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Adaptation to Steady-State Electrical Stimulation of the Vestibular System in Humans

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Objectives: Efforts are being made toward the development of a vestibular implant. If such a device is to mimic the physiology of the vestibular system, it must first be capable of restoring a baseline or "rest" activity in the vestibular pathways and then modulating it according to the direction and velocity of head movements. The aim of this study was to assess whether a human subject could adapt to continuous electrical stimulation of the vestibular system, and whether it was possible to elicit artificial smooth oscillatory eye movements via modulation of the stimulation.

Methods: One bilaterally deaf patient with bilateral vestibular loss received a custom-modified Med-El cochlear implant in which one electrode was implanted in the vicinity of the left posterior ampullary nerve. This electrode was activated with biphasic pulse trains of 400-μs phase duration delivered at a repetition rate of 200 pulses per second. The resulting eye movements were recorded with 2-dimensional binocular video-oculography.

Results: Successive "on-off" cycles of continuous electrical stimulation resulted in a progressively shorter duration of the nystagmic response. Once the adapted state was reached upon constant stimulation, amplitude or frequency modulations of electrical stimulation produced smooth oscillatory conjugated eye movements.

Conclusions: Although this is a case study of one patient, the results suggest that humans can adapt to electrical stimulation of the vestibular system without too much discomfort. Once the subject is in the adapted state, the electrical stimulation can be modulated to artificially elicit smooth eye movements. Therefore, the major prerequisites for the feasibility of a vestibular implant for human use are fulfilled.

Key Words: imbalance, prosthesis, rehabilitation, vestibular implant.

INTRODUCTION

For 3 decades, multichannel cochlear implants have been used for the rehabilitation of profoundly deaf patients. Since then, the "artificial ear" has demonstrated its effectiveness in adults and children. Based on a similar concept, a vestibular implant is being developed to help patients with bilateral vestibular loss. Motion sensors attached to an individual's head will capture information of self motion and, after adequate processing, this information will be transmitted to the central nervous system via electrodes placed in the vicinity of the vestibular end organs or their nerve branches. Several experiments on animal models have shown that electrical stimulation of the vestibular nerve can elicit responses that resemble the normally functioning vestibular apparatus.[1,2] More recently, similar observations were made in humans.[3,4] The subjects of these experiments were patients who had unilateral disabling Meniere's disease with recurrent spells of vertigo and with no useful hearing in the affected ear — making them eligible for surgical labyrinthectomy — or patients with profound bilateral hearing loss who were scheduled for cochlear implantation. Surgeries began under local anesthesia, and an electrode was placed in the vicinity of the posterior or lateral ampullary nerve via the external auditory canal. Eye movements were recorded by 2-dimensional video-oculography. As expected, electrical stimulation of the posterior and lateral ampullary nerve provoked, respectively, vertical and horizontal eye movements. However, in these short-term experiments the stimulation periods lasted only a few seconds and were not designed to demonstrate adaptation phenomena to constant electrical stimulation.

Physiologically, the vestibular part of the inner ear generates at rest a baseline neural activity of about 90 action potentials per second. This activity is modulated by head movements and increases or decreases by about 0.5 action potentials per second

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per degree of rotation of the head in one direction or the other.[5] A sudden loss of this rest activity causes important static and dynamic symptoms such as those observed after vestibular neuronitis, labyrinthectomy, or vestibular neurectomy (eg, deviation of the body toward the deafferented side; spontaneous nystagmus, accompanied by nausea and vomiting; impaired vestibulo-ocular reflexes from the side of the lesion). Over time, however, the central nervous system adapts to the new situation and static symptoms subside, although sometimes not totally.[6] If activity recovers spontaneously once the adaptation process to its absence is complete, as observed in some cases of vestibular neuronitis,[7] symptoms identical to those observed in cases of acute loss of activity can be observed, but with deviations in the opposite direction.

A vestibular implant will use electrical stimulation to restore neural activity in a deafferented vestibular system. Thus, if one wants to mimic the physiology of the natural system, the vestibular implant needs to restore baseline "rest" activity *and* its modulations. However, an abrupt restoration of activity might cause unbearable symptoms, similar to those observed after an acute unilateral loss of function. This expected phenomenon has been well documented in animal models.[8] An electrode was placed in the ampulla of the lateral semicircular canal of guinea pigs, and when continuous electrical stimulation was applied for the first time, the animals exhibited a nystagmus that took about 7 days to subside. Then, when stimulation was abruptly stopped, it resulted in the reappearance of a nystagmus in the opposite direction for a few days. Stimulation was then restarted and the nystagmus reappeared, but for a shorter period of time. Finally, after 4 on-off cycles, the nystagmus subsided in only a few minutes.[8] In conclusion, animal experiments show that the vestibular system can adapt to the presence or absence of artificially elicited neural activity and that the time required for adaptation is progressively reduced with sequential repetition of on-off cycles of stimulation.

The occurrence of prolonged periods of major imbalance or dizziness whenever the device is switched on or off would represent a serious limitation to the use of such a device with human subjects. Therefore, the main purpose of this experiment was to study whether a human patient could also adapt progressively to continuous electrical stimulation of the vestibular apparatus, as suggested by animal studies. The main difficulty of the experiment was to proceed with caution to avoid causing periods of uncomfortable dizziness in the patient.

In case the patient could adapt to continuous electrical stimulation of the vestibular apparatus, the second purpose of this study was to attempt amplitude and frequency modulations of the stimulation to see whether it was possible to elicit eye movements of different directions and speeds.

MATERIALS AND METHODS

Patient and Surgery. One male patient (69 years of age) with idiopathic bilateral deafness and vestibular loss who was scheduled for cochlear implantation on the left ear is the subject of this report. The experimental protocol was approved by the human study committee of our institution, and the patient gave his informed consent to participate in the proposed study. This gentleman, a retired lawyer, was eager to collaborate, was willing to give precise information, and had enough free time to participate in lengthy laboratory sessions.

His vestibular deficit was confirmed by the absence of nystagmic responses to a rotating pendular test (360° rotations, frequency of 0.05 Hz) and to a caloric test (10 mL in 20 seconds, at 44°C and 27°C with an automated irrigating device). In addition, the head impulse test was positive in the horizontal and vertical planes when a high-resolution infrared camera was used for the detection of eye saccades.[9]

The patient received a custom left-ear modification of a regular Med-El cochlear implant. The modification consisted of 1 extracochlear electrode for vestibular stimulation and 11 intracochlear electrodes for auditory nerve stimulation. (The standard device has 12 intracochlear electrodes.) When the implantation procedure was completed, the floor of the round window niche was drilled in its most rostral part to approach the canal of the posterior ampullary nerve, in a way similar to that used previously for short-term electrical stimulation.[3] The extracochlear electrode was placed into a small depression drilled near the posterior ampullary nerve, in the depth of the round window niche, and fixed with bone wax. No perioperative measurements of the nystagmic response were attempted, because the patient was under general anesthesia.

Electrical Stimulation. A custom Matlab program was written to control the Med-El Research Interface Board II interface used to drive the cochlear implant during the experiments. This software allowed activation of only the vestibular electrode, shutting off all intracochlear electrodes, and allowed control of the amplitude, rate, pulse width, and envelope of the trains of pulses used for vestibular stimulation. The first trials of electrical stimulation of the vestibular system were performed once the adaptation to

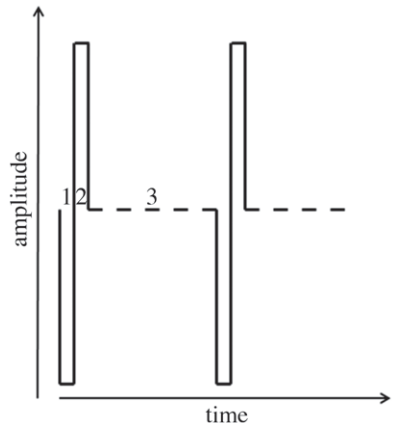

Fig 1. Electrical stimulus. Duration of phases 1 and 2 was set at 400 μs, and that of phase 3 at 4.2 ms. Thus stimulation consisted of trains of 400 μs per phase biphasic pulses, delivered at repetition rate of 200 pulses per second.

the cochlear implant was fully accomplished.

Electrical stimuli consisted of trains of biphasic pulses (400 μs per phase) delivered at a repetition rate of 200 pulses per second (Fig 1). First, to make sure that reliable nystagmic responses could be obtained upon stimulation of the posterior ampullary nerve, we performed some short-duration stimulation attempts. In this case, the envelope of the stimulation was modulated by 7 seconds on, and followed by 7 seconds off, to facilitate the analysis of the response. Then, trials of long-duration electrical stimulation of the vestibular system started. The patient was lying in a dark, soundproof room that was electrically shielded, and was wearing a black plastic face mask containing the videocameras in front of his eyes. Before the experiment was started, eye movements were checked to confirm the absence of spontaneous nystagmus. Then, long-duration electrical stimulation started. The nystagmic response was measured during specific intervals within the course of the session. To limit artifacts due to spontaneous eye movements and thereby allow better observation of the nystagmic responses, before each measurement period we gave the patient a tactile signal via a wristband vibrator prompting him to fix his gaze on a green visual target for 5 seconds. This target was turned off before the beginning of the measurement period, and the patient was instructed to try to keep his gaze in the same position. Between these periods, the patient was authorized to relax and to eventually close his eyes, although eye movements continued to be recorded during the whole session.

Eye Movement Recording. The eye movements were recorded by 2-dimensional binocular videooculography (Difra Instrumentation, Welkenraedt, Belgium) at 50 samples per second. The videocameras, mounted in a black plastic face mask, were maintained in front of the subject's eyes with an elastic cloth band. Right and left, horizontal and vertical eye movements were simultaneously recorded, as well as the envelope of the stimulus, to enable correlation with the eye movements.

Eye Movement Analysis. Recordings of eye movements were analyzed off-line to identify tracings without artifacts that were not altered by voluntary eye movements. To quantify "nystagmic activity," we estimated the slow component velocity using a home-made Matlab program that allowed manual measurement of the slope of each beat.[3,4] The slow component velocity values (expressed in degrees per second) presented in this report were computed as the average (and standard deviation) of 3 consecutive beats. Velocity was considered to be zero when no nystagmic beats, or only one, could be detected in a period of 5 seconds.

RESULTS

First, we checked that stimulation of the extracochlear electrode placed near the posterior ampullary nerve during surgery was capable of activating the vestibular system. The cochlear implant was turned off, and the prosthesis was used as a single-channel vestibular stimulator by means of custom software. The current threshold for vestibular activation was 300 μA. Short-duration stimulation attempts at 400 μA (ie, 2.5 dB above threshold) elicited nystagmic responses of large amplitude (Fig 2). At suprathresh-

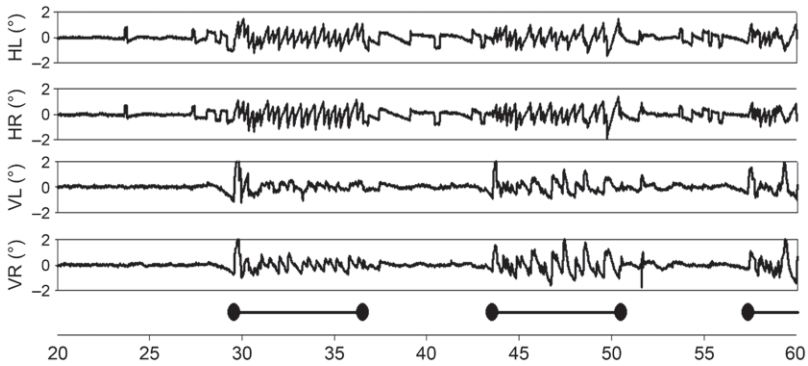

Fig 2. Nystagmic response to short-term electrical stimulation of extracochlear electrode. Electrical stimulation at 400 μA was delivered for 7 seconds and then turned off for 7 seconds. During periods of stimulation, left-beating horizontal nystagmus is observed that is absent when stimulation is turned off. There is also discrete vertical component of response. Black bars between dots represent periods of electrical stimulation. HL — horizontal left; HR — horizontal right; VL — vertical left; VR — vertical right.

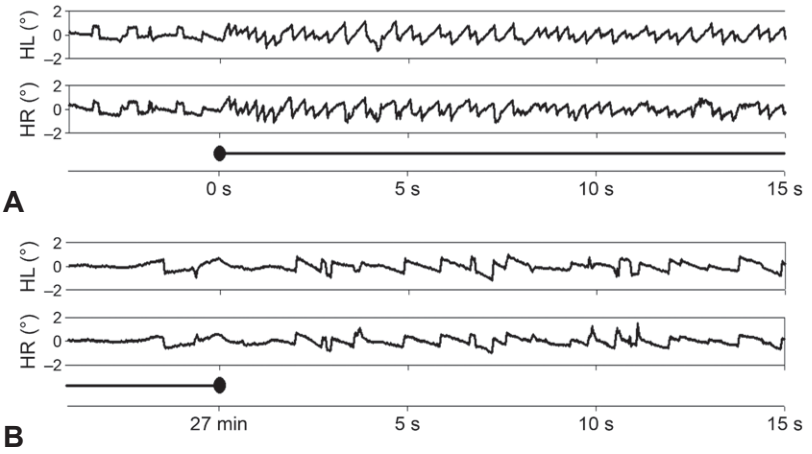

Fig 3. Nystagmic response to first attempt of constant electrical stimulation of vestibular system (stimulation level, 400 μA). Black bars between dots represent periods of electrical stimulation. **A)** Strong nystagmus response is observed at stimulation onset. **B)** After 27 minutes of continuous stimulation, nystagmic beats are (almost) absent when stimulation is on, and turning stimulation off elicits clear nystagmic response in opposite direction.

old stimulation levels, the patient also reported the perception of a high-frequency sound and a sensation of dizziness that increased with the intensity of the stimuli. Although the electrode had been tentatively placed near the posterior ampullary nerve, innervating a vertical canal, we observed nystagmic eye movements with a dominant component in the horizontal plane and a weaker component in the vertical plane. Note that the stimulating electrode was placed visually on the basis of anatomic landmarks and that we could not (in this case) perform perioperative nystagmic response measurements to finely adjust its location. Because the purpose of the experiment was to assess possible adaptation processes to continuous electrical stimulation in humans, we estimated that this was not a major limitation.

The next step was to attempt constant electrical stimulation of the vestibular system. When continuous electrical stimulation at 400 μA was turned on for the first time, a strong nystagmic response was observed at stimulation onset (Fig 3A). The response took several minutes to slow down, and it was only after 27 minutes of continuous stimulation that nystagmic beats were almost absent from the recordings. At this point, electrical stimulation was turned off and nystagmic beats of the opposite direction were observed (Fig 3B). This absence of nystagmic response upon continuous electrical stimulation and its reappearance (in the opposite direction) when stimulation is stopped is (to our knowledge) the first clear demonstration of adaptation to electrical stimulation of the vestibular system in a human being.

We waited for the disappearance of the nystagmic "off response" to the first stimulation attempt, and then we turned the stimulation on again. When stimulation was restarted, a strong nystagmus reappeared, but for a shorter period of time. After adaptation, the stimulation was stopped again, resulting in the reappearance of a nystagmus in the opposite direction and of shorter duration. At the fourth on-off attempt, a strong nystagmic response was still observed at onset, but the response seemed to slow down after only about 10 to 15 seconds (Fig 4A). The nystagmic response totally disappeared 7 minutes after stimulation onset, and again, when stimulation was turned off, nystagmic beats in the opposite direction were observed (Fig 4B).

We decided that such on-off periods of stimulation would be repeated until the duration of the "on" nystagmic response dropped to less than 5 minutes.

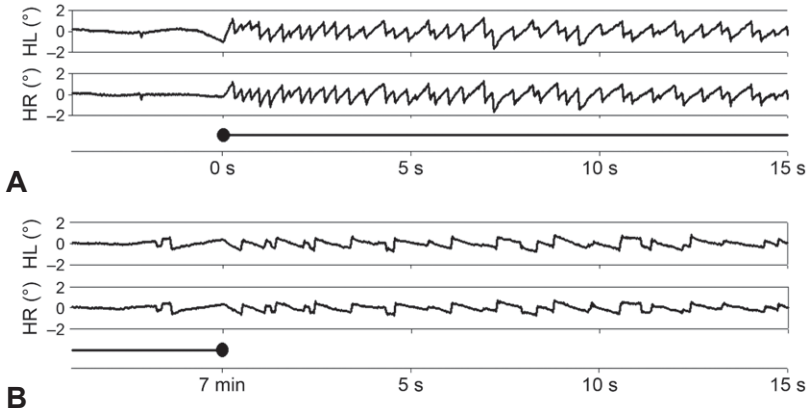

Fig 4. Nystagmic response to fourth attempt of constant electrical stimulation of vestibular system (stimulation level, 400 μA). Black bars between dots represent periods of electrical stimulation. **A)** Again, strong nystagmic response is observed at stimulation onset, which already seems to slow down after only 10 to 15 seconds of uninterrupted stimulation. **B)** After 7 minutes of continuous stimulation, nystagmic beats are (almost) absent when stimulation is on, and turning stimulation off again elicits clear nystagmic response in opposite direction.

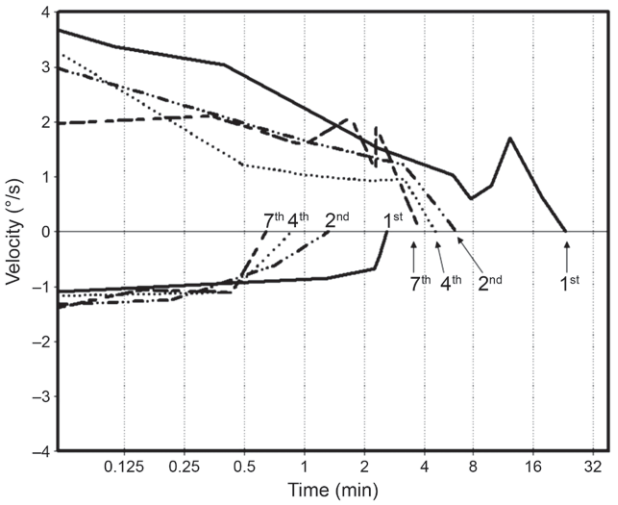

Fig 5. Measurements of slow component velocity during repetition of on-off cycles of continuous electrical stimulation of vestibular system. Cycles 1, 2, 4, and 7 are represented. Positive slow component velocity values describe slow eye movements to right. Nystagmic responses to onset of stimulation are stronger than nystagmic responses to offset of stimulation and have longer duration.

Figure 5 shows how the slow component velocity decreased after onset and after offset of the stimulation up to the seventh on-off cycle that was required to reach our stop-criterion. In spite of substantial variability in slow component velocity measurements, the data show that the nystagmic responses to the onset of stimulation have higher initial slow component velocities and a longer duration than nystagmic responses to the offset of the stimulation.

The final experiment was an attempt to modulate the stimulation signal, once the subject was in an adapted state. Figure 6 shows recordings of eye movement upon sinusoidal amplitude modulation (340 ± 60 μA) at 3 Hz. Clear small oscillatory eye movements were elicited by this type of electrical stimulation of the vestibular system. The oscillatory eye response is about 0.5° peak to peak (ie, well above the noise level) and of approximate sinusoidal shape. Frequency modulation (200 ± 120 pulses per second) of the stimulation signal produced similar eye movements, but of weaker amplitude (not shown). This is the first demonstration in a human being that smooth oscillatory eye movements can be driven by electrical stimulation of the vestibular system.

DISCUSSION

In this study, one patient received a modified cochlear implant with one stimulation electrode placed near the left posterior ampullary nerve. Although this is a case study on one patient that needs to be confirmed with additional subjects, the results obtained demonstrate that it is possible for humans to adapt to steady-state constant electrical stimulation of the vestibular system, and that once a patient is in an adapted state, it is possible to elicit smooth oscillatory eye movements by modulating the amplitude or frequency of the stimulation. To our knowledge, this is the first time that such results have been obtained with a human subject. These results theoretically open the way to the development of vestibular implants for human use.

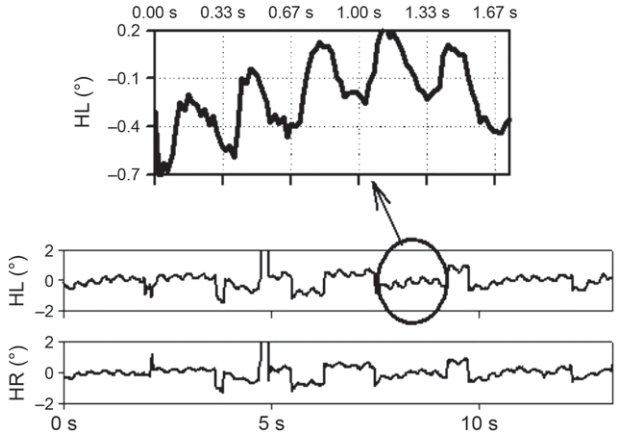

Fig 6. Eye movements elicited by sinusoidal amplitude modulation of electrical stimulation (340 ± 60 μA; modulated at 3 Hz). Once patient was in adapted state, modulation of stimulation elicited small clear and smooth eye movements of approximate sinusoidal shape.

If one wants to develop a vestibular implant, one needs to demonstrate that smooth eye movements can be driven by electrical stimulation of the vestibular apparatus. However, the process of reaching this goal is not straightforward. When electrical stimulation is attempted for the first time on a "fresh" vestibular system, one can observe a very long period of strong, uninterrupted nystagmic beats, during which no real control of eye movements is possible. Such observations were made with guinea pigs, a model in which the first nystagmic response lasted several days and the response finally dropped to a few minutes after several on-off cycles.[8] The same team also observed that the nystagmus decayed more rapidly in the squirrel monkey than in the guinea pig,[10] and even more rapidly in the rhesus monkey (D. Merfeld and R. F. Lewis, personal communication), suggesting that the time to adaptation is species-dependent. Fortunately, in humans, the time required to reach adaptation seems to be reasonably short (a few minutes) after the repetition of a few on-off cycles, and most important, this adaptation was obtained without causing major discomfort to the patient. This result is important because it is only when the adapted state is reached that one can attempt to modulate the output of the vestibular system and therefore hope to

control eye movements.

Merfeld et al[8,11] were the first to demonstrate in animal models (guinea pig and squirrel monkey) that controlled, oscillatory eye movements could be elicited by modulating the electrical stimulation signal, once the response to the constant-rate baseline stimulation had vanished. We made a similar observation in a human subject. The oscillatory response we observed in the patient was small (about 0.5° peak to peak) compared to those observed in animals (greater than 5° peak to peak). Such small eye movements would certainly be insufficient to provide full functional rehabilitation to a subject with bilateral vestibular loss. But one should remember that this is a first case study on one patient and that, of course, care was taken to maximize safety and minimize any possible discomfort. Therefore, all of the experiments reported here were conducted very close to the stimulation threshold. Constant stimulation was attempted at 400 μA, ie, only 2.5 dB above the stimulation threshold. Amplitude modulation was attempted at 340 μA, ie, at 1.09 dB above the threshold, by use of a modulation depth of only 18% in current units. In these conditions, we expected weak responses, and one needs in the future to extend these experiments to higher stimulation levels and to replicate them in more subjects.

Our intention was to place the stimulating electrode in such a way that it would stimulate the posterior ampullary nerve. Therefore, on the basis of the known physiology of the vestibular system,[1] as well as on clinical observations[12,13] and previous short-term attempts at electrical stimulation,[3] we expected to observe vertical eye movements in response to electrical stimulation of the posterior ampullary nerve. This was not the case in this patient, as stimulation elicited eye movements with a dominant horizontal component. In previous short-term experiments, we observed that minute changes in the placement of the stimulating electrode had drastic effects on the oculomotor responses.[3,4] We did not, in this case, perform any kind of perioperative fine-tuning of the electrode position, and it is possible that the electrode was positioned too close to the round window, resulting in a diffusion of the current to the end organs of the vestibule. The patient's perception of a high-frequency sound during the electrical stimulation suggests that the saccule was stimulated. Anatomic,[14] physiological,[15] and clinical studies[16] indicate that the saccule is a vestibular end organ. However, phylogenetically, it develops with the inferior part of the labyrinth, and some saccular fibers send projections into the cochlear nucleus[17] and are acoustically responsive.[18] This unexpected result underlines the necessity to position the electrode more precisely in future studies, by use of local anesthesia and perioperative recordings of the oculomotor responses.

In conclusion, our results extend those observed in animals and demonstrate that a human subject can adapt to electrical stimulation of the vestibular system without too much discomfort. Once adaptation is reached, either amplitude or frequency modulations of the stimulation can be used to artificially elicit smooth eye movements of different speeds and directions. This finding suggests that the major prerequisites for the feasibility of a vestibular implant for human use are fulfilled.

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