Adaptation to steady-state electrical stimulation of the vestibular system in humans

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Abstract
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.

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Adaptation to steady-state electrical stimulation of the vestibular system in the human

Running title: Adaptation to electrical stimulation of the vestibular system

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ABSTRACT

Objectives. Efforts towards the development of a vestibular implant are being made. To mimic the physiology of the vestibular system, such a device must be first capable to restore a baseline or “rest” activity in the vestibular pathways and then to modulate it according to 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 if it was possible to elicit artificially oscillatory smooth eye movements via modulation of the stimulation.

Methods. One bilaterally deaf patient with a bilateral vestibular loss received a custom modified Med-El\textsuperscript{®} cochlear implant in which one electrode was implanted in the vicinity of the posterior ampullary nerve. This electrode was activated with biphasic pulse trains of 400 µs phase duration delivered at a repetition rate of 200 pps. Resulting eye movements were recorded using 2D 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. While this is a case study on one patient, results suggest that humans can adapt to electrical stimulation of the vestibular system without too much discomfort. Once 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 – vestibular, implant, prosthesis, imbalance, rehabilitation
INTRODUCTION

For 3 decades multi-channel 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 suffering from a 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 resembling the normal functioning vestibular apparatus [1, 2]. Recently, similar observations were made in humans [3, 4]. Subjects of these experiments were patients suffering from unilateral disabling Ménière’s disease with recurrent spells of vertigo, with no useful hearing in the affected ear, making them eligible for a surgical labyrinthectomy or patients with a profound bilateral hearing loss programmed for a cochlear implantation. Surgeries started under local anesthesia and an electrode was placed into the vicinity of the posterior or lateral ampullary nerve via the external auditory canal. Eye movements were recorded using two dimensional video-oculography. As expected, electrical stimulation of the posterior and lateral ampullary nerve provoked, respectively, vertical and horizontal eye movements. However, in these acute experiments stimulation periods lasted only a few seconds and were not designed to demonstrate adaptation phenomena to chronic 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 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 a vestibular neuronitis, a labyrinthectomy or a vestibular neurectomy (e.g. deviation of the body towards the deafferented side; spontaneous nystagmus, accompanied by nausea and vomiting; impaired vestibulo-ocular reflexes from the ipsilesional side). 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 installed, as observed in some cases of vestibular neuronitis [7], symptoms identical to those observed in case of acute loss of activity can be observed, however with deviations in the opposite direction.
A vestibular implant will use electrical stimulation to restore neural activity in a de-afferented 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 following an acute unilateral loss of function. This expected phenomenon has been well documented in animal models [8]. An electrode was placed into the ampulla of the lateral semicircular canal of guinea pigs and when continuous electrical stimulation was applied for the first time, 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 four “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 repetitions 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 if 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 of 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.

**Material and Methods**

*Patient and surgery*

One male patient (69 years old) suffering from an idiopathic bilateral deafness and vestibular loss, and programmed to receive a cochlear implant 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 enthusiastic to collaborate, willing to give precise information as well as 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 cc in 20 sec, at 44 and 27° C using an automated irrigating device). In addition, the head impulse test was positive in the horizontal and vertical planes using a high resolution infra red camera for the detection of eye saccades [9].

The patient received a custom modification of a regular Med-El® cochlear implant. The modification consisted to have one extracochlear electrode for vestibular stimulation and 11 intracochlear electrodes for auditory nerve stimulation (while 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 already used previously for acute 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 per-operative measurements of the nystagmic response were attempted since the patient was under general anesthesia.

Electrical stimulation

A custom Matlab® program was written to control the Med-El® Research Interface Board II® (RIBII) interface used to drive the cochlear implant during the experiments. This software allowed to activate only the vestibular electrode, shutting off all intracochlear electrodes, and allowed to control 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 cochlear implant was fully accomplished.

Electrical stimuli consisted of trains of 400 μs/phase biphasic pulses, delivered at a repetition rate of 200 pulses per second (pps) (figure 1). First, to make sure that reliable nystagmic responses could be obtained upon stimulation of the posterior ampullary nerve some acute (“short” duration) stimulation attempts were done. 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 chronic (“long” duration) electrical stimulation of the vestibular system started. The patient was lying in a dark soundproof room electrically shielded. He was wearing a black plastic face mask maintaining the video cameras in front of his eyes. Before
the experiment was started, eye movements were checked to confirm the absence of spontaneous nystagmus. Then chronic electrical stimulation started. The nystagmic response was measured during specific intervals within the course of the session. To limit artefacts due to spontaneous eye movements and thereby to allow better observation of the nystagmic responses, the patient received - before each measurement period - a tactile signal via a wristband vibrator prompting him to fixate 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 movements recording

The eye movements were recorded using 2D binocular video oculography (Difra Instrumentation, Belgium) at 50 samples per second. The video cameras mounted in a black plastic face mask were maintained in front of the subject's eyes using 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 the correlation with the eye movements.

Analysis of eye movements

Recordings of eye movements were analyzed off-line to identify artifact free tracings that were not altered by voluntary eye movements. To quantify “nystagmic activity”, the slow component velocity (SCV) was estimated using a home made Matlab® program that allowed measuring the slope of each beat manually [3, 4]. The slow component velocity values (expressed in °/s) presented in this paper were computed as the average (and standard deviation) of 3 consecutive beats. Velocity was considered to be zero when no or only 1 nystagmic beat could be detected in a period of 5 s.

RESULTS

First, we checked that stimulation of the extracochlear electrode placed near the posterior ampullary nerve during surgery was capable to activate the vestibular system. The cochlear implant was turned off and the prosthesis was used as a single channel vestibular stimulator using custom software. The current threshold for vestibular activation was 300 µA. “Short” duration stimulation attempts at 400 µA (i.e. 2.5 dB above threshold.) elicited nystagmic responses of large amplitude (figure 2). At suprathreshold 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 anatomical landmarks and that we could not (in this case) perform per-operative nystagmic response measurements to finely adjust its location. Since the purpose of the experiment was to assess possible adaptation processes to continuous electrical stimulation in the human, we estimated that this was not a major limitation.

The next step consisted to attempt chronic 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 (figure 3, upper panel). The response took several minutes to slow down and it is 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 reversed direction were observed (figure 3, lower panel). This absence of nystagmic response upon continuous electrical stimulation and its reappearance (in opposite direction) when stimulation is stopped is (to our knowledge) the first clear demonstration of adaptation to electrical stimulation of the vestibular system in the human.

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 is still observed at onset, but the response seems to already slow down after only about 10-15 s (figure 4, upper panel). The nystagmic response totally disappeared already 7 minutes after stimulation onset and again, when stimulation was turned “off” nystagmic beats of reversed direction were observed (figure 4, lower panel).

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. Figure 5 shows how the SCV decreased after onset and after offset of the stimulation up to the seventh “on-off” cycles that were required to reach our stop-criterion. In spite of substantial variability in SCV measurements, the data show that the nystagmic responses to the onset of stimulation have
higher initial SCVs and last for longer duration than nystagmic responses to the offset of the stimulation.

The final experiment was to attempt to modulate the stimulation signal, once the subject was in adapted state. Figure 6 shows eye movement’s recordings upon sinusoidal amplitude modulation (340 µA ± 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 (i.e. well above the noise level) and of approximate sinusoidal shape. Frequency modulation (200 ppc ± 120 ppc) of the stimulation signal produced similar eye movements, but of weaker amplitude (not shown). This is the first demonstration in human 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 posterior ampullary nerve. While this is a case study on one patient that need to be confirmed with additional subjects, the results obtained demonstrate that: (i) it is possible for humans to adapt to steady-state chronic electrical stimulation of the vestibular system, and that (ii) once in adapted state, it is possible to elicit smooth oscillatory eye movements by (amplitude or frequency) modulating the stimulation. To our knowledge it is the first time that such results are obtained on a human subject. These results theoretically open the way to the development of vestibular implants for human use.

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 to reach 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 to finally drop to a few minutes after several ‘on-off” cycles [8]. The same team also observed that the nystagmus in the squirrel monkey decayed more rapidly than in the guinea pig [10] and even more rapidly in the rhesus monkey [Merfeld D and Lewis RF, personal communication], suggesting that the time of adaptation is species dependent. Fortunately in humans, the time 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 first to demonstrate on 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 on a human subject. The oscillatory response we observed on the patient was small, about 0.5° peak to peak, compared to those observed on animals (> 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 maximise safety and minimise any possible discomfort. Therefore all the experiments reported here were conducted very close to stimulation threshold. Chronic stimulation was attempted at 400 µA, i.e. only 2.5 dB above stimulation threshold. Amplitude modulation was attempted at 340 µA, i.e. at 1.09 dB above threshold, using 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 on more subjects.

Our intention was to place the stimulating electrode in such a way that it would stimulate the posterior ampullary nerve. Therefore, based on the known physiology of the vestibular system [1], as well as on clinical observations [12, 13] or previous acute attempts of 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 and stimulation did elicit eye movements with a dominant horizontal component. In previous acute experiments we observed that minute changes in the placement of the stimulating electrode had a drastic effects on the oculomotor responses [3, 4]. We did not, in this case, perform any kind of per-operative 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 endorgans of the vestibule. The fact that the patient perceived a high frequency sound during the electrical stimulation suggests that the saccule was stimulated. Anatomical [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, using local anesthesia and peroperative recordings of the oculomotor responses.

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


FIGURES LEGENDS

Figure 1: Electric stimulus. The 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/phase biphasic pulses, delivered at a repetition rate of 200 pulses per second (pps).

Figure 2: Nystagmic response to acute electrical stimulations of the extracochlear electrode. Electrical stimulation at 400 µA was delivered during 7 sec and then turned off for 7 seconds. During the periods of stimulation, a left beating horizontal nystagmus is observed which is absent when the stimulation is turned off. There is also a discrete vertical component of the response. (HL: horizontal left; HR: horizontal right; VL: vertical left; VR: vertical right).

Figure 3: Nystagmic response to the first attempt of chronic electrical stimulation of the vestibular system. Upper panel) A strong nystagmus response is observed at stimulation onset. Lower panel) After 27 minutes of continuous stimulation, nystagmic beats are (almost) absent when stimulation is “on”, and turning the stimulation “off” elicits a clear nystagmic response of opposite direction. (HL: horizontal left; HR: horizontal right; stimulation level: 400 µA).

Figure 4: Nystagmic response to the fourth attempt of chronic electrical stimulation of the vestibular system. Upper panel) Again a strong nystagmic response is observed at stimulation onset, which already seems to slow down after only 10-15 seconds of uninterrupted stimulation. Lower panel) After 7 minutes of continuous stimulation, nystagmic beats are (almost) absent when stimulation is “on”, and turning the stimulation “off” elicits again a clear nystagmic response of opposite direction. (HL: horizontal left; HR: horizontal right; stimulation level: 400 µA).

Figure 5: Measurements of the SCV during repetition of “on-off” cycles of continuous electrical stimulation of the vestibular system. Cycles 1, 2, 4, and 7 are represented. Positive SCV values describe slow eye movements to the right. The nystagmic responses to the onset of stimulation are stronger and have longer duration than nystagmic responses to the offset of the stimulation.

Figure 6: Eye movements elicited by sinusoidal amplitude modulation of the electrical stimulation (340 µA ± 60 µA; modulated at 3 Hz). Once in adapted state, the modulation of the stimulation elicited small clear and smooth eye movements of approximate sinusoidal shape. (HL: horizontal left; HR: horizontal right).
Figure 1
Figure 5