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Restoring the 3D Vestibulo-Ocular Reflex via Electrical Stimulation: The Johns Hopkins Multichannel Vestibular Prosthesis Project

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***Abstract*— Bilateral loss of vestibular sensation causes difficulty maintaining stable vision, posture and gait. An implantable prosthesis that partly restores normal activity on branches of the vestibular nerve should improve quality of life for individuals disabled by this disorder. We have developed a head-mounted multichannel vestibular prosthesis that restores sufficient semicircular canal function to partially recreate a normal 3-dimensional angular vestibulo-ocular reflex in animals. Here we describe several parallel lines of investigation directed toward refinement of this approach toward eventual clinical application.**

I. Introduction

The 3-dimensional angular vestibulo-ocular reflex (3D aVOR) helps stabilize gaze during head rotation by moving the eyes opposite the head to keep visual images stable on the retinae. Head rotations are normally sensed by the three semicircular canals (SCCs) of each inner ear, which modulate firing rates on ampullary branches of each vestibular nerve, driving central pathways that cause a reflex eye movement. Complementing the SCCs, the utricle and saccule normally sense gravitoinertial acceleration. While individuals with unilateral loss of vestibular sensation usually compensate well, bilateral loss can disable individuals whose vestibular hair cells are injured by ototoxic medications, infection, Ménière's disease or other insults to the labyrinth. Without input to vestibulo-ocular and vestibulo-spinal reflexes that normally stabilize the eyes and body, affected patients suffer blurred vision during head movement, postural instability, and chronic disequilibrium.

An implantable neuroelectronic vestibular prosthesis that senses head movement and modulates activity on the appropriate ampullary branches of the vestibular nerve could significantly improve quality of life for these otherwise chronically dizzy individuals. Current projects in the Johns Hopkins Vestibular NeuroEngineering Lab are advancing prosthetic vestibular stimulation toward clinical application by (1) creating a multichannel vestibular prosthesis able to restore the 3D aVOR for all directions of head rotation, (2) developing and refining a model of electric current flow in the implanted labyrinth to facilitate optimal design of electrodes and stimulus protocols, (3) developing optimal stimulation paradigms, (4) assessing the central nervous system's capacity to correct for distortion of prosthetically-generated vestibular nerve inputs, (5) assessing hearing outcomes after vestibular implantation, and (6) extending our approach to nonhuman primates with anatomy similar to humans. In what follows, we briefly review the status and trajectory of these efforts.

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II. Multi-Channel Prosthesis Device Development

The first-generation Johns Hopkins Multichannel Vestibular Prosthesis (MVP1) used three single-axis mutually orthogonal, micromachined gyro sensors to emulate transduction of 3D head angular velocity by the three SCCs of the implanted labyrinth [1]. While that device has proved adequate for research applications in which the processor and sensors are fixed to the skull externally and connected to implanted electrodes via a percutaneous connector, the size and power consumption of the MVP1's core circuitry (30 x 34 x 10 mm^3 and ~140 mW) were too large to meet requirements for encapsulation in a package implanted beneath scalp soft tissues (as is typical of existing cochlear implants).

We recently developed and described a second-generation device, the MVP2 [2]. The MVP2's circuitry is thin enough (29 x 29 x 5 mm^3) that it can fit within a hermetic container of thickness similar to housings of some cochlear implants currently in clinical use. The MVP2's power consumption has is ~50% less than the MVP1, which translates to extended battery life and/or reduced battery size. The MVP2 also includes multiple independent current sources allowing multipolar stimulation between arbitrary sets of its 12 electrodes, a tri-axis linear accelerometer and circuitry for measurement of electrically-evoked compound action potentials.

III. Computational Model of Current Flow and Nerve Activation in the Implanted Labyrinth

As has been the case for cochlear implants, suboptimal stimulation selectivity represents an important challenge to developers of a multichannel vestibular prosthesis. Definitively comparing the selectivity of different electrode array designs via *in vivo* experiments has been challenging, due to the large number of uncontrolled factors specific to each given animal (e.g., microanatomy, exact location of implanted electrodes, health of neural tissues in the implanted ear, etc.). To overcome this bottleneck and to achieve a more intuitive understanding of the biophysics of prosthetic vestibular nerve stimulation, we constructed an anatomically precise finite element/neuromorphic model of current flow in the implanted labyrinth [3].

We created model geometry for a standard chinchilla labyrinth via segmentation of microCT and microMRI images acquired with 30-48 mum and 12 mum voxels, respectively. Virtual electrodes can be inserted into this standard 3D anatomic model via co-registration of the standard anatomy with that assembled from a microCT of a given implanted animal. Meshing and finite element analysis for different electrode groupings and stimulus conditions are performed using customized versions of commercially available software packages. The model predicts potential field and current intensities through the labyrinth, then uses extracellular potential field predictions as input to a neuromorphic computational model that incorporates 2,415 model vestibular afferent fibers, each based on the Smith-Goldberg model of vestibular afferent spike initiation, [4] well-established morphophysiologic correlations between afferents terminal location and neural firing parameters, and a computationally efficient but robust model of action potential propagation by myelinated axons.

Testing the model's predictions against the measured 3D axes of eye rotation observed during prosthetic electrical stimulation via different electrode pairs implanted in chinchilla labyrinths, we found that many response features observed empirically were observed as emergent properties of the model, including effects of active and return electrode position, stimulus amplitude and pulse waveform shape on recruitment of targeted fibers and selectivity of stimulation with respect to nontarget fibers. The model's predictions aligned fairly well with the actual axis of eye rotation, with mean misalignment of $20 \pm 9°$. We are currently extending this approach to create similar models of the non-human primate labyrinth and human labyrinth with a goal of helping to optimize the likelihood of successful outcomes in the first human to receive an implant based on the MVP design.

IV. OPTIMIZATION OF STIMULUS WAVEFORMS AND TIMING

While cochlear implant electrode arrays and electronics have been continually improved over the past 30 years, much of the striking improvement in speech recognition outcomes over that time can be attributed to changes in stimulus protocols by which sounds are encoded by cochlear implants on the auditory nerve. While much is known about how primary vestibular nerve afferents normally encode head movement, the optimal stimulus encoding strategy for a multichannel vestibular prosthesis is not yet known.

We investigated effects of varying biphasic current pulse frequency, amplitude, duration, and interphase gap on VOR eye movements of chinchillas [5]. Increasing pulse frequency (which was modulated between 0 and 400 pulses/s to encode head angular velocity) increased response amplitudes while maintaining a relatively constant axis of 3D eye rotation, as might be expected from studies of [6]normal animals. Increasing pulse amplitude (over range 0-325 μA) also increased response amplitudes but incurred large increases in eye-head misalignment due to current spread beyond the target nerve. Shorter pulse durations (range 28- 340 μs) required less charge to elicit a given response amplitude while causing less axis shift than longer durations. Varying interphase gap had no apparent effect over a range of 25-175 μs.

Like cochlear implants, vestibular prostheses employing Pt/Ir metal electrodes must use biphasic current pulses that are charge-balanced over a short time scale, since they would otherwise drive irreversible electrochemical redox reactions at the metal-saline interface that can corrode the electrodes and liberate toxic ionized compounds that injure nearby neural tissue. Whereas normal hair cells can modulate afferent fibers' spike rates both up and down (via effectively analog control of neurotransmitter release), prosthetic biphasic pulses can only excite afferent fiber activity. The target nerve fibers' spontaneous activity therefore constitutes a floor beneath which biphasic current pulses cannot easily down-modulate firing rates. As a result, biphasic prosthetic stimuli delivered via MVPs have generally resulted in asymmetric responses, unless one accepts the added cost and surgical risk associated with bilateral implantation [7].

In an attempt to expand the dynamic range of both excitatory and inhibitory responses without incurring unacceptable increases in misalignment, we have recently examined effects of simultaneously modulating both pulse frequency and pulse current amplitude as functions of head angular velocity [8]. In chinchillas tested with a co-modulation paradigm, a combination of high baseline pulse rate and co-modulation of both current and pulse rate has shown promise for expanding the dynamic range of compensatory eye movements elicited during inhibitory head rotations.

V. MISALIGNMENT REDUCTION VIA ORTHOGONALIZATION OF THE SENSOR INPUT TO EYE MOVEMENT MAP

Despite optimization of electrode array geometry, surgical technique, and stimulus timing, some current spread still occurs and results in misalignment between the true axis of head rotation and that perceived by an implant user (for which the axis of VOR eye movement responses is a reasonable proxy). Since signals on each of the three ampullary nerves innervating the three mutually orthogonal semicircular canals in one labyrinth effectively represent three components of head rotation in a canal-based coordinate frame of reference, it should be possible to correct for much of the misalignment due to distortion of those signals by preprocessing them through multiplication by a "fitting matrix" comprising the inverse of the least-squares best-fit mapping between desired and observed 3D eye rotation response axes sampled over a range of stimuli that span the space of possible head rotations.

We recently found that this approach significantly improved both 3D misalignment and response amplitudes in chinchillas tested using a 3-channel vestibular prosthesis [6]. In the 4 chinchillas examined using this paradigm, responses were sufficiently linear and close to obeying vector superposition that standard linear algebraic orthogonalization techniques could be applied. As measured for 65 different stimulus axes in each of the animals, mean misalignment (i.e., angle between desired and observed 3D

VOR response axes) reduced after implementation of the pre-compensatory 3D coordinate transformation approach.

VI. Central Nervous System Neural Circuits Correct Residual Misalignment over a Week of Prosthesis Use

Even after optimization of electrode designs, surgical techniques, stimulus timing and 3D coding strategy, animals still exhibit some misalignment of VOR responses. However, the neural circuits mediating the VOR are highly adaptable and able to change not only the gain of the VOR but also its axis. For example, cats subjected to passive whole-body pitch rotations (i.e., nose up/down about an interaural axis) while viewing a visual surround moving synchronously but about a yaw axis (i.e., left and right) progressively shift the axis of VOR responses measured in response to whole-body pitch stimuli in darkness, with the eyes moving in yaw at speeds as much as 30% of the stimulus velocity [9].

Residual VOR misalignment due to current spread in animals using a multichannel vestibular prosthesis creates retinal slip signals analogous to those animals with normal labyrinths encounter when exposed to classic optical cross-axis adaptation paradigms like the one described above. Therefore, we hypothesized that chronic use of an MVP under normal viewing conditions would result in improved VOR alignment over time. We also hypothesized that VOR disconjugacy, which likely results from aberrant stimulation of the utricular and/or saccular nerve, would also improve.

To test these hypotheses, we rendered five chinchillas vestibular deficient by treating them with bilateral intratympanic injection of gentamicin and unilaterally implanted them with a head-mounted MVP [10]. Comparison of 3D VOR responses during 2 Hz, 50°/s peak horizontal sinusoidal head rotations in darkness on the first, third, and seventh days of continual MVP use revealed that the component of 3D VOR eye response about the intended axis remained stable (at about 70% of the normal VOR gain) while response components along inappropriate directions progressively receded so that misalignment improved significantly by the end of 1 week of prosthetic stimulation. Similar improvements were observed for probe stimuli about the axes of the other two implanted canals and for every stimulus frequency examined over the range (0.2-5 Hz. The extent of disconjugacy between the two eyes also improved during the same time window.

These observations confirm that the central nervous system rapidly adapts to multichannel prosthetic vestibular stimulation, improving 3D aVOR alignment and disconjugacy within the first week after activation. Considering the extent to which neural circuitry mediating the VOR has been conserved through vertebrate evolution, similar adaptive improvements are likely to occur in other species, including humans.

VII. Effects of Vestibular Prosthesis Electrode Implantation on Hearing

Cochlear implantation carries an acceptable risk of labyrinthine injury (which is probably lower with current-generation devices than the 1 per 28 implanted ears in a cohort studied at Johns Hopkins using earlier models, [11] however, whether the converse is true has yet to be established in humans. Whereas cochlear implant electrode arrays can be inserted near the auditory nerve while remaining completely in the scala tympani, implantation of electrodes near the semicircular canals' cristae probably disrupts the membranous labyrinth. In a previous study of hearing in chinchillas undergoing vestibular electrode implantation, we found that hearing was compromised in 4 of 6 animals [12]; however, differences in size and surgical approach preclude generalization of these data to humans with certainty.

To more accurately estimate the risk of hearing loss a human might face when contemplating vestibular prosthesis implantation, we measured auditory brainstem responses (ABR) and distortion product otoacoustic emissions (DPOAE) in four rhesus monkeys before and after unilateral implantation of vestibular prosthesis electrodes in each of 3 left semicircular canals [13]. Right ears served as controls.

Electrical stimuli comprised charge-balanced biphasic pulses at a baseline rate of 94 pulses/s, with pulse frequency modulated from 48 to 222 pulses/s by head angular velocity. Each of the four monkeys exhibited 3D aVOR responses in approximately the appropriate directions during stimulation of electrodes implanted in each semicircular canal.

ABR hearing thresholds to clicks and tone pips at 1, 2, and 4 kHz increased by 5-10 dB from before implantation to after implantation, and they increased another ~5 dB when measured during presentation of vestibular prosthesis current stimuli. No significant change was seen in right ears.

DPOAE amplitudes decreased (i.e., indicating reduced cochlear function) by 2-14 dB from before to after implantation in implanted ears, and there was a slight but statistically insignificant additional decrease of DPOAE amplitude during prosthetic stimulation.

From these observations, we can conclude that vestibular prosthesis electrode implantation and activation have less deleterious effects on hearing in rhesus monkeys than we would have predicted based on data from rodents. Considering the similarity of human and rhesus anatomy, it is likely that human hearing results will be similar to that observed in rhesus monkeys.

VIII. Extending the Approach toward Clinical Application

Results from the 4 monkeys we have implanted to date demonstrate that prosthetic stimulation of the primate labyrinth evokes aVOR responses with amplitudes and selectivity at least as good as that observed in chinchillas, both at the time of initial activation and after a week of adaptation for chronic use of a head-mounted MVP. [14, 15] An advantageous aspect of transitioning to rhesus monkeys is that they can participate in active head rotation training paradigms (similar to paradigms used on human patients [16]) to enhance VOR performance in the inhibitory direction. Interestingly, even passive participation in a paradigm of unilateral whole-body rotations toward the lesioned side can enhance VOR responses in otherwise normal rhesus monkeys after unilateral implantation [17] so it is likely that a comparable strategy can yield improvements in VOR performance for head rotation away from the implanted ear in animals using a unilateral MVP. Testing this hypothesis is a focus of current efforts.

IX. CONCLUSION

Progress to date strongly suggests that a multichannel vestibular prosthesis designed to take the place of lost semicircular canal function is feasible and will be an effective tool for treatment of patients who are otherwise unable to compensate for profound loss of labyrinthine sensation due to hair cell injury.

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