Hz and continuous INS for more than six hours have been performed in the auditory periphery without changing the compound action potential amplitude, which is a sensitive indicator for cochlear function [51]. Thus, we do not anticipate that thermal transients induced within the vestibular system using the upper limits for physiologically relevant laser parameters will result in thermal tissue damage.

Recently, we have shown that INS can also stimulate auditory neurons in the CNS. Investigators in our group have been able to measure evoked auditory brainstem responses following thirty minutes of continuous INS of the cochlear nucleus (the first center of auditory processing in the brain). This is the first demonstration of optical stimulation using INS of the CNS *in vivo* and we observed stable oABRs during thirty minutes of radiant exposure to the cochlear nucleus [52]. Optical stimulation of the vestibular periphery has not yet been demonstrated and future experiments in our laboratory will explore the efficacy and safety of INS in an animal model. Specifically, we plan to stimulate the individual semicircular canals using optical fibers surgically implanted and positioned near the ampulla of each canal and determine the feasibility of generating an optically-evoked vestibulo-ocular reflex (oVOR). The application of neuronal stimulation using infrared lasers may greatly improve current device technology as well as provide a powerful tool for research by eliminating electrical artifacts. The enhanced spatial selectivity may be advantageous when developing a peripheral vestibular prosthesis requiring the stimulation of all five vestibular end organs that sense angular and linear acceleration. Hybrid implants that combine optical and electrical stimulation may also warrant consideration.

3.1.2.3. Photostimulation of light-activated neurons: As previously noted, optical stimulation using radiant infrared energy most likely relies on photothermal mechanisms to trigger neuronal firing. An alternative approach is the use of visible light to activate neurons that express channel rhodopsin [53,54]. Photostimulation using pulsed light allowed for millisecond timescale control of neuronal spiking in hippocampal neurons expressing channel rhodopsin-2 (ChR2) in cell culture [53]. These cells were transfected using lentiviral gene delivery and expressed ChR2 in a stable manner [53]. Experiments in brain slices from transgenic mice expressing ChR2 have also demonstrated light-evoked action potentials with millisecond temporal resolution [54]. We hope that collaborations between our group and Dr. Boyden at MIT – a pioneer in this field – will soon explore the possibility of exploiting the improved spatial and temporal resolution of photostimulation in the vestibular periphery of ChR2 transgenic animals.

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3.2. Vestibular pacemaker

Results obtained during early studies of a sensory replacement prosthesis [31,55] suggested the idea of a vestibular pacemaker. Such a device might be designed to stabilize neural activity during transient attacks of vertigo and spatial disorientation due to abnormal variations in peripheral vestibular function, like those associated with Ménière's syndrome. Presently, irreversible lesions of the inner ear are used for severe cases of Meniere's syndrome; a vestibular pacemaker might provide a reversible way to alleviate the transient symptoms.

Requirements for such an implant include: 1) Surgical placement of electrodes/actuators must be minimally invasive. 2) Stimulation must be able to recruit/activate a large number of vestibular neurons from all components of the vestibular periphery. 3) Stimulation must minimally recruit/activate cochlear afferent and/or facial nerve afferents. 4) Patients must be able to adapt to the applied stimulation so that responses evoked by the stimulation are less disturbing than the symptoms experienced due to the abnormal peripheral variations.

Such a pacemaker might work by overriding disturbing abnormal variations in the vestibular signals and providing a stationary (i.e., not time varying) signal to the peripheral neurons that would allow the brain to acclimate. Specifically, the same pacemaker signal would be provided whenever the pacemaker was engaged, so a patient might be expected to adapt via the mechanisms of dual-state or context specific adaptation [56,57]. For such a device, it would be crucial that the patient "pre-adapt" (i.e., dual-adapt in a context specific manner) to the neural activity evoked by prosthetic stimulation. Data suggest that such pre-adaptation to electrical stimulation is feasible, [2] since animals repeatedly exposed to on/off stimulation transitions become less and less responsive to the stimulation transition as the number of on/off transitions increases [55].

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[2]While a pacemaker implant seems technologically and physiologically feasible, it would be even better if non-invasive stimulation (e.g., transmagnetic stimulation or a vibrator) could yield a similar influence.

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