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Research paper

Longitudinal performance of an implantable vestibular prosthesis

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ABSTRACT

Loss of vestibular function may be treatable with an implantable vestibular prosthesis that stimulates semicircular canal afferents with biphasic pulse trains. Several studies have demonstrated short-term activation of the vestibulo-ocular reflex (VOR) with electrical stimulation. Fewer long-term studies have been restricted to small numbers of animals and stimulation designed to produce adaptive changes in the electrically elicited response. This study is the first large consecutive series of implanted rhesus macaque to be studied longitudinally using brief stimuli designed to limit adaptive changes in response, so that the efficacy of electrical activation can be studied over time, across surgeries, canals and animals. The implantation of a vestibular prosthesis in animals with intact vestibular end organs produces variable responses to electrical stimulation across canals and animals, which change in threshold for electrical activation of eye movements and in elicited slow phase velocities over time. These thresholds are consistently lower, and the slow phase velocities higher, than those obtained in human subjects. The changes do not appear to be correlated with changes in electrode impedance. The variability in response suggests that empirically derived transfer functions may be required to optimize the response of individual canals to a vestibular prosthesis, and that this function may need to be remapped over time.

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1. Introduction

The vestibular system provides balance and orientation information that is critical for daily activity. The primary source of vestibular sensory information is in the inner ear, which contains five sensory end organs. In these organs, three semicircular canals (SCC) and two otolith organs, hair cells transduce rotation and/or linear accelerations of the head into neural activity. When these cells die, or experience transient changes in functional integrity due to conditions such as Meniere's disease, patients may experience a range of symptoms, including disequilibrium, oscillopsia, or vertigo. Furthermore, mammalian hair cells show only a small amount of spontaneous regeneration (Forge et al., 1993, 1998; Warchol et al., 1993; Rubel et al., 1995; Walsh et al., 2000; Oesterle et al., 2013; Kawamoto et al., 2009; Wang et al., 2010; Lin et al., 2011; Golub et al., 2012). For this reason, if there is a permanent loss of hair cell function, there is also a permanent loss of natural sensory input to the vestibular system. One strategy for treating hair cell loss is to bypass the missing receptor cells using direct electrical stimulation of the nerves innervating each end organ (Golub et al., 2010, 2013; Fridman and Della Santina, 2012; Merfeld and Lewis, 2012). This strategy has already achieved remarkable success for treating hair cell loss in another comparable sensory modality, hearing, with cochlear implants. For the vestibular system, an electrical stimulator could be used to replace the spontaneous activity of the missing end organ, or using a gyroscope or accelerometer to replace the dynamic modulation of vestibular input that results from head motion.

Much research effort by multiple groups has been spent on the development of an implantable single and multichannel vestibular neurostimulator over the past two decades (Fridman and Della Santina, 2012; Chiang et al., 2011; Cohen et al., 1964; Cohen and Suzuki, 1963; Bierer et al., 2012; Dai et al., 2011a,b,c; 2013; Davidovics et al., 2011, 2013; Della Santina et al., 2005, 2007;

List of abbreviations: SCC, semicircular canal; VOR, vestibulo-ocular reflex; SPV, slow-phase velocity; PPS, pulses per second

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Fridman et al., 2010; Gong and Merfeld, 2000, 2002; Gong et al., 2008; Lewis et al., 2001, 2002, 2010, 2013; Merfeld et al., 2006, 2007; Nie et al., 2011, 2013; Phillips et al., 2011, 2012; Rubinstein et al., 2012; Sun et al., 2011; Suzuki and Cohen, 1964; Thompson et al., 2012; Valentin et al., 2013; Phillips et al., 2013; Golub et al., 2013; Perez Fornos et al., 2014; Guyot et al., 2011a, b; 2012; Wall et al., 2007; van de Berg et al., 2012). The studies have described the efficacy of these devices in driving vestibulo-ocular reflex (VOR) mediated eye movements with electrical stimulation in a range of species, including humans. Stimulation from such a neurostimulator produces robust vestibular nystagmus in association with electrical stimulation trains of brief biphasic pulses, which is comparable to eye movements produced naturally through the VOR (Thompson et al., 2012; Phillips et al., 2011; Davidovics et al., 2013). In addition to VOR, electrical stimulation has been shown to drive other modalities of the vestibular system, including producing postural and head movements (Mitchell et al., 2013; Phillips et al., 2013) and perceptual responses (Lewis et al., 2013). Therefore, initial results in animal models and human subjects have been encouraging.

However, there are several limitations to the current literature. First, the majority of the papers that have been published have actually been reports based on a relatively small number of successful implantations. Indeed, many publications report results from multiple studies of the same animals over a relatively short period. Second, the majority of the papers have reported on only the initial findings in animals, which are quite promising when an implantation is successful. The long term efficacy of stimulation has only been studied in a few papers, and in these papers the slow phase eye velocities elicited during stimulation were either relatively low, or the duration of the study was relatively short (Merfeld et al., 2007; Lewis et al., 2010; Thompson et al., 2013; Dai et al., 2013). Also, the eye movements were often elicited in a natural rotational context, frequently including intermittent eyes open rotation, where residual vestibular function and adaptation play an important role in modifying the observed responses. Two of these studies were, in fact, specifically designed to elicit an increasingly accurate compensatory VOR response with electrical stimulation or to study adaptive changes in electrically elicited eye movements.

For these reasons, in this paper we describe the first full series of consecutive implantations of a large number of rhesus monkeys with a vestibular implant using a transient stimulation paradigm that was specifically constructed to reduce adaptive changes in the VOR response. This allowed us to evaluate the long-term efficacy of electrical stimulation with a vestibular prosthesis. We evaluated not only the slow phase velocity of the elicited eye movements across different currents and frequencies of stimulation, but also the impedance of the electrodes, over up to 644 days after implantation with the device. These results allow us to directly compare long term intermittent electrical stimulation elicited eye movement behavior across canals in single rhesus monkeys, across monkeys in the consecutive series, and with recently published data from human subjects using identical stimulation parameters, paradigms and devices. This comparison allows us to evaluate the rhesus monkey as a model system for the development of treatments using long-term electrical vestibular stimulation in human patients.

2. Methods

All experiments were performed in accordance with the recommendations of the National Research Council (1997, 2003) and the Society for Neuroscience, and exceeded the requirements recommended by the Institute of Laboratory Animal Resource and the Association for Assessment and Accreditation of Laboratory Animal Care International. All procedures were approved by the Institutional Animal Care and Use Committee of the University of Washington.

2.1. Implantation

Six rhesus macaque monkeys were implanted unilaterally with a vestibular neurostimulator in the right ear (Fig. 1A). All animals had normal vestibular function prior to implantation. Detailed descriptions of the implanted device used in this study (Nie et al., 2013), as well as the surgical implantation approach (Rubinstein et al., 2012), have been published previously. Briefly, the UW/Cochlear prosthesis was based on a Nucleus Freedom cochlear implant (Cochlear, Ltd., Sydney). The device contained a chronically implantable neurostimulator, which communicated with an external processor via an RF link. The neurostimulator includes a trifurcated lead. Located on the distal ends of each lead is a 2.5 mm electrode array with three stimulation sites (250 μm x 120 μm). During a sterile surgical implantation, a fenestration was made in the bony labyrinth adjacent to the ampulla of each semicircular canal, through which the tip of each lead was inserted. The electrode tip was small enough to allow for fluid flow within the membranous labyrinth. As such, the device was designed to preserve the sensitivity of the implanted end organ to natural rotational stimulation. Vestibular evoked compound action potentials and electrode impedance measurements were utilized during surgery to optimize the placement of the stimulating electrode within the canal (Nie et al., 2011). Finally, a remote ground ball electrode was placed under the temporalis muscle. If, following

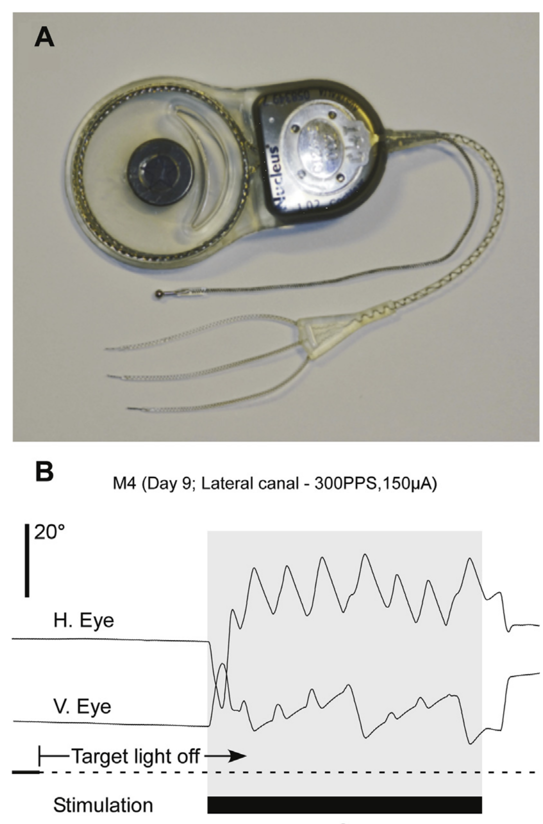

Fig. 1. The implantable portion of a multichannel vestibular neurostimulator based on a modified cochlear implant with a trifurcated lead for implantation into the three semicircular canals (A) and electrically evoked eye movement position traces (B). Eye position is plotted such that a negative value indicates a leftward eye movement for horizontal (H. Eye) and a downward eye movement for vertical (V. Eye) eye position traces.