The Vestibular Implant:

Feasibility in humans

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Contents

Chapter 1

Introduction and outline of the thesis

Introduction

Defining the problem and aim of this thesis

Bilateral vestibulopathy (BV) is a condition in which both vestibular organs do not sufficiently provide vestibular information to the brain due to a bilateral reduced or absent function of the vestibular organs, the vestibular nerves, or a combination of both (Agrawal et al., 2013; Hain et al., 2013; Zingler et al., 2008). It is a chronic condition with symptoms varying from osillopsia (the illusory movement of the visual environment) and imbalance, to cognitive deficits and autonomic symptoms (Jen, 2009; Kim et al., 2011; van de Berg et al., 2014; Zingler et al., 2009). BV is a major problem that substantially degrades quality of life and imposes a socioeconomic burden on society (Sun et al., 2014). Its prevalence of 28 per 100.000 adults is probably severely underestimated (Ward et al. 2013). Unfortunately, at this moment, treatment options are limited and with low yield (Porciuncula et al., 2012). Therefore, a vestibular implant has been postulated as a new therapeutic option that could potentially restore vestibular function (Fridman et al., 2010; Golub et al., 2014; Lewis et al., 2013; Wall et al., 2007). However, at the onset of this thesis, chronic vestibular implantation had only been investigated in animal studies. It was necessary to extend feasibility trials to humans, to be able to assess the unknown influence of other factors (e.g. different etiologies) and to assess the functional benefits of a vestibular implant. The aim of this thesis is therefore to investigate the feasibility of the vestibular implant as a clinically useful device in humans. A vestibular implant could potentially reduce the severe complaints and ultimately improve quality of life of patients suffering from BV.

Anatomy of the vestibular system

The vestibular apparatus is part of the labyrinth, which is located in the petrous portion of both temporal bones. This bony structure is filled with perilymph and contains an endolymph-filled membranous structure inside. It has five sensory organs: three semicircular canals which measure angular acceleration (each in a different plane) and two otolith organs which measure mainly linear acceleration and position with respect to gravity (Kingma et al., 2005; Lysakowski, 2005).

There is an anterior (or superior), lateral (or horizontal) and posterior semicircular canal. They have a widened part, which is called the ampulla. In this ampulla, haircells all have the same direction of polarization. This means that with an angular motion, afferent fibers of a canal will either be excited or inhibited (Kingma et al., 2005; Gong & Merfeld, 2002).

There are two otolith organs: the utriculus for measuring horizontal acceleration and the sacculus that measures vertical acceleration and position with respect to gravity.

Their sensory part is the macula, where haircells form groups that are sensitive for motion in different directions. During a linear motion, some of the otolith nerve fibers will be excited, while others are inhibited (Kingma et al., 2005; Wall et al., 2002).
There are two types of haircells: type I and type II. They mainly differ in structure and region. Type I haircells have a calyx, type II cells don't. Type I haircells are located more in the central zone of the sensory epithelium, instead of the periphery (Lysakowski, 2005). The haircells are synaptically connected with afferent nerve fibers. Nerves from the lateral and anterior ampulla form the ampullary nerve, which fuses with the utricular nerve to form the utriculoampullary nerve. Finally, a branch to the sacculus (Voit's anastomosis) joins to form the superior vestibulary nerve. Nerves from the posterior ampulla (the posterior ampullary nerve or singular nerve) fuse with the saccular nerve to form the inferior vestibulary nerve (Della Santina et al., 2007; Feigl et al., 2009; Kudo & Nomura, 1996).
The cell bodies of the inferior and vestibular nerve are located in the superior and inferior vestibular ganglion respectively, which are located at the bottom of the internal auditory meatus. Together, they form Scarpa's ganglion. In this ganglion, the spatial orientation of the five vestibular receptors is preserved (Sando et al., 1972).
From Scarpa's ganglion, nerve fibers travel to the vestibular nuclei in the brainstem, where they go into different directions: to the cerebellum (and from there to more centrally), to the spinal cord (for vestibulo-colic and vestibulo-spinal reflexes) and to other brainstem nuclei to initiate vestibular-mediated reflexes. These nuclei include the oculomotor nuclei for the vestibulo-ocular-reflex (VOR) (Kingma et al., 2005).

Physiology of the vestibular system

The vestibular system measures position of the head with respect to gravity within 0.5^{o} and acceleration of the head faster than $1^{o}/s^{2}$ (rotations) and $2cm/s^{2}$ (translations) (Kingma et al., 2005; Wall et al., 2002; Benson et al., 1989; Montandon, 1954; Carey & Della Santina, 2005). Together with other sensory systems such as vision, hearing and propriocepsis, it is involved in three major tasks: spatial orientation, gaze stabilization and facilitating balance, posture and gait. For spatial orientation, visual input is the most dominant clue, except that it needs the other ones to discriminate between movement of the head and movement of the environment. The vestibular system is very important for gaze stabilization since it facilitates the VOR, which controls the eye position in space. When moving the head to one side, the eyes are in a reflexive motion directed to the contralateral side, to stabilize images on the retina (Kingma et al., 2005; Della Santina et al, 2007; Carey & Della Santina, 2005). The VOR is a three-neuron reflex and has a very short latency of 7-9ms, in contrary to the 100ms that is inherent to visual processing. This reflex is the predominant mechanism with head movements faster than 1-3Hz. When the head is moved more slowly, vision based oculomotor systems like smooth pursuit (reflexive

following of images on the retinal fovea) and optokinetic nystagmus (eye rotation in response to optic flow of the visual scene) prevail. Because these are multi-synaptic reflexes, latency is long (100ms) and they therefore fail as gaze-stabilizer when head movements are >1Hz and >50^{o}/sec (Della Santina et al., 2007; Carey & Della Santina, 2005).

Vestibulo-spinal reflexes facilitate stabilization of the head and body. Their latency varies between 25-250ms. There are two major mechanisms. Firstly, the semicircular canals induce the vestibulo-collic reflex, which facilitates the correct position of the head during movement. Secondly, the otolith organs induce other vestibulo-spinal reflexes by which the correct posture is achieved. These reflexes are controlled by higher regions of the central nervous system, in order to create a harmony between posture and position of the head related to execution of motoric tasks (Kingma et al., 2005).

There are two types of vestibular afferent nerves: regular and irregular. They have different properties. Most important is their difference in sensitivity (change in spike rate for a change in stimulus). Regular afferents have a, on average, 6 times lower sensitivity to electrical stimulation than irregular ones (Goldberg et al., 1984). This means that they require higher current levels and charge delivery. However, since most of the vestibular afferents are regular ones, both types need to be stimulated in order to achieve a desired response.

The baseline firing rate of vestibular afferents in mammals average 50-200 spikes/sec (Carey & Della Santina, 2005). During rotation to the ipsilateral site, the firing rate is increased above the baseline. When rotated to the contralateral side, the rate is decreased below baseline. This range of firing rate varies from 0 to 300-400 spikes/sec (Gong & Merfeld, 2000; Shkel & Zeng, 2006).

The canals from the two labyrinths function complementary. For example, when the head is turned to the left, the firing rate for neurons of the left lateral canal will increase while that for the right decreases (as mentioned above). These neural responses are subtracted from each other in order to create a final response. This is effect is referred to as “push-pull” (Gong & Merfeld, 2002; Della Santina et al. 2007). The canals form three orthogonal pairs which work complementary: the left and right lateral, the left anterior and right posterior, the right anterior and left posterior (Della Santina et al. 2007).

The vestibular implant

The goal of the current vestibular implant design is to (partially) restore vestibular function when the vestibular organs have failed. This implies that the implant should be able to (partially) take over the function of the vestibular organs. In order to do so, motion has to be detected and processed into information that could be transferred to the vestibular nerves. Therefore, the vestibular implant consists of different

components: 1. Sensors that detect motion (gyroscopes and accelerometers); 2. A processor that converts the motion signals into electrical pulses; 3. Electrodes that convey the electrical pulses to the vestibular nerves (van de Berg et al., 2011). In the first trial, a modified cochlear implant (MED-EL, Innsbruck, Austria) was used to show the feasibility of the vestibular implant: motion sensors were added to the microphone and next to the cochlear array, extracochlear arrays were added (using some of the cochlear electrodes) which could be implanted in the vicinity of the branches of the vestibular nerve (Figure 1.1) (Perez Fornos et al., 2014; Guyot et al., 2016). This resulted in a vestibulocochlear implant that should be able to restore hearing as well as balance. In this first prototype, only the ampullary nerves were stimulated: the superior ampullary nerve (SAN), lateral ampullary nerve (LAN) and posterior ampullary nerve (PAN). The otolith organs were not yet stimulated. Different surgical strategies were applied in the group of VI-recipients. Firstly, an extralabyrinthine approach was used which comprised surgical approaches placing the electrodes directly to the nerves, without opening the labyrinth (Figure 1.1) (Wall et al., 2007; Guyot et al., 2011). Secondly, an intralabyrinthine approach was used in which the labyrinth was opened and the electrodes were brought in contact with the sensory epithelium of the ampullae (Figure 1.1). Since both surgical techniques still carry the risk of inducing hearing loss, the inclusion criteria for implantation included pre-operative deafness in the implanted ear (van de Berg et al., 2012).

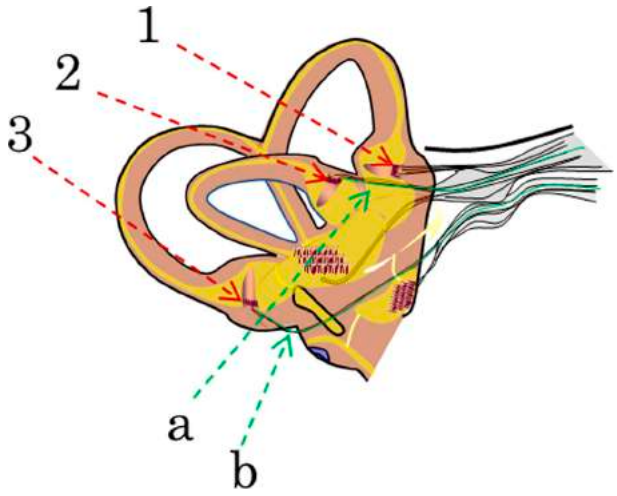

Figure 1.1 The human vestibular apparatus (drawing by J-P Guyot). The extralabyrinthine approach consists of placing the electrodes in contact with the nerves emerging from the ampullae of the lateral and superior semicircular canal (a) and posterior semicircular canal (b). For the intralabyrinthine approach, the electrodes are implanted inside the semicircular canals, in the vicinity of the superior (1), lateral (2) and posterior (3) ampullary nerves.

In order to stimulate the vestibular system, an optimal stimulus paradigm is still under development. The basic stimulus paradigm in this trial consisted of a cathodic-first, charge-balanced, biphasic, rectangular pulse, which was modulated in amplitude around a baseline. The amount of modulation depended on the dynamic range. This dynamic range was determined for each electrode by increasing the stimulus until it was perceived (lower threshold), and increasing it further until the upper threshold was reached. The upper threshold was defined by either the occurrence of facial nerve stimulation due to current spread, or the subject not being comfortable anymore with the strength of the perceived sensations: the upper comfortable level (UCL) (Perez Fornos et al., 2014). Baseline was set at approximately the middle of the dynamic range. This resulted in similar ranges for excitatory and inhibitory modulation. Normally, unilateral stimulation has an inherent asymmetry in response due to the baseline being far below the middle of the range, resulting in a stronger excitatory than inhibitory response. However by using a supranormal baseline, the effects on asymmetry due to unilateral stimulation could potentially be reduced (Gong & Merfeld, 2002; Della Santina et al. 2007; Lewis et al., 2002; 2010; Merfeld et al., 2006). The effects of the vestibular implant were mainly evaluated by investigating the characteristics of the VOR. Characteristics involved e.g. gain (peak eye velocity divided by peak head velocity), alignment (axis of eye movement with respect to the horizontal axis) and asymmetry (ratio between the excitatory and the inhibitory part of the stimulus). Eventually, this trial also included evaluation of functional benefits by investigating the dynamic visual acuity (DVA).

Stepwise approach to evaluate the feasibility of a vestibular implant

Chapter two: Bilateral Vestibular Hypofunction: Challenges in establishing the diagnosis in adults

The challenges when diagnosing BV in adults were reviewed and discussed to demonstrate the lack of diagnostic standards for BV and the urgent need for standardization at that time. Uniform criteria will eventually improve patient selection for implantation.

Chapter three: The vestibular implant: Quo vadis?

All available studies about the VI were reviewed and discussed to show the challenges involved in VI research and to illustrate that a basic VI in humans seemed feasible in the near future, at that time.

Chapter four: The modified ampullar approach for vestibular implant surgery: Feasibility and its first application in a human with a long-term vestibular loss

The pros and cons of the intralabyrinthine and extralabyrinthine surgical approaches for VI implantation were discussed. The intralabyrinthine approach was tested for the first time in a human with a long-term bilateral vestibular areflexia, in order to explore the feasibility of this approach in humans.

Chapter five: Vestibular implants: 8 Years of experience with electrical stimulation of the vestibular nerve in 11 patients with bilateral vestibular loss

VI characteristics of the first 11 patients implanted with a VI were examined to evaluate the efficacy and safety of the VI prototype.

Chapter six: Frequency-dependency of the electrically evoked vestibulo-ocular reflex in humans

The frequency-dependency of the electrically evoked VOR in 7 patients implanted with a VI was compared to the frequency-dependency of the “natural” VOR obtained in a group of seven age-matched volunteers, to explore whether complex stimulus processing strategies that consider frequency-dependent characteristics might be necessary.

Chapter seven: Vestibular implant input interacts with residual natural function

The interaction between vestibular implant input and residual “natural” input was investigated during the acute phase of stimulation. For this, 5 electrodes in 4 patients with a VI were tested. Understanding this interaction might be of benefit during the initial phase of “fitting” of the VI, and for investigation of the future possibility of counteracting vestibular asymmetry during disabling attacks of vertigo.

Chapter eight: Restoring visual acuity in dynamic conditions with a vestibular implant

The dynamic visual acuity while walking was tested in 6 patients fitted with a VI, to investigate whether a functional benefit could be obtained by using the VI.

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Chapter 2

Bilateral Vestibular Hypofunction: Challenges in establishing the diagnosis in adults

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ORL J Otorhinolaryngol Relat Spec. 2015;77(4):197-218

Abstract

Bilateral vestibular hypofunction (BVH) probably represents a heterogeneous disorder with different types of clinical pictures, with and without vertigo. In spite of increasingly sophisticated electrophysiological testing, still many challenges are met when establishing a diagnosis of BVH. Here, we review the main challenges, which are a reflection of its often difficult clinical presentation and the lack of diagnostic standards regarding the implementation and interpretation of vestibular tests. These challenges show that there is an urgent need for standardization. The resulting decisions should be used for the development of uniform diagnostic criteria for BVH, which are, at present, not yet available.

Introduction

Vestibular disorders and diagnosis

Vertigo and dizziness are frequently encountered in outpatient practices, affecting up to 36% of the population (Gopinath et al. 2009). However, even the more common vestibular diagnoses such as benign paroxysmal positional vertigo and vestibular migraine are often under- or misdiagnosed (Geser & Straumann 2012).[2] The difficulty of making the right vestibular diagnosis is reflected in the fact that in some populations, more than one third of the patients with a vestibular disease consult more than one physician (Grill et al., 2014) - in some cases up to more than fifteen (Roberts et al. 2013). It is necessary to have a correct diagnosis, since an incorrect diagnosis of a vestibular disease may eventually result in increased health care utilization and chronicity (Grill et al., 2014).
Bilateral vestibular hypofunction (BVH), currently a less common vestibular diagnosis, is also often under- or misdiagnosed (Vibert et al., 1995; Ward et al., 2013). It poses a diagnostic challenge (Kim et al., 2011). Even in the literature, reported prevalence rates vary from 28 to 81 per 100,000 people (Ward et al., 2013; Guinand et al., 2012a), and the percentages of BVH found in patients who underwent electronystagmography vary from 0.6 to 13.6% (Vibert et al., 1995; Porciuncula et al. 2012; McGath et al., 1989; Fujimoto et al., 2012). This article will discuss the challenges and pitfalls a physician meets when diagnosing BVH.

What Is BVH?

BVH is characterized by reduced or absent function of both vestibular organs, the vestibular nerves or a combination of both (Hain et al., 2013), which results in impairment or loss of the major functions of the vestibular organs: gaze stabilization, maintaining balance, postural control and spatial orientation (Kingma et al., 2005). The best-known symptoms are oscillopsia (blurred vision), chronic disequilibrium, postural instability and impaired spatial orientation (van de Berg et al., 2011; Della Santina et al., 2007; Lacour et al., 2009). Dandy was the first to describe BVH in 1941, after performing a bilateral vestibular neurectomy for Menière's disease. Nowadays, this symptom complex is known to have many causes, and BVH probably represents a functionally heterogeneous disorder with different combined or isolated deficits of the semicircular canals and/or otolith organs (Zingler et al., 2008). Most of the etiologies described are presented in Table 2.1. However, its etiology still remains unclear in approximately 50% of all cases (Kim et al., 2011; Jen 2009).

Table 2.1 Etiologies of BVH.*

Idiopathic (51%)	
Toxic/metabolic (13–21%)	Antibiotics, furosemide, cisplatin, aspirin, alcohol, vitamin B12 deficiency, folate deficiency, hypothyroidism , styrene poisoning, combination of nonsteroidal anti-inflammatory drug plus penicillin
Infectious (3.8–12%)	Meningitis/encephalitis/cerebellitis, lues, Behçet's disease, *Borrelia* infection, herpes simplex virus infection, bilateral neuritis
Autoimmune (10%)	Cogan's syndrome, Susac's syndrome, sarcoidosis, Wegener's granulomatosis, Sjögren's syndrome, colitis, celiac disease, polyarteritis nodosa, antiphospholipid syndrome, other systemic diseases
Neurodegenerative	CANVAS, superficial siderosis, episodic ataxia, multiple system atrophy, polyneuropathy, SCA3, SCA6, hereditary sensory and autonomic neuropathy type IV, other ataxias
Genetic	DFNA-9, DFNA-11, DFNA-15, DFNB-4, mutation chromosome 5q, 6q, 11q, 22q
Vascular	Supra- or infratentorial lesions, vertebrobasilar dolichoectasia
Neoplastic	Bilateral vestibular schwannoma, neurofibromatosis type 2, metastasis of lymphoma, malignant tumor
Trauma	Head trauma, iatrogenic (e.g. bilateral cochlear implantation)
Other ear pathology	Bilateral Menière's disease, otosclerosis, bilateral labyrinthitis, cholesteatoma
Congenital/syndromal	CHARGE, Usher, Turner, enlarged vestibular aqueduct, Alport syndrome
Other	Presbyvertigo, vestibular atelectasis, etc.

SCA = Spinocerebellar ataxia; CHARGE = coloboma, heart defects, atresia of the choanae, retardation of growth and development, genital and urinary abnormalities, ear abnormalities and/or hearing loss.

* Hain et al., 2013; Zingler et al., 2008a, 2008b, 2009; Jen 2009; Rinne et al., 1998; Szmulewicz et al, 2011; Weekamp et al., 2003; Kale et al., 2003; Black et al., 2004;, Lemaire et al., 2003; Jen et al., 2004; Gazquez et al., 2011; Watanabe et al., 1997; Guyot et al., 2001; Murofushi et al, 1997; Nuti et al., 1996; Tamagawa et al., 2002; Bischoff et al., 2006; Wenzel et al., 2014; Greco et al., 2014; Hirvonen & Aalto 2013; Hertel et al., 2013; Requena et al., 2014; Ahmed et al., 2012; Fischer et al., 2014; Baxter & Agrawal 2014; Viana et al. 2013.

Challenges in establishing a diagnosis of BVH

Challenge one: Recognizing the impact of BVH

The impact of BVH on quality of life is still controversial, and the handicap is not always recognized (Guinand et al., 2012a; Zingler et al., 2008; Grunfeld et al., 2000). Even the recent literature still reports on patients who underwent a bilateral vestibular neurectomy (Sun et al., 2014). Although effects on different aspects of life are not as yet completely well defined, increasing evidence shows that BVH affects different aspects of life significantly (Ward et al., 2013, Guinand et al., 2012a, Sun et al., 2014). Dizziness handicap inventory scores indicate that 44% of patients perceive the handicap due to BVH to be severe, while 41% view it as a moderate handicap (Guinand et al., 2012a). Quality of life is not only decreased with regard to vision or

ambulation dimensions, but also concerning functional and emotional dimensions (Sun et al., 2014). Therefore, physical activity, social functioning and vitality decrease (Ward et al., 2013; Guinand et al., 2012a); 55% of BVH patients miss school or work, and 75% are on disability. Besides an increased fear of falling, there is a 31-fold increased risk of falling (Ward BK, et al., 2013). It can be concluded that BVH not only substantially degrades quality of life but also imposes a socioeconomic burden on society (Sun et al., 2014).

If BVH occurs already early in life (e.g. via meningitis in childhood), it can impair the development of visual and somatosensory effectiveness in postural control due to its multimodal sensory interdependence (Rine & Wiener-Vacher 2013). Bilateral deficits in young children have been shown to lead to a delayed development of walking and postural control, delayed oculomotor control and learning difficulties (Rine & Wiener-Vacher 2013; Wiener-Vacher et al., 2012). Recognizing the impact of BVH emphasizes the need to make an accurate diagnosis and helps to understand the other symptoms associated with BVH (Rine & Wiener-Vacher 2013; Guerraz et al., 2001).

Challenge two: Recognizing the symptoms of BVH

Unlike when losing other sensory modalities such as vision, hearing or smell, symptoms of vestibular disorders are not always recognized by patients and physicians. Descriptions of the quality or type of dizziness have been found to be unclear, inconsistent and unreliable (Newman-Toker et al., 2007). For BVH, this may be due to several reasons.

Firstly, due to the heterogeneous origin of the disease, four different types of clinical pictures have been described: (1) recurrent vertigo and BVH – patients have episodes of vertigo occurring over several years, followed by symptoms of vestibular hypofunction; (2) slowly progressive BVH – patients have a gradual onset of symptoms of vestibular hypofunction, without any episodes of vertigo; (3) rapidly progressive BVH – patients have a sudden onset or a rapid progression of symptoms of vestibular hypofunction, with or without episodes of vertigo (this can be seen e.g. in autoimmune disorders or as an effect of vestibulotoxic medication), and (4) BVH with other neurological deficits, such as cerebellar ataxia and neuropathy – symptoms of BVH are combined with neurological symptoms. These four types show a broad variety of clinical pictures, and it is clear that vertigo does not have to be a symptom of BVH. Also, hearing loss or tinnitus does not regularly accompany BVH. While patients with associated episodes of vertigo or hearing loss might seek medical attention early in their clinical course, other patients may have subtle and poorly recognized symptoms, leading to a delay in diagnosis (Hain et al., 2013; Jen 2009; Hirvonen & Aalto 2013; Ahmed et al., 2012; Fischer et al., 2014).

Secondly, patients are often not aware that they have vestibular organs, until they start to fail. Vestibular controlled gaze stabilization and postural adjustments are

reflexes (vestibulo-ocular, vestibulocollic and vestibulospinal) and go unnoticed. This is why vestibular sensation is not included in the five vernacular senses (hearing, vision, smell, taste and touch) (Carey & Della Santina 2005). Also, when the vestibular organs fail, nonlabyrinthine inputs to the vestibular nuclei are enhanced, partially filling the gap left by the failing residual labyrinthine input, with sensory substitution (McCall & Yates 2011). Accurately defining the symptoms of vestibular failure can become more difficult, especially since vertigo does not have to be the presenting symptom (Guinand et al., 2012a; Kim et al., 2013). The main symptoms of BVH will now be explained in detail.

Oscillopsia

BVH leads to a reduced or absent vestibulo-ocular reflex (van de Berg et al. 2011). Normally, gaze is stabilized by the vestibulo-ocular reflex, which compensates head rotations with equal eye rotations to the opposite direction. In BVH, the vestibulo-ocular reflex is deficient, which leads to the eyes moving along with the head, forcing the patient to make a catch-up saccade (van der Stappen et al. 2000). Failure of gaze stabilization leads to excessive motion of images of stationary objects upon the retina during head movements, impairing vision. The illusion of movement of the seen world is called oscillopsia (Leigh & Zee 2006). BVH patients may complain of blurred vision during high-frequency head movements (Guinand et al., 2012b). From our experience we noticed that not all patients are able to recognize that oscillopsia due to BVH only occurs during high-frequency head movements. Therefore, some patients first go to the ophthalmologist to have their vision checked. Unfortunately, visual acuity is often measured in a static condition (without any head movements) and not in a dynamic condition (with head movements). As a result, oscillopsia is often not detected by ophthalmologists. However, it can be detected by testing visual acuity in dynamic conditions, using the test for dynamic visual acuity (DVA) (Demer et al., 1994), which will be explained in the section Challenge Three: Quantifying BVH.

Not all patients with BVH complain of oscillopsia. Percentages of BVH patients suffering from oscillopsia vary from 25 to 86%, and the degree of subjective complaints is not directly correlated with the severity of BVH as measured with objective tests (Vibert et al., 1995; Kim et al., 2011; McGath et al., 1989). Probably, mechanisms other than the vestibulo-ocular reflex may play a role in gaze stabilization during head movements (Telian et al., 1991).

Having these aspects in mind, oscillopsia can be difficult to acknowledge for patients as well as physicians. Moreover, not having oscillopsia does not rule out bilateral vestibulopathy.

Imbalance

BVH patients typically complain of unsteadiness or imbalance. Postural control and spatial orientation depend on vestibular, visual and proprioceptive inputs and on internal estimates based on motor efference. Due to failure of the vestibulospinal reflex in BVH, the multisensory process of postural control is hindered (Vibert et al., 1995; Kim et al., 2011; Zingler et al., 2008b; Rinne et al., 1998; Glasauer et al., 1994). Especially fast corrections become impaired, and the accuracy of gravity detection decreases. This leads to unsteadiness or imbalance during locomotion and to an increase in falls. Compensation is partially attempted by relying more on the remaining inputs and estimates (Guerraz 2005; Bisdorff et al., 1996; Cutfield et al., 2014). Therefore, unsteadiness or imbalance increases when the other inputs are challenged, e.g. while walking in the dark or on uneven surfaces (Ward et al., 2013; Jen 2009; Rinne et al., 1998). Imbalance and unsteadiness can also occur merely as the result of high-frequency head movements, due to failure of gaze stabilization. BVH patients may report a sensation of the 'image lagging behind' when the head is turned fast (e.g. while taking care crossing the street), which can result in imbalance or unsteadiness (Kim et al., 2011). Due to several factors, including the above-mentioned compensation and sometimes a slow progression of disease, unsteadiness or imbalance can be subtle in some patients, not being the key symptom of presentation. This can interfere with making the right diagnosis.

Visual vertigo

BVH patients rely more on other sensory inputs such as vision (Cutfield et al., 2014; Göttlich et al., 2014; Dieterich et al., 2007). However, an increased visual dependence can result in symptoms of vertigo that are provoked or aggravated by specific visual contexts (e.g. supermarkets, movement of objects, driving, crowded places, scrolling down a computer screen, moving windshield wipers). This is called 'visual vertigo'. Patients suffering from visual vertigo have been shown to have abnormally large perceptual and postural responses to disorienting visual environments. This could reflect a difficulty in resolving a visually induced sensory conflict between visual and vestibuloproprioceptive inputs as a result of an increased visual dependence (Kingma et al., 2005; Guerraz et al., 2001; Cutfield et al., 2014). Unfortunately, many vestibular patients are diagnosed with a pure psychological disorder as a cause of these symptoms (Bronstein 1995). It is therefore important to recognize visual vertigo as a possible symptom of vestibulopathy.

Cognitive deficits

BVH patients often suffer from cognitive deficits such as difficulty concentrating, being in a 'brain fog' or being more tired (Guinand et al., 2012a; McCall & Yates 2011; Hanes

& McCollum 2006). Since patients are continuously compensating and trying to avoid imbalance and falling, walking, for instance, is prioritized over secondary tasks such as cognitive ones. It is often said that a patient 'stops walking when talking' (Bessot et al., 2012; Lundin-Olsson et al., 1997). Also spatial learning and memory are affected by loss of labyrinthine input, probably influenced by the hippocampus, which is subject to functional and structural changes (McCall & Yates 2011; Zheng et al., 2013; Viard et al., 2011). A bilateral atrophy of the hippocampus was found in 17% of a BVH population, which correlated with spatial memory deficits (Zheng et al., 2012, Brandt et al. 2005). The anterior hippocampus is also critically involved in emotional processes. Therefore, the hippocampus could be one of the main structures in which the cognitive and emotional effects of vestibular loss interact (Smith et al., 2013, Fanselow & Dong 2010). Other parts of the brain show changes in resting-state connectivity due to BVH, which may also account for the persistent deficits in visuospatial attention and spatial orientation as well as unsteadiness (Göttlich et al., 2014). In other words, cognitive deficits can be related to vestibulopathy and should not be disregarded while taking the history of a patient.

Psychological or psychiatric symptoms

The chronic disequilibrium as well as difficulty performing routine daily activities as a result of BVH can have a psychological impact (Grill et al., 2014; Guinand et al., 2012a; Sun et al., 2014). This is shown by a high prevalence of psychiatric symptoms among vertiginous patients (Baijens et al., 2015; Ketola et al., 2015). For instance, BVH patients more often report autonomic symptoms and somatic anxiety (Guerraz et al., 2001). Besides those, psychiatric conditions such as depression could play a confounding role in the reported health status of patients (Sun et al., 2014). In the chronic phase, it is mainly the psychiatric disorders which worsen the clinical picture along a more disabling and debilitating course, not the vertigo symptoms (Ketola et al., 2015). Taking these factors into account, BVH and psychological and psychiatric symptoms coexist and interfere with each other. Therefore, having a patient with mainly psychological or psychiatric symptoms in addition to dizziness does not directly exempt a physician from performing a vestibular workup.

Neurological symptoms

BVH may be associated with neurological diseases, such as neurodegenerative diseases [e.g. spinocerebellar ataxia, multiple system atrophy, CANVAS (cerebellar ataxia, neuropathy and vestibular areflexia syndrome)], infectious diseases (e.g. meningitis, encephalitis, cerebellitis), neoplasms, vascular lesions, and others (Table 2.1). Up to 39% of BVH patients may have a vestibular deficit combined with a neurological disorder (Hain et al., 2013; Zingler et al., 2009). In some cases, BVH may precede cerebellar ataxia. Often, BVH is underdiagnosed in cerebellar disorders,

probably partly because cerebellar and vestibular disorders have overlapping signs and symptoms (Rinne et al., 1998; Requena et al., 2014). Vestibular disorders may even be improperly diagnosed as a cerebellar syndrome (Hain et al., 2013). Therefore, if imbalance is in excess of that expected for the severity of the neurological disorder, one should consider a coexisting BVH (Szmulewicz et al., 2011).

Autonomic symptoms

With the vestibulosympathetic reflex, the peripheral vestibular system also has widespread effects on homeostatic regulatory physiology (Highstein & Holstein 2012). It has projections to sites involved in the central regulation of respiratory and cardiovascular activity (blood pressure and heart rate) as well as to sites that mediate the affective and emotional aspects of vestibuloautonomic function (Highstein & Holstein 2012; Holstein et al., 2011). Therefore, BVH can, for instance, lead to orthostatic hypotension and to a disturbance in the association between vertigo and panic (Highstein & Holstein 2012; Balaban 2004).

Challenge Three: Quantifying BVH

For several reasons, BVH is a diagnostic challenge. Firstly, each test has its own limitations in terms of sensitivity, specificity, patient acceptance, costs and duration, and there is still no consensus about diagnostic criteria for BVH (Kim et al., 2011). Secondly, since BVH probably represents a functionally heterogeneous disorder with different combined or isolated deficits of the vestibular system, different results from laboratory tests can be expected for different types of BVH (Zingler et al., 2008a; Fujimoto et al., 2009a; Priesol et al., 2014). Thirdly, the output parameters of laboratory tests such as the caloric test, rotatory chair tests and (video) head impulse testing [(V)HIT] show a considerable overlap between patients and healthy subjects (Weber et al., 2009). Fourthly, clinical vestibular testing primarily measures reflexes [e.g. caloric test, rotatory chair tests, vestibular evoked myogenic potentials (VEMPs)], while perceptual thresholds are not yet routinely used to evaluate vestibular disorders (Priesol et al., 2014). However, they might be better correlated with complaints (Priesol et al., 2014). These tests could complement the standard vestibular testing battery used in clinical practice. The main examinations for determining BVH will now be discussed.

Neuro-otological and vestibular physical examination

A complete and thorough neuro-otological and vestibular examination is necessary to find any signs of vestibular hypofunction or any neurological diseases, particularly ataxia. During the neuro-otological assessment, one should pay especially close attention to the oculomotor examination, since abnormal oculomotor findings may be

the only or first presenting central signs that may explain the vestibular symptoms (Kattah et al., 2009). The oculomotor examination is best performed before inducing the substantial head movements that are typical for some major components of the vestibular examination. The vestibular examination includes the Dix-Hallpike and the lateral roll test, positional testing, (V)HIT, the test for DVA, the visually enhanced vestibulo-ocular reflex test, fixation suppression, the Valsalva maneuver (straining against the closed glottis and blowing out against pinched nostrils), the head shake test, the vibration test, the hyperventilation test and the Romberg test on foam rubber or in tandem (Petersen et al., 2013; Kheradmand & Zee 2012). The Romberg test mainly diagnoses ataxia and is not specific for a vestibular loss, since it also detects cerebellar and proprioceptive impairment (Petersen et al., 2013; Khasnis & Gokula 2003). However, the sensitivity for detecting vestibular deficits increases when the patient stands on foam rubber (Lanska & Goetz 2000). The Romberg test on foam rubber has a sensitivity of up to 79% and a specificity of up to 80% for detecting both patients with unilateral and those with bilateral vestibular loss (Petersen et al., 2013, Fujimoto et al., 2009b). Although abnormalities in the other vestibular tests during physical examination can be found (Kheradmand & Zee 2012; Szmulewicz et al., 2014), this review will not focus on them, since the main challenges for diagnosing and quantifying BVH are not encountered in these tests, except for HIT and the test for DVA; they will be discussed separately below.

Head impulse testing

A brief, high-acceleration head 'impulse' can test vestibular function of all semicircular canals. Depending on the semicircular canal tested, the head is rotated in a different direction (Halmagyi & Curthoys 1988;, Migliaccio & Cremer 2011). A corrective catch-up saccade is made in case of vestibular hypofunction. HIT can be performed with or without the use of a noninvasive video-oculography device (i.e. VHIT). This device consists of goggles that contain a high-speed infrared video camera that tracks eye movements and accelerometers that track head movements (MacDougall et al., 2009).

Although applying HIT may sound simple at first, some challenges are met when performing it. The first challenge is to adequately deliver the stimulus: it should be a high-acceleration (1,000–6,000°/s^2), rapid (100–200°/s), low-amplitude (10–20°) head rotation. When using VHIT, one should pay attention by avoiding a loose strap, wrong calibration, pupil tracking loss, (mini-)blinks, touching the goggles, patient inattention and investigator-induced bounce; if these are not avoided, they will result in artifacts (Mantokoudis et al., 2015).

The second challenge is not to be fooled by pre-programmed compensatory saccades ('covert saccades') that can be invisible to the naked eye of the examiner and can occur (not only) in BVH patients. Consequently, BVH may be missed (Weber et al.,

2008). A recent study by Strupp et al. indicated that HIT observed by the naked eye of experts is false negative for about 50% of the patients when compared to VHIT [pers. commun. H.K. with Michael Strupp]. This clearly supports the use of the VHIT device, which is able to track these saccades. Examples of normal and abnormal VHIT recordings with overt and covert saccades are presented in Figure 2.1a–c.

The third challenge is to correctly interpret the traces. VHIT traces can have many artifacts, leading up to 42% of uninterpretable traces (Mantokoudis et al., 2015). Besides these artifacts, eye movements in patients with a vestibular hypofunction can show patterns that challenge interpretations. Ideally, vestibulo-ocular reflex gain is calculated by peak eye velocity divided by peak head velocity (Weber et al., 2009). However, artifacts and abnormal patterns distort the process of correct gain calculation, and commercially available software is not yet able to adequately compensate for it. An example of an eye movement pattern that interferes with gain calculation is presented in Figure 2.2. In order not to miss a BVH, a physician should not yet solely rely on software processing for gain calculation, but should be trained in assessing the raw data and should be aware of the impact of deviant eye movement patterns and measurement artifacts (Mantokoudis et al., 2015).

The fourth challenge is to correctly interpret the end result. HIT provides a stimulus for measuring gain of the vestibulo-ocular reflex which is different from those used in other vestibular tests such as the rotatory chair tests or the caloric test; it includes many more high-frequency components than the rotatory chair tests and the caloric test. Differences in response to the caloric test versus the rotation tests versus HIT are especially pointing to this difference in frequency content. It has been shown that a bilateral vestibular loss can be measured with the caloric test, while the responses as measured with HIT are relatively preserved (Agrawal et al., 2013; McGarvie et al., 2015). In other words, it is necessary to understand that the presence of a normal vestibulo-ocular reflex as measured with HIT does not rule out a vestibular deficiency.

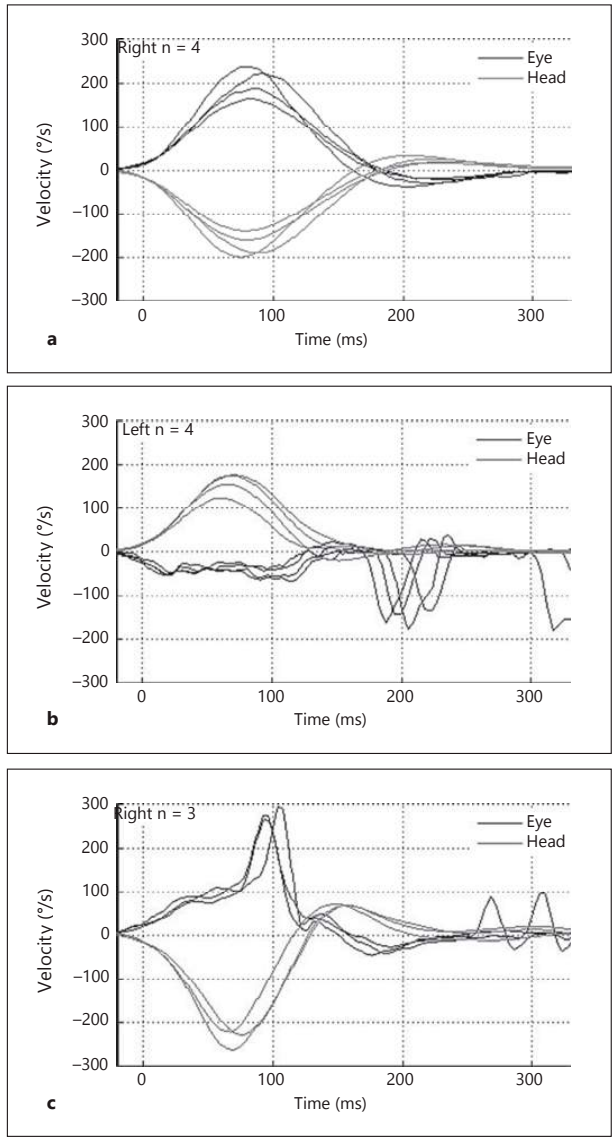

Figure 2.1 Raw VHIT recordings of different subjects, recorded with the EyeSeeCam system (EyeSeeCam VOG; EyeSeeCam, Munich, Germany). Head velocity traces are shown in gray, eye velocity traces in black. **A)** VHIT recordings of head impulses to the right in a healthy subject. The eye movements compensate for the passive head movements. **B)** VHIT recordings of head impulses to the left in a patient with a peripheral vestibular deficit, resulting in overt saccades (peaks in eye velocity after head movements). The eye movements do not compensate for the passive head movements. **C)** VHIT recordings of head impulses to the right in a patient with a peripheral vestibular deficit, mainly resulting in covert saccades (peaks in eye velocity during head movements).

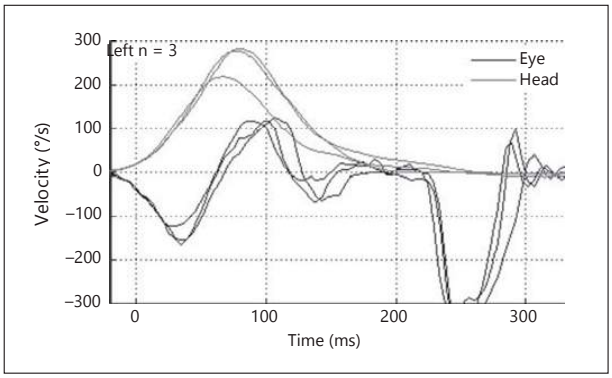

Figure 2.2 Example of an eye movement pattern that interferes with gain calculation. Raw VHIT recordings of head impulses to the left in a patient with BVH are presented. Head velocity traces are shown in gray, eye velocity traces in black. Normally, gain is calculated by peak eye velocity divided by peak head velocity. In this case, gain calculation is challenged, since at the moment the peak head velocities are reached, the eyes are actually moving along with the head in the same direction. The passive head movements are not compensated by the eye movements. Although this is clearly an abnormal HIT, there is not yet any consensus about how to determine (or whether it is even possible to determine) the real peak eye velocity which is necessary for gain calculation.

Dynamic visual acuity

During head movements, efficient stabilization of the image on the retina is necessary to preserve visual acuity (Guinand et al., 2012a). In BVH patients, gaze stabilization fails and can lead to significant deterioration in visual acuity during head movements (Aaronson et al., 1998; Jacobson & Newman 1990). Visual acuity in dynamic conditions can be assessed by testing for DVA. DVA testing can be performed in many ways: the patient has to read letters from a visual acuity chart or a computer screen during active or passive, vertical or horizontal head movements, or while walking on a treadmill at different velocities (Guinand et al., 2012b; Tian et al., 2002). Passive high-angular-velocity movements (150°/s) have been shown to be most useful for discrimination between healthy subjects and patients with a unilateral or bilateral vestibular loss. However, that study did not include DVA testing by walking on a treadmill (Vital et al., 2010). A decline of more than 2 lines on the optotype chart is considered abnormal (Fife et al., 2000), although a loss of 2 lines (0.2 logMAR) is not unusual for healthy subjects. In order to trade sensitivity for specificity, 4 lines may be required (Hain et al., 2013). Moreover, DVA may show false-negative results due to mechanisms that at least partially compensate for the retinal instability during head movements (Petersen et al., 2013; Vital et al., 2010). However, in subjects with unilateral and bilateral vestibular loss, computerized DVA testing reached a sensitivity of 94.5% and a specificity of 95.2% (Herdman et al., 1998). In another group of BVH

patients, DVA was impaired in 96% of the cases (Kim et al., 2011). To conclude, DVA can help establishing the diagnosis of BVH, but a normal DVA does not definitely rule out BVH, and an impaired DVA does not imply vestibular hypofunction per se. It is still not understood by which specific vestibular deficits (which semicircular canals, which otolith organs and which frequencies) DVA decreases.

Caloric test

The caloric test, first described by Barany, is believed to evaluate the low-frequency part (0.003 Hz) of the horizontal semicircular canal function, which is much lower than the frequency spectrum of natural head movements. This, together with the fact that the caloric stimulus is monaural, implies that the test is considered a non-physiological vestibular test (Kim et al., 2011; Furman & Cass 1996; Hamid 1988; Bárány 1906). On the other hand, the caloric test is the only widely used clinical test that exclusively stimulates only one side, in contrast to HIT and all other head rotation tests. Based on extensive research in the previous century, the caloric response is believed to be induced by convection (Wit et al., 1990), aspecific thermic stimulation of hair cells (Wit & Segenhout 1988) and endolymph expansion (Scherer & Clarke 1985).
Many challenges are met when using the caloric test for diagnosing BVH. Firstly, it should be performed in a standardized way, since, in order to get reproducible results, all parameters have to be optimized. Therefore, if possible, one should stop medication that influences the vestibular response (e.g. vestibulosuppressants, some antidepressants). Furthermore, the room must be completely dark, preventing the patient from being able to visually suppress the elicited vestibulo-ocular reflex, and calibration must be performed prior to each irrigation. A 5-min stimulus interval should be kept between successive irrigations to reduce the residual effects of the previous irrigation. At each irrigation of preferably 30 s, the stimulus must have the same characteristics: the same total volume of at least 250 ml water and the same temperatures for cold and warm irrigations (30 and 44°C, respectively) (van der Stappen et al., 2000; Maes et al., 2007). A 1-degree variation in temperature from the intended 30 or 44°C can already result in a 14% difference in stimulation magnitude (Gonçalves et al., 2008; Souza et al., 2000). The required thermic stimulus is best achieved by the use of water and not by air (Maes et al., 2007; Greven et al., 1979; Norré & Renier 1979; Zangemeister & Bock 1980). Statistically higher slow component values of the vestibulo-ocular reflex are obtained for water than for air, and evidence shows that air has a poorer test-retest reliability and greater inter-subject variability (Coats 1986; Cooper & Mason 1979). Based on our extensive clinical experience in comparing air calorics to water calorics in many hundreds of patients, we advise using water calorics. However, responses to water calorics also show considerable test-retest variation and variability between healthy subjects (Maes et al., 2007). In the past, responses were quantified by slow-phase velocity (in the culmination phase) of

the caloric nystagmus, the maximum nystagmus frequency and the total number of nystagmus beats. The maximum slow-phase velocity at the time of maximum response (culmination phase) occurs generally about 50-60s after the start of irrigation and is the preferred parameter to be determined. Ice water calorics is not preferred, since it can induce a pseudocaloric nystagmus by activating a latent spontaneous nystagmus (Kim et al., 2011; Greisen 1972; Möller & Odkvist 1989) and the absence of an ice water response does not prove a complete vestibular areflexia, as was thought in the past. After all, it does not exclude normal vestibular responses to the rotatory chair tests or VHIT at all. Besides delivering the right stimulus, all tests should be performed by a trained, attentive and dedicated technician who is able to interpret results to a certain extent. The patient's state of alertness is very important, since cortical activity influences the vestibulo-ocular reflex: the reflex is inhibited by drowsiness. The technician should therefore keep the patient aroused e.g. by asking him/her to perform mental tasks or to focus on the vestibular sensation of rotation. If during irrigation the patient has not been attentive enough, it has to be repeated (van der Stappen et al., 2000; Barnes 1993). If not repeated, the measured vestibulo-ocular reflex may be lower than in case of optimal alertness, which could lead to a false-positive diagnosis of vestibular hypofunction.

The second challenge is to have the right frame of reference regarding caloric test outcomes. Therefore, a vestibular laboratory must obtain its own up-to-date normative data, since in the literature it has been shown that, due to local factors, caloric test outcomes may vary widely between laboratories (van der Stappen et al., 2000, Maes et al., 2007). The average maximum slow-component velocity varies between laboratories from 14.9 to 29.7°/s for cold irrigations and from 12.1 to 30.9°/s for warm irrigations laboratories (van der Stappen et al., 2000; Sills et al., 1977; Press et al., 1979; Karlsen et al., 1992). These normative data will probably reveal a high variability among values. For example, in one vestibular laboratory, the 95% prediction interval of the average maximum slow-component velocity may vary from 3.4 to 32.9°/s for cold irrigations and from 6.9 to 55.0°/s for warm irrigations. There is as yet no unanimity among investigators about correcting values for age (Bruner & Norris 1971; Mulch & Petermann 1979; Peterka et al., 1990; Mallinson & Longridge 2004). Also, the asymmetry between labyrinths may be up to 19%, and still be within the normal range (van der Stappen et al., 2000). This variability may partly be due to uncontrollable factors such as differences in anatomy of the temporal bone (differences in temperature conduction), blood flow and middle ear fluids - all the more reason to have controllable factors such as stimulus parameters and technical skills optimized and to absolutely avoid any visual suppression (van der Stappen et al., 2000).

The third challenge is, again, to correctly interpret the values. For BVH, it is first of all important to not only look at the asymmetry. Some laboratories only report the asymmetry between ears, without reporting the total response. This could result in

false-negative errors (Hain et al., 2013). However, while it is necessary to take the total response into account, there is still no consensus on the range of responses required for the diagnosis of BVH (Kim et al., 2011; McGath et al., 1989; Möller & Odkvist 1989; Myers 1992). A criterion often suggested for diagnosing BVH is to have a sum of 4 irrigations that is less than 20°/s (Kim et al., 2011; Hain et al., 2013; Zingler et al., 2008a; Agrawal et al., 2013). While this is highly specific, it could still lead to false-positive results (partly due to the anatomical variations mentioned above) and also, very importantly, to false-negative results. The sum of 4 irrigations in one laboratory can already vary from 27 to 169°/s (van der Stappen et al., 2000). This implies that using a sum of less than 20°/s will possibly lead to 'milder' types of BVH being missed. One of the main problems with the caloric test is the fact that a physician will hardly ever know what would have been the initial response values of a patient for the caloric test. A patient often visits a physician for the first time, when vestibular complaints are already present. It is therefore not known when the measured response is low, whether it is a reflection of already induced vestibular damage or just the physiological initial response. This remains a challenge. Depending on the criteria for BVH, some authors show that the caloric test only has a sensitivity of 64.6%. This could be the result of highly specific criteria, anatomical differences or measuring a nonphysiological stimulus, but it could also be due to the fact that only the lateral semicircular canal is tested by the caloric test (Priesol et al., 2014). Other parts of the vestibular system are not tested, such as the remaining semicircular canals and the otolith organs.
To summarize, using the caloric test for diagnosing BVH is challenging, due to the high standards necessary for testing and difficult interpretation as a result of inter- and intra-subject variation for which the present diagnostic criteria for BVH are not always sufficient. When the high testing standards are not adhered to, and the inter- and intra-subject variability is not taken into account, this will lead to unnecessary false-positive and false-negative diagnoses of BVH.

Rotatory chair tests

Rotatory chair tests could demonstrate residual vestibular function in patients with severe BVH, when (almost) no vestibular response is measured with the caloric test (Eviatar 1970; Baloh et al., 1979; van de Berg et al., 2012). It can also provide additional data about central processing of vestibular input from both labyrinths (van der Stappen et al., 2000). Two frequently used algorithms are the sinusoidal harmonic acceleration test (SHAT) and the velocity step test (VST) (Maes et al., 2008). The SHAT is often promoted as a real multi-frequency rotation test. However, compared to the optimum frequency sensitivity of the semicircular canals (ranging from about 0.1 to 10 Hz), the SHAT uses only low-frequency stimuli ranging from 0.005 to a maximum of 0.64 Hz. Another complicating factor is that the total SHAT takes considerable time.

Therefore, the frequency response might be affected by changes in alertness of the patient during the test.

The VST involves more high-frequency components compared to the SHAT (step function) and comes closer to HIT. The first challenge when performing rotatory chair testing is to conduct it in a standardized way. One should always stop medication that influences the vestibular response, if possible. Furthermore, the room should be completely dark to avoid fixation suppression and optokinetic stimuli. The patient must be alert, since alertness during rotation increases the gain of the measured vestibulo-ocular reflex (van der Stappen et al., 2000). It is necessary to have a well-trained, dedicated and attentive technician who is able to interpret results to a certain extent. In this way the patient can be kept alert and measurements can be directly repeated when suboptimal responses are encountered. If the patient is not alert and the technician does not recognize this, the measured vestibulo-ocular reflex may be lower than in reality. This could result in a false-positive diagnosis of vestibular hypofunction. Many vestibular laboratories prefer to have the eyes of the patient open during testing, since closing the eyes decreases gain of the vestibulo-ocular reflex (Möller et al., 1990). For the VST, it is preferred to use the first rotation for familiarization with the test to get responses as accurate as possible (Maes et al., 2008).

The second challenge is to have the right frame of reference for the rotatory tests. Regarding gain of the vestibulo-ocular reflex, its values differ very much between vestibular laboratories for the SHAT as well as for the VST. It is therefore necessary for each vestibular laboratory to have its own normative data (Maes et al., 2008; Wall et al., 1984; Henry & DiBartolomeo 1993). Furthermore, in the SHAT and the VST, gain is considered to be the most variable parameter between and within subjects, probably as a consequence of factors such as fatigue, alertness, stress and habituation (Barnes 1993; Maes et al., 2008; Li et al., 1991; Su et al., 2000). Gain is also reduced by the test itself; rotating in the dark is an artificial condition that reduces gain (Leigh 1992, 1996). Moreover, gain is frequency dependent: it increases to a certain extent with an increasing modulation frequency (Barnes 1993; van de Berg et al., 2014). Taking all these facts into account, normative data for a vestibular laboratory can vary widely: for the SHAT, a mean gain of 58.77% with a standard deviation of 13.98% (0.1 Hz, 50°/s peak velocity), and for the VST, a mean gain of 67.66% with a standard deviation of 18.14% (200°/s^2 deceleration after a continuous velocity of 100°/s rotating to the right). However, it has been indicated that SHAT and VST gain parameters can be highly reliable, despite the fact that they are influenced by many other factors (Maes et al., 2008). Regarding other parameters, directional preponderance can vary widely within one vestibular laboratory, up to a 95% prediction interval of 26% (0.05 Hz, 50°/s peak velocity) (van der Stappen et al., 2000). Parameters that are believed to be more consistent and reproducible are ‘phase’ in the SHAT and ‘time constant’ in the VST. They are not influenced by the arousal state of the patient (Maes et al., 2008; Li

et al., 1991; Bouveresse et al., 1998; Jenkins & Goldberg 1988; Wolfe et al., 1977). The literature about the influence of sex differences on response parameters is not really consistent (Li et al., 1991).
All these facts show that interpreting the results correctly is the last challenge when using the rotatory chair for diagnosing BVH. Some authors suggest that rotatory chair tests should be the gold standard (Hain et al., 2013; Furman & Kamerer 1989). If any abnormalities are found in BVH patients, the strongest effects are often found at low frequencies, with a decrease in gain and an increase in phase (Hain et al., 2013). However, depending on the criteria, only 53% of BVH patients show abnormal responses on the rotatory chair. This emphasizes the need for establishing a standardized protocol for the diagnosis of BVH patients. Until now, the modulation frequencies necessary to be tested and the cutoff criteria have not yet been established (Kim et al., 2011; Perez Fornos et al., 2014). As with caloric testing, a borderline low response, for instance, may be the result of damage due to a vestibular disorder or be just a physiological phenomenon. Without knowing the initial values of a patient, the etiology of the low response will remain questionable.
To summarize, use of the rotatory chair is challenging. In order to get reproducible and consistent results, a high standard for testing is necessary. Due to inter- and intra-subject variation in some parameters, interpretation of the results remains difficult and the diagnostic criteria for BVH are not yet established for this test. It seems that the rotatory chair can be used complementarily with other vestibular tests (Clark KF, 1986), but not as the only test in the diagnostic process of BVH.

Vestibular evoked myogenic potentials

VEMPs are electromyogenic potentials elicited by high-intensity, transient acoustic stimuli and recorded from surface electrodes over tonically contracted muscles. Different types of VEMP are recorded from neck muscles [cervical VEMPs (cVEMPs)] or ocular muscles [ocular VEMPs (oVEMPs); for an overview, see Curthoys et al. 2010], and both have been incorporated as part of the vestibular testing battery in many clinics worldwide. A major difference is that the oVEMP is a contralateral response, whereas the cVEMP is an ipsilateral response. This is shown in a study in which the oVEMP was absent on the contralateral side in patients with unilateral vestibular function, but present on the ipsilateral side (Iwasaki et al., 2007). Furthermore, the cVEMP is an inhibitory response and the oVEMP is excitatory, as shown in a single-motor unit recording study (Colebatch & Rothwell 2004). The more uncertain parts of the tests are related to the end organ responsible for the response. It has been proposed that the oVEMP is mainly mediated by utricular stimulation, while the cVEMP is a saccular response (Curthoys & Vulovic 2011).
In order to use VEMPs as a diagnostic tool, it is imperative to identify, understand, and when possible, control the pitfalls in VEMP testing. Firstly, it is important to realize

that there is no standardized testing method, not for the cVEMP and even less so for the oVEMP (Rosengren et al., 2010; Todd et al., 2007). Many variables have been described to influence the outcome (patient position, electrode placement, frequency and intensity of the stimulus, etc.). Although general guidelines have been published (Papathanasiou et al., 2014), improvements are needed before VEMPs can be considered a reliable test. Since no standardized method is used, it is difficult to compare outcomes between studies. Therefore, it necessary for each laboratory to gather its own normative database from which pathological outcomes can be evaluated. This database should contain VEMP responses of healthy subjects of varying age groups, since both cVEMPs and oVEMPs show reduced outcomes with increasing age (Li et al., 2015; Welgampola & Colebatch 2001).

Secondly, different VEMP outcome metrics can be used to assess vestibular function. Recent studies have described the use of the inter-aural asymmetry ratio to compare the left with the right ear in order to aid in identifying the affected ear in Menière's disease (Taylor et al., 2011). In strictly unilateral diseases this could be a helpful outcome; however, when there is a suspicion or chance that both ears are affected, this ratio could underestimate the disease (Lin et al., 2006). Therefore, in BVH this outcome measurement has little value. Peak-to-peak amplitude is another method of assessing the VEMP waveform, in which the distance between positive and negative peaks is measured. For cVEMPs as well as oVEMPs, the peak-to-peak amplitude changes when the vestibular apparatus is affected, and this response varies by the stimulus frequency (Singh & Barman 2013). Therefore, it is preferable to measure VEMPs with multiple stimulus frequencies (McCaslin et al., 2013; Rauch et al., 2004). In most of the current literature, only a single measurement, made at one frequency, was used to assess VEMP response (mostly at 500Hz), which substantially limits the sensitivity of the test. Peak-to-peak amplitude also co-varies with muscle contraction intensity, which can be a significant confounding variable. Recent studies have shown that normalization of the VEMP response during signal processing to correct for the muscle activity significantly reduces the variability in cVEMPs in healthy subjects (van Tilburg et al., 2014). Also, VEMP thresholds at multiple frequencies yield, at least in Menière's disease patients, a more sensitive measure with less inter-subject variability (in normals), further increasing the clinical utility of the cVEMP [van Tilburg et al., submitted paper]. Threshold measurements in oVEMPs have also been shown to differ between healthy and pathological subjects (Winters et al., 2012). Furthermore, using only a present/absent criterion, the degree of damage to the otoliths is not measurable. A recent study showed that there was a significant decrease in cVEMP threshold in Menière's disease patients when these patients were tested 2 times with at least 3 months between tests, suggesting a progressive decrease in otolith function [van Tilburg et al., submitted paper]. The unaffected ear showed no significant difference in threshold.

Thirdly, it is important to correctly interpret the results. Some studies use VEMPs in the evaluation of BVH; however, the application of VEMPs is often not optimal, making it difficult to interpret the results. Two papers described patients with absent cVEMPs and normal caloric responses, demonstrating a new subtype of idiopathic bilateral vestibulopathy called 'dissociated bilateral vestibulopathy' (Fujimoto et al., 2009a, 2012). However, some patients were older than 70 years, in which case age could also be a very likely (physiological) explanation for the absent responses. Other patients had vertigo attacks, and even though they did not have hearing loss, this could be a first sign of Menière's disease, since some of them were still young (below 45 years). Although it is most likely that BVH can affect different parts of the vestibular system separately (Zingler et al., 2008a; Jen 2009), an absent response of VEMPs does not indicate a vestibular deficit per se.
In conclusion, VEMP testing is an emerging and valuable addition to the vestibular function testing 'toolbox', since it permits an assessment of each otolith organ in a way not previously available. The details of the underlying physiology and the precise methods of performing, analyzing and interpreting VEMP responses are still evolving and not yet standardized. More research is needed to determine how VEMPs are most accurately performed and interpreted.

Other diagnostic tests

The value of posturography in the diagnosis of BVH is limited, since it lacks specificity. It does not discriminate very well between vestibular disorders and other causes of imbalance such as cerebellar ataxia (Hain et al., 2013). The accuracy of subjective visual vertical testing for BVH has still to be refined (Funabashi et al., 2012). Many other tests can also be used in the diagnostic process if necessary: audiometry, measuring blood pressure, measuring orthostatic hypotension, blood tests (including autoantibodies, complement factors, folate, vitamin B_{12}, renal function, thyroid function, glucose, genetics, etc.), imaging (e.g. magnetic resonance imaging, computed tomography), lumbar puncture, sensory nerve action potentials, speech assessment, etc. (Zingler et al., 2008a, 2009; Jen 2009; Szmulewicz et al., 2011, 2014; Requena et al., 2014). However, these tests are mainly used for determination of coexisting problems or the etiology of BVH (Table 2.1), not for an evaluation of vestibular function. Since they do not specifically contribute to establishing the presence of BVH, they are not within the scope of this review.

Challenge four: Establishing the diagnosis of BVH

To establish a correct diagnosis in vestibular patients is difficult: a clear diagnosis is not possible in up to 40% of vertigo patient subgroups (Roberts et al., 2013). As may be concluded from the challenges mentioned above, establishing the diagnosis of BVH is not an exception to this: it can be complicated. This results from its often difficult

clinical presentation (e.g. vertigo does not always occur), the lack of uniform criteria for BVH, the heterogeneity of BVH, different settings in which patients are seen (otorhinolaryngology, neurology, ophthalmology, etc.), the trade-off between sensitivity and specificity for each test which determines the cut-off criteria, the (inherent) shortcomings of the tests and the fact that patients' subjective sensations do not always match up with the objective laboratory measures (Grill et al., 2014; Kim et al., 2011; Zingler et al., 2008a; van der Stappen et al., 2000). Regarding criteria for BVH, different ones can be used which could probably complement each other. Three examples extracted from the literature are shown in Table 2.2 (Kim et al., 2011; Hain et al., 2013; Fujimoto et al., 2009a; Brantberg & Löfqvist 2007).

As shown, there are still challenges regarding all the options. For example, the criteria in Table 2.2a do not take tests of otolith function into account. This could lead to an underestimation of BVH when considering the option of dissociated bilateral vestibulopathy. Furthermore, the cut-off criterion for reduced caloric responses probably mainly yields a high specificity. Sensitivity may be put at a disadvantage in less severe cases of BVH or in individuals with high initial caloric responses (before they developed BVH). Also, the criterion of a reduced gain for rotatory chair testing is not defined. The (partial) definition on the basis of the parts affected displayed in Table 2.2b only uses the present/absent criterion for VEMPs, which could lead to an underestimation of BVH. On the other hand, it does not yet consider a physiological or age-related absence of VEMPs, which could lead to an overestimation of BVH. Table 2.2c shows a (partial) definition of BVH on the basis of severity. However, it is a challenge to define vestibular loss; for instance, caloric and rotatory chair tests have a broad range of normative data. It is questionable to determine the extent of vestibular loss if the initial values are not known. Also, the definition does not specify whether it comprises only vestibular loss or also loss in functional parameters. After all, as stated earlier, patients' subjective sensations do not always match the results of the laboratory tests (Kim et al., 2011). One of the factors contributing to this issue could be the basic health condition of patients. For example, in obstructive sleep apnea, this is given as one of the explanations why some patients are able to withstand a certain amount of sleep disruption better than others (Richtlijn OSAS, 2009). Therefore, the severity of obstructive sleep apnea may be determined by objective laboratory findings, combined with daytime sleepiness as measured by a short questionnaire (Richtlijn, 2009). For some vestibular patient groups, such an influence of their basic health condition has already been known for physical as well as mental domains: imbalance is often greater in patients with CANVAS, due to the comorbidity of polyneuropathy and ataxia (Szmulewicz et al., 2014), and patients with an anxious, introverted temperament could be more prone to develop chronic subjective dizziness (Staab et al., 2014). However, also less well-known factors could belong to the basic health condition, such as the ability to effectively use mechanisms that at least partially compensate for the consequences of vestibular hypofunction

(Vital et al., 2010). The severity of BVH can therefore most likely be determined not only by objective laboratory findings but also by using a combination of objective laboratory findings together with a specification of the handicap related to the dizziness. For hearing-impaired patients, functional hearing ability is partially assessed by speech audiometry. Since there is as yet no vestibular 'speech audiogram', functional impairment due to BVH is at this moment probably best measured by using questionnaires.

Table 2.2 Examples of BVH criteria extracted from the current literature.

a.	BVH defined as a combination of history and laboratory findings (Kim et al., 2011)
	1. Symptoms only during locomotion Unsteadiness and/or Oscillopsia 2. Bedside evaluation Positive HIT and/or Impaired DVA 3. Laboratory tests Reduced caloric responses (sum SPV <20°/s) and/or Reduced gain on rotatory chair 4. Other causes excluded
	Evaluation Definite diagnosis: met all 4 diagnostic criteria Probable diagnosis: met criterion 2 or 3 in addition to criteria 1 and 4
b.	BVH (partially) defined on the basis of the affected parts of the vestibular organs (Fujimoto et al., 2009a, Brantberg et al., 2007)
	Affected parts Superior vestibular nerve plus inferior vestibular nerve Only superior vestibular nerve Only inferior vestibular nerve Dissociated BVH
c.	BVH (partially) defined on the basis of severity (Hain et al., 2013)
	Severe: 75–100% vestibular loss Moderate: 50–75% vestibular loss Mild: 0–50% vestibular loss

SPV = Slow-phase velocity.

Overall, establishing the diagnosis of BVH in a patient with a severely affected vestibular system could very well be possible, since patient history and vestibular tests, when correctly applied and interpreted, will all be indicative of BVH. However, in many cases, the vestibular system is less severely affected, or strong compensatory mechanisms or psychological comorbidity play a role. In these patients, establishing the diagnosis of BVH is a great challenge at this moment. It still remains up to the physician, who has to combine the clinical picture and outcomes of (not all congruent) objective laboratory tests, to decide whether a patient suffers from BVH or not.

Future in diagnosing BVH

There is an urgent need for diagnostic standardization regarding the implementation and interpretation of vestibular tests. The resulting decisions should be used for the development of uniform diagnostic criteria for BVH. Regarding vestibular tests, besides standardizing their implementation, an evaluation of cut-off points for BVH is necessary. At this moment, cut-off points are mainly in favor of a high specificity, putting sensitivity at a disadvantage, especially in caloric and rotatory chair tests. For VHIT, defining the interpretation of traces is necessary; quantification is not always possible, and physicians cannot yet solely rely on software. Concerning DVA, determining various aspects could be helpful in establishing the diagnosis of BVH. It has not been extensively investigated in milder clinical presentations of BVH, lacking evidence of its value in these patients. Also, the best way to perform DVA testing is not uniform (e.g. passively shaking the head, walking on a treadmill). For VEMPs, criteria should be defined as to how to perform, analyze and interpret them. Once this is established, VEMPs must be included in the criteria for BVH, especially taking the possibility of otolith involvement into account.
Regarding criteria, we would propose BVH to be established on the basis of a combination of patient history, physical examination, vestibular tests (including VEMPs) and perceived handicap as measured by questionnaires (e.g. the Dizziness Handicap Inventory). Once established, BVH could be classified according to severity, taking not only objective measures but also functional impairment into account. A classification according to severity could be important, since much progress has been made in developing a vestibular implant (Perez Fornos et al., 2014; Fridman & Della Santina 2012; Golub et al., 2014; Lewis et al., 2011) and such a classification could facilitate patient selection. If necessary, a subdivision into probability groups (e.g. definite BVH, probable BVH, etc.) can be made to facilitate decision making in cases with less congruent test results. The role of measurements of vestibular perceptual thresholds is not yet certain, but if they will develop into one of the standard routine vestibular tests, they might become the ‘speech audiogram’ for vestibular disorders. In close cooperation with other societies and institutions, the International Standardization Committee of the Bárány Society has defined new international standards for several vestibular syndromes (e.g. benign paroxysmal positional vertigo, Menière’s disease, vestibular migraine). It is, among others, currently working on a definition of BVH, including diagnostic criteria.

Conclusions

Many challenges are met when establishing the diagnosis of BVH. These reflect its often difficult clinical presentation (e.g. vertigo does not always occur) and the lack of diagnostic standards regarding the implementation and interpretation of vestibular

tests. Therefore, there is an urgent need for standardization. The resulting decisions should be used for the development of uniform diagnostic criteria for BVH, which are, at present, not yet available.

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Chapter 3

The vestibular implant: quo vadis?

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Front Neurol. 2011;2:47

Abstract

Objective
To assess the progress of the development of the vestibular implant (VI) and its short-term feasibility.

Data sources
A search was performed in Pubmed, Medline, and Embase. Key words used were “vestibular prosth*” and “VI.” The only search limit was language: English or Dutch. Additional sources were medical books, conference lectures and our personal experience with peroperative vestibular stimulation in patients selected for cochlear implantation.

Study selection
All studies about the VI and related topics were included and evaluated by two reviewers. No study was excluded since every study investigated different aspects of the VI.

Data extraction and synthesis
Data was extracted by the first author from selected reports, supplemented by additional information, medical books conference lectures. Since each study had its own point of interest with its own outcomes, it was not possible to compare data of different studies.

Conclusion
To use a basic VI in humans seems feasible in the very near future. Investigations show that electric stimulation of the canal nerves induces a nystagmus which corresponds to the plane of the canal which is innervated by the stimulated nerve branch. The brain is able to adapt to a higher baseline stimulation, while still reacting on a dynamic component. The best response will be achieved by a combination of the optimal stimulus (stimulus profile, stimulus location, precompensation), complemented by central vestibular adaptation. The degree of response will probably vary between individuals, depending on pathology and their ability to adapt.

Background and objective

The last decade, interest increases in developing an implantable vestibular prosthesis for people with a vestibular disorder, which functions analog to the cochlear implant in patients with severe sensorineural hearing loss (Gong and Merfeld, 2000, 2002; Rubinstein and Della Santina, 2002; Wall et al., 2002; Merfeld et al., 2006, 2007; Shkel and Zeng, 2006; Wall and Guyot, 2007; Gong et al., 2008; Tang et al., 2009; Fridman et al., 2010; Lewis et al., 2010; Dai et al., 2011a,b; Davidovics et al., 2011; Guyot et al., 2011a,b). The objective of this review is to assess the progress of the development of the vestibular implant (VI), its feasibility short-term, and to provide useful practical information for researchers in this field. For these purposes, the following aspects were evaluated: type of prosthesis, stimulus profile (pulse characteristics, current, frequency), stimulus site, and adaptation of the central vestibular system.

Materials and methods

Data sources

A search was performed in Pubmed, Medline, and Embase. In order to create a very sensitive search, the key words “vestibular prosth*” and “VI” were used. The only search limit was language: English or Dutch. In order to keep up to date during writing of the review, the search was monthly reperformed until May 2011.

Study selection

Since research of the VI is still in an experimental phase, very few studies have been published yet. Therefore all studies about the VI were included and evaluated by two reviewers. This resulted in a non-comparative and expert opinion study, not randomized controlled. No study was excluded since every study investigated different aspects of the VI.
Literature references of the selected studies were also evaluated. In case references were needed to understand the selected study, these were also selected and evaluated by the two reviewers.

Data extraction and synthesis

Data extraction was done by the main author. Since every study had its own point of interest with its own outcomes, it was not possible to compare data of different studies. Whenever the same research group presented data about the same subject, the data most recently obtained were used for the review.

Introduction to data

Studies about the VI are sparse because its research is still in an experimental phase. Therefore, a systematic review about this subject was not an option. However, this narrative review deals with the most up to date knowledge about the most important aspects of the VI.

The need for a vestibular implant

There are a couple of patient groups who could benefit from the VI, since no definite therapeutic options are available for them at the moment.
The first and most important group are patients with complete or near complete acquired bilateral loss of vestibular function. This is called bilateral vestibulopathy. It leads to oscillopsia (blurred vision), chronic disequilibrium, postural instability, and impaired spatial orientation as a result of failing vestibulo-ocular and vestibulo-spinal reflexes and a reduced perception of motion and tilt (Della Santina et al., 2007; Lacour et al., 2009). Many of these patients are able to make optimal use of sensory substitution and can cope with these problems, but a substantial number of these patients show a moderate to severe reduction of their quality of life as monitored with the Dizziness Handicap Inventory (data to be published). Besides, it also increases the risk of falling, which is especially dangerous in the elderly.
Also patients with a fluctuating vestibular function such as Meniere's disease (Wall et al., 2002), elderly with presbyvertigo and patients with an incomplete centrally compensated unilateral hypofunction of a labyrinth are possible candidates for a vestibular prosthesis. (Wall et al., 2002; Agrawal et al., 2009).
No articles have been published about the selection of patients. Inclusion criteria for studies in humans in Maastricht University Medical Centre include a mean peak slow phase velocity of ≤5˚/s in bilateral bithermal caloric irrigations, low or no gain at rotatory chair tests and pathological head-impulse-test (HIT) for horizontal and vertical canals in which presence of correction saccades are considered pathological (not yet published).

General aspects of the design of the vestibular implant

The ultimate goal is to develop a VI which restores the vestibular function partially or completely. It directly stimulates the vestibular neural pathways by electrical pulses and has many analogies with the cochlear implant (Gong and Merfeld, 2000). However, whereas a simple microphone acts as the primary artificial sound sensor in a CI, the design of an artificial motion sensor for a VI is much more complex.

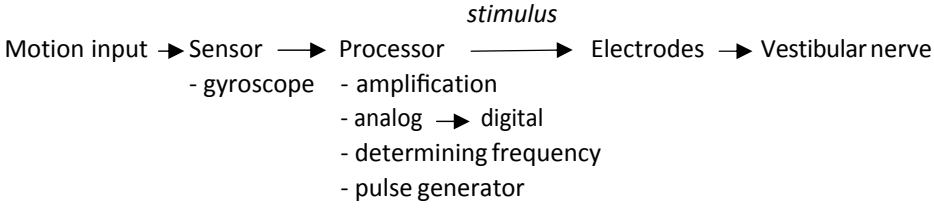
Firstly, motion (3D translations and 3D rotations) and orientation relative to the gravity vector should be detected by a combination of sensors (e.g., accelerometers, gyroscopes, Hall elements) resulting in a 6 degree of freedom (DOF) artificial labyrinth. The major problems with the design of such an artificial labyrinth are problems with drift, limited ranges of temporal and spatial sensitivity and high power consumption. The latter might hamper an easy continuous use of an implant over time. At current, separate components or combinations of them are commercially available but still no ideal complete 6 DOF sensor fulfilling all requirements exists. New sensors specially designed to be used in a VI are in development and several are tested now experimentally. We are convinced however that all these technological problems will be solved in the very near future.

The output signals of the artificial labyrinth have to be converted into an adequate stimulus for the hair cells and/or nerve. This is achieved by analog-digital conversion of the sensor outputs and feed them into a programmable digital microprocessor and signal generator. The microprocessor and signal processor enables a programmable conversion of the sensor output into analog electrical pulses to stimulate the nerves or hair cells. In this way, a stimulus with the optimal temporal characteristics and amplitude can be delivered to the vestibular nerve or hair cells by implanted electrodes (Gong and Merfeld, 2000, 2002; Lewis et al., 2002, 2010; Wall et al., 2002; Merfeld et al., 2006, 2007; Shkel and Zeng, 2006; Della Santina et al., 2007; Gong et al., 2008; Fridman et al., 2010; Dai et al., 2011a; Guyot et al., 2011b). A crucial problem might arise from the fact that the linear accelerometers in the artificial labyrinth like the statolith organs do not sense a difference between tilt and translation. It is yet unclear to which extend this aspect has to be dealt with within the signal processing unit of the VI, or that the brain will be able to do the necessary signal processing itself.

Optimal location of electrodes is yet to be determined (Wall et al., 2002; Wall and Guyot, 2007; Feigl et al., 2009; Guyot et al., 2011a). Monopolar as well as bipolar stimulation is possible. Bipolar stimulation is safer, provides more selective stimulation, but requires a higher current (Della Santina et al., 2007).

The prosthesis can be implanted unilaterally or bilaterally (Gong et al., 2008).

In short:



In the next chapters, the most important aspects will be discussed in more detail.

Pulse characteristics

Until now, the most commonly used waveform for electroneurostimulation is the charge-balanced, biphasic, rectangular, cathodic-first, current pulse (Figure 3.1; Gong and Merfeld, 2000, 2002; Lewis et al., 2002, 2010; Wall et al., 2002; Merfeld et al., 2006, 2007; Shkel and Zeng, 2006; Della Santina et al., 2007; Wall and Guyot, 2007; Dai et al., 2011a; Davidovics et al., 2011; Guyot et al., 2011b).

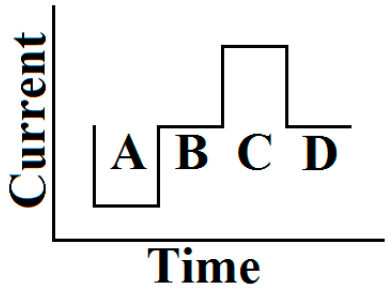


Figure 3.1 Biphasic rectangular pulse. This means that there are two phases with charge delivery. The first phase is the cathodic (negative) one (A), after that there is a delay (B). The anodic (positive) phase follows (C), which has the same charge as the cathodic one, but with a positive charge instead of a negative. In this way the charge remains balanced. The last phase is the resting phase (D). The duration of it determines the frequency of the stimulus. A longer duration of phase D implies less pulses per second (pps) and thus a lower stimulus frequency. The shape of all the phases are rectangular and a current is delivered, instead of a voltage.

Charge-balance, monophasic, and biphasic

With neural stimulation, chemical reversibility is a requirement. Processes occurring at an electrode, induced by a pulse, should therefore be reversed by a pulse of opposite polarity (Robblee, 1990). Monophasic and any DC-current can consequently lead to neural damage as a result of accumulated charge which induces irreversible reactions. Therefore, stimuli should be charge-balanced, which excludes the use of monophasic pulses (Shepherd et al., 1991; Shepherd and Javel, 1999; Merrill et al., 2005; Davidovics et al., 2011). A biphasic stimulus is capable of stimulating a nerve more selectively, but requires a higher current than a monophasic stimulus (Gorman and Mortimer, 1983; Shepherd and Javel, 1999).

Pulse width and amplitude

The duration and amplitude of the pulse should be long and high enough to deliver the sufficient amount of charge to stimulate a nerve, but not too long and high to

avoid damage and to limit power consumption per se. It is observed that a short high amplitude stimulus requires less charge than a wide stimulus of low amplitude in order to excite a nerve membrane (Crago et al., 1974; Mortimer, 1981; Macherey et al., 2006; Davidovics et al., 2011). However, in case of a high current, there is an increased “current spread” and “crosstalk” (see below Current).
A short pulse train with a high frequency is also a more powerful stimulus than a long pulse train of low-frequency (Suzuki et al., 1969). In order to achieve a high frequency, pulse width can not be too long. The optimal frequency characteristics, fall and rise time, or shape of the pulses for vestibular nerve or hair cell stimulation in humans still have to be explored in detail [see “Delay Between Cathodic and Anodic Phase (Interphase Gap)”].

Polarity

The cathodic phase is the part of the pulse which induces the neural response. The anodic phase is added in order to effect balanced charge stimulation to avoid tissue damage (Brummer and Turner, 1975; Merfeld, 2004; Macherey et al., 2006; Shkel and Zeng, 2006). The anodic phase is also capable of eliciting a response, but it is less efficient and requires higher currents. During tests in bilaterally plugged squirrel monkeys it was shown that the cathodic phase is the determining phase (Gong et al., 2008). Still, this does not mean that in all patients a biphasic–cathodic-first stimulus should be used.
After all, central processes are shown to be more sensitive to anodic stimuli than to cathodic ones, while for intact peripheral axons it is just the opposite (Rattay et al., 2001; Macherey et al., 2006). When many peripheral axons have been degraded, an anodic stimulus could therefore be more efficient than a cathodic (Macherey et al., 2006). It is important to understand the pathology of a patient to know whether peripheral axons have degraded. This could imply a different stimulus profile for different pathologies. During investigations on polarity in cochlear implants, there was often no difference between anodic and cathodic stimuli, although sometimes a cathodic stimulus created a better response. This “central activation hypothesis” is therefore still questioned (Macherey et al., 2006), but remains a factor to take into consideration.

Delay between cathodic and anodic phase (interphase gap)

The delay between the cathodic and anodic phase is a delicate balance. It should be long enough to prevent slow action potentials from the cathodic phase to be inhibited by the anodic phase (Macherey et al., 2006; Della Santina et al., 2007; Gong et al., 2008). However, it should not be too long, otherwise the anodic phase will generate action potentials instead of balancing the charge (Della Santina et al., 2007). Also, it should be

as short as possible in order to reduce the damage to electrodes (Gong and Merfeld, 2002). How short the delay can be, is not yet known (Gong et al., 2008). In chinchillas, varying interphase gap has not shown a discernible effect on VOR response or axis misalignment (Davidovics et al., 2011).

Other waveforms than rectangular

Next to rectangular, many different waveforms have been described and applied (Balter et al., 2004; Macherey et al., 2006). Rise and fall time and pulse shape are significant factors in frequency characteristics, stimulus efficiency, and reducing power consumption, while maintaining charge-balance (Macherey et al., 2006). Most of these waveforms are only tested in cochlear implants and not (yet) with a VI. The most well-known and eligible waveforms are now discussed.

Monophasic

A single cathodic or anodic pulse (Figure 3.2). As indicated already above, since charge-balance is not maintained, this is an obsolete waveform for stimulating vestibular afferents.

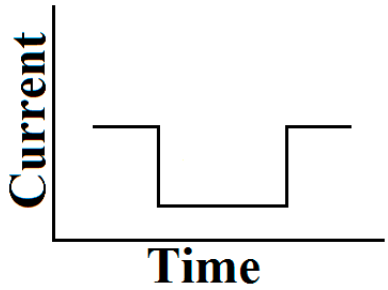


Figure 3.2 Monophasic pulse.

Pseudomonophasic

A short phase of polarity, directly followed by a longer phase with lower amplitude of opposite polarity (Figure 3.3). In cochlear implants, pseudomonophasic stimulation has shown to be more efficient by producing lower thresholds than a biphasic rectangular waveform. It also reduces spread of excitation (Frijns et al., 1996; Macherey et al., 2006).

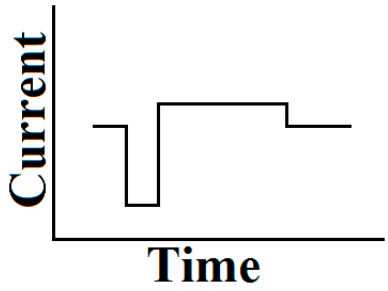


Figure 3.3 Pseudomonophasic pulse.

Delayed pseudomonophasic

A customized pseudomonophasic waveform, where the longer phase is presented midway between the short phases of two consecutive phases (Figure 3.4). As a result of the delay between the short and long phase, its stimulation efficiency in cochlear implants is even better than a pseudomonophasic waveform. This results in a reduction of power consumption. The first phase is the dominant phase. Lengthening or lowering of the second phase does not change the produced thresholds. A delayed pseudomonophasic is not capable of producing frequencies as high as a biphasic rectangular waveform, as a result of the prolonged second phase (Macherey et al., 2006).

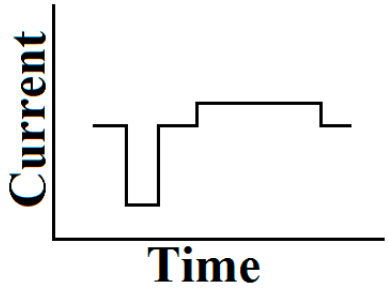


Figure 3.4 Delayed pseudomonophasic pulse.

Continuous 1-co-sinusoidal stimulation

This waveform has been tested with galvanic vestibular stimulation via large surface electrodes placed on the skin retro-auricular. It produced the most reproducible galvanic induced body sway at around 0.5Hz. It was compared with low-frequency block pulses, trapezoidal pulses, short pulses, and 1-co-sinusoidal pulses (Balter et al., 2004). This stimulus is currently used to explore electrical excitability in patients with

bilateral vestibulopathy, but clearly differs from the frequency range applied for direct stimulation of the labyrinth or nerve. It has to be noted that the body sway frequency response also depends on specific mechanical properties of the body (resonance frequency, mass inertia, etc.; Figure 3.5).

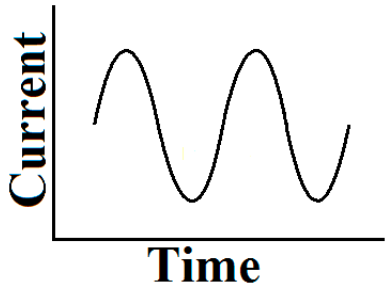


Figure 3.5 Continuous 1-co-sinusoidal stimulation.

Current

Voltage sources are simpler and more efficient than current sources. However, in contrary to current sources, they are not able to control the amount of charge delivery when impedance of electrodes varies. Therefore, a current source is the selected stimulation modality (Wall et al., 2002).

The amplitude of the current has yet to be determined. In nature, physiologically, the conversion from the analog hair cell receptor potential via synapses into spike trains in the afferent fibers can be considered as comparable to a process of analog to digital conversion. Here the sensory information in the spike train is coded in terms of frequency and phase of spikes. The amplitude of the spikes seems then of limited importance: it will show an on–off characteristic. This implies that maybe also the amplitude of the artificial electrical nerve fiber stimulation only needs to pass a minimum threshold to be effective. No clear relationship then would exist between pulse amplitude and frequency and phase content of the original sensor signal. However, the amplitude of the electrode pulses determines also the current spread and by that the number of fibers that will be excited with possibly different thresholds (irregular and regular units) per fiber. It is well known that synchronization of activity between fibers play an important role in the ultimate response. So increasing amplitude will activate more fibers and initiate synchronization.

There are three key factors which play a role in the pulse amplitude: “safety,” a “sufficient response” and “current spread, synchronization, and crosstalk.” Regarding safety, the amplitude of the current must not be too high (>40 mC), otherwise it will

cause electrode dissolution and neural damage (Gong and Merfeld, 2000; Wall et al., 2002; Davidovics et al., 2011). However, if the current is too low, only the irregular afferents will be stimulated and there will not be a sufficient response. Most units are regular and they require a higher current (Bronte-Stewart and Lisberger, 1994; Fridman et al., 2010). Investigations have shown that when the amplitude of current increases, magnitude of VOR also increases, which leads to a higher gain and a more sufficient response (Bronte-Stewart and Lisberger, 1994; Gong and Merfeld, 2000; Della Santina et al., 2007; Merfeld et al., 2007; Wall and Guyot, 2007; Gong et al., 2008; Fridman et al., 2010). When current becomes too high again, the electricity will be spread among other than the targeted anatomical structures ("current spread") and they will be stimulated and react accordingly ("crosstalk"). With the VI, crosstalk mainly appears in the facial nerve, cochlear nerve, and the other ampullary nerves (Lewis et al., 2002; Merfeld et al., 2006; Shkel and Zeng, 2006; Della Santina et al., 2007; Wall and Guyot, 2007; Fridman et al., 2010; Davidovics et al., 2011). This limits selective stimulation (Fridman et al., 2010). In order to find a way of avoiding crosstalk from the facial nerve while having the most optimal current, the amplitude has been increased until facial twitching was observed. After that, it was decreased with a few microamperes until no twitching was present anymore. This experiment was done in squirrel monkeys and chinchillas, without observing interference with the cochlear nerve (Merfeld et al., 2007; Fridman et al., 2010). To avoid crosstalk with the other ampullary nerves, different strategies have been proposed which can be used simultaneously: decreasing current, electrode position and isolation, current steering, and precompensation. The first two speak for themselves: by decreasing the current until no or acceptable shift from the intended VOR-axis is obtained (which means that there is no or little stimulation of the other ampullary nerves) or by locating a well isolated electrode as near as possible to the ampullary nerve so little current is necessary to adequately stimulate the ampullary nerve, crosstalk can be limited (Della Santina et al., 2007; Merfeld et al., 2007; Wall and Guyot, 2007; Feigl et al., 2009). Current steering is the use of stimulating multiple electrodes at the same time, in order to steer the current to a location that is in between the targeted area's of the electrodes when all the stimulating current is delivered to either one of them. The center of activity can therefore be shifted by changing the delivered current to an electrode (Bonham and Litvak, 2008). This is already investigated in cochlear implants, but not yet with the VI. With precompensation, current spread from an electrode targeting one ampullary nerve, is overcome by adjusting the input of the electrodes targeting the other ampullary nerves using vector summation. By using vector summation, it is possible to significantly restore the VOR-axis and to reduce errors in the speed of eye movement responses (obtaining a bigger amplitude). This process of accurately correcting the misalignment of VOR-axis, is called precompensation. Whether precompensation is needed in human subjects is still unknown, since current spread to other ampullary nerves is believed to be less due to bigger distances

between anatomical structures in humans compared to monkeys and chinchillas (Merfeld et al., 2007; Fridman et al., 2010). Besides, neuroplasticity is also able to counterbalance effects of current spread to an extent (Merfeld et al., 2006, 2007). Also adaptation ability to adjust the 3D VOR has shown to be impressive: the human horizontal VOR can be inverted completely within several days when wearing glasses with inverted prisms (Melvill Jones et al., 1988). This will be discussed subsequently.

Pulse frequency

Firstly, increase of pulse frequency induces an increase of VOR magnitude (Cohen et al., 1965; Gong and Merfeld, 2000; Wall et al., 2002; Wall and Guyot, 2007), mimicking the natural response. Secondly, pulsatile stimulation composed of high-frequency components yields less current spread than low-frequency stimulation (Rubinstein and Spelman, 1988; Merfeld et al., 2006). Therefore, the stimulation frequency should be a high pulsatile stimulation which can be varied along the whole frequency range of the afferent fiber (0-400pps). Whether there is a maximum of stimulation frequency below the natural range is uncertain. Some data suggest that there is a maximum around 200pps for the posterior ampullary nerve (PAN) in humans (Wall and Guyot, 2007), although this limitation was not encountered in other experiments in animals (Merfeld et al., 2007; Fridman et al., 2010; Lewis et al., 2010; Davidovics et al., 2011).

A third important fact is the baseline firing rate of vestibular afferents not being centered in the middle of its frequency range (Gong and Merfeld, 2000, 2002; Shkel and Zeng, 2006). As a result, the dynamic range below the baseline is much less than above. In other words: there is less space to maneuver below baseline than above. This is not a problem with a bilateral implant, because the “push–pull” effect is used (Gong and Merfeld, 2002; Della Santina et al., 2007; Gong et al., 2008). However, a unilateral implant is probably not able to give adequate information about yaw-rotations in contralateral direction because the dynamic range below baseline is too small. Since a unilateral implant is preferred because it requires less surgery, risks, costs, etcetera, it could be worth solving this problem. Therefore, the baseline can artificially be set at a higher frequency (supranormal frequency) than the normal average firing rate at a frequency between baseline and maximum. It provides a broader range to modulate below baseline and could therefore be sufficient to provide adequate bidirectional vestibular sensations with a unilateral prosthesis (Gong and Merfeld, 2000, 2002; Lewis et al., 2002, 2010; Della Santina et al., 2007; Merfeld et al., 2007). Investigations show that it is possible to increase the baseline firing rate and that the nervous system is able to adapt. At first a brisk nystagmus occurs after setting a new baseline, which decreases over time while it is still possible

to create a response by modulating above and below the baseline. The fact that a brisk contralateral nystagmus occurs when the supranormal baseline stimulation stops, suggests that central compensation is able to accept a new baseline (Gong and Merfeld, 2002; Lewis et al., 2002, 2010; Merfeld et al., 2006, 2007). Others believe that it is not necessary to use supranormal baseline frequencies because the asymmetry is usually well compensated by the adaptive capacity of vestibulocerebellar circuits. It is enough to suffer little of disability when having a single normal labyrinth (Curthoys and Halmagyi, 1995; Black et al., 1996; Fridman et al., 2010). Besides, modulating around a supranormal baseline frequency provides the vestibular system with information that differs markedly from that encountered in everyday life. This could lead to slower and less complete adaptation (Dai et al., 2011a). Therefore, in their opinion, the advantages of a supranormal frequency (broad dynamic range, symmetric responses) do not counterbalance the major advantage of a normal firing rate, which is higher gain and more sufficient adaptation (Fridman et al., 2010; Dai et al., 2011a). It is indeed observed that static compensation is quite good, but in contrast, dynamic compensation remains poor: e.g., the HIT (image stabilization) remains abnormal even after complete central compensation and adaptation. Also, many patients report a reduced automatization of balance, orientation, and navigation even in centrally good compensated unilateral vestibular lesions (Lacour et al., 2009).

The fourth fact is that when modulating around the baseline, an adequate modulation sensitivity should be chosen. Modulation sensitivity is the amount of modulation in firing frequency as a function of angular head velocity. In other words: for each degree per second that a head turns, the firing rate is modulated up- or downward in pulses per second (pps). The amount of pulses per second increase of firing rate for a given angular velocity is called the sensitivity. Sensitivity is therefore noted as pps/˚/s (Gong and Merfeld, 2000; Lewis et al., 2002; Merfeld et al., 2007). The firing frequency of vestibular neurons forms a hyperbolic curve: it is linear for a broad range of angular velocities, only at higher velocities the response saturates and sensitivity is lower. Therefore, a wide range of velocities can be covered with a fixed frequency range and a fixed sensitivity (Gong and Merfeld, 2000, 2002; Merfeld et al., 2007). In the natural system, type I neurons have a baseline firing rate of 90 pps, with a modulation sensitivity of 0.5 pps/˚/s (Goldberg and Fernandez, 1971; Guyot et al., 2011a). Thus, an increase 0-20 ˚/s in head velocity results in an increase from 90 to 100 pps. It is possible to artificially increase the sensitivity (Gong and Merfeld, 2000, 2002; Lewis et al., 2002, 2010; Merfeld et al., 2007). This results in a significantly higher gain but lower range and implies that less angular velocities can be covered as maximum stimulation is then achieved sooner at slower velocities (Merfeld et al., 2007; Lewis et al., 2010).

Stimulus site

The optimal stimulus location in humans has not been determined yet, because there are three difficult basic requirements. Firstly, when stimulating at a certain position, it should be selective and give as less crosstalk as possible. This is important, because stimulation in the vestibular area can interfere with hearing and stimulate the facial nerve and other vestibular branches than the intended one (Wall et al., 2002; Merfeld et al., 2006, 2007; Della Santina et al., 2007; Wall and Guyot, 2007; Feigl et al., 2009; Guyot et al., 2011b). This can be solved by inserting the electrode as close as possible to the vestibular nerve (Merfeld et al., 2006; Della Santina et al., 2007; Wall and Guyot, 2007; Feigl et al., 2009; Guyot et al., 2011a,b). However, it could interfere with the second basic requirement: as few surgical risks as possible. Major complications of some surgical techniques are deafening the patient and damage to the facial nerve (Gacek, 1974; Parnes and McClure, 1990, 1991; Wall and Guyot, 2007; Feigl et al., 2009; Tang et al., 2009; Dai et al., 2011b). To prevent the hearing loss, experiments in humans are still done with deaf patients (Wall and Guyot, 2007; Guyot et al., 2011a,b). Since the ultimate goal is to develop an implant which can also be used in patients with only a vestibular problem, it is important to refine surgical techniques and eventually weigh the pros of reducing crosstalk against its contras which are the complications involved.

Thirdly, it is still uncertain which part of the nerve should be stimulated. It could depend on pathology since different parts of the vestibular sensory system are affected to a different extent. Gradual and partial loss (e.g., presbyvertigo) seem to implicate slow transganglionic degeneration of vestibular fibers with lower postural deficits and faster compensation than a sudden and total loss (e.g., neurectomy) which leads to fast Wallerian degeneration and needs deep reorganization of the neuronal networks to recover (Lacour et al., 2009).

Therefore, it is necessary to understand the pathological processes of diseases, in order to determine electrode position (Wall et al., 2002; Lacour et al., 2009).

Studies show that loss of vestibular hair cells leads to some degeneration of vestibular nerve and ganglion cells (Schuknecht, 1982; Cass et al., 1989), while a significant number of surviving cells still responds to electrical stimulation, without change of threshold (Wall et al., 2002). This information has to be combined with studies about the specific diseases. Presbyvertigo is associated with an age-related reduced elasticity of the cupula and statolith membrane, a change in viscosity of the endolymph, linear loss of hair cells, nerve fibers, ganglion cells, and the degeneration of within the cerebellum and vestibular nuclei. The mechanical changes in the labyrinth (elasticity and viscosity) reduce the sensitivity, especially for the higher frequencies (fast head movements). In the cristae, type II cells are lost at a greater rate than in the maculae, in contrary to type I cells which have an equal loss in the cristae and maculae. Total reduction of sensory hair-cell population averages 20% for

the maculae and 40% for the cristae, with pronounced inter-individual variations. Reduction in number of vestibular nerve fibers averages 37% in individuals between 75 and 85 years compared to younger persons and the vestibular nuclei show a neuronal loss with an average of 3–5% per decade between the ages of 40 and 93 years (Lacour et al., 2009). The superior division of Scarpa is significantly more affected than the inferior division (Velazquez-Villasenor et al., 2000; Rauch et al., 2001). Temporal bone studies on patients with Menière's disease show next to presbyvertigo degeneration, also a significant loss of hair cells and ganglion cells, with the utricular macula being relatively spared (Leake et al., 1999; McCall et al., 2009). Regarding ototoxicity, degeneration depends on type of drug, drug dosage, and duration of treatment. However, especially hair cells seem to degenerate without affecting ganglion cells on the short-term (Tsuji et al., 2000a; Lacour et al., 2009).

These differences in survival and plasticity of neurons lead to different amounts of neurons available for the electrostimulation. This will result in a wide variation of inter-individual responses to vestibular prosthetic stimulation (Fridman et al., 2010).

Taken all these data into account, it is suggested that after hair cell insult, peripheral dendrites will initially remain intact, after which they "die back" to Scarpa's ganglion (Wall et al., 2002). Electrically stimulating the vestibular nerve could probably prevent rapid loss of spiral ganglion nerves (Leake et al., 1999; Shepherd et al., 2008). Therefore, depending on pathology, direct stimulation after a vestibular insult at different stimulation sites should be considered (Wall et al., 2002). Main sites are locations along the course of the vestibular branches or Scarpa's ganglion (Gacek, 1974; Parnes and McClure, 1990, 1991; Kudo and Nomura, 1996; Gong and Merfeld, 2000, 2002; Lewis et al., 2002, 2010; Wall et al., 2002; Merfeld et al., 2006, 2007; Della Santina et al., 2007; Wall and Guyot, 2007; Feigl et al., 2009; Fridman et al., 2010; Guyot et al., 2011a). The most commonly used surgical approaches will now be discussed briefly, as well as some proposed techniques.

Approach to the canals/ampullotomy

Most investigations use an approach to the ampullae in which the facial nerve and middle ear structures are spared. The surgical procedure involves a cortical mastoidectomy after which the semicircular canals are exposed and opened. Depending on the study, a fenestration at the thin segment or near the junction of the thin segment and the ampulla is made and the electrodes are inserted and placed near the crista of the ampulla.

Animal studies confirm that an electrically evoked nystagmus can be induced, which corresponds to the plane of the stimulated canal (Gong and Merfeld, 2000, 2002; Lewis et al., 2002, 2010; Rubinstein and Della Santina, 2002; Merfeld et al., 2006, 2007; Gong et al., 2008; Tang et al., 2009; Fridman et al., 2010; Davidovics et al., 2011).

However, there are two major risks. Firstly, as mentioned earlier, stimulating the ampullae could lead to an insufficient response since the ampullae can be too far away from a vital part of the vestibular nerve (Schuknecht, 1982; Cass et al., 1989; Leake et al., 1999; Wall et al., 2002; Lacour et al., 2009). Secondly, there could be interference with hearing. This can be the result of opening the labyrinth or by activating the cochlear nerve due to current spread of the electrodes. A study in rhesus monkeys shows that implantation can lead to a hearing loss but is not likely to be more than 10 dB. This hearing loss has not yet been proven to be significant. Regarding stimulation of the cochlear nerve, levels of ABR (auditory brain stem response) and DPOAE (distortion product otoacoustic emissions) increased during stimulation with 0-5 and 2-14 dB respectively (statistically not significant; Dai et al., 2011b).
Research in Maastricht University Medical Centre has focused on modifying this technique to a well-defined ampullar approach which has proven to generate an electrically evoked nystagmus in the plane of the stimulated canal in a human (not yet published).

Approach to the posterior ampullary nerve by Gacek, modified by Guyot er al. (2011a,b)

Gacek (1974) described the surgical approach to the PAN, in order to treat patients with disabling benign paroxysmal positional vertigo. By modifying this technique, it is possible to achieve a robust vertical nystagmus which corresponds to a large extent to an axis perpendicular to the plane of the posterior semicircular canal, without any apparent crosstalk (Wall and Guyot, 2007). A transmeatal approach is used, in which the lateral bony ridge overhanging the round window niche is removed to expose the whole membrane of the round window. The canal of the PAN is then approached by drilling in the most rostral part of the floor of the round window niche. Next, it is "blue-lined" by leaving approximately 100µm of bone on it. After that, an electrode is inserted. This approach has been successfully tested in humans (Wall and Guyot, 2007).
The major risk of this technique is sensorineural hearing loss, which varies from 3.7 (Gacek and Gacek, 2002) to 38% (Epley, 1980).

Approach of the lateral ampullary nerve and superior ampullary nerve by Guyot et al. (2011a,b)

A new technique was proposed by Guyot et al. (2011a,b) in order to reach the lateral ampullary nerve (LAN) and superior ampullary nerve (SAN) with little risk of damage to the facial nerve and without affecting the oval window. It is a transmeatal approach with a partial atticotomy in which the head of the malleus and the incus are removed.

The LAN and SAN are then approached by drilling at the spot ventral to the prominence of the lateral semicircular canal, superior to the horizontal tympanic segment of the facial canal and inferior to the tegmental roof. The drill is directed ventrally, medially, and inferiorly. Once the nerves are reached, electrodes can be inserted. A temporal bone study showed that the canal of the nerve was directly reached in few cases (5-12.5%). Mostly, it was indirectly accessible through the osseous ampulla by removing parts of the bony wall of the lateral semicircular canal, but with preservation of the membranous labyrinth (70-90%).
This technique has recently been tested in three humans. It was shown that a nystagmus is evoked by stimulating the nerves at the desired location. When LAN was separately stimulated, a horizontal nystagmus was obtained. However, in two out of three cases, LAN and SAN were simultaneously stimulated since their fiber bundles are in close proximity of each other (Wall et al., 2002; Della Santina et al., 2007; Guyot et al., 2011a). This resulted in a predominantly horizontal nystagmus with a vertical component. Being not able to selectively stimulate the nerves might not be a problem, since cross-axis adaptation would possibly align the nystagmus to the desired axis. Stimulation range varied between 120 and 1000µA. Regarding risks, sensorineural hearing loss and damage to the facial nerve will probably be the main risk of this technique because the membranous labyrinth can be damaged accidentally and drilling is performed closely to the facial nerve (Feigl et al., 2009). Also, the ossicular chain has to be reconstructed as parts of the chain are removed during the procedure. This results in an air-bone gap, which can be expected to be less than 20 dB in more than 90% of cases (Zheng et al., 1996; Guyot et al., 2011a).

Approaches to Scarpa's ganglion

Since the spatial orientation of the five vestibular receptors is preserved in Scarpa’s ganglion (Sando et al., 1972), it could be possible to implant electrodes at that location and provide adequate stimulation. However, current spread could be an issue because the fiber bundles are (just like LAN and SAN) in close proximity of each other. It would also require very invasive approaches to get the electrodes in position: a translabyrinthine or middle fossa approach (Wall et al., 2002). These are not yet investigated regarding the VI and will therefore not be discussed. Since in many pathological processes a significant number of vestibular nerve cells survive (Schuknecht, 1982; Cass et al., 1989; Tsuji et al., 2000a,2000b; Velazquez-Villasenor et al., 2000; Rauch et al., 2001; Lacour et al., 2009) and approaches to Scarpa’s ganglion are very invasive, research has only been done about approaches to the ampullae and vestibular nerves (Suzuki et al., 1969; Kudo and Nomura, 1996; Gong and Merfeld, 2000; Lewis et al., 2002, 2010; Merfeld et al., 2006, 2007; Wall and Guyot, 2007; Gong et al., 2008; Feigl et al., 2009; Tang et al., 2009; Fridman et al., 2010; Dai et al., 2011b; Guyot et al., 2011a).

Until now, most research has focused on stimulating the nerves of the semicircular canals and not the ones of the otolith organs. This results from the fact that the sensory part of the otolith organs, the macula, consists of hair cells which are sensitive for motion in different directions (Wall et al., 2002; Kingma, 2005; Lysakowski, 2005). This means that their nerves have axons which represent different directions. Therefore, they are difficult to stimulate. It would result in much crosstalk and require extra electrodes and accelerometers (Wall et al., 2002; Della Santina et al., 2007). Some state that it is also much more important to emulate the angular VOR from the semicircular canals, than the linear VOR from the otolith organs. After all, when one is fixating at a target greater than ~1 m away, retinal image slip due to angular motion of the eyes and head dominate slip due to translation (Della Santina et al., 2007; Fridman et al., 2010).
Although the brain is able to adapt to a suboptimal stimulus (see below), striving for an optimal stimulus seems important in order to reduce the burden on central compensation (Fridman et al., 2010). Finding the best stimulus site is an important step in this process.

Results

Studies have shown that electric stimulation of the canal nerves induces a nystagmus which corresponds to the plane of the canal which is innervated by the stimulated nerve branch (Gong and Merfeld, 2000, 2002; Lewis et al., 2002, 2010; Wall et al., 2002; Della Santina et al., 2007; Merfeld et al., 2007; Wall and Guyot, 2007; Gong et al., 2008; Fridman et al., 2010; Guyot et al., 2011a). The outcomes still demonstrate inter-subject variability, just like with cochlear implant patient outcomes. However, there are many consistencies (Merfeld et al., 2007). The characteristics of the evoked VOR will now be discussed. Main results are presented in Table A3.1 in Appendix 3.1.

Gain

The gain of the electrically evoked VOR varies from very low (e.g., 0.07) to near normal. It is influenced by many factors. Apart from the efficacy of the electrode–nerve system, there are factors that can be modified more easily in order to achieve a higher gain.

Current

As stated earlier, gain is increased by a higher current (Bronte-Stewart and Lisberger, 1994; Gong and Merfeld, 2000; Wall et al., 2002; Della Santina et al., 2007; Merfeld et al., 2007; Wall and Guyot, 2007; Gong et al., 2008; Fridman et al., 2010). Current should be high enough to stimulate the regular units of the nerve, but low enough to

avoid electrode dissolution, neural damage, and too much crosstalk by current spread (Gong and Merfeld, 2000; Lewis et al., 2002; Wall et al., 2002; Merfeld et al., 2006, 2007; Shkel and Zeng, 2006; Della Santina et al., 2007; Wall and Guyot, 2007; Fridman et al., 2010; Davidovics et al., 2011). Methods to overcome these factors, like electrode position and isolation, current steering, and precompensation are still investigated (Suzuki et al., 1969; Kudo and Nomura, 1996; Gong and Merfeld, 2000; Wall et al., 2002; Della Santina et al., 2007; Merfeld et al., 2007; Wall and Guyot, 2007; Bonham and Litvak, 2008; Feigl et al., 2009; Fridman et al., 2010; Guyot et al., 2011a).

Frequency

Gain increases with stimulus frequency. A frequency range has not be determined yet, since it varies with experimental set-up and tested subject (Cohen et al., 1965; Gong and Merfeld, 2000; Wall et al., 2002; Wall and Guyot, 2007). However, it might be necessary to increase the dynamic range, which implies an increase of the baseline firing rate of vestibular afferents to a supranormal level (Gong and Merfeld, 2000, 2002; Lewis et al., 2002, 2010; Della Santina et al., 2007; Merfeld et al., 2007). As discussed above, this might however result in unacceptable lower gains (Fridman et al., 2010).

Modulation sensitivity

A significantly higher gain is achieved by adjusting the settings of the vestibular prosthesis to a higher modulation sensitivity (Gong and Merfeld, 2002; Lewis et al., 2002, 2010; Merfeld et al., 2007). It can result in near normal gain and for each doubling of stimulation sensitivity, gain roughly doubles (Merfeld et al., 2007).

Stimulation period and transitions

Gain is significantly increased by stimulation period and transitions between stimulation states. When stimulating for a longer time, gain at first decreases, but slowly increases over the ensuing time (Lewis et al., 2002, 2010). Considering transitions between different stimulation states (investigated transition cycle: off – low sensitivity → low sensitivity – high sensitivity → high sensitivity – off → off – low sensitivity, etc.), it was shown that the gain at the onset of stimulation with a new off-to-on transition was generally greater than that recorded after the previous off-to-on transition. With each new cycle, gain initially increased followed by a rapid drop. After that, it either slowly increased or remained relatively stable at a level which was above the one of the previous cycle. Which transition is most important in increasing the gain, is not yet determined (Lewis et al., 2010).

Bilateral stimulation

Bilateral stimulation increases the gain. The electrically evoked responses by bilateral stimulation turn out to be equal to a linear summation of responses evoked by unilateral right ear and unilateral left ear stimulation. Advantages of bilateral stimulation are a higher sensitivity (more precise stimulation) and the fact that it is probably not necessary anymore to use a supranormal baseline firing rate. Disadvantages are additional risks (e.g., perform surgery on two sides), higher costs, and more complexity. After all, the efficacy of the electrode–nerve system is hardly ever equal on both sides, which requires different currents on each side in order to restore the push–pull nature of the complementary functioning labyrinths (Gong and Merfeld, 2002; Della Santina et al., 2007; Gong et al., 2008).

Age

VOR-gain declines with advancing age (Dimitri and Oas, 1996; Lewis et al., 2010). However, there seems to be no good parallel between imbalance in the elderly and caloric response. This could imply that age-related decline in vestibular response is the result of a decline in central vestibular processing instead of a loss of peripheral vestibular function, or that VOR-gain is only affected in the higher frequencies (Mallinson and Longridge, 2004).

Adaptation to baseline

When the vestibular afferents are chronically stimulated by a tonic continuous (supra)normal baseline pulse-rate, at first a brisk nystagmus occurs. This nystagmus decreases, dependent on the laboratory animal setting, over a period from 20 min to 1 day until no nystagmus is recorded anymore (Gong and Merfeld, 2000; Lewis et al., 2002, 2010; Merfeld et al., 2006, 2007; Della Santina et al., 2007; Gong et al., 2008; Guyot et al., 2011b). During PAN stimulation in a human with repeated “on–off” transitions, nystagmic response disappeared after only a few minutes without major discomfort (Guyot et al., 2011b). When stimulation was stopped, a nystagmus in the contralateral direction occured, which attenuated within minutes to hours. This “after-effect” suggests a form of neural plasticity and adaptation (Merfeld et al., 2006, 2007; Guyot et al., 2011b). The fact that this “after-effect” has a more rapid decay, is suggested to be the result of the “recall” of the previous adaptive state (no stimulation; Gong and Merfeld, 2002).

Motion modulates responses

Although the nervous system adapts to the tonic baseline firing rate, it does not adapt to the motion-modulated part of stimulation. VOR develops significantly when the

stimulation frequency is modulated around the baseline. When stimulated for a couple of months, motion-modulated responses still remain. Gain is initially high and declines rapidly, after which it slowly increases (Lewis et al., 2002, 2010; Merfeld et al., 2006, 2007; Gong et al., 2008; Guyot et al., 2011b).

Dual state adaptation

Transitions between stimulation states do not only have a favorable effect on gain, but also on the evoked nystagmus when the prosthesis is activated or inactivated. After a couple off-to-on and on-to-off and transitions, nystagmus, and the "after-effect nystagmus" are less intense and the return to baseline occurs more rapidly. After many of these transitions, only little nystagmus is evoked when stimulation starts or stops. The nervous system of laboratory animals seems to recognize the absence or presence of stimulation and react adequately to it. This adaptation to two states ("on" or"off ") in which no major undesired nystagmus response is evoked by a transition, is called "dual state adaptation." This might be relevant for patients who only need the prosthesis on a stand-by system to overrule fluctuations (e.g., Meniere's disease), or when a change of batteries or stimulation parameters is necessary (Merfeld et al., 2006, 2007; Lewis et al., 2010; Guyot et al., 2011b).

Cross-axis adaptation

It is possible to develop an eye response which is aligned with the axis of head motion, by stimulating a canal which is orthogonal to the motion axis. This is called "cross-axis adaptation" (Lewis et al., 2002; Della Santina et al., 2007; Dai et al., 2011a). In an experiment with squirrel monkeys, the PAN was stimulated while the velocity sensor of the prosthesis was oriented parallel to the axis of the lateral canals. At first a vertical VOR of 0.05 was measured, as well as a small horizontal response. Over 7 days, the horizontal gain increased to 0.1 and the vertical gain decreased (Lewis et al., 2002). This indicates that cross-axis adaptation is possible. It could play a role in correcting misalignments of the device (Della Santina et al., 2007; Dai et al., 2011a).

Time constant

The time constant of the evoked VOR is smaller than the time constant of the prosthesis and does not change significantly during chronic stimulation, bilateral stimulation, and by multiple transitions in modulation sensitivity (Merfeld et al., 2007; Gong et al., 2008; Lewis et al., 2010). Probable underlying mechanisms are that the velocity storage integrator is not engaged by prosthetic input and the high levels of tonic stimulation which are likely to reduce the efficacy of synaptic transmission in the central vestibular pathways by constantly releasing synaptic vesicles (Lewis et al., 2010). Since the time constant of the prosthesis can be made arbitrarily long, it has

been suggested that the smaller time constant of the evoked VOR might not be a limitation (Merfeld et al., 2007). However, much depends also to which extent involvement of the velocity storage is crucial for further central processing.

VOR-symmetry

When stimulation starts, a substantial VOR-asymmetry is present. Head turns away from the stimulated ear produce larger VOR-gains than head turns toward the stimulated ear. This phenomenon was observed in squirrel monkeys, which also showed a decline in difference between the ipsilateral and contralateral gains of 71-78%, when stimulated chronically for 2 weeks in low sensitivity mode [0.9-1.2pps/˚/s (Lewis et al., 2010)]. In another experiment with chinchilla's, VOR-asymmetry did not change significantly during 1 week of prosthetic use. Improvement in VOR-symmetry when using a prosthesis is therefore still uncertain (Dai et al., 2011a).

VOR-axis

When the prosthesis is activated for the first time, there is a rapid deviation of the intended VOR-axis. This results from current spread and reduction of the intended VOR-gain (e.g., reduction of horizontal VOR-gain when the horizontal semicircular canal is stimulated; Fridman et al., 2010; Lewis et al., 2010).
In chinchillas it was shown that VOR-axis remained nearly constant when modulating the intensity of frequency from 20 to 100%, but misalignment increased with increasing current amplitude and pulse duration. Therefore, the response of an electrode which elicits suboptimal selective stimulation and moderate to severe misalignment (probably because it was implanted not very close to the ampullary nerve), can be optimized by using a lower pulse duration. However, an electrode eliciting highly selective stimulation, maintains low misalignment over a wide range of pulse duration (Davidovics et al., 2011).
During chronic stimulation, the VOR-axis shifts back toward the intended axis (Lewis et al., 2010; Dai et al., 2011a). In another experiment with chinchillas, misalignment of VOR-axis improved significantly after 1 week of multichannel prosthetic stimulation. This indicates a rapid adaptation of the central nervous system to prosthetic stimulation (Dai et al., 2011a).
As stated earlier, precompensation might be able to significantly correct the misalignment of VOR-axis. Also, modulating around a normal baseline instead of a supranormal one could lead to faster and more complete adaptation (Fridman et al., 2010; Dai et al., 2011a).

Acclimation to peripheral vestibular stimulation by a prosthesis

Still little is known about the ability of the brain to adapt to changes in the peripheral vestibular signal (Lewis et al., 2002). Particularly Merfeld and colleagues have done extensive research to adaptation in guinea pigs and squirrel monkeys (Gong and Merfeld, 2000, 2002; Lewis et al., 2002, 2010; Wall et al., 2002; Merfeld et al., 2006, 2007; Gong et al., 2008).

Investigations show that the brain is at least partly able to adapt to changes in peripheral vestibular signal by a prosthesis. Examples are: a significant increase in gain as a result of chronic stimulation and multiple transitions between stimulation states, the "after-effect" and "recall", "dual state adaptation", "cross-axis adaptation", an increase of VOR-symmetry, and a better alignment of VOR-axis during chronic stimulation.

Summarizing: the brain is able to adapt the VOR when motion-modulated prosthetic vestibular input is used. It adapts to a higher baseline stimulation, while still reacting on the dynamic component. Due to adaptation, VOR-gain, rotational axis, and symmetry increase during chronic stimulation (Merfeld et al., 2007; Gong et al., 2008; Fridman et al., 2010; Lewis et al., 2010; Dai et al., 2011a; Guyot et al., 2011b).

Knowing these adaptive capabilities of the brain opens new perspectives, not only for the engineering part (it is probably not necessary to completely mimic natural stimuli) but also for how and when to use the VI in the future. For example, patients could regularly turn their VI on and off in order to facilitate a more rapid adaptation and patients with Meniere's disease could use their VI as a "vestibular pacemaker" in which it is only turned on when necessary. These findings also suggest that when a vestibular prosthesis is installed, a period of adaptation is necessary in which the patients adapt to the new stimuli. Probably, a specific adaptation protocol is necessary, just like with the cochlear implant. Defining the optimal protocol will require human patient studies (Merfeld et al., 2006).

Future research

Future research should focus on engineering as well as biomechanical issues (Wall et al., 2002). At this point, engineering issues concerning power are of main concern. Therefore, only this aspect will now be discussed since other engineering issues are outside the scope of this article. Power problems can be solved by decreasing demand and increasing supply. Regarding demand, especially the sensors have a relatively high power consumption which has to be reduced. Besides, when developing these sensors, it should be taken into account that the sensors become as small as possible so they can be attached to the head. An optimal stimulus profile can also reduce power consumption by using the lowest current and frequency as possible with a

power-efficient waveform (Wall et al., 2002; Macherey et al., 2006; Davidovics et al., 2011). Regarding power supply, batteries should become more powerful and there must be found a way to deal with instantaneous loss of power which could lead to dangerous situations for the patient. An external battery pack has been used previously (Merfeld et al., 2006).
Concerning biomechanical issues, determining the stimulus site in humans is the most important aspect of the biomechanical issues at this point. This can be combined by investigating the optimal stimulus profile, which could differ for each site since the distance to a nerve and current spread vary for each location. Once the prosthesis is implanted, an acclimation protocol should be established and the efficacy of the prosthesis must be evaluated by different vestibular, visual, proprioceptive, auditory, cognitive, and hearing tests. Analyzing these tests will give information about what to expect from the implant (Wall et al., 2002).
Furthermore, ethical issues should be tackled. They comprise for example safety regulations during (human) research, patient selection, alternatives for an implantable prosthesis, and costs for society.
In all aspects of the biomechanical and ethical issues, the ENT-surgeon will play an important role.

Conclusion

To use a basic VI in humans seems feasible in the very near future. Investigations show that electric stimulation of the canal nerves induces a nystagmus which corresponds to the plane of the canal which is innervated by the stimulated nerve branch. The brain is able to adapt to a higher baseline stimulation, while still reacting on a dynamic component. The best response will be achieved by a combination of the optimal stimulus (stimulus profile, stimulus location, precompensation), complemented by central vestibular adaptation. The degree of response will probably vary between individuals, depending on pathology and their ability to adapt.

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Table A3.1 Main results of vestibular implant research.

Findings	Animal research	Type of animal	Main results and references	Human research	Main results and references
Electric stimulation of the canal nerves induces a nystagmus which corresponds to the plane of the canal which is innervated by the stimulated nerve branch	Yes	Guinea pig	Stimulation of the anterior canal shows vertical eye movements (Gong and Merfeld, 2000)	Yes	Blue-lined stimulation of the posterior ampullary nerve shows a primarily vertical response (Wall and Guyot, 2007) Stimulation of LAN and SAN shows a predominantl horizontal response with a vertical component (Guyot et al., 2011a)
		Squirrel monkey	Stimulation of the horizontal canal evokes primarily horizontal responses (Gong and Merfeld, 2002; Lewis et al., 2002, 2010; Merfeld et al., 2007; Gong et al., 2008)		
		Chinchilla	Acute stimulation using a multichannel prosthesis shows eye responses already aligned somewhat with head rotation axes, but significant misalignment is evident (Della Santina et al., 2007; Fridman et al., 2010; Dai et al., 2011a)		
Gain is increased by a higher current	Yes	Guinea pig	Eye movements are measurable at a current of 19 µA and become greater at higher current levels (Gong and Merfeld, 2000)	Yes	Blue-lined PAN stimulation evokes a fairly linear increase of response with increasing input amplitude over the range of 300 µA to 1 mA (Wall and Guyot, 2007; Guyot et al., 2011b)
		Squirrel monkey	The magnitude of the response is roughly proportional to stimulation current pulse level (Gong et al., 2008)		LAN-stimulation ranges from 120 to 1000 µA, which might be enough to encode eye movements of different velocities (Guyot et al., 2011a)
		Chinchilla	Increasing stimulus current amplitude increases VOR magnitude (Della Santina et al., 2007; Fridman et al., 2010)		
Gain increases with stimulus frequency and modulation sensitivity	Yes	Guinea pig	Increases in the stimulation frequency are matched by increases in the magnitude of the eye movement responses. Clear eye responses are observed from 40.5 Hz (Gong and Merfeld, 2000)	Yes	Blue-lined stimulation of PAN shows that slow component velocity rapidly increases with increasing pulse repetition rate from 25 pps to a maximum of 200 pps (Wall and Guyot, 2007)
		Squirrel monkey	Gain roughly doubles for each doubling of the stimulation sensitivity (Lewis et al., 2002, 2010; Merfeld et al., 2007)		

Table A3.1 (continued)

Findings	Animal research	Type of animal	Main results and references	Human research	Main results and references
Gain is significantly increased by stimulation period and transitions between stimulation states	Yes	Squirrel monkey	The VOR shows adaptive capabilities during chronic stimulation and cycling of stimulation state, evidenced by an increase in gain (Lewis et al., 2010)	No	
		Chinchilla	3D VOR response remains relatively high and constant during 7 days of continuous stimulation (Dai et al., 2011a)		
Bilateral stimulation increases the gain	Yes	Squirrel monkey	VOR responses evoked by bilateral stimulation are the summation of the responses evoked by bilateral stimulation, demonstrating a gain constant of 0.24 (normal = 0.26; Gong et al., 2008)	No	
The vestibular system adapts to (supra)normal baseline stimulation	Yes	Guinea pig	The first time stimulation is turned on, all guinea pigs acclimate within a day or so (Merfeld et al., 2006)	Yes	When continuous electrical stimulation at 400 µA is turned on for the first time, strong nystagmic beats are almost absent from recordings after 27 min (Guyot et al., 2011b)
		Squirrel monkey	The nystagmus evoked by baseline stimulation disappears within 6 h to 1 day of the chronic stimulation turned on (Lewis et al., 2002, 2010; Merfeld et al., 2007)		
		Chinchilla	Activation of prosthesis causes a brisk nystagmus, which adapts to a slow phase velocity of <5˚/s in all components within 20 min. (Della Santina et al., 2007)		
The vestibular system adapts to static baseline stimulation, but not to dynamic modulation	Yes	Guinea pig	Sinusoidally modulated stimulation yields a sinusoidally modulated VOR, even after acclimation to the baseline stimulation (Merfeld et al., 2006)	Yes	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 (Guyot et al., 2011b)
		Squirrel monkey	Animals show horizontal VORs for periods exceeding 90 days when pulse-rate is modulated, while nystagmus evoked by baseline stimulation has disappeared (Merfeld et al., 2007; Lewis et al., 2010)		

Table A3.1 (continued)

Findings	Animal research	Type of animal	Main results and references	Human research	Main results and references
The vestibular system adapts to different stimulation states	Yes	Guinea pig	After many off-to-on or on-to-off transitions, little nystagmus is evoked by turning the stimulation on or off (Merfeld et al., 2006)	Yes	Successive "on–off" cycles of continuous electrical stimulation result in a progressively shorter duration of the nystagmic response (Guyot et al., 2011b)
		Squirrel monkey	The spontaneous nystagmus evoked by stimulation gradually attenuates and remains relatively small during subsequent periods of chronic stimulation of different stimulation states (Lewis et al., 2010)		
Cross-axis adaptation is possible in the vestibular system	Yes	Squirrel monkey	A horizontal VOR can develop even if the stimulated posterior canal is orthogonal to the velocity sensor of the prosthesis (Lewis et al., 2002)	No	
		Chinchilla	Cross-axis adaptation considerably improves 3D VOR alignment during the first week of chronic stimulation (Dai et al., 2011a)		
Time constant of the evoked VOR is smaller than the time constant of the prosthesis	Yes	Squirrel monkey	The time constant of the VOR response was smaller than the time constant of the prosthesis (Merfeld et al., 2007; Gong et al., 2008; Lewis et al., 2010)	No	
Improvement in VOR-symmetry is still uncertain	Yes	Squirrel monkey	During the first 2 weeks of stimulation, No there is a decline in difference between the ipsi- and contralateral gains of 71–78% when stimulated in the low sensitivity mode (Lewis et al., 2010)	No	
		Chinchilla	VOR-asymmetry did not change significantly during 1 week of prosthetic use (Dai et al., 2011a)		
Misalignment of VOR-axis improves significantly during prosthetic use	Yes	Squirrel monkey	During chronic stimulation, the initial No VOR-axis (45˚–56˚) is shifted in the plane closer to the compensatory orientation of 90˚ (73˚–83.5˚; Lewis et al., 2010)	No	
		Chinchilla	Seven days of continuous prosthetic use shows a significant improvement in VOR alignment (Dai et al., 2011a)		

Chapter 4

The modified ampullar approach for vestibular implant surgery: feasibility and its first application in a human with a long-term vestibular loss

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Abstract

Objective
To assess, for the first time in a human with a long-term vestibular loss, a modified approach to the ampullae and the feasibility of evoking a VOR by ampullar stimulation.

Materials and methods
Peroperative stimulation of the ampullae, using the ampullar approach, was performed under full anesthesia during cochlear implantation in a 21-year-old female patient, who had experienced bilateral vestibular areflexia and sensorineural hearing loss for almost 20 years.

Results
The modified ampullar approach was performed successfully with as minimally invasive surgery as possible. Ampullar stimulation evoked eye movements containing vectors congruent with the stimulated canal. As expected, the preliminary electrophysiological data were influenced by the general anesthesia, which resulted in current spread and reduced maximum amplitudes of eye movement. Nevertheless, they confirm the feasibility of ampullar stimulation.

Conclusion
The modified ampullar approach provides safe access to the ampullae using as minimally invasive surgery as possible. For the first time in a human with long-term bilateral vestibular areflexia, it is shown that the VOR can be evoked by ampullar stimulation, even when there has been no vestibular function for almost 20 years. This approach should be considered in vestibular surgery, as it provides safe access to one of the most favorable stimulus locations for development of a vestibular implant.

Introduction

For more than a decade, research has been conducted into development of an invasive vestibular prosthesis (vestibular implant) (Gong and Merfeld, 2000, 2002; Lewis et al., 2002, 2010; Wall et al., 2002; Della Santina et al., 2007; Merfeld et al., 2007; Wall et al., 2007; Gong et al., 2008; Fridman et al., 2010; Davidovics et al., 2011; Guyot et al., 2011a), since non-invasive vestibular prostheses present many drawbacks in restoring vestibular function (Janssen et al., 2010). The proposed vestibular implant is analogous with the cochlear implant as it directly stimulates the neural pathways through electrical pulses (Gong and Merfeld, 2000).

Firstly, motion is detected by gyroscopes which send their signals to a processor. Secondly, the signals are processed to create an adequate stimulus with the right pulse characteristics (frequency, current, shape). Thirdly, the stimulus is delivered by electrodes to the vestibular nerve (Gong and Merfeld, 2000, 2002; Lewis et al., 2002, 2010; Wall et al., 2002; Merfeld et al., 2006, 2007; Shkel and Zeng, 2006; Della Santina et al., 2007; Fridman et al., 2010).

Studies have shown that it is possible to induce a nystagmus which corresponds to the plane of the canal innervated by the electrically stimulated nerve branch (Gong and Merfeld, 2000, 2002; Lewis et al., 2002, 2010; Wall et al., 2002; Della Santina et al., 2007; Merfeld et al., 2007; Wall et al., 2007; Fridman et al., 2010; Davidovics et al., 2011; Guyot et al., 2011a). Moreover, the brain seems to adapt the VOR to motion modulated vestibular input and is able to increase VOR gain (maximum peak eye velocity divided by the maximum stimulus velocity), rotational axis, and symmetry during chronic stimulation (Merfeld et al., 2007; Gong et al., 2008; Fridman et al., 2010; Lewis et al., 2010). However, some hurdles have still to be overcome in relation to biomechanical and engineering issues (Wall et al., 2002). One of the main biomechanical issues is presented by the stimulus site, which is not yet properly determined. The ideal stimulus site should be a location with a well-considered compromise between three basic requirements:

1. To be close to the vestibular nerve, in order to give selective stimulation and have as little crosstalk as possible (the spread of the current to other than the targeted anatomical structures which leads to unintended activation of them) to the facial nerve, cochlear nerve, and other ampullary nerves (Wall et al., 2002; Merfeld et al., 2006, 2007; Della Santina et al., 2007; Wall et al., 2007; Feigl et al., 2009; Guyot et al., 2011a).
2. To be reached with as few surgical risks as possible. Damage to the facial nerve and deafening the patient are the main risks involved in the surgical approach of some specific locations (Gacek, 1974; Parnes and McClure, 1990, 1991; Wall et al., 2007; Feigl et al., 2009; Tang et al., 2009; Dai et al., 2010).
3. To stimulate a vital part of the vestibular nerve. Studies show that, depending on pathology and elapsed time since onset of disease, different parts of the

vestibular sensory system are affected to a different extent. This results in varying amounts of neurons available for the electrodes. Therefore, it is believed that different stimulus locations should be considered. Proposed locations are the ampullae, along the course of the vestibular branches, or Scarpa's ganglion (Gacek, 1974; Schuknecht, 1982; Cass et al., 1989; Leake et al., 1999; Gong and Merfeld, 2000, 2002; Tsuji et al., 2000a,b; Velazquez-Villasenor et al., 2000; Rauch et al., 2001; Lewis et al., 2002, 2010; Wall et al., 2002; Merfeld et al., 2006, 2007; Della Santina et al., 2007; Wall et al., 2007; Feigl et al., 2009; Lacour et al., 2009; McCall et al., 2009; Guyot et al., 2011a).

Previously, two types of approach have been developed for implantation of a vestibular implant:

1. An approach to the lateral ampullary nerve (LAN), superior ampullary nerve (SAN), and posterior ampullary nerve (PAN), for extralabyrinthine stimulation.
2. An approach to the ampullae of the semicircular canals (ampullar approach), for intralabyrinthine stimulation.

Approach to LAN/SAN/PAN

In Geneva an approach to the PAN, LAN, and SAN has been developed and tested in humans (Wall et al., 2007; Feigl et al., 2009; Guyot et al., 2011a,b).
This surgery involves two different approaches, one for the PAN, the other one for the LAN and SAN. The PAN is reached by a transmeatal approach in which the floor of the round window niche is drilled in its most rostral part. Then, the nerve is "blue-lined" and an electrode is inserted. This technique is extracted from that described by Gacek to treat benign paroxysmal positional vertigo (Gacek, 1974; Wall et al., 2007). The LAN and SAN are reached by a transmeatal approach with removal of the head of the malleus and incus. After that, drilling is started at the spot ventral to the prominence of the lateral semicircular canal, inferior to the tegmental roof, and superior to the prominence of the facial canal. Once the nerves are reached, electrodes are inserted.
It is shown that electric stimulation from these locations induces a nystagmus which corresponds to the plane of the canal innervated by the stimulated nerve branch, and that it is possible to elicit smooth oscillatory eye movements by modulating the amplitude or frequency of the stimulation (Wall et al., 2007; Feigl et al., 2009; Guyot et al., 2011a,b).
There are a number of possible drawbacks to this type of approach. Firstly, there is a risk of sensorineural hearing loss, especially when drilling out the osseous ampulla which could result in accidental damage to the membranous labyrinth. For the approach to the PAN, the risk of sensorineural hearing loss varies from 3.6 to 38% (Epley, 1980; Gacek and Gacek, 2002). Secondly, parts of the ossicular chain are removed and, despite ossicular chain reconstruction, a certain degree of conductive

hearing loss may be caused. Thirdly, drilling is in the vicinity of the facial nerve, which carries the risk of damaging the nerve (Feigl et al., 2009). Fourthly, the ampullary nerves are sometimes unreachable (5-18%; Kudo and Nomura, 1996; Feigl et al., 2009).
The main advantage, however, is the very close proximity of the electrodes to the nerves, which could allow for highly selective stimulation with little current, leading to little current spread and crosstalk (Merfeld et al., 2006; Della Santina et al., 2007; Wall et al., 2007; Feigl et al., 2009; Guyot et al., 2011a). Also, in the case of peripheral dendrites which have "died back" to Scarpa's ganglion, stimulation through this type of approach is relatively proximal to this structure, and could offer stimulation of more vital structures (Wall et al., 2002).

Ampullar approach

In other studies, an approach to the ampullae of the semicircular canals was used (Gong and Merfeld, 2000, 2002; Lewis et al., 2002, 2010; Rubinstein and Della Santina, 2002; Merfeld et al., 2006, 2007; Gong et al., 2008; Tang et al., 2009; Fridman et al., 2010; Davidovics et al., 2011; Nie et al., 2011; Rubinstein et al., 2011). It comprises a cortical mastoidectomy, after which the semicircular canals are exposed and opened via a fenestration at the thin segment or near the junction of the thin segment and the ampulla. The electrodes are inserted and placed near the crista of the ampulla.
In animals, it was shown that it was possible to induce an electrically evoked nystagmus which corresponded to the plane of the stimulated canal. However, there are still some drawbacks that have to be investigated. For example: deafening the patient, and creating a sufficient response (Gong and Merfeld, 2000, 2002; Lewis et al., 2002, 2010; Rubinstein and Della Santina, 2002; Merfeld et al., 2006, 2007; Gong et al., 2008; Tang et al., 2009; Dai et al., 2010; Fridman et al., 2010). When the canal is fenestrated, perilymph oozes out of the canal. Depending on the case, sensorineural hearing loss could occur, which is not always reversible (Parnes and McClure, 1990, 1991; Tang et al., 2009; Dai et al., 2010). Regarding a sufficient response, as stated earlier, a vital part of the vestibular nerve should be stimulated. When peripheral dendrites have "died back" to Scarpa's ganglion (Wall et al., 2002), a location near the ampulla could be too far from a vital structure to create a sufficient response.
The main advantages of this type of approach are that the facial nerve remains relatively safe from damage and that the middle ear structures are preserved (Wall et al., 2007; Feigl et al., 2009; Guyot et al., 2011a).
The ampullar approach appears to be relatively safe, with few drawbacks, and easier to use than the LAN/SAN/PAN-approach. However, the drawbacks and possible risks of the ampullar approach, namely more current spread, sensorineural hearing loss (Tang et al., 2009; Dai et al., 2010), and damage to the facial nerve and ossicular chain, have not yet been extensively investigated in humans. A few studies have shown that,

using the appropriate surgical technique and equipment, there is a risk of hearing loss, but that this is neither severe nor permanent (Parnes and McClure, 1990, 1991; Gacek and Gacek, 2002; Tang et al., 2009; Dai et al., 2010; Rubinstein et al., 2011). Also unknown is whether it is possible to stimulate a vital part of the nerve, when there has not been any vestibular function for many years. Therefore, the goal of this study was to evaluate for the first time, in a human with a long-term vestibular loss, the ampullar approach, and the feasibility of evoking a VOR by ampullar stimulation. This was achieved by:

1. Performing the ampullar approach in a human, and specifying/modifying the technique in order to minimize surgical drilling and damage to the otic capsule;
2. Showing and discussing the preliminary results of ampullar stimulation under general anesthesia.

Materials and methods

Surgical procedure: The ampullar approach

The ampullar approach has previously been performed by using a cortical mastoidectomy, exposition of the semicircular canals, extensive bluelining of the semicircular canals, and fenestrating them at the thin segment or adjacent to the ampullary ends (Gong and Merfeld, 2000, 2002; Lewis et al., 2002, 2010; Rubinstein and Della Santina, 2002; Merfeld et al., 2006, 2007; Gong et al., 2008; Tang et al., 2009; Fridman et al., 2010; Davidovics et al., 2011; Nie et al., 2011; Rubinstein et al., 2011). In this trial, the approach was specified more clearly, since the use of fixed anatomical markers as a reference prevents the surgeon from drilling unnecessarily and minimizes damage to the otic capsule. Drilling was performed in a direct angle to the ampullae, without bluelining relatively large portions of the canals, resulting in as minimally invasive surgery as possible and, therefore, minimizing the chance of accidentally entering the canals. Intra-operative facial nerve monitoring was used.

Approach to the ampullae of the superior and lateral canal

When the superior and lateral semicircular canals fuse at the vestibule, they make a “V-shape.” Therefore, after the mastoidectomy and posterior tympanotomy, minimally invasive bluelining of the anterior ends of the canals (adjacent to each ampullary end) was obtained by drilling cranially at the dome of the lateral canal and following it, until the “V” appeared. A small diamond burr (2 mm) was used. As the anterior end of the superior canal was located by following the lateral canal, no more drilling of the superior canal was necessary. Eventually, approximately only 3 mm of

the anterior ends of both canals were blue-lined. After that, a small fenestration adjacent to each of the ampullary ends was made. In this case, a manually positioned temporary electrode was inserted (see below). Permanent electrodes would be inserted in the case of a vestibular implant (Figures 4.1 and 4.2).

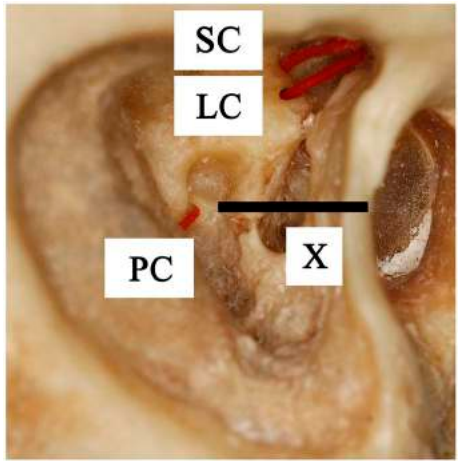

Figure 4.1 Lateral view of a right temporal bone. It shows the superior canal (SC), lateral canal (LC), and posterior canal (PC) which are fenestrated near the ampullary ends and marked with inserted plastic wires. Line X is the imaginary line through the stapes footplate, which indicates the location of the posterior ampulla, medial to the facial nerve.

Approach to the posterior ampulla

The ampulla of the posterior canal is located nearby the oval window and stapes. Therefore, it is located medial to the facial nerve, at an imaginary almost horizontal line through the stapes footplate, between the sigmoid sinus and the facial nerve (Figure 1, line X). Using the stapes as a reference, minimally invasive surgery was obtained by directly undermining the facial nerve below the lateral semicircular canal and drilling a hole in the direction of the stapes. After bluelining the anterior end of the canal, a small fenestration adjacent to the ampulla was made. Again, temporary electrodes were then inserted (Figure 4.3). However, it would also be possible to insert permanent electrodes, according to the requirements of the case.

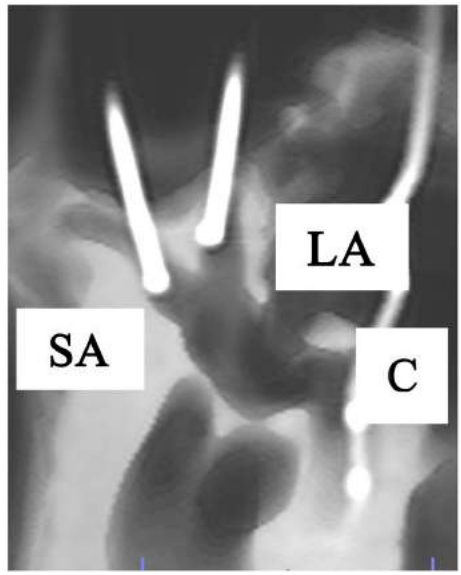

Figure 4.2 Anterolateral view of a right temporal bone using cone beam CT-scan. It shows the fenestration and insertion of the cochleovestibular electrodes in the superior ampulla (SA), lateral ampulla (LA), and cochlea(C).

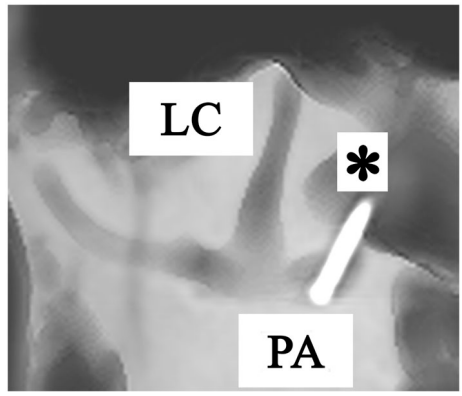

Figure 4.3 Anterolateral view of a right temporal bone using cone beam CT-scan. It shows the fenestration and insertion of the electrode (*) in the posterior ampulla (PA). (LC=lateral canal).

Human subject

The subject of this experiment was a 21-year-old woman undergoing surgery for cochlear implantation, performed by the last author in Maastricht University Medical

Centre. Due to meningitis in her childhood, she became bilaterally deaf with bilateral vestibular areflexia. She reported no vestibular complaints.
Three inclusion criteria were fulfilled:

1. Mean peak slow phase velocity of ≤5˚/s in bilateral bithermal caloric irrigations;
2. Pathological Head-Impulse-Test (HIT) for horizontal and vertical canals;
3. Low or no gain on rotatory chair tests.

Electronystagmography (ENG) was used for vestibular testing. Bilateral bithermal (30˚and 44˚) caloric irrigations were performed by experienced technicians in standardized conditions. Rotatory chair tests consisted of horizontal and vertical torsion swing (0.11Hz, ωmax=100˚/s) and bilateral velocity steps (ω=250˚/s). Manual HITs were recorded with a high-speed camera [CASIO Exilim, Pro EX-F1, 12× optical zoom, high speed camera, 300 frames per second (fps)] in the three semicircular canal planes. The presence of correction saccades was considered as pathological. She showed no response to bilateral vestibular galvanic stimulation. These vestibular tests were only performed pre-operatively.
Informed consent, and approval from the Medical Ethical Committee, in accordance with the Helsinki Declaration, were obtained (protocol name and number: “Electric stimulation of the ampullary nerves in patients with bilateral vestibular loss” – NL31405.068.10; World Medical Association General Assembly, 2000). The study was registered at the Dutch Trial Register: www.trialregister.nl.

Experimental testing

Stimulation equipment, paradigm

To check the locations of the fenestrations, and to show the feasibility of evoking a VOR by stimulating the ampullary nerves via the ampullae, a monopolar electrode was used to electrically stimulate the ampullae. It was manually positioned on the cristae of the ampullae for intralabyrinthine stimulation. The return electrode was placed on the patient’s back. When measurements were completed, the canals were closed with bone wax and Tissucol® (Baxter, aprotinin, trombin).
Matlab© software was used to drive a real-time processor (RP2.1 Real-Time Processor, Tucker-Davis Technologies©) which was connected to a galvanic stimulator (Maastricht Instruments b.v.©) where the stimulus was converted to a current. A monopolar stimulator (Standard Prass Flush-Tip Stimulator Probe, Medtronic©) of 500µm was used to deliver the current to the nerves. Biphasic pulses of 200 µs phase duration with a repetition rate of 200 Hz were used. Current was modulated step by step from 0 to a maximum of 1mA. Pulse train duration was 10s with on/off periods of 0.5s.

Eye movements, recording, and analysis

The horizontal, vertical, and torsional eye movements were recorded using video oculography (Clinical Video Eye Tracker, Maastricht Instruments b.v.©) at 50 samples/s. Recordings were analyzed off-line with algorithms written in Matlab© software. Horizontal, vertical, and torsional components were estimated at suprathreshold stimulation parameters.

Anesthetics

The whole procedure was performed under general anesthesia. Propofol 6mg/kg/h and Remifentanil 0.35mcg/kg/min were administered during the surgical approach. When electric stimulation and measurements commenced, Propofol was stopped, and Remifentanil was continued at the same dosage. After electric stimulation, the cochlear implantation procedure was resumed with Propofol only (8mg/kg/h).

Results

The modified ampullar approach was performed successfully: the ampullae from the anterior, lateral, and posterior canal were reached, with minimal bluelining of the anterior ends of the canals. No damage to the facial nerve, ossicular chain, or inner ear structures was observed.

Stimulation with 700μA elicited tonic eye deviation in all three ampullae, confirming the positioning of the electrode and feasibility of ampullar stimulation by this approach.

Maximum vertical and horizontal amplitudes of the eye during ampullar nerve stimulation of the canals ranged from 6.6˚ to 19˚. These results are presented for each canal in Figure 4.4.

Stimulation of the LAN showed a horizontal component which was away from the stimulation side. The vertical component was upward. For the stimulation of the SAN, the vertical component was upward and the horizontal component was away from the stimulation side. Maximum amplitude of torsion was 17˚. Stimulation of the PAN elicited tonic eye deviation with a downward vertical component and a horizontal component away from the stimulation side. When the current was increased to obtain maximum amplitudes, facial twitching was observed in most of the cases.

When stimulation was stopped, the eye returned back to its starting position. Examples are presented in Figures 4.5A,B, which refer to stimulation of the SAN. The horizontal component was delayed (5s) compared to the vertical component.

Regarding the anesthetics, it was clearly observed that after the Propofol was stopped, reactions became more profound once the Propofol was cleared from the body.

During post-operative follow-up, the patient did not suffer from any change in vestibular symptoms. Facial nerve function was preserved.

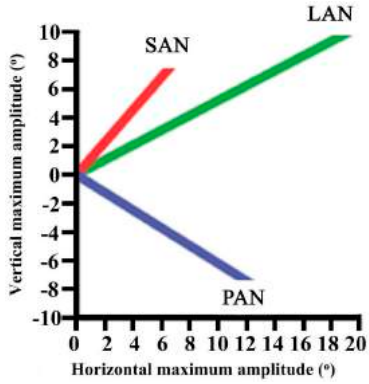

Figure 4.4 Maximum vertical and horizontal amplitudes of the eye during ampullar nerve stimulation of each canal.

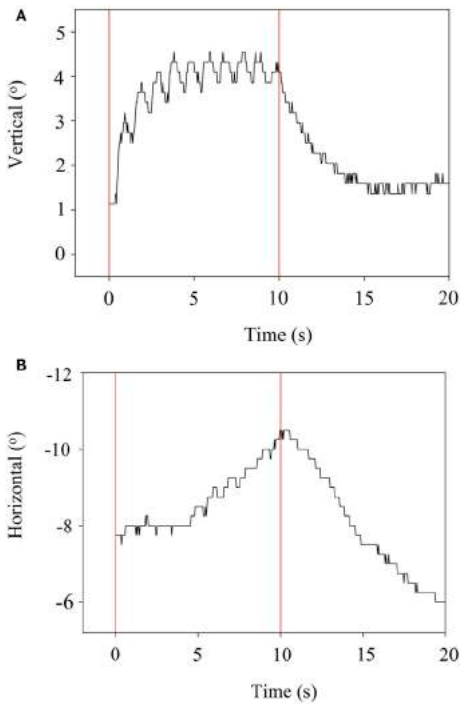

Figure 4.5 (A) VOR vertical component during suprathreshold stimulation of the SAN. Vertical bars indicate the start and end of stimulation. (B) VOR horizontal component during suprathreshold stimulation of the SAN. Vertical bars indicate the start and end of stimulation.

Discussion

This study shows, for the first time in a human with a long-term vestibular loss, the modified ampullar approach with minimally invasive surgery and the feasibility of ampullar stimulation. There is an important difference between this human subject and subjects in previous research: previous subjects still had some residual function, or bilateral vestibulopathy was induced by canal plugging or ototoxic medication prior to implantation (Gong and Merfeld, 2002; Lewis et al., 2002, 2010; Wall et al., 2002; Merfeld et al., 2006, 2007; Della Santina et al., 2007; Gong et al., 2008; Tang et al., 2009; Dai et al., 2010, 2011; Davidovics et al., 2011; Rubinstein et al., 2011). Our human subject had exhibited no vestibular function for almost 20 years. Therefore, it was very important to show whether stimulation in this subject would be feasible. This study shows that a VOR can be evoked by electrically stimulating the ampullae under general anesthesia, in a human with a long-term vestibular loss, and in whom galvanic stimulation did not elicit any response during vestibular testing pre-operatively. This suggests that stimulation of the ampullae is probably close enough to vital parts of the vestibular nerve to elicit a response in the majority of cases. “Dying back” of the nerves could be less of an issue than previously assumed. However, it could influence the stimulation range (change of stimulation thresholds) and inter-individual differences in responses to the vestibular implant. The modified ampullar approach seems to be a safe approach.

Firstly, the facial nerve remains relatively safe from damage when intra-operative facial nerve monitoring is employed. Secondly, middle and inner ear structures are preserved. Thirdly, surgery of the vestibular system is already well known by neuro-otologic surgeons compared to the extralabyrinthine approach to the LAN/SAN/PAN. Fourthly, accidental damage to the canals is reduced, by modifying the ampullar approach into a procedure with minimally invasive surgical drilling, using the “V-shape” of the superior and lateral canal, together with the imaginary horizontal line through the stapes footplate as a reference. This facilitates safe bluelining of only the anterior ends of the canals, adjacent to the ampullary ends. Further advantages of the ampullar approach are that multiple electrodes can be inserted into the ampulla, and that fixating them will be less challenging than with the extralabyrinthine approach. For example, if the array of electrodes shifts accidentally during surgery, another electrode with the best response could be selected for stimulation. In addition, using more electrodes could also facilitate current-steering and precompensation (correcting the misalignment of the VOR-axis by vector summation; Fridman et al., 2010).

One potential disadvantage of intralabyrinthine ampullar stimulation is the general belief of deafening the patient. However, more studies show that with appropriate surgical technique and equipment, opening the canals carries a risk of hearing loss that is neither severe nor permanent (Parnes and McClure, 1990, 1991; Gacek and

Gacek, 2002; Tang et al., 2009; Dai et al., 2010; Rubinstein et al., 2011). In the future, intralabyrinthine stimulation could thus become an option in hearing patients, after more thorough investigations in humans. Therefore, the ampullar approach should be considered in vestibular implant surgery since it carries low risks. It opens up new perspectives on the development of a 3D vestibular implant with selective intralabyrinthine stimulation of the vestibular nerve.

It should be noted that the ampullar approach does not rule out the extralabyrinthine approach to the LAN/SAN/PAN. They could be used as complementary procedures (a combination of both approaches in one patient) or as alternatives (the appropriate technique is selected for each patient), depending on the results of future research.

These preliminary results show that ampullar stimulation is possible in a person with a long-term vestibular loss. Stimulation leads to a tonic eye deviation with mixed components and variable maximum amplitudes. Although components are mixed, stimulation always evoked a vector which is congruent with the canal: a horizontal component during LAN-stimulation, an upward component during SAN-stimulation, and a downward component during PAN-stimulation. This component was not always the predominant vector. However, in Figure 4.4 it is shown that stimulation of each ampulla has its own vector. Studies show that this is more important than having the right vector, since cross-axis adaptation can occur. This is the phenomenon that eye responses which are aligned with the axis of head motion, can be evoked by stimulating a canal which is orthogonal to the axis of motion (Lewis et al., 2002, 2010; Della Santina et al., 2007; Dai et al., 2011). Research in chinchillas showed that there was a significant improvement of the VOR-axis after 1 week of multichannel prosthetic stimulation, indicating that the central nervous system rapidly adapts to prosthetic stimulation (Dai et al., 2011).

Crosstalk is an important factor. Figure 4.5B shows a delayed horizontal component (after 5s) during SAN-stimulation, suggesting current spread resulting in delayed recruitment of the LAN. In addition, Figure 4.4 shows mixed components during ampullar stimulation as a result of significant crosstalk between the ampullary and/or otolith nerves. However, it is difficult to interpret the crosstalk between nerves. For example, the horizontal component of SAN-stimulation could be the result of simultaneous LAN-stimulation, utricular stimulation, or both. Factors which could play a role in the misalignment are both the pulse duration and the current. In this experiment, biphasic pulses of 200µs phase duration and 10s pulse train duration were used. Animal research has shown that misalignment is reduced by using a lower pulse duration and current (Davidovics et al., 2011). In future research, pulse phase and train duration could be lowered, especially as a pulse train duration of 10s does not mimic physiological conditions. As presented in Figure 4.5B, the horizontal component is not visible until 4–5s after SAN-stimulation. Normal head motions do not last for 5s. This could suggest that during physiological conditions, in which head motions generally have a shorter duration, recruitment of the other ampullary nerves

is less likely as a shorter time does not allow the current spread to reach the other nerves. Regarding current, a higher current was necessary in order to cope with the effects of general anesthesia. This resulted in current spread to the other ampullary and/or otolith nerves as well as to the facial nerve. Once a prosthesis is implanted, it is believed that a lower current could be maintained during daily use, resulting in less current spread. If misalignment of a vestibular prosthesis should remain after adjusting for the factors mentioned above, precompensation could also be used since it has been shown to significantly restore the VOR-axis (Fridman et al., 2010).
We were able to evoke a VOR under full anesthesia by replacing Propofol by Remifentanil. This is a useful finding since, at least in our clinic, both patients and ethical committees are more likely to cooperate when surgical procedures and investigations are performed under general anesthesia. Although anesthesia will influence the reactions to electrical stimuli (Poon and Irwin, 2009) (e.g., changing thresholds and stimulation range, lowering maximum amplitudes of eye movements), this anesthetic protocol can be used in future investigations. It could facilitate vestibular implant surgery when intra-operative ampullar stimulation is necessary to investigate electrode position or when electrically evoked compound action potentials (ECAPs) are not obtained during surgery (Nie et al., 2011). The feasibility of applying ampullar stimulation in cases of vestibular nerve degeneration could also be assessed. However, it can only be used for qualifying, and not for quantifying, electrophysiological reactions. For example, under normal conditions, maximum amplitudes of 6.6˚–19˚ would be suboptimal for the use of a vestibular implant. When Propofol was stopped, reactions became more profound once the Propofol was cleared from the body. The effect of Remifentanil remained. Therefore, we can only state that stimulation is feasible; realistic maximum amplitudes cannot be given. However, the maximum amplitudes that were obtained under general anesthesia seem very promising.

Conclusion

The modified ampullar approach provides safe access to the ampullae using as minimally invasive surgery as possible. For the first time in a human with long-term bilateral vestibular areflexia, it has been shown that the VOR can be evoked by ampullar stimulation, even when there has been no vestibular function for almost 20 years. This approach should be considered in vestibular surgery, since it provides safe access to one of the most favorable stimulus locations for development of a vestibular implant.

Acknowledgments

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Chapter 5

Vestibular implants: 8 years of experience with electrical stimulation of the vestibular nerve in 11 patients with bilateral vestibular loss

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Abstract

Background
The concept of the vestibular implant is primarily to artificially restore the vestibular function in patients with a bilateral vestibular loss (BVL) by providing the central nervous system with motion information using electrical stimulation of the vestibular nerve. Our group initiated human trials about 10 years ago.

Methods
Between 2007 and 2013, 11 patients with a BVL received a vestibular implant prototype providing electrodes to stimulate the ampullary branches of the vestibular nerve. Eye movements were recorded and analyzed to assess the effects of the electrical stimulation. Perception induced by electrical stimulation was documented.

Results
Smooth, controlled eye movements were obtained in all patients showing that electrical stimulation successfully activated the vestibulo-ocular pathway. However, both the electrical dynamic range and the amplitude of the eye movements were variable from patient to patient. The axis of the response was consistent with the stimulated nerve branch in 17 out of the 24 tested electrodes. Furthermore, in at least 1 case, the elicited eye movements showed characteristics similar to those of compensatory eye movements observed during natural activities such as walking. Finally, diverse percepts were reported upon electrical stimulation (i.e., rotatory sensations, sound, tickling or pressure) with intensity increasing as the stimulation current increased.

Conclusion
These results demonstrate that electrical stimulation is a safe and effective means to activate the vestibular system, even in a heterogeneous patient population with very different etiologies and disease durations. Successful tuning of this information could turn this vestibular implant prototype into a successful artificial balance organ.

Introduction

Bilateral loss of the vestibular function (BVL) has a dramatic impact on the quality of life. The affected patients complain predominantly of chronic imbalance and blurred vision in dynamic conditions (Guinand et al., 2012a, 2012b). They fear to fall and frequently report having difficulties reading signs or recognizing faces when they are walking. Some even report feeling ashamed to be seen in public as others often think they are drunk. Moreover, due to multifocal cortical and thalamic projections of vestibular afferents, emotions, memory, cognitive abilities and personality can also be affected (Fuller et al., 2004; Smith & Darlington 2013; Smith & Zheng 2013). In most cases, a BVL cannot be compensated and sensory substitution is insufficient so that there is no or little spontaneous improvement to be expected in the long term (Zingler et al., 2008). As a consequence, BVL imposes a significant social and economic burden on patients and society (Sun et al., 2014). Unfortunately, there currently is no evidence for an efficient treatment.

The concept of a vestibular implant to artificially restore the vestibular function is similar to that of cochlear implants, which have a proven track record for hearing rehabilitation in cases of profound deafness. Briefly, in a vestibular implant, head motion is captured with motion sensors (i.e., gyroscopes) and transformed to a pattern of electrical currents by an external processor. This information is then wirelessly transmitted to an implanted stimulator that incorporates vestibular electrodes. Electrical stimulation delivered through these vestibular electrodes would trigger action potentials in the vestibular nerve that, in theory, would be interpreted by the central nervous system as head motion, ultimately allowing the 'artificial' restoration of the vestibular function.

Intensive efforts towards the development of a vestibular implant for clinical applications have been undertaken during the past decade (Merfeld & Lewis 2012). Devices with single or multichannel independent vestibular arrays have been designed and/or manufactured (Gong & Merfeld 2000, 2002; Della Santina et al., 2007; Valentin et al., 2013; Rubinstein et al., 2012). Different motion sensor fixation and signal processing strategies have been proposed, leading to the recent filing of several patents (Jaeger et al., 2013, 2015; Garnham et al., 2012; Merfeld et al. 2003; Pelizzone et al., 2014). Finally, several animal and human studies have established the feasibility of this concept. Electrical stimulation was identified as an effective means for activating the vestibular system in animals already in the 1960s (Cohen & Suzuki 1963; Suzuki et al., 1964). Most recent animal research efforts have concentrated on meticulously investigating the effects of electrical stimulation parameters on vestibular responses (Davidovics et al., 2011), focusing mainly on vestibulo-ocular responses (Lewis et al., 2002; Merfeld et al., 2006, 2007; Gong et al., 2008; Lewis et al., 2010a; Saginaw et al., 2011; Lewis et al., 2012; Fridman et al., 2010; Dai et al., 2011a, 2011b, 2013; Davidovics et al., 2012; Phillips 2015), but also on orientation

percepts and postural responses (Thompson et al., 2012; Lewis et al., 2013; Mitchell et al., 2013). In humans, extralabyrinthine and intralabyrinthine surgical routes to the lateral (LAN), posterior (PAN) and superior (SAN) ampullary branches of the vestibular nerve have been described and validated in peroperative stimulation trials (Kos et al., 2006; Wall et al., 2007; Feigl et al., 2008, 2009; Guyot et al., 2011a; van de Berg et al., 2012). Our group has reported on the results of the first chronic implantations of a vestibular implant prototype in human subjects (Guyot et al., 2011b), followed by a group at the University of Washington (Golub et al., 2014). Our most recent results demonstrated that it is possible to elicit an artificial, motion-controlled vestibulo-ocular reflex in implanted patients (Perez Fornos et al., 2014). Postural responses to electrical stimulation have also been reported in human subjects (Phillips et al., 2013).
Our research group has participated in vestibular implant development for over 10 years. Today, we have a unique pool of 11 BVL patients implanted with a vestibular implant prototype. In this paper, we report on our main results, gathered over a period of 8 years.

Materials and methods

Patients and surgery

Eleven patients with bilateral or unilateral deafness (3 females and 8 males, mean age at implantation years, range 34–71 years) and concomitant BVL were recruited between 2007 and 2013 at the Service of Otorhinolaryngology, Head and Neck Surgery, Department of Clinical Neurosciences, Geneva University Hospital in Switzerland and at the Division of Balance Disorders of Maastricht University Medical Centre in the Netherlands. The demographics of the patient population are presented in Table 5.1. They all fulfilled 3 inclusion criteria: (1) mean peak slow-phase velocity of ≤5°/s in bilateral bithermal caloric irrigations, (2) pathological Head Impulse Test for all 6 horizontal and vertical canals, and (3) low (<0.2) or no gain in rotatory chair tests. Standard videonystagmography and electronystagmography were used for vestibular testing. Bilateral bithermal (30 and 44°C) caloric irrigations were performed by highly experienced technicians in standardized conditions. Rotatory chair tests consisted of standard clinical horizontal torsion swing tests (0.05–0.1 Hz, ωmax = 60°/s). The Head Impulse Test was performed with the Video Head Impulse Test of Ulmer (Synapsis©, Marseille, France), the EyeSeeCam Video Head Impulse Test (EyeSeeCam VOG©, Munich, Germany) and/or the ICS Impulse (Otometrics, Denmark).
The patients received a custom-modified cochlear implant (MED-EL, Innsbruck, Austria) with 1, 2 or 3 vestibular electrodes derived from the main cochlear array (Figure 5.1). A minimum of 9 electrodes was thus left for the cochlear stimulation, which should not jeopardize the auditory outcome (Shannon RV, et al., 1995).

Table 5.1 Demographics and implant details for each patient.

Patient	Sex	Hearing loss	Etiology	Onset	Age at implant	Implant year	Implanted side	Vestibular electrodes	Surgical approach
S1	M	B	idiopathic	progressive	68	2007	left	PAN	EL
S2	M	B	congenital / idopathic	progressive	34	2008	right	PAN	EL
S3	M	B	congenital / idopathic	progressive	46	2008	left	PAN	EL
S4	M	B	Menière's	progressive	71	2011	left	PAN	EL
S5	M	U	traumatic	acute (<1 year ago)	63	2012	right	PAN LAN	EL
S6	F	B	mastoidectomy (L) traumatic (R)	acute (<1 year ago)	67	2013	left	PAN LAN SAN	IL
S7	F	U	meningitis	acute (47 years ago)	48	2012	right	PAN LAN SAN	IL
S8	M	B	DFNA9	progressive	67	2012	left	PAN LAN SAN	IL
S9	F	B	DFNA9	progressive	68	2013	left	PAN LAN SAN	IL
S10	M	B	DFNA9	progressive	66	2013	left	PAN LAN SAN	IL
S11	M	B	DFNA9	progressive	64	2013	left	PAN LAN SAN	IL

B = bilateral; U= unilateral; EL = extralabyrinthine; IL = intralabyrinthine

In 5 patients (S1–S5), an extralabyrinthine transmeatal surgical approach was performed (Kos et al., 2006; Feigl et al., 2009). The PAN (S1–S5) and the LAN (only S5) were exposed. In these patients (except S1), this part of the surgery was done under local anesthesia, and a probe electrode (125 µm diameter, 90% platinium-10% iridium Tefloncoated wire; MicroProbes for Life Science, Gaithersburg, Md., USA) was used to perform acute peroperative electrical stimulation. The depth and direction of drilling was adjusted following the observation of nystagmic responses obtained upon electrical stimulation. Once the optimum electrode position was found, general anesthesia was induced and the custom-modified device was implanted using a conventional retro-auricular approach with a regular mastoidectomy, a posterior tympanotomy and a cochleostomy. The cochlear array was inserted into the cochlea and the vestibular electrodes were put in contact with the PAN (and LAN in S5) and secured with fascia from the temporal muscle and/or glass ionomer (Ketac, 3M, Saint Louis, Minn., USA).

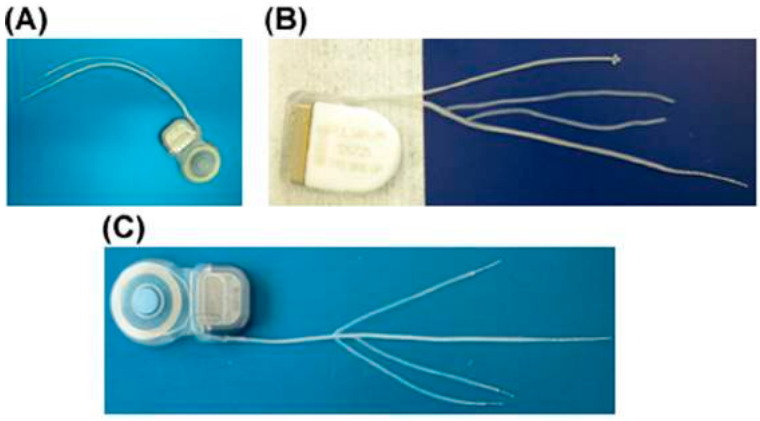

Figure 5.1 The three generations of vestibular implant prototypes developed in collaboration with MED-EL (Innsbruck, Austria) based on existing cochlear implant technology. A standard cochlear implant was customized by removing 1–3 electrodes from the cochlear array. Each of these 'vestibular' electrodes was located on the distal tip of separate leads to allow implantation in the posterior ampullary nerve (extralabyrinthine approach, **a**), in the posterior and lateral ampullary nerves (extralabyrinthine approach, **b**), or in the ampullae of the posterior, lateral, and superior semicircular canals (intralabyrinthine approach, **c**).

In 6 patients (S6–S11), an intralabyrinthine approach was used to put 1 electrode in each ampulla (van de Berg et al., 2012). The entire procedure was performed under general anesthesia. Briefly, this approach consisted of a regular mastoidectomy, a posterior tympanotomy and a cochleostomy. The 3 semicircular canals were blue-lined and an inframillimetric 'canalotomy' was performed close to each ampulla. Electrodes were then inserted into each ampulla. At this stage, the patient was kept under intravenous remifentanil only, allowing to maintain general anesthesia while preserving the slow phase of the vestibulo-ocular reflex (e.g., tonic eye deviation). Peroperative electrical stimulation delivered via the vestibular electrodes was performed and the direction of the resulting tonic eye deviation was used to adjust the electrode position. Finally, electrodes were secured with hydroxylapatite bone cement (Otomimix, Walter Lorenz Surgical, Jacksonville, Fla., USA) and fibrin sealant (Tissucol, Baxter International Inc., Deerfield, Ill., USA), or with fascia from the temporal muscle.

Device activation took place no earlier than 4 weeks postoperatively, when healing of the surgery site was assumed to be complete. For simplicity purposes, from now on, we will refer to PAN, LAN and SAN for electrical stimulation delivered with each of the vestibular electrodes.

Electrical stimulation

The setup for the electrical stimulation of the PAN, LAN and SAN was composed of a desktop computer that allows customization of the stimulation parameters (current intensity, pulse rate, phase width, modulation depth and modulation frequency). The computer communicated this information to the implanted stimulator via the manufacturer's research interface Board (RIB II, MED-EL) and the system's antenna.
Cochlear electrodes were always switched off during the experimental procedure. Stimulation was delivered to each electrode separately, and consisted of trains of charge-balanced, cathodic-first, biphasic pulses (400 μs/phase) presented at 200 pulses/s. During the device activation, the current amplitude was incremented by steps of a maximum of 50 μA (lowered to 25–10 μA if necessary) to minimize patient discomfort. Vestibular threshold was determined as the first (lowest) level of electrical current where the first vestibular symptom was observed (e.g., a change in nystagmus slow-phase velocity >2°/s) or reported (e.g., 'I feel like turning'). Particular attention was given to the first reported perception. Then stimulation was again increased by 10- to 25-μA steps until the upper comfortable level (e.g., occurrence of pain or facial nerve stimulation) was reached. The dynamic range was determined as the current range from the vestibular threshold up to the upper comfortable level (Guyot et al., 2011).
The next step consisted of characterizing the eye movements that could be elicited by electrical stimulation delivered through each electrode (single-electrode stimulation). A 'baseline' stimulation (constant amplitude electrical stimulation) was given at an amplitude arbitrarily chosen in the middle of the dynamic range. Once patients were adapted to this 'baseline' stimulation (Guyot et al., 2011), the amplitude of the stimulus was modulated using a sinusoidal signal with a frequency of 3 Hz and a modulation depth corresponding to 75% of each patient's dynamic range. At the end of the experiments, 'baseline' stimulation was gradually decreased to zero.

Eye movement recording and analysis

Two-dimensional eye-in-head angular position was recorded using a fast monocular 2D video oculography system (EyeSeeCam VOG). Ideally, 3D binocular movements should be reported (Haslwanter 1995). However, we decided to use 2D video oculography for several reasons. First, although the search coil technique is considered as the gold standard for 3D ocular recording (Robinson 1963), it is invasive and is generally not well tolerated for use longer than 20–30 min; therefore, we did not consider it acceptable to add this burden to our test patients who had to undergo long, repeated testing sessions. Secondly, search coil measurements require a relative complex infrastructure consisting of a cubic structure (about $1m^3$) incorporating the 3D coils by which the magnetic field is generated. For accurate measurements, the patient's head must stay in the linear area (center) of this magnetic field. This is a

major drawback as our future goal is to test patients at least partly moving freely in their environment. Moreover, previous studies have demonstrated that 2D analysis of eye movements is sufficient to assess the vestibulo-ocular reflex during natural activities (Crane & Demer 1997). Thirdly, several portable, light-weight, high-speed, infrared monocular video oculography systems, incorporating motion sensors have recently been developed, providing accurate measurements of 2D eye movements and 6D head movement (Weber et al., 2009; Bartl et al., 2009), but the detection of the eye torsion (3rd dimension) by video eye trackers is still more troublesome, less reliable and less accurate. Therefore, being aware of its limitations, we considered it acceptable to use monocular 2D video oculography as a first approach. All eye movement recordings were done in darkness with patients sitting in an upright position.

A segment of 10 cycles was analyzed for each experimental trial. Eye position data were first filtered at 30Hz with a low-pass moving average filter (zero-phase shift). Eye velocity and acceleration were then obtained via the first and second derivatives of the eye position. Blinks and quick eye movements (e.g., saccades and nystagmus quick phases) were detected as segments where eye acceleration was >1,000°/s. These segments were removed from the data and were not replaced by interpolated values (Figure 5.2a).

Peak horizontal and vertical velocity (respectively, PVhorizontal and PVvertical) were estimated using best-fit frequency-fixed sinusoids (Figure 5.2b). Total peak velocity was then computed as the vector norm of these 2D components:

$$\left(\sqrt{PV_{horizontal}{}^2 + PV_{vertical}{}^2} \right).$$

The axis of eye movements (angle with respect to the horizontal) was computed as:

$$tan^{-1} \left(\frac{PV_{vertical}}{PV_{horizontal}} \right)$$

Eye movements with an angle >45° were considered as predominantly vertical and those with an angle <45° as predominantly horizontal. Finally, asymmetry was presented using the index

$$\frac{PV_E - PV_I}{PV_E + PV_I},$$

where PV_E and PV_I stand for the excitatory and inhibitory peak of the sinusoidal eye movement, respectively (i.e., away from and towards the implanted ear). These excitatory/inhibitory peak velocities were calculated using best fits to stimulus half-cycles (e.g., only positive or only negative), similar to previous studies (Dai et al., 2011b;

Stir

Perez Fornos et al., 2014). Individual patient results did not always follow a normal distribution; therefore, results were reported as median values (25th–75th percentiles). Mean results across patients followed a normal distribution (Shapiro-Wilk $p>0.05$) and were therefore presented as mean values (± standard deviation).

Ethics considerations

Experiments were designed and conducted in accordance with the 1964 Declaration of Helsinki. Local Ethics Committees of the Geneva University Hospitals (NAC 11-080) and of the Maastricht University Medical Centre (NL36777.068.11/METC 11-2-031) approved this experimental protocol. All participants gave their informed consent prior their inclusion in the study.

Results

A total of 24 vestibular electrodes were available for electrical stimulation in 11 patients. At the time of writing this paper, the longest follow-up period was 8 years (patient S1, implantation in July 2007), and the shortest was 2 years (S10 and S11, implantation in July 2013). No complications related to the surgery or to the experimental procedure were reported.

Measured dynamic range

A vestibular threshold could be determined in 21 of the 24 available electrodes (blue circles in Figure 5.3). In 19 of these electrodes, the upper comfortable level corresponded to facial nerve stimulation (red circles in Figure 5.3). In 2 electrodes, no upper comfortable level could be determined even at the highest current amplitude tested (550μA; red triangles in Figure 5.3). The dynamic range was highly variable across patients and across electrodes (gray columns in Figure 5.3). It was null for 1 electrode. In 3 electrodes, no vestibular reaction was observed nor reported, even at the highest stimulation currents tested (550μA; blue triangles in Figure 5.3).

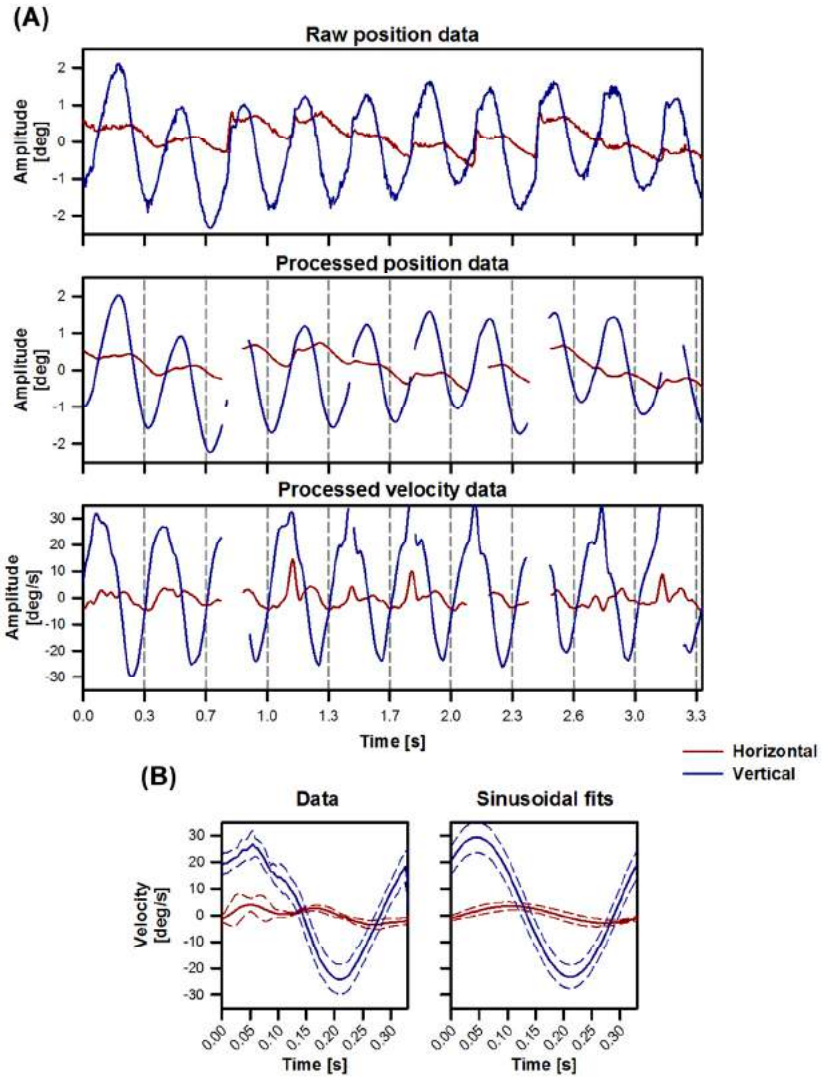

Figure 5.2 Illustration of eye movement data processing. The panels present eye movement data tracings for patient S7, gathered during the amplitude modulation experiments (frequency 3Hz, modulation strength corresponding to 75% of the patient's dynamic range). **A** Three steps are illustrated: raw eye position (e.g., before any processing was performed), processed eye position data (e.g., eye position data after low-pass filtering and after blinks and quick eye movements >1,000°/s had been removed), and processed eye velocity data (e.g., obtained from the derivative of the processed eye position data). **B** Average cycle data ± standard deviation (left) and their corresponding sinusoidal fits (right).

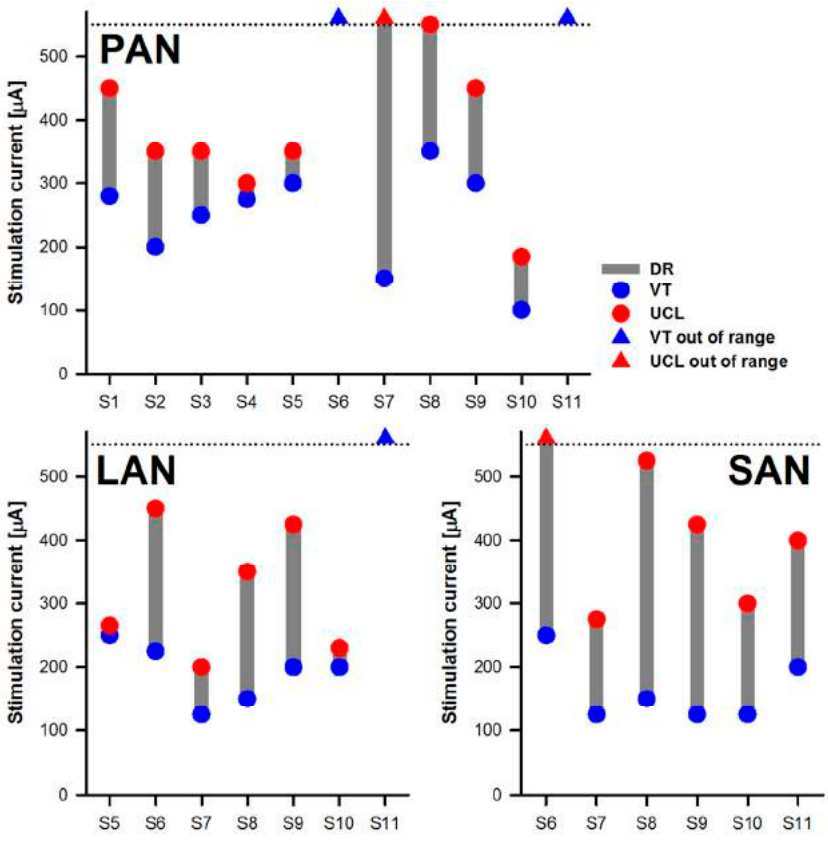

Figure 5.3 Vestibular thresholds (VT –blue circles), upper comfortable level (UCL – red circles) and corresponding dynamic range (DR – gray columns) are shown. Twenty-one out of the 24 available electrodes were responsive, and a dynamic range could be established. No response was obtained with 3 electrodes (blue triangles), even at the highest current tested (550µA, dotted lines in each panel). In 2 electrodes, no UCL could be determined, even at 550µA (red triangles). Note that in the case of the LAN electrode of subject S5, both the VT and the UCL were at the same current level (250µA) so the blue and red circles had to be slightly offset for visibility.

Electrically elicited eye movements

The main characteristics of the electrically elicited eye movements (total peak velocity and axis) are presented in Figure 5.4. The largest eye movements per electrode were observed in patient S7 for PAN (26°/s; 24.4–26.5°/s) and LAN (32.7°/s; 25.2–39.4°/s) and in patient S6 for SAN (21.3°/s; 18.5–23.4°/s). Consistent with the very variable dynamic ranges measured, the range of eye velocities was also very variable. Mean

peak velocities per electrode across patients were 8.7 ± 7.6°/s for PAN (n=11), 13 ± 12.5°/s for LAN (n=6), and 11.9 ± 6.6°/s for SAN (n=5).

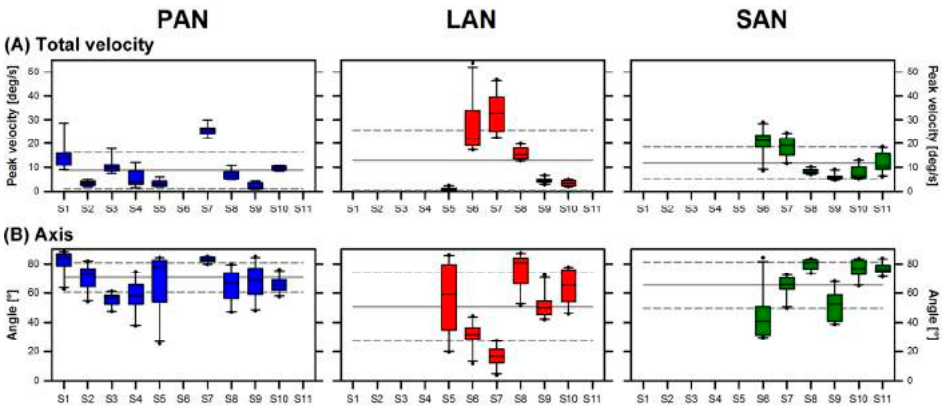

Figure 5.4 Main characteristics of electrically evoked eye movements. Each individual panel shows individual data for a given electrode (PAN: first column, blue box plots; LAN: middle column, red box plots; SAN: right col-umn, green box plots). Box plots indicate median values, 25th and 75th percentile values (colored box), 10th and 90th percentile values (error bars), and 5th and 95th percentile values (black circles). Mean values across patients, per electrode, are presented as gray solid lines (± standard deviation, gray dashed lines). **A** Total peak velocity. **B** Axis (angle with respect to the horizontal plane) of the elicited eye movements, calculated over 10 consecutive cycles.

As expected from previous experiments (Wall et al., 2007, Guyot et al., 2011), stimulation via 15 out of the 16 PAN and SAN electrodes resulted in eye movements with a predominantly vertical component. The mean angle for PAN stimulation was 70.6 ± 10° and of 65.4 ± 15.8° for SAN stimulation. Note, however, that for 1 SAN electrode, the angle was predominantly horizontal (S6: 40.8°; 31.1– 50.5°). In contrast, stimulation of LAN electrodes resulted in a larger misalignment from the expected angle. The mean angle for LAN stimulation was 50.6 ± 23.3°; only 2 out of the 6 LAN electrodes elicited eye movements predominantly in the horizontal plane (S6: 31.7°, 28.5– 36°; S7: 16.5°, 12.4–21.5°).

The asymmetry index of the responses is presented in Figure 5.5. The most symmetrical responses were observed with PAN stimulation (0.04 ± 0.07). SAN stimulation (0.08 ± 0.15) and LAN stimulation (0.14 ± 0.11) showed a slightly higher asymmetry index. The less symmetrical responses per electrode were observed in patient S3 for PAN stimulation (0.15, 0.01–0.19), in patient S5 for LAN stimulation (0.34, 0.22–0.55), and in patient S10 for SAN stimulation (0.20, –0.08 to 0.24).

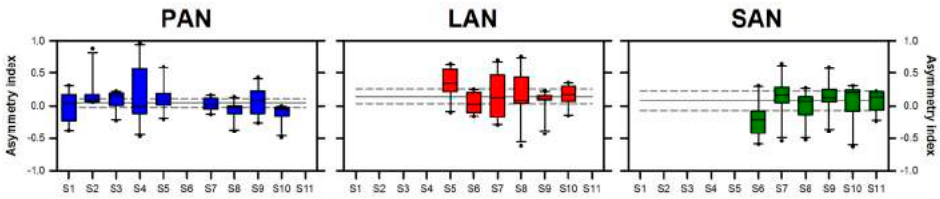

Figure 5.5 Asymmetry of the eye movements elicited via electrical stimulation of the PAN (left panel, blue box plots), the LAN (middle panel, red box plots), and the SAN (right panel, green box plots). Box plots indicate median values, 25th and 75th percentile values (colored box), 10th and 90th percentile values (error bars), and 5th and 95th percentile values (black circles). Mean values across patients, per electrode, are presented as gray solid lines (± standard deviation, gray dashed lines). This index was calculated using best fits to excitatory/inhibitory stimulus half cycles (see Materials and Methods).

Evoked percepts

The first-reported perceptions for each electrode are summarized in Table 5.2. During PAN stimulation, sound was most frequently the first reported perception (6 out of 9). For LAN and SAN stimulation, diverse perceptions were reported, such as rotatory sensation, sound, tickling or pressure. The intensity of the perception reported for each electrode was also very variable. In general, the intensity of the reported percepts increased as the stimulation current increased. However, it was rarely consistent with evoked ocular responses.

Table 5.2 First-reported sensation upon stimulation of each of the vestibular electrodes.

	PAN	SAN	LAN
S1	sound, vertigo	n.a.	n.a.
S2	sound	n.a.	n.a.
S3	sound	n.a.	n.a.
S4	sound	n.a.	n.a.
S5	sound	n.a.	needle in the ear
S6	none	rotatory sensation	rotatory sensation
S7	eyes moving	eyes moving, ‘tickling’ sensation	ear ‘tickling’
S8	‘tickling’ sensation	‘tickling’ sensation	‘tickling’ sensation
S9	vibration, sound	vibration, sound	‘current-flow’ sensation
S10	rotatory sensation,	sound	Sound
S11	none	pressure	Pressure

n.a. = Not applicable.

Discussion

The results presented here demonstrate that the concept of a unilateral vestibular implant is feasible in human patients. Motion information provided by the vestibular system is artificially mimicked by delivering a constant 'baseline' stimulation, which can be up- or downmodulated to evoke vestibulo-ocular responses. This allowed eliciting controlled eye movements in the 11 patients suffering from a BVL who received a vestibular implant. A particularly promising outcome of this study is that eye movements could be successfully evoked in a heterogeneous group of patients regarding the etiology of the deficit or the duration of the disease. This is particularly relevant since a significant concern was that vestibular dendrites could degenerate with time, precluding electrical stimulation of the vestibular nerve after long periods of sensory deprivation.

Efficacy of electrical stimulation

The efficacy of stimulation was very different across patients and across electrodes. Eye movements evoked by electrical stimulation of an ampullary nerve were expected to have an axis orthogonal to the plane of the corresponding semicircular canal. This was optimally achieved for PAN, LAN and SAN stimulation in 1 patient (S7). Moreover, in this case, mean peak eye velocities were 26, 32.7, and 19.1°/s for PAN, LAN, and SAN stimulation, respectively. This is a very promising finding, since in this case, evoked eye movements were within the range of compensatory eye movements previously reported during important dynamic daily activities, such as walking or running (20–30°/s) (Crane & Demer 1997; Grossman et al., 1989). Group results, however, showed some misalignment and lower mean peak eye velocities. Animal research reports suggest that adaptive processes could help improve the overall characteristics of the artificial eye movements in the long term (Lewis et al., 2010a; Dai et al., 2011a, 2013). Furthermore, particular stimulation strategies (e.g., incorporation of precompensatory 3D coordinate transformations (Fridman et al., 2010), comodulation of the amplitude and pulse rate of the stimulation (Davidovics et al., 2012) have also been suggested as possible alternatives to improve the characteristics of the electrically evoked vestibulo-ocular response.

It was expected that only very small eye movements could be elicited via electrodes with a narrow dynamic range (e.g., LAN responses for S10). However, surprisingly, eye movement responses were minimal in some cases with a relatively large dynamic range (e.g., LAN stimulation for S9). Despite this, patients still reported strong sensations related to vestibular stimulation (e.g., being pulled to the side or rotatory sensations). Such a dissociation between eye movement amplitude and sensation has also been reported by the team of the University of Washington (Rubinstein 2014). This suggests that electrical stimulation might be activating vestibular structures other

than those involved in the generation of the vestibulo-ocular reflex. This finding deserves further investigation.

Three out of the 24 implanted electrodes were unresponsive. Some hypotheses can be put forward. In subject S6, the PAN electrode was unresponsive. A CT scan revealed an intraotic fracture line crossing the posterior ampulla and fibrosis filling the canal was found during surgery. Traumatic section or severe posttraumatic degeneration of the dendrites as well as fibrosis of the ampulla might drastically reduce the excitability of the vestibular nerve. The other 2 unresponsive electrodes were those implanted in the PAN and LAN of patient S11. This patient was suffering from DFNA9, an autosomal dominant nonsyndromic congenital disease due to COCH gene mutations (Manolis et al., 1996). This adult-onset disorder is characterized by a progressive bilateral loss of cochlear and vestibular function. Severe loss of cochleovestibular nerve dendrite is a characteristic histological feature of this disease (Merchant et al., 2000). This might preclude the success of intralabyrinthine electrical stimulation, due to the distance between the ampulla and the Scarpa ganglion. This hypothesis is reinforced by the fact that 7 out of the 9 vestibular electrodes of BVL patients diagnosed with DFNA9 (S9–S11) showed the smallest responses.

Finally, another factor that can significantly influence the effectiveness of electrical stimulation is optimal positioning of stimulating electrodes. Indeed, it has been observed that minimal position changes of the electrodes resulted in drastic changes of nystagmic responses (Wall et al., 2007). So far, peroperative stimulation under local and general anesthesia was performed to improve the electrode positioning. Peroperative vestibular electrically evoked action potentials could be an additional tool to improve the electrode positioning in the future (Nie et al., 2011).

Perception evoked via electrical stimulation

Patients were actively requested to describe what they felt during the stimulation sessions. After unsuccessfully attempting to categorize the percepts described by the first implanted patients, raw description of any perception was documented. As can be seen in the results, described percepts were quite heterogeneous. This could be at least partially explained by the concomitant, spurious activation of nonvestibular neural structures due to current spread (i.e. the cochlear nerve, the branches of the glossopharyngeal nerve, and, to some extent, possibly also the vagal and the facial nerves).

Extralabyrinthine versus intralabyrinthine electrode placement

In 5 patients, electrodes (n=6) were implanted close to vestibular nerve branches (extralabyrinthine approach), while in 6 patients, electrodes (n=18) were implanted in the ampullae (intralabyrinthine approach). The first approach was initially chosen in

the perspective of reducing the risk of inducing hearing loss (estimated around 4% as observed by Gacek and Gacek in 252 neurectomies of the PAN for intractable benign paroxysmal positional vertigo (Gacek & Gacek, 2002)). In contrast, the intralabyrinthine approach might allow better selectivity of the stimulation but the risk of inducing hearing loss in this case is still unclear. Results of animal studies are controversial: some demonstrate that intralabyrinthine electrode insertion with or without electrical stimulation impairs hearing in most of the cases (Tang et al., 2009; Dai et al., 2011c; Tran et al., 2012), while others show that it is possible to preserve auditory and vestibular function (Bierer et al., 2012). The results in human patients are not very encouraging in this respect. The group at the University of Washington has implanted 4 patients diagnosed with an intractable Menière's disease. They all had some preoperative residual vestibular and hearing function. An intralabyrinthine approach was used and postoperative hearing (reported only for 1 out of the 4 implanted patients) was almost totally lost (Golub et al., 2014; Phillips et al., 2013). Nevertheless, there are reports showing that hearing is preserved after plugging of a dehiscent superior semicircular canal, plugging of the posterior superior semicircular canal for intractable benign paroxysmal positional vertigo (Limb et al., 2006; Agrawal et al., 2001), and plugging of the lateral superior semicircular canal in patients with severe Menière's disease (Charpiot et al., 2010). Since most patients suffering from a BVL have normal or near-normal hearing, it is crucial that the incidence of hearing loss upon vestibular implant surgery is thoroughly investigated and reported in the near future.

Additional considerations

In the natural vestibular system, motion is coded by modulation of the discharge rate of the spontaneous 'baseline' neural activity (i.e., number of spikes per second) of the vestibular nerve. For the lateral semicircular canal, the discharge rate increases with ampullopetal movements of the endolymph and decreases with movements of opposite direction. For example, for the horizontal semicircular canal, a head rotation in the direction of the canal (i.e., rightwards for the right ear) will result in an increase in the neuronal discharge rate. Conversely, a horizontal head rotation in a direction opposite to the canal (i.e., leftwards for the right ear) will result in a decrease in the discharge rate. The reverse is true for the vertical semicircular canals (Goldberg & Fernandez 1971). In light of this physiological motion modulation scheme, discharge rate modulation has often been chosen as the stimulation method (Fridman et al. 2010; Lewis et al. 2010b). However, in our experiments, eye movements were produced using amplitude modulation, not discharge rate modulation. This choice was motivated in a previous observation that in humans, discharge rate modulation resulted in smaller eye movements than amplitude modulation (Guyot JP, 2011).

Furthermore, our prototype vestibular implants are modified cochlear implants, which are designed to use amplitude modulation.
Consistent with previous data (Lewis et al., 2010a; Dai et al., 2011b; Perez Fornos et al., 2014), some asymmetry was observed in the responses obtained upon stimulation with the majority of the electrodes. It is still unclear whether lack of symmetry will turn out to be a clinically relevant issue that will fundamentally limit the patient's benefit with the system. Furthermore, the vestibular system itself might be able to adapt to the electrical stimulus and improve the characteristics of the response with time (Lewis et al., 2010a; Dai et al., 2011b, 2013). The use of different signal processing strategies (e.g., logarithmic vs. simple linear transfer functions) could also provide a potential solution.

Conclusion

These results confirm the feasibility of the concept of a vestibular implant for human use. We observed no medical complications related to the surgery or the device. Furthermore, the implant was successful at eliciting vestibulo-ocular responses even after long periods of implantation and in a very heterogeneous patient population. This, taken together with previous work (Perez Fornos et al., 2014), suggests that our objective of providing a first clinical tool to patients with a BVL might not be so far away.

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Chapter 6

The vestibular implant: frequency-dependency of the electrically evoked vestibulo-ocular reflex in humans

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Abstract

The vestibulo-ocular reflex (VOR) shows frequency-dependent behavior. This study investigated whether the characteristics of the electrically evoked VOR (eVOR) elicited by a vestibular implant, showed the same frequency-dependency. Twelve vestibular electrodes implanted in seven patients with bilateral vestibular hypofunction (BVH) were tested. Stimuli consisted of amplitude-modulated electrical stimulation with a sinusoidal profile at frequencies of 0.5, 1, and 2 Hz. The main characteristics of the eVOR were evaluated and compared to the "natural" VOR characteristics measured in a group of age-matched healthy volunteers who were subjected to horizontal whole body rotations with equivalent sinusoidal velocity profiles at the same frequencies. A strong and significant effect of frequency was observed in the total peak eye velocity of the eVOR. This effect was similar to that observed in the "natural" VOR. Other characteristics of the (e)VOR (angle, habituation-index, and asymmetry) showed no significant frequency-dependent effect. In conclusion, this study demonstrates that, at least at the specific (limited) frequency range tested, responses elicited by a vestibular implant closely mimic the frequency-dependency of the "normal" vestibular system.

Introduction

Bilateral vestibular hypofunction (BVH) is most often a chronic condition in which patients can suffer from blurred vision (oscillopsia), impaired spatial orientation and postural instability (Brandt et al., 2010; van de Berg et al., 2011; Hain et al., 2013). These and other symptoms lead to an important decrease in physical activity, social functioning and vitality that dramatically impact the patients' quality of life (Guinand et al., 2012; Ward et al., 2013). The prognosis of BVH is poor and more than 80% of the patients do not improve (Zingler et al., 2008; McCall & Yates, 2011). Until now, treatment options are limited and with low yield (Porciuncula et al., 2012).

A vestibular implant, in a concept analogous to that of the cochlear implant, has been postulated as a possible therapeutic alternative. This idea is currently investigated by research groups in Europe and the United States. Research both from animal and human studies have demonstrated that electrical stimulation is an effective means to activate the vestibular system (Fridman et al., 2010; Guyot et al., 2011; Lewis et al., 2013; Golub et al., 2014). Considerable research efforts have been devoted to the investigation of the electrically evoked vestibulo-ocular reflex (eVOR). Promisingly, results showed that it is possible to elicit a VOR which corresponds to the plane of the canal which is innervated by the electrically stimulated nerve branch (Gong and Merfeld, 2002; Della Santina et al., 2007; Merfeld et al., 2007; Wall et al., 2007; Fridman et al., 2010; van de Berg et al., 2011; Perez Fornos et al., 2014). Current efforts focus on optimizing stimulation paradigms (Davidovics et al., 2011, 2012), on improving the alignment of the eVOR (Migliaccio et al., 2011; Dai et al., 2013; Davidovics et al., 2013), and on investigating the adaptive properties of the eVOR (Merfeld et al., 2006, 2007; Lewis et al., 2010; Guyot et al., 2011; Dai et al., 2013). Important efforts are also undertaken to improve surgical techniques (Feigl et al., 2009; Dai et al., 2011a; Bierer et al., 2012; Rubinstein et al., 2012; van de Berg et al., 2012) and to solve biomechanical issues (Wall et al., 2003; Hayden et al., 2011; van de Berg et al., 2011; Fridman & Della Santina, 2013).

The Geneva-Maastricht group has recently demonstrated that it is possible to restore the VOR in patients with BVH, using a chronically implanted vestibular implant prototype (Perez Fornos et al., 2014). During these experiments, some frequency dependent effects were observed. Frequency-dependency is a well-known feature of the vestibular system. Gain of the semicircular canals (peak eye velocity/peak head velocity) is high for middle frequencies, but decreases with lower and higher frequencies, consistent with the mechanical properties of the semicircular canals (Barnes, 1993). Interestingly, these middle frequency movements are often encountered by individuals in daily life, for example during voluntary head movements and locomotor activities (Barnes, 1993; Crane & Demer, 1997). Therefore, it is important to further investigate the frequency-dependent behavior of the eVOR

and how it compares to the frequency-dependent characteristics of the “natural” VOR in healthy subjects. This was the main objective of this study.

Materials and methods

Implanted patients

Between 2007 and 2013, 11 volunteers with BVH received a vestibular implant prototype consisting of a modified cochlear implant (MED-EL, Innsbruck, Austria) with extra-cochlear branches for vestibular stimulation (Guinand et al., 2015). The devices, inclusion criteria, and surgical techniques have been described in detail previously (Perez Fornos et al., 2014; Guinand et al., 2015). Seven of them were available for this study (age 46–68 years; mean age 61.4 years; see Table 6.1). Twelve electrodes at different anatomical locations were tested: four electrodes implanted in the vicinity of the superior ampullary nerve (SAN), three electrodes implanted in the vicinity of the lateral ampullary nerve (LAN) and five electrodes implanted in the vicinity of the posterior ampullary nerve (PAN).

Table 6.1 Main characteristics of the tested patients with bilateral vestibular hypofunction.

Subject	Sex	Tested electrode(s)	Age at implantation	Etiology	Year of implantation	Surgical approach
BVH1	M	SAN; LAN	67	DFNA-9	2012	Intralabyrinthine
BVH2	F	PAN	48	Meningitis	2012	Intralabyrinthine
BVH3	M	SAN; LAN; PAN	66	DFNA-9	2013	Intralabyrinthine
BVH4	F	SAN; PAN	68	DFNA-9	2013	Intralabyrinthine
BVH5	F	SAN; LAN	67	Traumatic	2013	Intralabyrinthine
BVH6	M	PAN	46	Idiopathic	2008	Extralabyrinthine
BVH7	M	PAN	68	Idiopathic	2007	Extralabyrinthine

Healthy subjects

Seven age-matched healthy volunteers with a blank history for vestibular disorders were selected for the comparison experiments. These tests involved three men and four women (age 59–69 years; mean age 62.7 years).

Electrical stimulation

Electrical stimulation was delivered exclusively to one vestibular electrode at a time. The activation procedure has been previously described (Guyot et al., 2011; Perez Fornos et al., 2014). Briefly, the generation of bi-directional eye movements (e.g., both leftwards and rightwards for stimulation of the LAN) with unilateral electrical stimulation requires first that a “baseline stimulation” (i.e., constant amplitude) is

delivered by the vestibular electrode. Then, up- and down-modulation of this "baseline stimulation" effectively results in the generation of smooth, bi-directional eye movements.

Stimulation consisted of amplitude modulated, charge-balanced, cathodic-first, biphasic pulses (200 µs/phase) presented at a pulse rate of 400 pulses/sec. "Baseline stimulation" amplitudes corresponded to the middle of each patient's dynamic range (see Perez Fornos et al., 2014; Guinand et al., 2015); for details on the determination of thresholds, upper comfortable level and resulting dynamic range). Modulation strengths for each patient/electrode were selected to correspond to 50-75% of the corresponding dynamic range and were kept constant throughout the experiments. Figure 6.1 illustrates this electrical stimulation procedure.

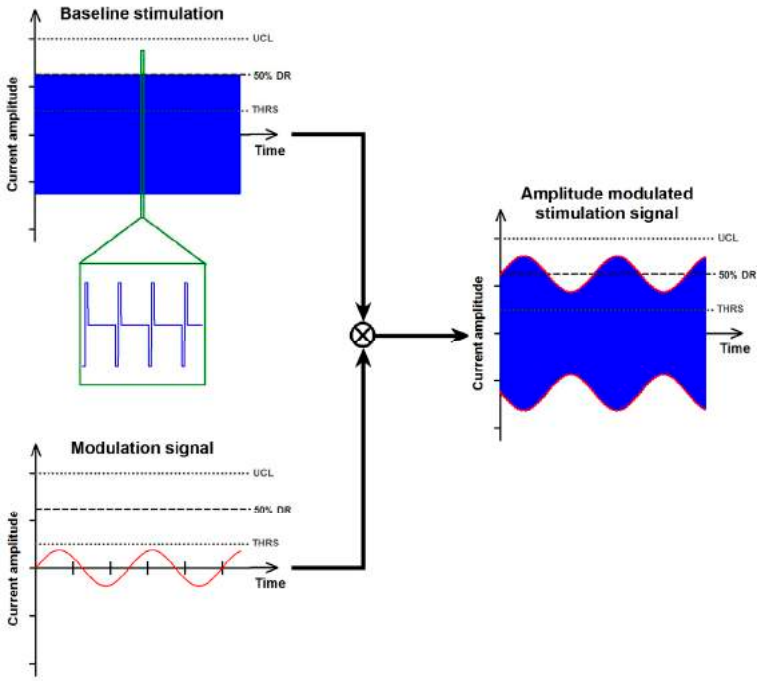

Figure 6.1 Illustration of the electrical stimulation paradigm. Stimulation was delivered to one vestibular electrode at a time. Patients first received baseline electrical stimulation that consisted of constant amplitude trains of biphasic, cathodic-first pulses (upper-left panel). Baseline stimulation was presented at a fixed pulserate of 400 pulses per second. Its intensity corresponded to 50% of each electrode's previously measured dynamic range (DR; current range between the vestibular threshold-THRS-and the upper comfortable level-UCL-). Once patients were in "adapted" state, the baseline stimulation could be modulated in amplitude using a signal with a sinusoidal profile (see lower-leftpanel). The strength (i.e., intensity) of the modulation was kept constant and its frequency was varied between 0.5 and 2Hz.The right panel shows an example of such an amplitude modulated stimulation signal (bluetrace). The envelope of the modulation signal (red dotted lines) has been highlighted for clarity.

Study design

All tests were conducted in a controlled laboratory setting and performed in complete darkness. All participants (from both groups) were instructed to sit still, look in front of them and keep their eyes open during the trials. If necessary, alerting tasks were given to improve concentration and general level of arousal, in order to obtain as reproducible results as possible.

In order to test the eVOR as specifically as possible without any influences of other inputs like residual vestibular function, the eVOR-experiments were conducted in stationary conditions (e.g., without any head or body movement). Patients sat comfortably in a stationary chair while the implant was activated. Each electrode was separately tested with a fixed sequence of approximately 60 sinusoidal cycles of amplitude modulated electrical stimulation (see details in Section Electrical Stimulation). The strength (i.e., intensity) of modulation was kept constant throughout experimental trials and 3 modulation frequencies (0.5, 1, and 2Hz) were tested. Lower modulation frequencies were intentionally excluded, since previous investigations (in exactly the same conditions) showed only very small eVOR responses at these frequencies (Perez Fornos et al., 2014). Furthermore, 60-cycle trials at low modulation frequencies below 0.5Hz resulted in very long sessions, which severely compromised the attention of the patients for the rest of the testing session (Perez Fornos et al., 2014). All tests for a given electrode were performed on the same day.

Modulation of the frequency of the electrical stimulus would correspond in real life to modulation of the frequency of the head velocity stimulus in dynamic situations. Therefore, the eVOR obtained by electrical stimulation in patients with BVH was compared to the “natural” VOR obtained in healthy volunteers during velocity controlled whole body rotations. Healthy volunteers were subjected to 60-cycle trials of horizontal whole body rotations in a custom-made, velocity-controlled rotatory chair (Nystagliner Pro; Erich Jaeger Gmbh). Rotations followed the same sinusoidal profile as electrical stimuli (same frequency range of 0.5, 1, and 2Hz) and had a peak velocity of 30°/s.

Eye movement recording and analysis

Bidimensional eye movements (i.e., horizontal and vertical eye position, no torsion) were recorded with the EyeSeeCam system (EyeSeeCam VOG; Munich, Germany) (Bartl et al., 2009; Perez Fornos et al., 2014). Motivation for this choice, as well as the dataprocessing using cycle-by-cycle analysis and calculation of gain were described previously (Perez Fornos et al., 2014; Guinand et al., 2015). An example of eye movement data processing is presented in Figure 6.2. Analysis was performed on as many valid cycles (free of saccades and blinks) as possible (minimum 43, maximum 60).

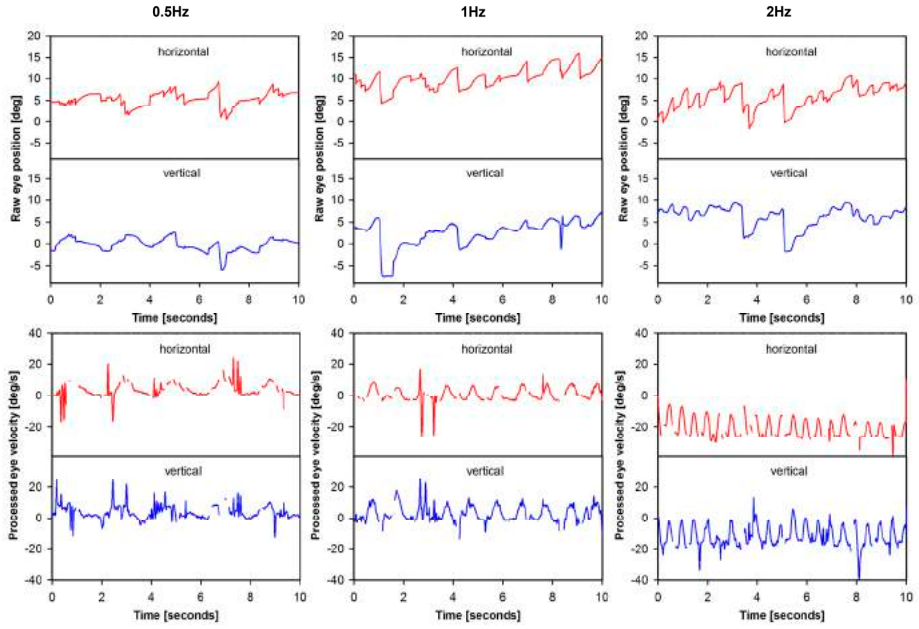

Figure 6.2 Illustration of eye movement data processing. The figure presents eye movement data tracings for patient BVH1-LAN.Two steps are illustrated for each modulation frequency: raw eye position (e.g., before any processing was performed) and processed eye velocity data.

Total peak eye velocity was calculated as the square root of the sums of the squares of horizontal and vertical peak eye velocity. To facilitate the analysis of the frequency-dependent behavior of peak eye velocities of different magnitudes, peak eye velocities per modulation frequency were normalized to the highest measured peak eye velocity per electrode. Angle of the (e)VOR (with respect to the horizontal axis) was defined as the angle between the horizontal and vertical peak eye velocity (Guinand et al., 2015). The habituation-index was determined by the mean peak eye velocities of the last 10 cycles, divided by the mean peak eye velocities of the first 10 cycles. The asymmetry-index (ratio of excitatory/inhibitory half cycle gain) of the most prominent component (horizontal or vertical) was calculated as (excitatory half cycle gain—inhibitory half cycle gain)/(excitatory half cycle gain inhibitory half cycle gain) (Dai et al., 2011b) and converted into an absolute value.

Statistics

Since normality tests conducted on individual results often failed the normality assumption, individual results (per subject/electrode) were presented as median

values, as well as the 25th–75th percentiles. Group results conformed to normal distributions and were therefore presented as mean values standard error of the mean (SEM).
Statistics were performed using analysis of variance (ANOVA) modules from IBM SPSS Statistics v.22 (IBM Corporation, New York, United States of America). Raw scores were used as input for comparative tests regarding angle, habituation-index and asymmetry-index. For total peak eye velocity, variance differed between the groups. Therefore, data were first normalized before proceeding to statistical analysis. A significance level of 0.05 was chosen to detect significant differences within and across groups.

Ethical considerations

This study was in accordance with the Declaration of Helsinki (amended version 2013). The testing protocol was approved by the ethical committees of the Maastricht University Medical Center (NL36777.068.11/METC 11-2-031) and the Geneva University Hospital (NAC 11-080).

Results

Characteristics of the eVOR

The first objective of this paper was to describe the main characteristics of eVOR-responses. Four main characteristics were studied: total peak eye velocity, angle of the eVOR (with respect to the horizontal axis), the habituation-index over 60 cycles, and the asymmetry (ratio of excitatory/inhibitory half cycle gain) of the response.
Total peak eye velocity results obtained per electrode are presented in Table 6.2. Consistent with previous observations (Guinand et al., 2015), inter-subject variability was high. The medians of the total peak eye velocity for the electrodes ranged from 0.6°/s (BVH4-PAN, 0.5 Hz) up to 21.5°/s (BVH5-SAN, 2 Hz).
To facilitate comparison of the results across patients and across frequencies, total peak eye velocity results were normalized to the highest values per electrode. Individual and pooled results revealed a clear frequency-dependent behavior for the three stimulation sites (Figure 6.3). In general, the lowest peak eye velocities were obtained with a modulation frequency of 0.5 Hz. Peak eye velocities progressively increased with increasing modulation frequency, reaching a maximum at 2 Hz. Note however that interestingly, patient BVH2 showed an opposite behavior (stimulation of the PAN). There was a statistically significant effect of modulation frequency [$F_{(2,27)}$=16.25, $p<0.001$] but not for stimulation site. Post-hoc pairwise comparisons

(Tukey) indicated that the difference in mean normalized peak eye velocities was statistically significant ($p<0.05$; 0.5Hz: 0.53 ± 0.08; 1Hz: 0.72 ± 0.05; 2Hz: 0.98 ± 0.02).

Table 6.2 Medians, 25th percentiles and 75th percentiles of total peak eye velocity (°/s) for all electrodes, per modulation frequency.

Electrode	Frequency	Median	25th percentile	75th percentile
BVH1-SAN	0.5Hz	4.2	2.4	5.3
	1Hz	5.4	3.3	7.6
	2Hz	6.9	5.2	9.1
BVH1-LAN	0.5Hz	6.9	5.3	8.6
	1Hz	9.1	7.1	10.4
	2Hz	9.3	7.3	11.4
BVH2-PAN	0.5Hz	8.5	6.4	9.8
	1Hz	8.3	7.8	9.0
	2Hz	6.9	6.2	7.7
BVH3-SAN	0.5Hz	1.1	0.9	1.5
	1Hz	3.9	3.1	5.0
	2Hz	5.6	4.6	7.2
BVH3-LAN	0.5Hz	0.9	0.6	1.2
	1Hz	1.8	1.4	2.5
	2Hz	3.6	2.2	4.8
BVH3-PAN	0.5Hz	2.0	1.5	2.5
	1Hz	5.7	5.2	6.4
	2Hz	8.6	8.0	9.7
BVH4-SAN	0.5Hz	0.8	0.5	1.1
	1Hz	1.4	1.0	1.7
	2Hz	3.6	2.4	4.4
BVH4-PAN	0.5Hz	0.6	0.5	0.8
	1Hz	1.0	0.6	1.3
	2Hz	1.5	1.0	2.3
BVH5-SAN	0.5Hz	12.4	10.8	14.1
	1Hz	13.5	10.8	17.4
	2Hz	21.5	16.6	24.9
BVH5-LAN	0.5Hz	6.8	6.0	8.1
	1Hz	8.0	6.8	9.5
	2Hz	11.1	9.0	12.9
BVH6-PAN	0.5Hz	10.2	8.1	13.5
	1Hz	12.5	10.6	14.7
	2Hz	12.0	9.8	14.6
BVH7-PAN	0.5Hz	4.0	3.5	4.4
	1Hz	4.0	2.8	5.0
	2Hz	5.7	4.6	7.5

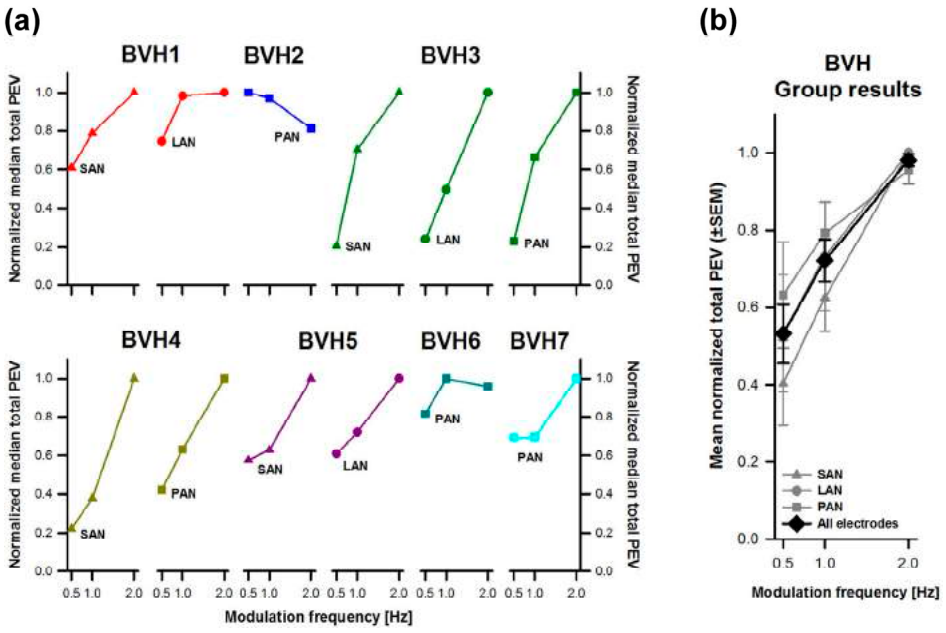

Figure 6.3 Normalized total peak eye velocity (PEV) vs. modulation frequency. **a** Each panel represents individual results obtained during stimulation for each stimulation site (SAN, LAN, PAN). **b** Mean results (±SEM) calculated across patients for each stimulation site (gray plots) and for all electrodes together (black plot).

Figure 6.4A shows individual angle results (with respect to the horizontal axis) for each stimulation site. Results for each stimulation site were very variable across subjects. No clear effect of modulation frequency could be distinguished either. For example, stimulation of the SAN in BVH3 (dark green triangles in Figure 6.4A) showed, as expected, angles with a predominantly vertical component ranging from 59 to 83°. The eye movement response progressively shifted toward the vertical axis (the angle increased) as modulation frequency increased. However, results for the same stimulation site were completely different in the case of patient BVH5 (purple triangles in Figure 6.4A). Surprisingly, this patient showed median angles with a predominantly horizontal component, ranging from 12 to 14° during stimulation of the SAN. Furthermore, median angles remained relatively stable across modulation frequencies for this patient. Similar inter-subject variability was observed for stimulation of the LAN and the PAN.

Mean results across stimulation sites (gray plots in Figure 6.4B) showed that overall, the stimulation site with the most vertical eVOR response was the PAN (58.6 ± 5.5°). There were only very small differences in angles between stimulation of the SAN and the LAN (respectively 46.8 ± 6.1° and 40.4 ± 7.1°). Differences across modulation

frequencies were small, both when each stimulation site was considered separately and when data from all stimulation sites was pooled (black plot in Figure 6.4B). There was no statistically significant main effect of modulation frequency or stimulation site.

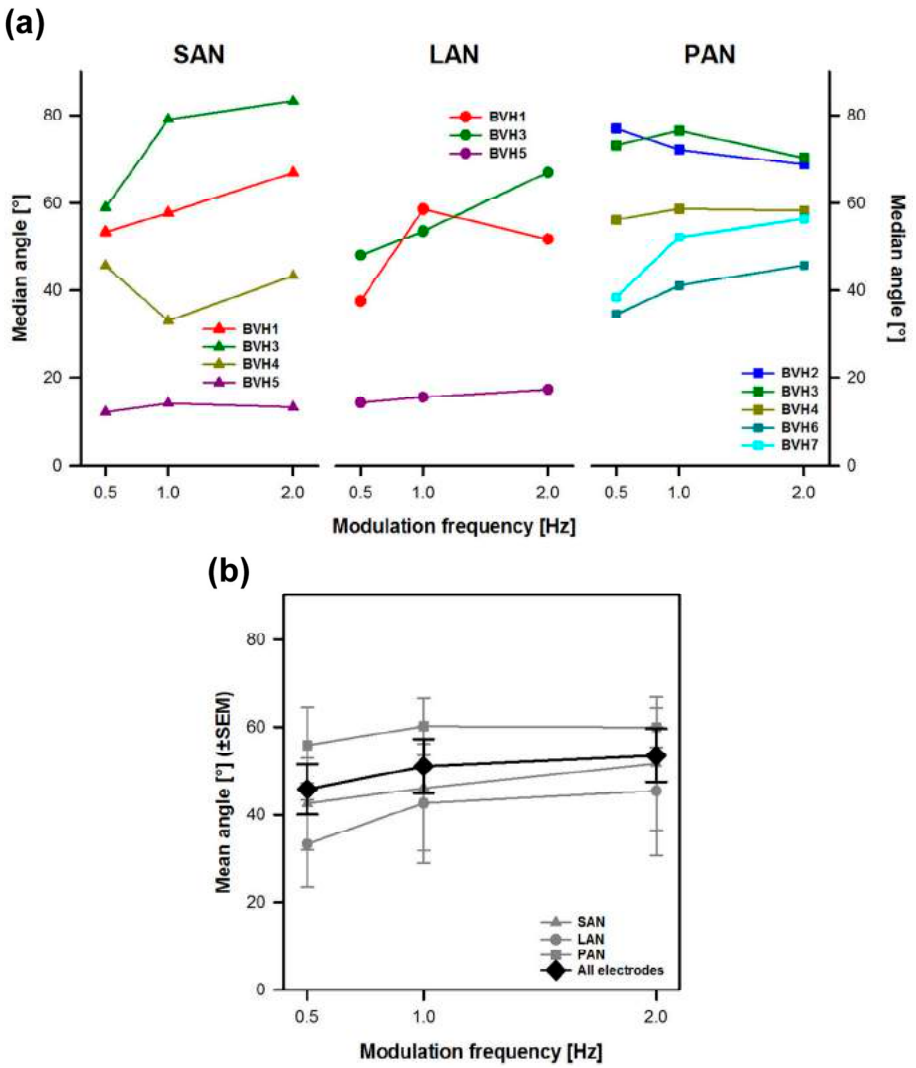

Figure 6.4 Angle of eye movements vs. modulation frequency. **a** Each panel represents individual results obtained during stimulation for each stimulation site (SAN, LAN, PAN). **b** Mean results (±SEM) calculated across patients for each stimulation site (gray plots) and for all electrodes together (black plot).

Figure 6.5A shows individual median habituation-indexes per patient and for each stimulation site. Results across subjects and across stimulation sites were again quite variable. Results were very variable from one stimulation site to another in the same patient (e.g., results for patient BVH3, dark green plots in Figure 6.5A). Habituation could also be very different when comparing the same stimulation site between patients (e.g., compare results for stimulation of the PAN, squares in Figure 6.5A).

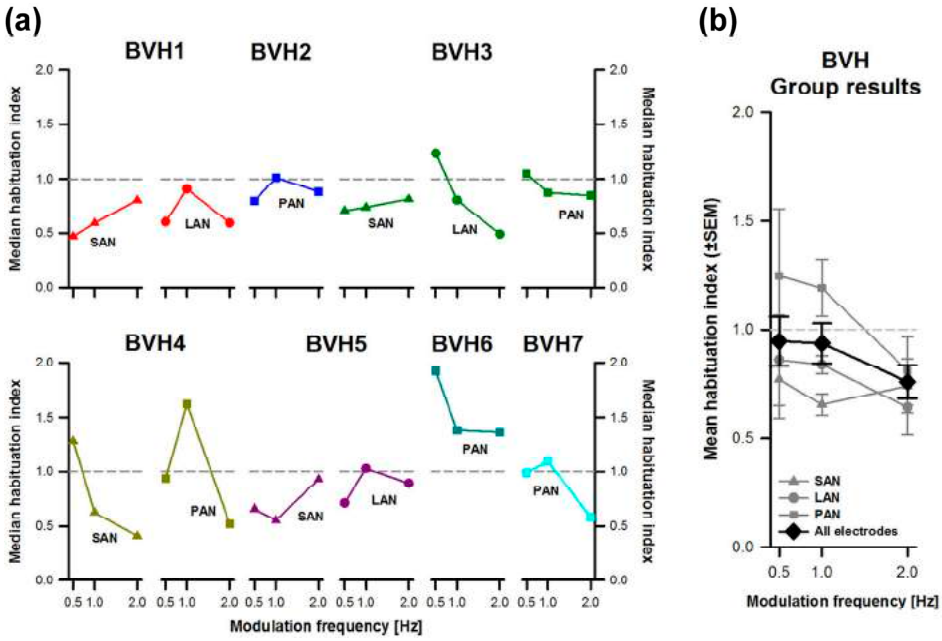

Figure 6.5 Habituation-index vs. modulation frequency. **a** Each panel represents individual results obtained during stimulation for each stimulation site (SAN, LAN, PAN). **b** Mean results (±SEM) calculated across patients for each stimulation site (gray plots) and for all electrodes together (black plot).

No clear effect of modulation frequency could be distinguished either. While in some cases habituation seemed to be more important (i.e., indexes became lower) at higher modulation frequencies (e.g., BVH4-SAN, olive green triangles in Figure 6.5A), in other cases the inverse trend was observed (e.g., BVH1-SAN). Mean results across stimulation sites and for all stimulation sites together showed a clearer picture (Figure 6.5B). Habituation- indexes for stimulation of the PAN were in general higher (1.08 ± 0.09), reflecting less adaptation than stimulation of the SAN and the LAN (respectively 0.72 ± 0.11 and 0.78 ± 0.12). This difference was only statistically significant between stimulation of the SAN and the PAN ($p<0.05$). Another interesting observation from

pooled results was that in general, habituation was more important for the 2 Hz modulation frequency than for 0.5 and 1 Hz. However, the effect of modulation frequency, as well as the interaction effect between modulation frequency and stimulation site, were not statistically significant.

Figure 6.6 displays asymmetry-indexes for each patient and each stimulation site. Values were <0.3 in all cases. The patient showing the most asymmetrical responses was BVH5 (purple plots in Figure 6.6A) and the one with the most symmetrical responses was BVH4 (olive green plots in Figure 6.6A), particularly for stimulation of the SAN. No systematic frequency-dependent behavior was observed in individual results. Group results (Figure 6.6B) confirmed that asymmetry was in general low, and some variability between stimulation sites was also observed. There were no significant effects of modulation frequency or stimulation site. The interaction effect between modulation frequency and stimulation site was not statistically significant either.

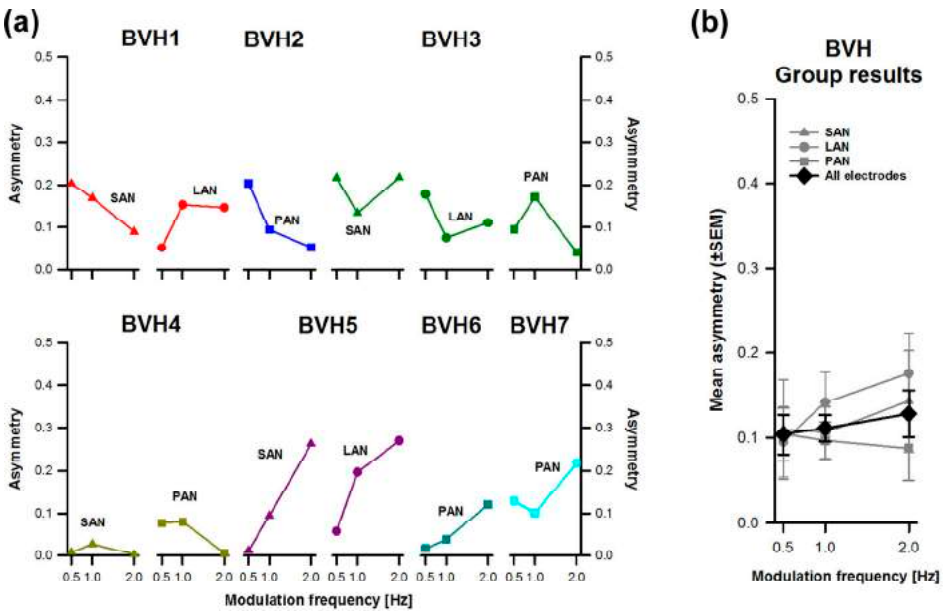

Figure 6.6 Asymmetry-index vs. modulation frequency. **a** Each panel represents individual results obtained during stimulation for each stimulation site (SAN, LAN, PAN). **b** Mean results (±SEM) calculated across patients for each stimulation site (gray plots) and for all electrodes together (black plot).

The eVOR vs. the “natural” VOR

The second goal of this study was to compare the previously described eVOR-characteristics with those of the “natural” VOR observed in the group of healthy volunteers. The results of this comparison are summarized in Figure 6.7.

Figure 6.7A compares the frequency-dependent behavior of the normalized total peak eye velocity of the eVOR to that of the "natural" VOR. From this figure it is clear thar both show a strikingly similar frequency-dependent behavior, with the lower peak eye velocities measured at 0.5Hz (0.53 ± 0.08 for the BHV-group and 0.54 ± 0.05 for the group of healthy volunteers).

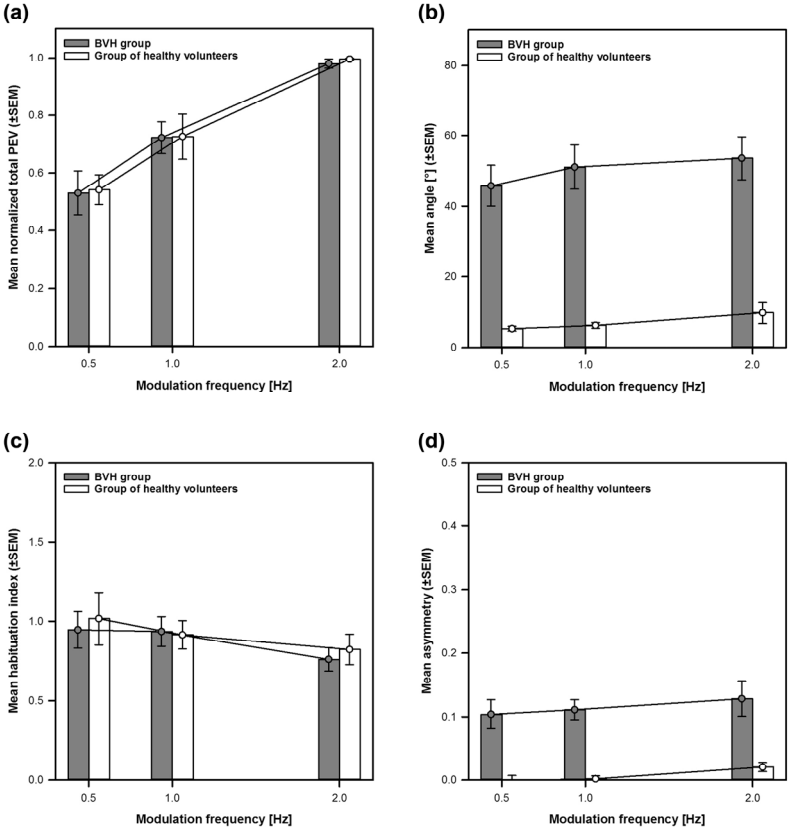

Figure 6.7 Comparison of the main characteristics of the eVOR to the “natural” VOR. The eVOR is represented as mean group results of the BVH-group (gray bars and circles ±SEM). The “natural” VOR is represented as mean group results of the group of healthy volunteers (white bars and circles ±SEM). **a** Normalized total peak eye velocity (PEV) vs. modulation frequency. **b** Angle of the VOR responses vs. modulation frequency. **c** Habituation-index vs. modulation frequency. **d** Asymmetry-index vs. modulation frequency.

Peak eye velocities increased progressively with increasing frequency reaching a maximum at 2Hz (BVH-group: 0.72 ± 0.06 at 1Hz and 0.98 ± 0.01 at 2Hz; Group of healthy volunteers: 0.73 ± 0.08 at 1Hz and 0.99 ± 0.003 at 2Hz). A Two-Way between-groups ANOVA confirmed a significant effect of frequency [$F_{(2, 51)}$ 29.39, $p<0.001$], but no significant difference between both groups. The interaction between both variables was not significant either.

Figure 6.7B compares eVOR angles to those of the "natural" VOR. The angles of the "natural" VOR are close to zero (i.e., practically horizontal) and remained relatively stable across modulation frequencies, consistent with the direction of applied whole body rotations. As described previously, mean eVOR angles were much higher, with a predominantly vertical component and also remained relatively stable across modulation frequencies. A Two-Way between-groups ANOVA confirmed a significant difference between both groups [$F_{(1, 51)}$ 84.91, $p<0.001$], but no significant effect of frequency. The interaction effect was not significant either.

Figure 6.7C compares the habituation-index of the eVOR to that of the "natural" VOR. Habituation-indexes were close to one (i.e., meaning very little adaptation) for both groups at 0.5 and 1Hz and only slightly decreased at 2Hz. There was no significant difference between groups or across modulation frequencies. The interaction effect was not significant either.

Finally, Figure 7D compares the asymmetry-indexes of the eVOR to those of the "natural" VOR. Mean asymmetry for the eVOR ranged between 0.10 (0.5Hz) and 0.13 (2Hz). Mean asymmetry for the "natural" VOR was much lower and close to 0, although values slightly increased at 2Hz. A Two-Way between-groups ANOVA confirmed a significant difference between both groups [$F_{(1, 51)}$ 37.64, $p<0.001$], but no significant effect of modulation frequency. The interaction effect was not significant either.

Discussion

The goal of this study was to investigate how the characteristics of the eVOR change as a function of modulation frequency in the first group of patients implanted with a vestibular implant prototype, and to compare these results to the "natural" VOR responses obtained in healthy age-matched volunteers.

These results demonstrate that at least in this specific (limited) frequency range, the vestibular implant closely mimics the natural frequency-dependency of the vestibular system. Frequency showed a significant effect on the total peak eye velocity: total peak eye velocity increased with increasing frequency for both groups, without any significant effect between the groups. No significant frequency-dependent changes

were observed in angle, habituation-index or asymmetry. This behavior was similar in the eVOR and in the "natural" VOR.

The increase of peak eye velocity with frequency has already been well documented in normal subjects (Barnes, 1993), but it had never been systematically evaluated in human patients with a vestibular implant. It is reasonable to hypothesize that this effect probably reflects the properties of vestibular afferents, which are the main target of electrical stimulation by a vestibular implant (Goldberg et al., 1984; Kim et al., 2011). However, it cannot be excluded that a small residual population of hair cells and more central connections can contribute to this effect (Aw et al., 2008). The eVOR angle (with respect to the horizontal axis) was very variable across the BVH-group for the whole tested frequency range. The resulting misalignment has already been described in animals as well as humans and is attributed mainly to current spread or imprecise electrode placement (Fridman et al., 2010; Lewis et al., 2010, 2013; Dai et al., 2011c, 2013; Davidovics et al., 2011; van de Berg et al., 2011; Guinand et al., 2015). Current spread is particularly relevant in the case of the LAN and the SAN (Figure 6. 4A) because of their close anatomical position relative to each other (van de Berg et al., 2012). Many strategies to minimize misalignment have been investigated, such as different stimulus waveforms, precompensation (vector summation), current steering and improving electrode design, but none of these seem totally infallible (Fridman et al., 2010; Dai et al., 2011c, 2013; Davidovics et al., 2013). Fortunately, chronic stimulation experiments in animals have shown that the brain is very adaptive: it is able to significantly improve eVOR alignment, making it possible to develop an ocular response which is aligned with the axis of head motion, even when stimulating the nerve branch of a canal that is orthogonal to the axis of motion. This phenomon is called "cross-axis adaptation." (Lewis et al., 2003, 2010, 2013; Della Santina et al., 2007; Dai et al., 2011c; van de Berg et al., 2011; Guinand et al., 2015). Therefore, taking the adaptability of the brain into account, it should still be determined to which extent complex stimulation strategies to improve eVOR alignment will have to be incorporated into a device suited for human clinical use.

Repeated exposure to the same sinusoidal stimulus can cause a long-lasting decrease in VOR gain in animals and humans. This habituation can be frequency-specific (Dow & Anastasio, 1999). While significant habituation has been observed for low-frequency stimuli (Buettner et al., 1981; Jäger & Henn, 1981a,b; Dow and Anastasio, 1997, 1999; Clément et al., 2002), repeated stimulation at higher modulation frequencies shows little or no change in VOR gain (Ito et al., 1974; Jäger & Henn, 1981a; Dow & Anastasio, 1999). Consequently, some authors suggest sinusoidal oscillations should be limited to a few cycles or having a delay between two series of tests (Clément et al., 2002). Other key factors involved in the result of vestibular tests are general level of arousal and instruction set (Wall & Furman, 1989; Weissman et al., 1989; Barnes, 1993; Zee & Leigh, 2006). For example, it is well known and documented that results can be compromised during long testing trials. In this study,

low modulation frequencies that would result in long testing times were excluded. Sixty-cycle trials were used and a delay between tests was obeyed. In these testing conditions, no significant habituation was observed. It is therefore reasonable to assume that habituation does not constitute a limiting factor in the tested frequency range.

No significant frequency-dependent changes in asymmetry were observed. However, the BVH-group showed significantly more asymmetry than the group of healthy volunteers. This could be expected, since acute unilateral vestibular stimulation (BVH-group) was compared to bilateral vestibular stimulation (group of healthy volunteers). However, it is interesting to note that the asymmetry index in the BVH-group remained relatively low (maximum 0.27) compared with previous data in unilaterally implanted monkeys (Dai et al., 2013; Guinand et al., 2015). The major difference between both studies was the level of baseline stimulation used. Baseline stimulation in this study was set supranormally at 50% of the dynamic range, while the animal study used a lower baseline in order to mimic the physiology of normal rhesus monkey vestibular afferent fibers (Sadeghi et al., 2007; Dai et al., 2013). With a supranormal baseline, the decrease in excitatory response is counterbalanced by the increase in inhibitory response, which should improve the symmetry of the response. In other words, using a supranormal baseline corresponding to 50% of the total dynamic range, allows an equal range of stimulation currents to code head movements toward the implanted side and toward the unimplanted side. Consequently, head compensation in all directions should be enhanced (Davidovics et al., 2012). At this point it is important to point out that it is still not clear yet whether asymmetry will be an issue of clinical relevance for vestibular implants. Results in patients with a unilateral vestibular loss show that response asymmetry is generally well compensated (Curthoys & Halmagyi, 1995; Black et al., 1996; van de Berg et al., 2011). It is therefore reasonable to hypothesize that even an asymmetric eVOR might be enough to restore useful vestibular function.

Knowing the minor frequency effects on angle, habituation and asymmetry could open doors for future research. It allows these eVOR-parameters to be determined at only specific frequencies, without the need for testing the whole frequency range. This is likely to result in more precise measurements, since (1) some modulation frequencies which have specific drawbacks (i.e., low gain for low-frequencies or challenging head stabilization during rotatory tests at higher-frequencies) could be left out of the analysis and (2) time is saved in the already long testing sessions, resulting in improved patients' concentration which has to be optimal for all tests.

The fact that a vestibular implant can closely mimick the "natural" frequency-dependency of the vestibular system, is also a promising finding for device development. Since the VOR is appropriately compensated in a frequency range which is important for every-day activities (Crane & Demer, 1997), there might be no need

of implementing complex stimulus processing strategies that consider frequency-dependent characteristics.

Additional considerations

In this study, the threshold for vestibular activation was the current where the first vestibular symptom was reported or observed (Guinand et al., 2015). This could be a change in nystagmus slow peak eye velocity or a clearly vestibular related sensation that could be below the threshold of activation of the VOR-pathway. This latter case suggests that other pathways can be activated before the VOR-pathway. These sub-VOR-threshold perceptions deserve to be investigated more in the future (Guinand et al., 2015).

Some healthy volunteers were unable to adequately stabilize their heads at 2Hz. This resulted in an increase in the vertical peak eye velocity component, which is in accordance with clinical experience that effectively stabilizing the head above a certain rotation frequency becomes challenging. A bite bar could be added to improve head stabilization. However, it was decided not to use a bite bar since we considered that this would impose an additional unnecessary burden to subjects. Furthermore, adding a bite bar would hinder communication with subjects. Both these considerations are particularly relevant for our long, repeated testing sessions performed in complete darkness.

Finally, a potential caveat of this study is that results are based on a small number of subjects. This suggests that results of statistical tests should be interpreted with caution. Nevertheless, the trends reported were similar across subjects and inter-subject variability was smaller than the observed effects. In these conditions, adding more subjects to the study would certainly give more statistical power to the results, but it would not fundamentally change the observed trends.

Conclusion

A strong and significant frequency-dependency effect in total peak eye velocity was observed in the tested frequency range (0.5–2Hz). This effect was comparable to the one observed for the “natural” VOR. (e)VOR-angle, habituation-index and asymmetry showed no significant frequency-dependent effect in any group. This study demonstrates that, at least in the specific (limited) frequency range tested, the vestibular implant closely mimics the natural frequency-dependency of the vestibular system.

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Chapter 7

The vestibular implant input interacts with residual natural function

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Abstract

Objective
Patients with bilateral vestibulopathy (BV) can still have residual “natural” function. This might interact with “artificial” vestibular implant input (VI-input). When fluctuating, it could lead to vertigo attacks. Main objective was to investigate how “artificial” VI-input is integrated with residual “natural” input by the central vestibular system. This, to explore (1) whether misalignment in the response of “artificial” VI-input is sufficiently counteracted by well-aligned residual “natural” input and (2) whether “artificial” VI-input is able to influence and counteract the response to residual “natural” input, to show feasibility of a “vestibular pacemaker.”

Materials and methods
Five vestibular electrodes in four BV patients implanted with a VI were available. This involved electrodes with a predominantly horizontal response and electrodes with a predominantly vertical response. Responses to predominantly horizontal residual “natural” input and predominantly horizontal and vertical “artificial” VI-input were separately measured first. Then, inputs were combined in conditions where both would hypothetically collaborate or counteract. In each condition, subjects were subjected to 60 cycles of sinusoidal stimulation presented at 1 Hz. Gain, asymmetry, phase and angle of eye responses were calculated. Signal averaging was performed.

Results
Combining residual “natural” input and “artificial” VI-input resulted in an interaction in which characteristics of the resulting eye movement responses could significantly differ from those observed when responses were measured for each input separately ($p<0.0013$). In the total eye response, inputs with a stronger vector magnitude seemed to have stronger weights than inputs with a lower vector magnitude, in a non-linear combination. Misalignment in the response of “artificial” VI-input was not sufficiently counteracted by well-aligned residual “natural” input. “Artificial” VI-input was able to significantly influence and counteract the response to residual “natural” input.

Conclusion
In the acute phase of VI-activation, residual “natural” input and “artificial” VI-input interact to generate eye movement responses in a non-linear fashion. This implies that different stimulation paradigms and more complex signal processing strategies will be required unless the brain is able to optimally combine both sources of information after adaptation during chronic use. Next to this, these findings could pave the way for using the VI as “vestibular pacemaker.”

Introduction

Bilateral vestibulopathy (BV) is defined as severely reduced or totally absent function of the bilateral vestibular organs, vestibular nerves or a combination of both (Hain et al., 2013). Associated symptoms are postural instability, blurred vision (oscillopsia) and impaired spatial orientation abilities (van de Berg et al., 2011; van de Berg et al., 2015). Up to 84% of the patients report a significant reduction in quality of life and there are considerable physical and socioeconomic impacts (Guinand et al., 2012; Sun et al., 2014). Since central vestibular compensation and sensory substitution are often not sufficient to counterbalance the lack of vestibular information (McCall et al., 2011), prognosis is poor in most cases (Zingler et al., 2008). Therapeutic options are limited and remain ineffective for high-frequency and unpredictable movements (Porciuncula et al., 2012; Herdman et al., 2007). In this context, restoring vestibular function using a vestibular implant (VI) might be beneficial for BV patients. Many research groups around the world are now investigating the feasibility, technical aspects and biomechanical issues of this option (Golub et al., 2014; van de Berg et al., 2012; Gong et al., 2002; Fridman et al., 2012). The first results of a motion-modulated vestibular prosthesis in humans were previously published by the Geneva-Maastricht group and provided clear evidence for the feasibility of a clinically useful VI in humans (Perez Fornos et al., 2014; Guinand et al., 2015; Guyot et al., 2016; van de Berg et al., 2014; Nguyen et al., 2016). The prototype implants investigated in animals and humans still have many challenges to overcome. A key challenge is to design, surgically implant and adjust the VI in such a way that the desired electrically evoked eye movements closely mimic the characteristics (e.g., gain, angle, phase) of the "natural" vestibulo-ocularreflex (VOR) response observed upon motion stimuli (Guinand et al., 2015; van de Berg et al., 2014; Dai et al., 2013; Davidovics et al., 2012; Della Santina et al., 2007; Feigl et al., 2009; Rubinstein et al., 2012; Wall et al., 2002). In order to achieve this, two factors might be relevant. First, VI-stimulation can show significant misalignment in the eye movement response as a result of current spread from the electrode location to adjacent nerves (van de Berg et al., 2011; Guinand et al., 2015; van de Berg et al., 2014). Second, residual "natural" input can still be present in BV (Zingler et al., 2008). This latter includes residual vestibular function and extravestibular cues such as proprioception (Fridman et al., 2012). This residual "natural" function might interact with the "artificial" VI-input, possibly influencing the response to the "artificial" VI-input. A fluctuating residual "natural" function could also give complaints (e.g., attacks of vertigo). It has been hypothesized that the VI could counteract the fluctuating residual "natural" function, and serve as a "vestibular" pacemaker (Golub et al., 2014). Therefore, a crucial point to be investigated in VI research is how this "natural" input (e.g., residual vestibular function as well as extravestibular cues) interacts with the "artificial" VI-input, to generate vestibular responses (i.e., the combined VOR). From a basic science point of

view, this could facilitate basic knowledge about how the central vestibular system integrates information of these two inputs. From a clinical point of view, it could facilitate knowledge about how the central vestibular system copes with misalignment of the “artificial” VI-response in the presence of well-aligned residual “natural” input. This could help determining whether a specific stimulation paradigm is needed to correct for the misalignment. Next to this, it could facilitate knowledge about whether the “artificial” VI-input is able to influence the response to residual “natural” input. This could pave the way for using the VI as a “vestibular pacemaker” in the future (Golub et al., 2014). Literature on this matter is still scarce in this relatively novel field. In previous animal investigations, vestibular function was ablated in a broad frequency range by canal plugging or ototoxic medication. In such experimental settings, only little vestibular function was preserved (van de Berg et al., 2012; Della Santina et al., 2007; Fridman et al., 2010; Lewis et al., 2002; Merfeld et al., 2006). Therefore, the interactions between “artificial” VI-input and residual “natural” input have not been completely investigated. In previous human investigations conducted by the Geneva-Maastricht group (Perez Fornos et al., 2014; van de Berg et al., 2014; Guyot et al., 2011), no interactions between the “artificial” and the “natural” inputs were investigated either. The current study was therefore designed to fill this gap by exploring how the “artificial” VOR generated by the VI, is modulated by the interaction between “artificial” VI-input and “natural” residual input during stimulation trials in the first hours after activating the VI (acute activation). In order to answer the clinical relevant questions mentioned above, predominantly horizontal residual “natural” input was combined with “artificial” VI-input that was congruent (predominantly horizontal) and incongruent (predominantly vertical, and inversed).

Methods

Patients and device

This study was conducted in four BV patients implanted with a modified cochlear implant incorporating three vestibular electrodes (MED-EL, Innsbruck, Austria). The inclusion criteria, surgical procedures and device characteristics were previously described (Perez Fornos et al., 2014; Guinand et al., 2015; van de Berg et al., 2014). The vestibular electrodes were located at various anatomical sites: two electrodes were implanted in the vicinity of the lateral ampullary nerve (LAN), two electrodes were implanted in the vicinity of the superior ampullary nerve (SAN), and one was implanted in the vicinity of the posterior ampullary nerve (PAN) (Table 7.1). These tested electrodes will be referred to as: BV1-LAN, BV1-SAN, BV2-PAN, BV3-LAN, and BV4-SAN. Note that electrodes implanted at different anatomical sites were purposefully used in the experiments in order to be able to study the interaction

between predominantly horizontal residual “natural” input with both horizontal (LAN stimulation) and vertical (SAN and PAN stimulation) “artificial” VI-input (see Introduction and Study Design and Experimental Procedure).

Electrical stimulation

As previously described, baseline stimulation of the vestibular nerve was restored in order to be able to generate bidirectional eye movements (i.e., upwards/downwards when stimulating the vertical nerve branches, and rightwards/leftwards when stimulating the lateral ampullary branch) with only unilateral vestibular stimulation (Perez Fornos et al., 2014; Guyot et al., 2011; Guinand et al., 2015). In this study a supraphysiological baseline was used, consisting of constant amplitude trains of biphasic charge-balanced pulses (200 μs/phase) presented at a rate of 400 pulses per second. The amplitude was set in the middle of the dynamic range measured for each patient (Guinand et al., 2015). This has shown to be effective in generating bidirectional vestibular sensations with a unilateral prosthesis (van de Berg et al., 2011; Guinand et al., 2015). It was previously reported that activating an implant does not often result in major discomfort and that nystagmus disappears within minutes, especially after repeated “on-off” transitions (Guinand et al., 2015; Guyot et al., 2011). Therefore, it was waited until the subjects were in the adapted state (e.g., when the spontaneous nystagmus had disappeared) (Guyot et al., 2011). Then an electrical signal was used to up- and down-modulate the amplitude of the train of pulses delivered by the vestibular electrodes. The modulation signal was generated by a 3D gyroscope (LYPR540AH; ST Micro-electronics; Geneva, Switzerland) fixated to a velocity-controlled rotatory chair (Nystagliner Pro; Erich Jaeger Gmbh) used to deliver precise sinusoidal rotations in the horizontal plane. For short, gyroscopes only capturing yaw-plane motion of the rotatory chair, served as input for modulation. Modulation was then applied to the electrodes located in horizontal as well as vertical semicircular canals. Therefore, yaw-plane motion led to an electrical response in all implanted semicircular canals. In this study, a linear transfer function was used in which the modulation strength (i.e., function slope) was chosen in such a way that at the fastest motion stimuli (30°/s, see experimental procedure below) the amplitude of electrical stimulation corresponded to 50-90% of the dynamic range of that specific electrode. This characteristic remained constant during the experiments. Note that this stimulation paradigm implied symmetric or equal modulation for excitatory and inhibitory stimuli (Perez Fornos et al., 2014; van de Berg et al., 2014). The specific electrical stimulation details for each tested electrode in each patient are presented in Table 7.1.

Table 7.1 Main characteristics of the tested BV-patients with a modified cochlear implant.

Subject	Sex	Etiology	Age at implantation	Surgical approach	Tested electrode(s) and side of implantation	Baseline and modulation amplitude
BV1	F	Trauma	67	Intralabyrinthine	LAN – Left side	250μA +/- 30μA
					SAN – Left side	400μA +/- 75μA
BV2	F	Meningitis	48	Intralabyrinthine	PAN – Right side	150μA +/- 50μA
BV3	M	DFNA-9	67	Intralabyrinthine	LAN – Left side	120μA +/- 60uA
BV4	M	Trauma	53	Intralabyrinthine	SAN – Right side	350μA +/- 125μA

Study design and experimental procedure

Patients were tested in a controlled laboratory setting, in complete darkness. They were instructed to sit still, keep their head straight up (not fixed), look in front of them and keep their eyes open during the trials. As the trials required substantial time, it was chosen to not fixate the patients' head on the chair or to use biteboard fixed gyroscopes. Therefore, it was first confirmed in a control experiment that, at the relative low rotational amplitudes and frequencies used in this study, head motion closely followed the motion stimulation profile. In addition, alerting tasks (e.g., counting down from 100 by 7, to name boy names starting with an "A," etc.) were given to all subjects during experimental trials to improve level of concentration and arousal. During experimental trials, patients were subjected to 60 sinusoidal cycles with a peak velocity of 30°/s and presented at a frequency of 1Hz, delivered by the velocity-controlled rotatory chair. Trials were performed in four experimental conditions:

1. *VOR condition*: patient sitting on the rotatory chair (i.e., subject to horizontal whole-body rotations), without electrical stimulation. This condition was used to quantify the patients' residual "natural" vestibular function in horizontal plane (including any contribution of extravestibular cues).
2. *Electrically evoked VOR condition (eVOR condition)*: patient sitting aside in an immobile chair (static, no motion) while the amplitude of the electrical stimulation delivered through one vestibular electrode was modulated by the gyroscope fixed to the rotatory chair. Since electrodes at different anatomical sites were used, the eVOR response could be cross-axial to the residual "natural" response measured in the VOR condition. The eVOR condition, as well as the paradigm of electrical stimulation, has been previously described (van de Berg et al., 2014). This condition was designed to quantify the VOR response generated exclusively by VI-input (i.e., no contribution of residual "natural" and/or extravestibular cues).
3. *Total VOR condition with "regular" modulation (totalVOR+)*: patient sitting on the rotatory chair (i.e., subject to horizontal whole-body rotations), while the amplitude of the electrical stimulation delivered through one vestibular electrode

was modulated by the gyroscope fixed to the rotatory chair [see also "Perez Fornos et al., 2014"]. In this condition, the alignment of the gyroscopes corresponded to the side of implantation. For example, during whole-body rotations to the left, the VI provided an excitatory stimulus for patients implanted on the left and an inhibitory stimulus for patients implanted on the right. Whole-body rotations to the right led to the opposite. This condition was designed to quantify the VOR response when the residual "natural" input and the "artificial" VI-input worked together to generate the response.

4. *Total VOR condition with inversed modulation (totalVOR−)*: this experimental condition was similar to the totalVOR+ condition, except that the orientation of the gyroscopes was reversed for the horizontal plane: Instead of delivering an excitatory stimulus during a whole-body rotation to the implanted side, an inhibitory stimulus was delivered by the VI. An excitatory stimulus was elicited by a rotation to the opposite side. In this condition, the "artificial" VI-input could hypothetically counteract the input of the residual "natural" and extravestibular inputs.

The testing sequence was identical for all patients since the after-effects of VI-stimulation are still undetermined (Merfeld et al., 2006; Lewis et al., 2013): VOR, eVOR, totalVOR+, and finally totalVOR−. Trials were repeated if necessary to obtain as many reliable results as possible. Indications for repeating a trial were equal to those used in a clinical setting (van de Berg et al., 2015; van de Berg et al., Videobook).

Data acquisition and pre-processing

Bidimensional eye movements were recorded during experimental trials using the EyeSeeCam system (EyeSeeTec; Munich, Germany) at a sampling rate of 220Hz. The eye movement signal was then preprocessed off-line using Matlab R2011b (The Mathworks, Natick, MA, USA). The eye position signal was smoothed first using an 11th order Sawitzky-Golay filter, followed by an 11th order median filter. Then, the signal was differentiated to obtain the eye velocity. Blinks, saccades and quick phases were detected as segments where eye acceleration was above 1,000°/s and eye velocity was above 600°/s, and subsequently removed. Piecewise cubic Hermite interpolation was used to fill the missing values. Finally, eye velocity, head velocity, and time data were then transferred to Mathematica 10.4 (Wolfram Research, Champaign, IL, USA), where any cycles with remaining blink artifacts were manually removed in consensus by two authors (Raymond van de Berg and Dmitrii Starkov).

Data analysis of the remaining cycles

Signal averaging was performed by calculating the mean of all cycles for each sample point of the mean cycle. To visualize the average signals, results were plotted separately for horizontal and vertical eye and head velocities. After a first qualitative analysis by three authors (Raymond van de Berg, Marc van Hoof, and Herman Kingma), it was decided to develop a signal analysis algorithm based on peak total eye and peak total head velocities. These were calculated as the square roots of the sums of the squares of horizontal and vertical eye and head velocities. Peak total eye velocities and peak total head velocities per cycle were determined using a peak detection paradigm where the maximum excitatory and inhibitory velocities were identified. After detecting the first peak, the second peak was selected using a weighted distance and amplitude function in relationship to the first peak and to half of the cycle [amplitude × (amount of samples to first peak/amount of samples of half the cycle)]. Cycles were only included if an inhibitory and excitatory peak were present. Gain of each cycle was calculated by dividing peak total eye velocity by peak total head velocity, not corrected for time delay. Since the eVOR condition did not contain sinusoidal head movements (the head was kept stationary) and to allow comparison, the gain in the eVOR condition was based on the peak total eye velocity divided by a hypothetical 1Hz sinusoidal head movement with a peak velocity of 30°/s.

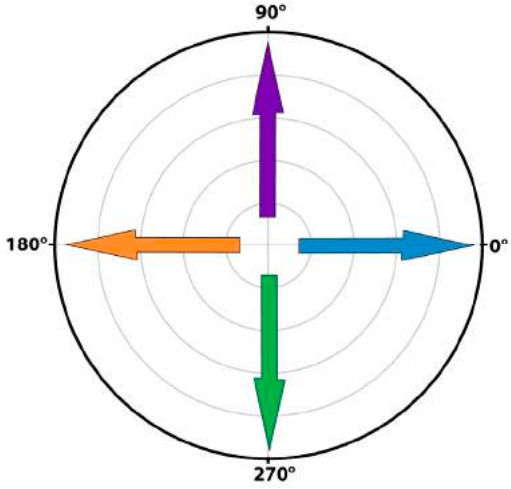

Figure 7.1 Polar plot illustrating the angles of eye movements. A horizontal eye movement to the right corresponded to an angle of 0^{o} (blue arrow), a horizontal eye movement to the left to an angle of 180^{o} (orange arrow). A completely vertical eye movement upwards corresponded to an angle of 90^{o} (purple arrow) and a completely vertical eye movement downwards to an angle of 270^{o} (green arrow).

Statistics

Medians and interquartile ranges were determined. Confidence intervals for medians were bootstrapped 1000 times. *P*-values were calculated using the Mann-Whitney *U* Test for the medians. Bonferroni correction was applied (alpha value of 0.05 divided by 36 to correct for multiple testing). An alpha value of 0.0014 was thus considered statistically significant.

Ethical considerations

This study was in accordance with the Declaration of Helsinki (amended version 2013). Approval was obtained from the ethical committees of Maastricht University Medical Center (NL36777.068.11/METC 11-2-031) and Geneva University Hospitals (NAC 11-080). All participants provided written informed consent prior to the study.

Results

Qualitative analysis of signal shapes

Figures 7.2 and 7.3 present the preprocessed eye and head movement signals of each condition for each subject, before and after averaging. Pure "artificial" VI-input (eVOR condition) could lead to non-linearities in the eye movement response: sinusoidal electrical stimulation did not often evoke sinusoidal eye movements (e.g., eVOR of BV1-LAN, BV1-SAN, BV4-SAN). These non-linearities involved asymmetries between the excitatory phase and the inhibitory phase of stimulation. For example, the eVOR condition for BV4-SAN showed a high peak in the vertical eye velocity during the excitatory phase but a lower and less pronounced peak in the inhibitory phase. Asymmetrical responses were also often observed in the combined totalVOR+ and totalVOR− conditions (e.g., BV1-SAN).

Characteristics of the responses obtained in the different experimental conditions

Gain

Table 7.2 and Figure 7.4 present, respectively, the median peak total eye velocities and the vectors of the obtained eye movements in the excitatory and inhibitory phases of stimulation, plotted for each electrode in each condition. As expected, little residual "natural" function (VOR condition) was present in all cases. The median gain value was ≤0.25 for all cases, except for BV3-LAN where it reached around 0.4 for both phases of stimulation. When residual "natural" function was combined with "artificial" VI-input, gains increased in totalVOR+ and total- VOR− in all cases, except a

non-significant decrease of gain in the excitatory phase of totalVOR− in BV2-PAN. The increases were significant (p<0.00001) for both the excitatory and the inhibitory phases of stimulation of totalVOR+ and totalVOR− in BVL1-LAN, BVL1-SAN, and BV4-SAN. In BV2-PAN, the increase was significant for both phases in totalVOR+, and the inhibitory phase in totalVOR− (p≤0.0001).

Only the gain in the excitatory phase of stimulation for the totalVOR+ condition was significantly higher (p=0.0004) than VOR for BV3-LAN. When comparing responses of "artificial" VI-input only (eVOR) to the combined conditions totalVOR+ and totalVOR−, gain could increase or decrease with respect to eVOR. These changes were significant in BV1-LAN and BV1-SAN in totalVOR− for both phases (p≤0.0002), but not in totalVOR+. In BV2-PAN only the gain of the excitatory phase of totalVOR− was significantly different from eVOR (p<0.00001). In BV3-LAN the gains of the inhibitory phases of totalVOR+ and totalVOR− were significantly different from eVOR (p≤0.0002), but not the excitatory phases. In BV4-SAN, both totalVOR+ and totalVOR− were significantly different from eVOR (p<0.00001), except the excitatory phase of totalVOR+. In all electrodes, the excitatory phase always showed a higher gain than the inhibitory phase in totalVOR+. In totalVOR− this was always the opposite. To summarize, gain often significantly changed when combining residual "natural" function with "artificial" VI-input, compared to residual "natural" function only.

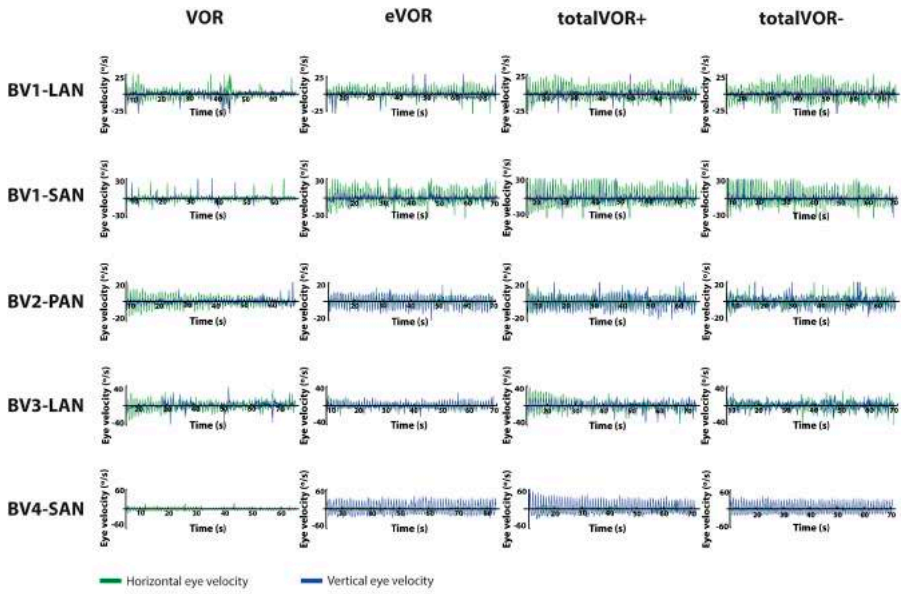

Figure 7.2 Plots presenting for all subjects the raw eye movement signals of each condition in the horizontal and vertical planes. Positive horizontal velocities correspond to movements to the right and negative horizontal velocities to movements to the left. Positive vertical velocities correspond to movements upwards and negative vertical velocities to movements downwards.

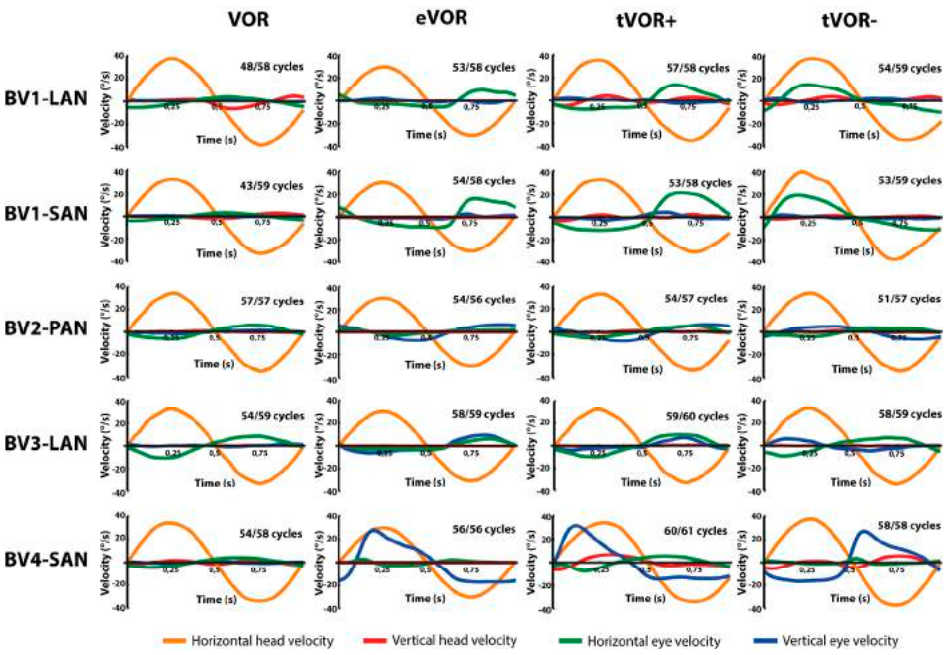

Figure 7.3 Averaged eye and head movement signals of each condition in the horizontal and vertical planes. Positive horizontal velocities correspond to movements to the right and negative horizontal velocities to movements to the left. Positive vertical velocities correspond to movements upwards and negative vertical velocities to movements downwards. Note that since the electrically evoked vestibulo-ocularreflex (eVOR) condition involved no head movements, a hypothetical horizontal head movement is plotted corresponding to the electrical stimulus of the vestibular implant. The amount of cycles measured is given, as well as the number of cycles available for analysis after data cleaning.

Angles

Three electrodes elicited eye movement responses that were in the plane of the stimulated canal: a predominantly horizontal response in BV1-LAN, and predominantly vertical responses in BV2-PAN and BV4-SAN. Two other electrodes showed clear misalignment: BV1-SAN elicited a predominantly horizontal response, and BV3-LAN elicited a mixed horizontal and vertical response (Table 7.3 and Figure 7.4). When combining residual “natural” input and “artificial” VI-input in totalVOR+, the angles remained predominantly horizontal in BV1-LAN and BV2-SAN. In BV2-PAN, BV3-LAN, and BV4-SAN predominantly horizontal eye movements of VOR were combined with predominantly vertical eye movements of eVOR.

Table 7.2 Median peak total eye velocities (°/s) and confidence intervals in the excitatory and inhibitory phases of stimulation, of each electrode in each condition.

		Excitation				*Inhibition*		
	VOR	*eVOR*	*totalVOR+*	*totalVOR-*	*VOR*	*eVOR*	*totalVOR+*	*totalVOR-*
BV1-LAN	5.7	14.2	15.0	11.3	6.7	5.8	9.4	16.8
	(5.0-7.2)	(11.6-16.2)	(11.6-16.2)	(10.3-11.0)	(5.1-8.1)	(5.4-8.0)	(8.2-10.3)	(15.2-18.6)
BV1-SAN	4.3	20.7	24.9	12.4	4.8	12.3	13.1	23.3
	(3.8-4.9)	(16.6-23.2)	(22.8-28.0)	(11.4-13.3)	(4.2-5.3)	(10.4-13.4)	(11.8-13.9)	(20.9-27.3)
BV2-PAN	7.2	10.0	12.2	7.1	6.7	7.2	9.2	10.2
	(6.4-8.3)	(9.2-10.5)	(11.6-12.8)	(6.4-7.7)	(6.6-7.7)	(6.8-7.8)	(8.2-10.0)	(9.7-11.3)
BV3-LAN	11.7	12.3	16.6	12.9	13.0	10.0	14.5	16.1
	(10.3-13.3)	(10.8-13.5)	(15.1-18.7)	(11.3-16.5)	(11.9-16.1)	(6.8-12.2)	(12.6-17.2)	(13.6-18.2)
BV4-SAN	4.6	28.1	32.7	17.3	4.4	18.3	16.3	28.0
	(4.1-5.4)	(27.1-29.5)	(31.1-34.8)	(16.3-18.1)	(3.8-5.8)	(17.5-19.9)	(15.0-17.4)	(27.4-28.5)

Table 7.3 Median angles (°) and confidence intervals in the excitatory and inhibitory phases of stimulation, of each electrode in each condition.

	Excitation				*Inhibition*			
	VOR	eVOR	*totalVOR+*	*totalVOR-*	*VOR*	*eVOR*	*totalVOR+*	*totalVOR-*
BV1-LAN	25.6	358.4	352.9	178.6	165.5	180.4	165.1	354.8
	(12.5-39.2)	(4.5-345.9)	(348.8-355.3)	(173.7-188.4)	(147.7-173.6)	(163.6-188.6)	(157.6-173.5)	(351.4-359.7)
BV1-SAN	7.4	10.5	0.3	190.3	171.4	190.2	185.2	0.4
	(18.1-353.8)	(0.0-15.1)	(5.6-357.6)	(187.3-193.5)	(167.4-185.8)	(180.6-195.7)	(182.0-191.6)	(5.4-358.1)
BV2-PAN	193.0	248.3	241.1	126.2	12.6	76.3	53.8	278.5
	(190.0-200.0)	(243.4-254.9)	(229.9-244.3)	(111.3-131.8)	(6.2-15.5)	(75.1-78.7)	(45.6-65.4)	(269.0-283.6)
BV3-LAN	358.2	55.8	28.1	331.5	184.3	244.4	191.7	146.2
	(3.9-349.6)	(52.5-59.0)	(25.8-37.0)	(313.6-352.0)	(176.3-191.5)	(227.5-255.4)	(188.0-199.7)	(122.6-152.8)
BV4-SAN	13.6	64.3	48.7	9.9	357.9	275.3	287.2	88.4
	(182.9-188.1)	(88.0-90.8)	(99.0-101.7)	(268.1-275.9)	(2.5-354.8)	(272.2-277.2)	(285.5-290.2)	(86.5-89.7)

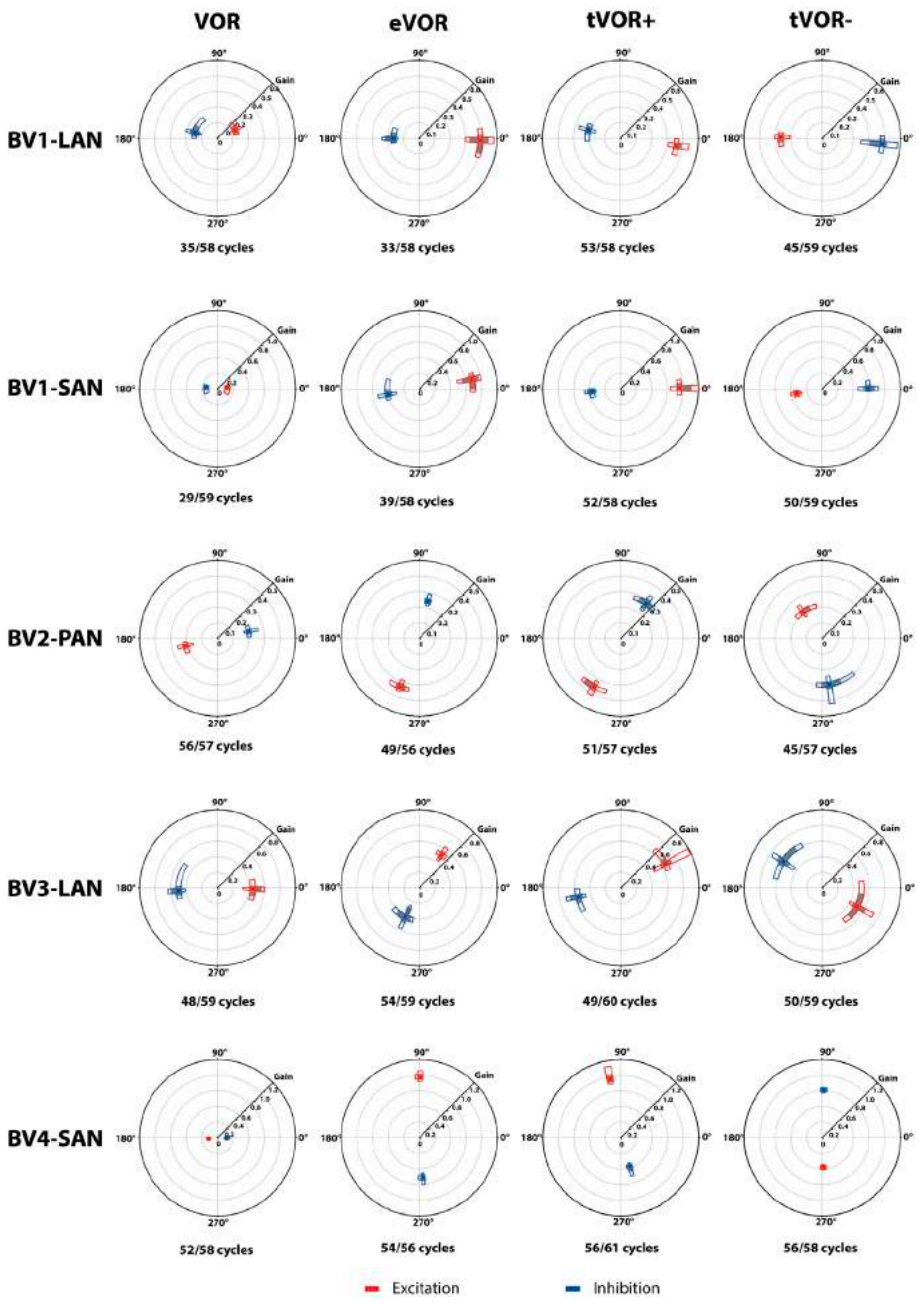

Figure 7.4 Vectors of peak total eye velocities in the excitatory and inhibitory phases of stimulation, plotted for each electrode in each condition (VOR, eVOR, tVOR+, tVOR-). The gain is represented by the vector magnitude. The angle of the response is represented by the vector

angle (according to the polar plot in Figure 7.1). Dots represent the medians, grey bars the 95% confidence intervals and the open bars the interquartile ranges of the vectors of peak total eye velocities. Red represents peak total eye velocities obtained during the excitatory phases of stimulation, blue during the inhibitory phases. The amount of analyzed excitatory and inhibitory peak total eye velocities is given, as well as the amount of peaks available for analysis after data cleaning. Note that, to improve visibility, the scale of the polar plots for each subject was optimized for individual responses, and consequently is not uniform across subjects.

This resulted in a shift of the predominantly vertical median peak total eye velocities of eVOR, to the horizontal axis. When inverting the gyroscopes of the VI in totalVOR−, different responses were obtained. In BV1-LAN, BV1-SAN, and BV4-SAN, inversion of the gyroscopes resulted in an almost 180° difference of the angles of the median peak total eye velocities of the excitatory and inhibitory phases, compared to totalVOR+. In other words, the eyes moved to the opposite direction than in totalVOR+. In BV2-PAN and BV3-LAN, inversion of the gyroscopes resulted in an inversion of the vertical peak total eye velocities, but not of the horizontal peak total eye velocities. For example in BV2-PAN: when the head was moving to the right in totalVOR+, the eyes moved downwards and to the left. When the head was moving to the right in totalVOR−, the eyes now went upwards, but remained moving to the left. To summarize, the resulting angle of the eye responses in the combined conditions was a non-linear mix of the responses resulting from residual “natural” input and “artificial” VI-input across subjects.

Asymmetry

Figure 7.5 presents the asymmetry of the eye movement responses plotted for each electrode in each condition. A significantly higher asymmetry in eye movement response was found in eVOR compared to VOR in all electrodes ($p \leq 0.0002$). When comparing VOR with conditions that involved “artificial” VI-input combined with residual “natural” input (totalVOR+ and totalVOR−), a significant asymmetry was found in totalVOR+ in almost all electrodes ($p \leq 0.001$) except BV3-LAN, and in totalVOR− in BV2-PAN and BV4-SAN ($p \leq 0.0013$). Asymmetry of responses of “artificial” VI-input only (eVOR) did often not significantly differ from totalVOR+ (only BV4-SAN, $p=0.0003$), but always from totalVOR− ($p \leq 0.0011$). In the combined conditions, the median asymmetry always inverted from a positive value in total-VOR+, to a negative one in totalVOR−. This asymmetry between totalVOR+ and totalVOR− significantly differed in almost all electrodes ($p<0.0001$) except BV3-LAN. To summarize, “artificial” VI-input often introduced a significant asymmetry to the resulting eye responses across subjects.

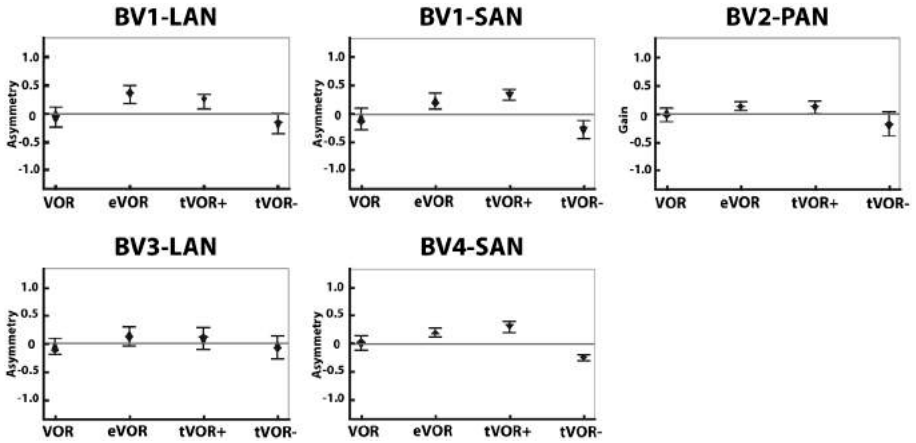

Figure 7.5 Asymmetry of the eye movement responses plotted for each electrode in each condition (VOR, eVOR, tVOR+, tVOR-). The widest part of each diamond represents the median, upper and lower parts of the diamond the 95% confidence intervals, and the bars the interquartile ranges. Red represents the excitatory phase, blue the inhibitory phase. The amount of analyzed excitatory and inhibitory peak total eye velocities is the same for each electrode and condition as in Figure 7.3.

Phase

Figure 7.6 illustrates the phases of the eye movement responses plotted for each electrode in each condition. Regarding horizontal phases (horizontal phase of BV4-SAN not presented in this figure), all electrodes showed a phase lag in VOR and a "hypothetical" phase lead in eVOR (since the eye movement response was compared with a hypothetical horizontal head movement). They significantly differed from each other in all electrodes (p<0.0001). In the predominantly horizontally aligned electrodes BV1-LAN and BV1-SAN, the median phase of the horizontal eye movement response in totalVOR+ was significantly more in counter phase (showing a phase difference closer to 180°) than the eye movement response in VOR and eVOR (p<0.00001). No significant difference between VOR and totalVOR+ was found in the other electrodes with more vertical components in the response. Responses of "artificial" VI-input only (eVOR) always significantly differed from totalVOR+ regarding horizontal phases. Inversion of the gyroscopes in totalVOR− induced some clear phase shifts. In the electrodes with a predominantly horizontal response (BV1-LAN and BV1-SAN), the horizontal eye movement response was almost in counter phase in totalVOR+, and almost in phase in totalVOR−.

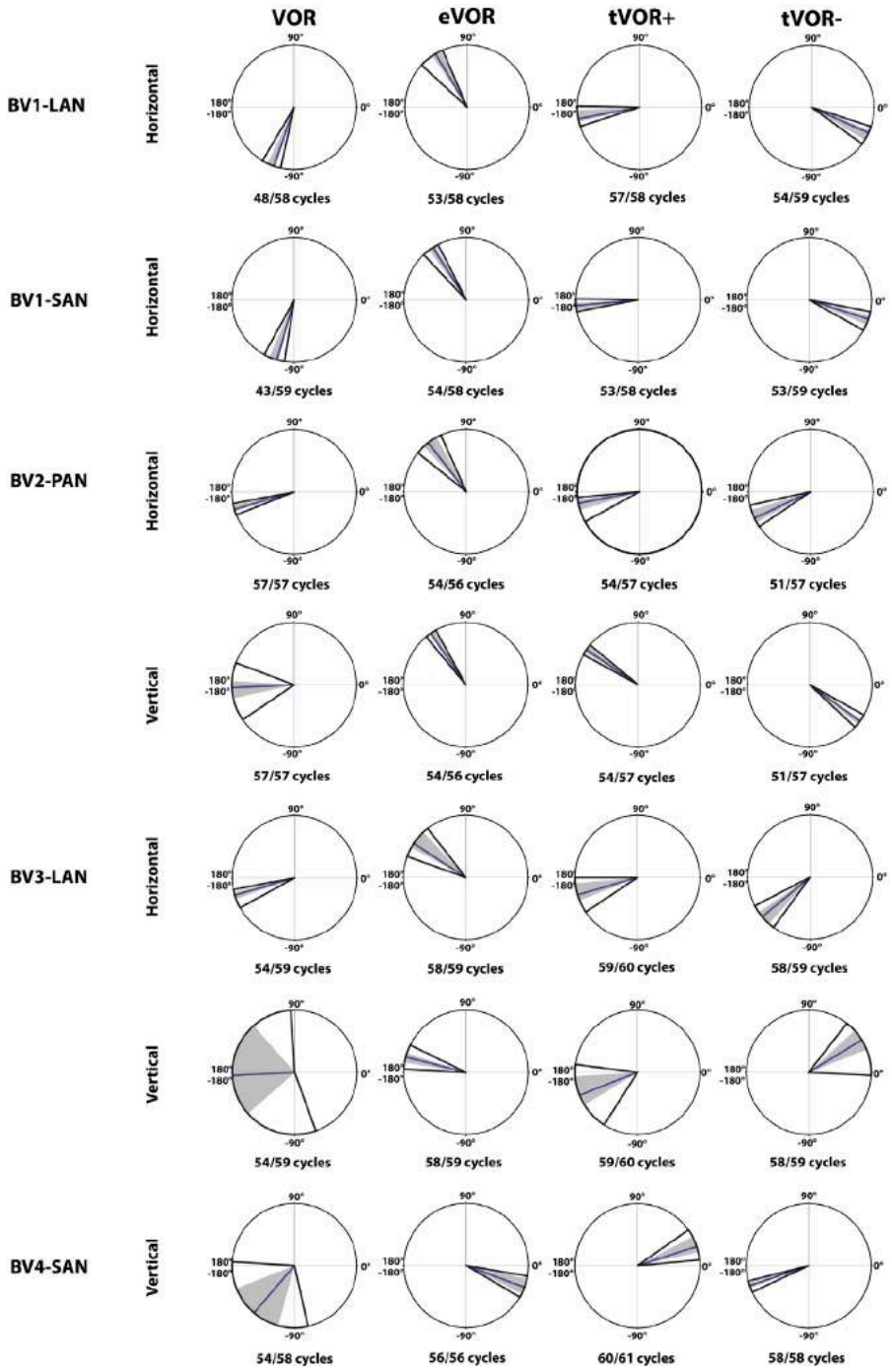
VOR
eVOR
tVOR+
tVOR-
BV1-LAN
Horizontal
48/58 cycles
53/58 cycles
57/58 cycles
54/59 cycles
BV1-SAN
Horizontal
43/59 cycles
54/58 cycles
53/58 cycles
53/59 cycles
BV2-PAN
Horizontal
57/57 cycles
54/56 cycles
54/57 cycles
51/57 cycles
Vertical
57/57 cycles
54/56 cycles
54/57 cycles
51/57 cycles
BV3-LAN
Horizontal
54/59 cycles
58/59 cycles
59/60 cycles
58/59 cycles
Vertical
54/59 cycles
58/59 cycles
59/60 cycles
58/59 cycles
BV4-SAN
Vertical
54/58 cycles
56/56 cycles
60/61 cycles
58/58 cycles

Figure 7.6 Phases of the eye movement responses plotted for each electrode in each condition (VOR, eVOR, tVOR+, tVOR-). Zero corresponds with "in phase", +/-180º with "counter phase". Positive values correspond with a phase lead, negative values with a phase lag. The middle bar represents the median, the grey area the 95% confidence interval and the outer bars the interquartile ranges. Depending on the case, horizontal, vertical or both phases are presented. The amount of cycles measured is given, as well as the amount of cycles available for analysis after data cleaning.

In other words, when the head was moving to the left in totalVOR+, the eyes were moving to the opposite direction, but when the head was moving to the left in totalVOR−, the eyes were moving in the same direction. In BV4- SAN (mainly vertical response), vertical phases were nearly in phase in totalVOR+, and nearly in counter phase in totalVOR−. In the electrodes BV2-PAN and BV3-LAN, horizontal phases did not differ significantly between VOR and totalVOR−. However, the vertical eye movement response changed from near counter phase (totalVOR+), to near in phase (totalVOR−). To summarize, the electrodes with a predominantly horizontal response were able to significantly decrease the phase lag of the residual "natural" function. Inverting the gyroscopes could introduce an almost 180° horizontal or vertical phase shift, depending on the electrode.

Discussion

The main outcome of this study is the demonstration of significant interactions between the VI-generated VOR and residual "natural" function during the acute stimulation of vestibular nerve branches. It was shown that horizontal residual "natural" input was not sufficient to fully counteract the misalignment of the "artificial" VI-input. However, "artificial" VI-input was able to significantly influence the response to residual "natural" input. The interaction between "artificial" VI-input and residual "natural" input has not been extensively studied before in humans, although all BV patients can still have some residual "natural" input that can significantly contribute to the response. This study was designed as an initial exploratory test to investigate the possible interaction, by inducing conflicts between vectors of eye movements. It was illustrated that when both inputs combined (measured in VOR and eVOR conditions), an interaction occurred in which some of the characteristics of the resulting eye movement responses (totalVOR+ and totalVOR− conditions) significantly differed from one or both inputs. This interaction was not linear: the vectors obtained in the totalVOR conditions did not seem to be a clear linear summation of the vectors obtained in the VOR and eVOR conditions, as illustrated in Figure 7.7. It could be hypothesized that when vectors containing different components are combined, the "strongest" components might be represented more in the resulting totalVOR, than the "weaker" components. This

could clearly be observed in the totalVOR− conditions of the “artificial” VI-inputs with an almost equal magnitude with respect to their corresponding residual “natural” inputs (BV2-PAN and BV3-LAN). In these cases, the resulting vectors of eye movements in totalVOR− showed angles of which the horizontal component was dominated by the input with the strongest median horizontal peak eye velocities, and the vertical component was dominated by the input with the strongest median vertical peak eye velocities (Figure 7.7). This was also found in the “artificial” VI-inputs with a much higher magnitude than their corresponding residual “natural” inputs (BV1-LAN, BV1-SAN, BV4-SAN): after combining both inputs, the resulting totalVOR conditions were often dominated by components of the “artificial” VI-input. Especially in the totalVOR− conditions of these electrodes, in which clear phase shifts were observed, it was shown that “artificial” VI-input was able to “counteract” residual “natural” input (Figure 7.7).

Some electrodes showed clear misalignment (e.g., BV1-SAN with a predominantly horizontal response). Although highly interesting, the background for this was previously extensively described and not within the scope of this article (van de Berg et al., 2011; Guinand et al., 2015; Nguyen et al., 2014). However, this misalignment (next to purposely selecting electrodes with a predominantly vertical response and inverting the gyroscopes) facilitated an interaction between horizontal residual “natural” input and predominantly vertical and/or inversed “artificial” VI-input. Within this interaction, the brain was not able to fully suppress conflicting vestibular information in the acute phase of stimulation (Lacour et al., 2009). In other words: horizontal residual “natural” input was not sufficient to fully counteract the misalignment of the “artificial” VI-input. In these cases, the central vestibular system did not thoroughly distinguish between input that was congruent with the axis of whole-body rotation (the residual “natural” input) or with input that was sometimes conflicting with the axis of whole-body rotation (the “artificial” VI-input). In animals, “cross-axis adaptation” has been described, in which vertical eye movement responses gradually shifted toward alignment with the axis of horizontal head rotation after long periods of chronic use. This indicates that the central nervous system rapidly adapts to VI-input (Dai et al., 2011). Cross-axis adaptation takes several days to occur in animals (van de Berg et al., 2011; Lewis et al., 2002). In humans, it has not been reported for stimulation periods longer than these 60-cycle trials, in which cross-axis adaptation did not occur in the electrodes with predominantly vertical eye responses. This should be evaluated in future studies involving longer periods of chronic stimulation. However, the interaction between residual “natural” input and “artificial” VI-input could possibly enhance faster adaptation than previously described in animals (Dai et al., 2013; Lewis et al., 2002; Dai et al., 2011; Lewis et al., 2010).

In case the human brain is not able to correct for the misalignment after adaptation during chronic use, more complex stimulation paradigms might be necessary. These

findings do imply that the response to residual “natural” input can be influenced by “artificial” VI-input. This might pave the way for using the VI as a “vestibular pacemaker.” Future studies could address this subject by using the VI to reduce vestibular asymmetry as occurring during disabling attacks of vertigo (Golub et al., 2014). However, whether this interaction is beneficial or counterproductive in these situations has not been determined yet. In most electrodes, “artificial” VI-input significantly increased gain in totalVOR+ (the condition in which the VI should work in daily life). The totalVOR response did not seem to result from a simple, linear interaction between VOR and eVOR responses (e.g., the horizontally aligned electrodes BV1-LAN and BV1- SAN; Figure 7.4). Next to this, gain did not often reach the value of 1. This was due to a lower response to electrical stimulation, as well as the natural frequency-dependency of the vestibular system. After all, gain in healthy individuals does not necessarily have to reach the value of 1 at 1Hz modulation (van de Berg et al., 2014). Furthermore, in the electrodes generating a predominantly horizontal eye movement response, phase could significantly be restored. This is an important finding since BV patients often show phase abnormalities in their VOR response (Hain et al., 2013). The improvement of gain and phase of the eye movement response in totalVOR+ (the condition in which the VI should work in daily life) is encouraging for the future rehabilitation prospects of the VI. A previous study of our group also supported this by showing a significantly increased performance during a reallife task (walking), resulting from VI-stimulation (Guinand et al., 2016). An additional important finding of this study was the observation of non-linearities induced by VI-stimulation. “Artificial” VI-input (present in eVOR, totalVOR+ and totalVOR−) often resulted in asymmetrical shapes of eye movements, not fully replicating the shape of the sinusoidal stimulation signal. This implies that traditional methods of signal analysis like fitting with a sinus or application of Fast Fourier transform (Perez Fornos et al., 2014; Davidovics et al., 2012) might be insufficient for evaluation of eye movements obtained by the VI. Several facts could contribute to this asymmetry. Firstly, a linear transfer function was chosen, from the lower threshold, to baseline, to the upper threshold. However, neural responses to electrical stimulation rarely follow a linear relationship (DiGiovanna et al., 2016). Secondly, the VI unilaterally stimulates the ampullary nerves in a non-physiological way: it involves a relatively non-selective electrical stimulus that bypasses all biophysical properties of the peripheral end-organ and selected pulse rates were supra- physiological (Wilson et al., 1979). Thirdly, another contributing factor could be the paradigm of determining the dynamic ranges: the lowest threshold for stimulation was determined as the first (lowest) level of electrical current where the first vestibular symptom was observed or reported (Guinand et al., 2015). However, in recent experiments it was observed that perception can have a lower threshold than the VOR (van de Berg et al., 2016). This implies that when baseline stimulation is set at half the dynamic range, it might not be halfway the dynamic range for eliciting a VOR. This could result in an

asymmetrical eVOR response since the eVOR might reach saturation earlier during the inhibitory phase of stimulation than during the excitatory phase of stimulation.

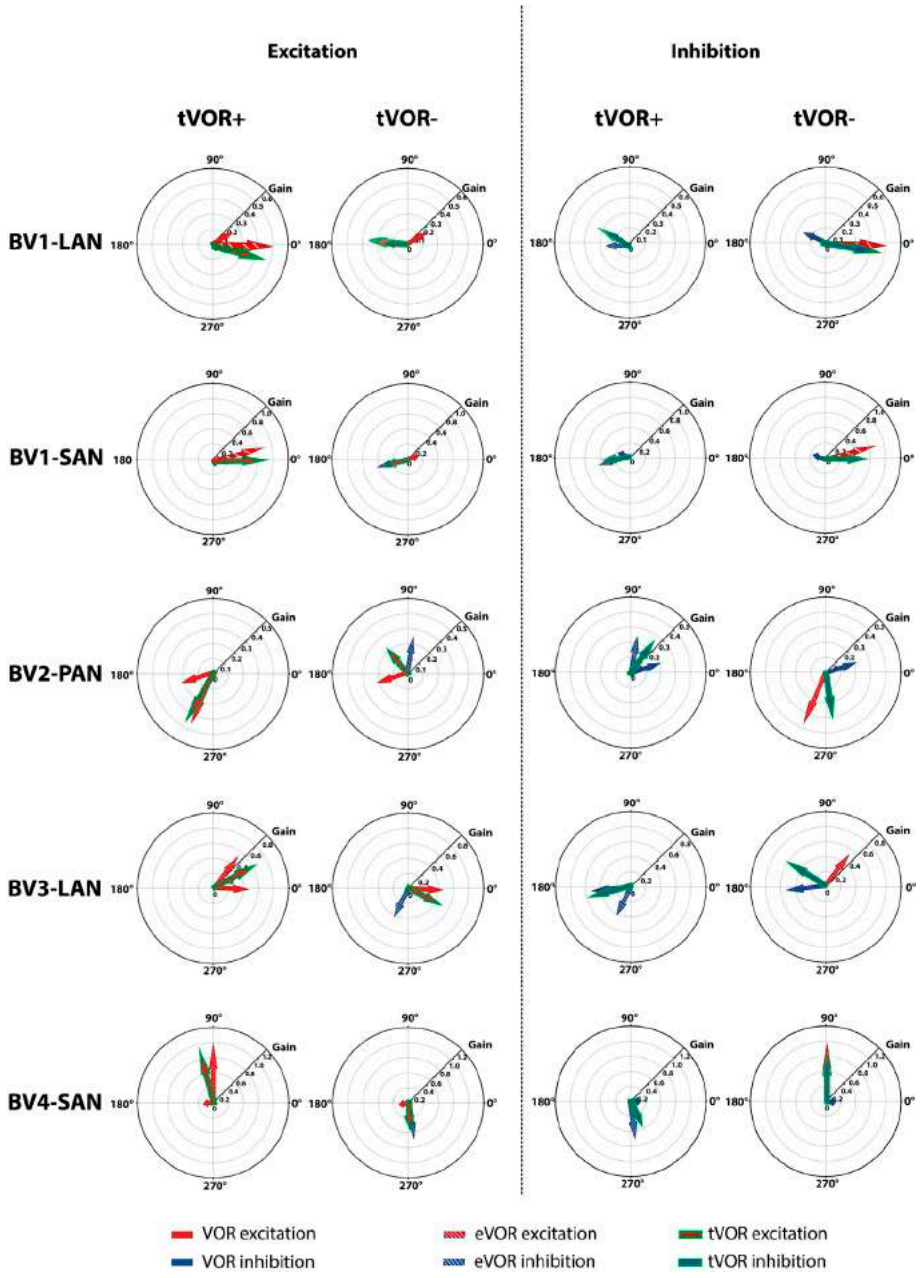

Figure 7.7 Schematic representation of the interaction between residual "natural" input and "artificial" VI-input in the excitatory and inhibitory phases of the tVOR+ and tVOR- conditions of all electrodes. Arrows show the median vector of peak total eye velocities obtained during excitatory and inhibitory phases of the experimental trials. Excitatory vectors contain a red color; inhibitory vectors contain a blue color. VOR is represented by a plain arrow, eVOR by a striped arrow, and tVOR by a green edged arrow. In the excitatory phases of tVOR+, the excitatory phases of VOR and eVOR were combined. In the excitatory phases of tVOR-, the excitatory phases of VOR were combined with the inhibitory phases of eVOR, since the gyroscopes were inversed during the tVOR- condition. In the inhibitory phases of tVOR+, the inhibitory phases of VOR and eVOR were combined. In the inhibitory phases of tVOR-, the inhibitory phases of VOR were combined with the excitatory phases of eVOR.

Other considerations and limitations

Patients in this study still had some residual "natural" input. They fitted the stringent inclusion criteria for implantation, including a gain of less than 0.25 on rotatory chair tests using the typical clinical frequency of 0.1Hz (Perez Fornos et al., 2014). By increasing the stimulation frequency to 1Hz, gain of the residual "natural" input increased (van de Berg et al., 2014). This facilitated a higher residual "natural" input, to interact with the "artificial" VI-input. It also explains why some patients (e.g., BV3) showed a higher VOR response than would initially be expected from the inclusion criteria. Motivation for not using a bite bar was previously described (van de Berg et al., 2014). Unfortunately, head movement artifacts (vertical head movements or differences in velocity) were observed in some VOR, totalVOR+, and totalVOR− conditions. These unwanted head movements affected mainly angle. Therefore, no statistical analysis was performed regarding angle of the obtained eye movements. Only a 1Hz sinusoidal stimulus was chosen for this study. It was previously shown that the eVOR has an acceptable gain at 1Hz compared to lower frequencies where alertness and arousal may influence the gain substantially more. Next to this, head fixation to the rotatory chair becomes more necessary at higher frequencies to avoid artifacts by head inertia. In contrary to lower frequencies, patients' arousal is also less compromised during 60-cycle trials at 1Hz. Besides, other parameters like angle and asymmetry show no significant frequency dependency and habituation does not play a key factor in the eVOR analysis when using this paradigm (van de Berg et al., 2014). However, this also implies that the findings of this study might be specific for this frequency (Agrawal et al., 2013; MgGarvie et al., 2015) and that they cannot directly be extrapolated to other frequencies.

Conclusion

In the acute phase of VI-activation, residual "natural" input and "artificial" VI-input interact to generate eye movement responses in a non-linear fashion. The observed interaction implies that different stimulation paradigms and more complex signal

processing strategies (e.g., non-linear transfer functions) will be required unless the brain is able to optimally combine both sources of information after adaptation during chronic use. Next to this, these findings could pave the way for exploring the use of the VI as a “vestibular pacemaker.”

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Chapter 8

Restoring visual acuity in dynamic conditions with a vestibular implant

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Abstract

Vestibular implants are devices designed to rehabilitate patients with a bilateral vestibular loss (BVL). These patients lack a properly functioning vestibulo-ocularreflex (VOR), which impairs gaze stabilization abilities and results in an abnormal loss of visual acuity (VA) in dynamic situations (i.e., severely limiting the patient's ability to read signs or recognize faces while walking). We previously demonstrated that the VOR can be artificially restored in a group of BVL patient sfitted with a prototype vestibular implant. This study was designed to investigate whether these promising results could be translated to a close-to-reality task, significantly improving VA abilities while walking. Six BVL patients previously implanted with a vestibular implant prototype participated in the experiments. VA was determined using Sloan letters displayed on a computer screen, in four conditions: (1) with the patient standing still without moving (static), (2) while the patient was walking on a treadmill at constant speed with the vestibular implant prototype turned off (systemOFF), (3) while the patient was walking on a treadmill at constant speed with the vestibular implant prototype turned on providing coherent motion information (systemON$_{motion}$), and (4) a "placebo" condition where the patient was walking on a treadmill at constant speed with the vestibular implant prototype turned on providing reversed motion information (systemON$_{sham}$). The analysis (one-way repeated measures analysis of variance) revealed a statistically significant effect of the test condition [$F_{(3,12)}$ 30.5, $p<0.001$]. Significant decreases in VA were observed with the system OFF condition when compared to the static condition (Tukey *post-hocp*<0.001). When the vestibular implant was turned on, delivering pertinent motion information (systemON$_{motion}$) the VA improved to close to normal values. The improvement disappeared in the placebo condition (systemON$_{sham}$) and VA-values also dropped significantly in this condition (Tukey*post-hocp*<0.001). These results are a significant step forward in the field, demonstrating for the first time in humans that gaze stabilization abilities can be restored with a vestibular implant prototype. The vestibular implant shows considerable promise of being the first-ever effective therapeutic alternative for patients with a BVL in the near future.

Introduction

The vestibular implant is a device designed to artificially restore the vestibular function using motion modulated electrical stimulation of the peripheral vestibular system. In the past two decades, several groups have demonstrated that three key aspects of vestibular function: the vestibulo-ocular reflex (VOR; Merfeld et al., 2007; Lewis et al., 2010; Dai et al., 2011; Perez Fornos et al., 2014), specific postural responses (Phillips et al., 2013), as well as vestibular percepts (Guinand et al., 2015) can be artificially elicited and restored using a vestibular implant. This confirms that it is possible to effectively transmit motion information to the central nervous with such a device. The vestibular implant concept could be applicable in cases of severe bilateral loss of the vestibular function (BVL), a very disabling and poorly recognized condition for which no effective treatment exists (Guinand et al., 2012a; Sun et al., 2014). Our group has recently demonstrated partial restoration of the VOR in a group of BVL patients fitted with a prototype vestibular implant, using motion modulated electrical stimulation of the vestibular nerve (Perez Fornos et al., 2014). In certain cases the velocity of the elicited eye movements was within the range of compensatory eye movements observed in healthy subjects during walking or running (Grossman et al., 1989; Guinand et al., 2015) and the electrically evoked VOR displayed a similar frequency response as the physiological VOR (Van de Berg et al., 2015). These results can be considered as a milestone in the development of a vestibular implant, confirming in humans pioneering findings obtained in animal research (Gong and Merfeld, 2002; Dai et al., 2011). The next fundamental question was whether this artificial vestibular reflex could be useful to improve performance on a clinically significant, more complex task. The majority of patients diagnosed with a BVL describe a clinical manifestation consisting of blurred vision or oscillopsia. For example, they experience difficulties recognizing faces or reading signs while walking. This is mainly attributed to the loss of the vestibular reflexes, in particular of the VOR that holds a crucial role in the mechanism of gaze stabilization. In the clinic, this can be quantified as a pathological drop of visual acuity (VA) in dynamic conditions compared to a static condition (Guinand et al., 2012b). Some testing protocols use passive, unpredictable high velocity yaw or pitch head movements as stimuli for the dynamic condition. They have demonstrated high sensitivity in revealing a BVL (Schubert et al., 2006; Vital et al., 2010). The vestibular implant is a device designed to artificially restore the vestibular function using motion modulated electrical stimulation of the peripheral vestibular system. In the past two decades, several groups have demonstrated that three key aspects of vestibular function: the vestibulo-ocular reflex (VOR; Merfeld et al., 2007; Lewis et al., 2010; Dai et al., 2011; Perez Fornos et al., 2014), specific postural responses (Phillips et al., 2013), as well as vestibular percepts (Guinand et al., 2015) can be artificially elicited and restored using a vestibular implant. This confirms that it is possible to effectively transmit motion

information to the central nervous with such a device. The vestibular implant concept could be applicable in cases of severe bilateral loss of the vestibular function (BVL), a very disabling and poorly recognized condition for which no effective treatment exists (Guinand et al., 2012a; Sun et al., 2014). Our group has recently demonstrated partial restoration of the VOR in a group of BVL patients fitted with a prototype vestibular implant, using motion modulated electrical stimulation of the vestibular nerve (Perez Fornos et al., 2014). In certain cases the velocity of the elicited eye movements was within the range of compensatory eye movements observed in healthy subjects during walking or running (Grossman et al., 1989; Guinand et al., 2015) and the electrically evoked VOR displayed a similar frequency response as the physiological VOR (Van de Berg et al., 2015). These results can be considered as a milestone in the development of a vestibular implant, confirming in humans pioneering findings obtained in animal research (Gong and Merfeld, 2002; Dai et al., 2011). The next fundamental question was whether this artificial vestibular reflex could be useful to improve performance on a clinically significant, more complex task. The majority of patients diagnosed with a BVL describe a clinical manifestation consisting of blurred vision or oscillopsia. For example, they experience difficulties recognizing faces or reading signs while walking. This is mainly attributed to the loss of the vestibular reflexes, in particular of the VOR that holds a crucial role in the mechanism of gaze stabilization. In the clinic, this can be quantified as a pathological drop of visual acuity (VA) in dynamic conditions compared to a static condition (Guinand et al., 2012b). Some testing protocols use passive, unpredictable high velocity yaw or pitch head movements as stimuli for the dynamic condition. They have demonstrated high sensitivity in revealing a BVL (Schubert et al., 2006; Vital et al., 2010).

However, a drawback of these methods is that the stimuli used are not physiological. Another more representative method of the everyday challenge faced by BVL patients is the evaluation of VA while walking on a treadmill at controlled velocities (Lambert et al., 2010). This original method has been shown to be reliable and sensitive to detect BVL (Hillman et al., 1999), even at low walking speeds of 2 km/h (Guinand et al., 2012b). Demonstrating the restoration of gaze stabilization abilities in BVL patients, particularly in a close-to-reality task would constitute a significant step forward in the rehabilitation of vestibular deficits. In the present study, we investigated whether motion-modulated electrical stimulation could be used to normalize VA abilities while walking in a group of BVL patients chronically implanted with a vestibular implant.

Materials and methods

Patients and device

Twelve BVL patients, unilaterally or bilaterally deaf, were recruited at the Service of Otorhinolaryngology and Head and Neck Surgery at the Geneva University Hospitals and at the Division of Balance Disorders at the Maastricht University Medical Center. Strict inclusion criteria were implemented, and have been described in detail previously (Guinand et al., 2015). Patients were fitted with prototype vestibular implants. These devices consisted of a modified cochlear implant (MED-EL, Innsbruck, Austria) that provided, in addition to the cochlear array, extra-cochlear electrodes for "vestibular" stimulation. Extra- or intra-labyrinthine implantation of the electrodes in the vicinity of the ampullary branches of the vestibular nerve, as previously described (Kos et al., 2006; Van de Berg et al., 2012), was performed.The vestibular implant was activated no earlier than 3 weeks after surgery. Six out of the twelve implanted patients were available for dynamic VA experiments presented in this paper(Table8.1). A regular cochlear implant processor (Tempo+MED-EL, Innsbruck, Austria) was used to control the electrical stimulation delivered by the selected electrode using a customized transformation unit connected to the auxiliary input of the processor (Pelizzone et al., 2013). Angular head motion was captured with a three-axis gyroscope (device based on the sensor LYPR540AH; ST Micro-electronics; Geneva, Switzerland), fixed to the patient's head using a customized helmet.

Table 8.1 Demographics and implantation details of participating patients.

Patient	Sex	Etiology	Age (at implantation)	Implantation year	Active electrode	Surgical approach	Baseline stimulation amplitude (Dynamic range; μA)
S1	M	Idiopathic	68	2007	PAN	EL	360 (170)
S2	M	Congenital/ idiopathic	46	2008	PAN	EL	300 (100)
S3	F	Traumatic	67	2013	SAN	IL	410 (300)
S4	F	Meningitis	48	2012	SAN	IL	200 (180)
S5	M	DFNA9	66	2013	PAN	IL	120 (80)
S6	M	Traumatic	53	2015	SAN	IL	350 (450)

PAN, posterior ampullary nerve; EL, extra-labyrinthine; SAN, superior ampullary nerve; IL, intra-labyrinthine.

Electrical stimulation

As the predominant components of head movements during walking are pitch and vertical translation (Grossman et al., 1989), electrodes in the vicinity of the posterior (PAN) or superior (SAN) ampullary nerves were selected to deliver motion information using electrical currents. Theoretically, stimulation of these vertical vestibular nerve

branches should generate vertical compensatory eye movements (Suzuki et al., 1964). Only one vestibular electrode was active during the experiments and all cochlear electrodes were turned off. As already described in previous publications, to generate bidirectional eye movements (i.e., upwards and downwards when stimulating the vertical nerve branches) when using unilateral vestibular stimulation, it was necessary to first restore and maintain a *baseline stimulation* of the vestibular nerve (Guyot et al., 2011; Perez Fornos et al., 2014; Guinand et al., 2015). In this study, we chose a supra physiological baseline stimulation profile consisting of trains of biphasic, charge-balanced (200 µs/phase) pulses presented at a rate of 400 pulses per s. These stimulation parameters were selected because they have proved to be particularly effective for activating the vestibular system in our particular setting. The amplitude of the baseline stimulation was set in the middle of the dynamic range measured for each patient (Guinand et al., 2015).Once in the *adapted* state (Guyot et al., 2011), the motion signal captured by the head mounted gyroscope could be used to up- and down-modulate the amplitude of the train of pulses delivered via the SAN or PAN vestibular electrodes.

We arbitrarily chose to implement a simple linear transfer function between measured pitch head velocity and electrical stimulation delivered via the SAN or PAN electrode. It was defined based on the previously measured dynamic range and eye movement response characterized for each subject (Guinand et al., 2015). Amaximumof 85% of each patient's dynamic range was used to code for 30◦/s, based on previous data on the main characteristics of the VOR during locomotion (Grossman et al., 1989). For safety reasons, maximum stimulation delivered was hard coded to be limited to 90% of the patient's dynamic range, to avoid excessively high currents in case any abrupt, rapid head movement occurred.

Visual Acuity Measurements

During the experiments, patients had to read aloud sequences of Sloan optotypes (CDHKNORSVZ) of decreasing size displayed in a random order one at a time on a computer screen (15 inches). The screen was positioned at eyes' height, 2.8 m in front of the patient. The sequence started with a five letters presentation at 1 logMAR (logarithm of the Minimum Angle of Resolution). If the letter recognition rate was above chance ($>$10%), the letter size was decreased by a step of 0.1 logMAR and five new letters were presented one at a time. The same procedure was continued until the recognition rate for a given letter size dropped below chance ($\leq$10%). Two almost identical additional runs were repeated.

The experiments were carried out on a treadmill in four conditions: (1) with the patient standing still (static), (2) while the patient was walking at a constant speed with the vestibular implant turned off (systemOFF), (3) while the patient was walking at a constant speed with the vestibular implant turned on and delivering *coherent*

motion information to the patient's vestibular nerve (i.e., amplitude of the baseline stimulation modulated using the signal coming from the pitch axis of the gyroscope; $systemON_{motion}$), and (4) while the patient was walking at a constant speed with the vestibular implant turned on and delivering *incoherent* motion information to the patient's vestibular nerve (i.e., amplitude of the baseline stimulation modulated using the reversed signal coming from the pitch axis of the gyroscope; $systemON_{sham}$). Walking speed was set between 2 and 4 km/h, at the maximum where the patient felt safe and could walk without holding the handrails in the systemOFF condition. Once the maximum safe speed for the patient was selected, it was kept constant for all the dynamic conditions. The order in which each of the three dynamic conditions was conducted was determined using a Latin square design, randomized across patients. All experiments were written in MATLAB (R2010a; Mathworks, Natick MA, USA) using the Psychtoolbox (Brainard, 1997; Pelli, 1997; Kleiner et al., 2007).
Raw data, expressed in logMAR, were converted to decimal VA-values and normalized to VA obtained in static conditions (Holladay, 1997). A one-way repeated measures analysis of variance (ANOVA) was conducted to compare VA across conditions. All statistical analyses were performed with the statistics package for SigmaPlot 13.0 (Systat Software, Inc., Chicago, IL, USA).

Ethics Statement

All subjects gave written informed consent in accordance with the Declaration of Helsinki. Approval of the ethical committees of the Geneva University Hospitals (NAC 11-080) and of the Maastricht University Medical Center (NL36777.068.11/METC 11-2-031) was obtained.

Results

All patients were able to complete the procedure at their own maximum safe walking velocity (2–4 km/h). Absolute VA-values obtained in each condition are presented in Table 8.2. Please note that lower logMAR-values indicate better scores.

Table 8.2 Absolute VA-values obtained in each condition per patient [logMAR].

Patient	Static VA	SystemOFF	$SystemON_{motion}$	$SystemON_{sham}$	MSWV
S1	0.04	0.18	0.04	0.14	2
S2	−0.07	0.19	0.04	0.13	4
S3	−0.21	0.07	−0.14	−0.02	3
S4	−0.34	−0.17	−0.31	−0.31	4
S5	−0.13	0.00	−0.11	−0.05	4
S6	0.06	0.31	0.22	0.33	3

Maximum safe walking velocities [MSWV (km/h)] in each case are also indicated.

Compared to the static condition, all six patients experienced a drop in VA while walking on the treadmill in the systemOFF condition, ranging from 0.13 to 0.28 logMAR in absolute value (a loss of 0.1 logMAR corresponds to a loss of one line on a standard letter chart used for the measurement of the VA). In the $systemON_{motion}$ condition, the VA improved in all patients compared to the systemOFF condition, and even equaled the value of the static condition in one patient (S1). The VA differences between the static and the $systemON_{motion}$ conditions ranged from 0 to 0.16 logMAR. The VA differences between the static and the $systemON_{motion}$ conditions were smaller than the VA differences between the static and the $systemON_{sham}$ conditions in all six patients. The VA differences between the static and the $systemON_{sham}$ conditions were smaller than the VA difference between the static and the systemOFF conditions, except for S6. The range of the VA differences between the static and the $systemON_{sham}$ condition was 0.03 to 0.28 logMAR.

Normalization of individual VA scores to values obtained in the static condition allows a better representation and facilitates comparison of the previously mentioned trends for each patient (**Figure 8.1A**). The ANOVA analysis showed a statistically significant difference between conditions [$F_{(3,\ 12)}=30.49$, $p<0.001$]. *Post-hoc* tests (Tukey) revealed a significant ($p<0.001$) increase of the VA loss in the system OFF and in the $systemON_{sham}$ conditions, compared to the static and the $systemON_{motion}$ conditions. No significant differences were found, either between the static and the $systemON_{motion}$ conditions, or between the system OFF and the $systemON_{sham}$ conditions (see **Figure 8.1B**).

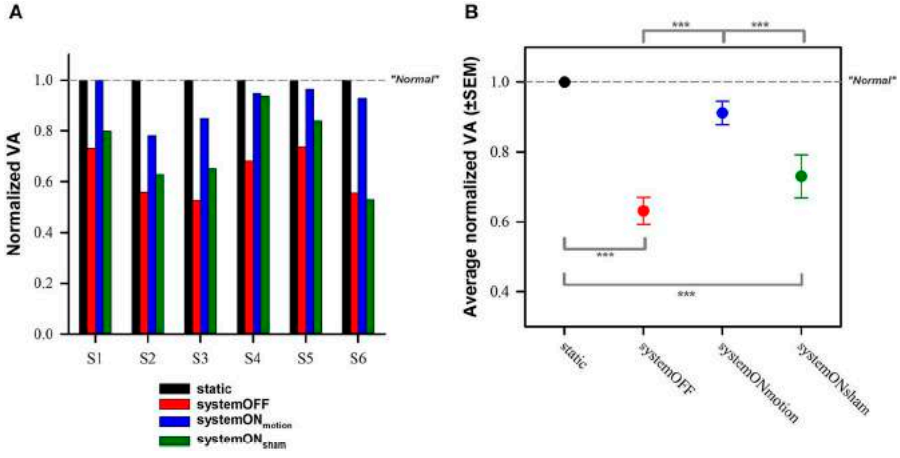

Figure 8.1 Normalized visual acuity results. (A) Individual results obtained in the dynamic conditions (colored bars; red—systemOFF, blue—$systemON_{motion}$, green—$systemON_{sham}$) for the six participating subjects, normalized to results obtained in the static condition (black bar). (B) Average normalized results (± standard error of the mean, *SEM*). ***Indicates significant differences between conditions in the *post-hoc* tests (Tukey). Dotted gray lines indicate theoretical performance of "normal" subjects (i.e., no loss of visual acuity in dynamic situations).

Discussion

These results clearly indicate that the vestibular implant successfully transfers motion information to the brain, leading to restoration of VA abilities in a dynamic situation (walking in standardized conditions). This represents the first demonstration of functional rehabilitation using the concept of motion- modulated electrical stimulation of the vestibular nerve in humans, and therefore constitutes a fundamental milestone in the field.

To investigate whether it was possible to improve gaze stabilization abilities in BVL patients wearing a prototype vestibular implant, a protocol representative of one of the most common complaints was implemented. When walking, patients with a BVL present a significant loss of VA which is correlated with the presence of oscillopsia (Guinand et al., 2012b). Using motion modulated electrical stimulation, the VA measured in dynamic conditions (i.e., while walking) was significantly improved to a value close to that measured in static conditions in all six patients tested. The fact that the VA improvement decreased significantly in the systemON$_{sham}$ condition further confirms that observed improvements were due to the properly functioning vestibular implant. Interestingly however, the VA loss observed in the systemON$_{sham}$ condition was slightly smaller than that observed in the systemOFF condition (non-significant), suggesting that some useful motion information could still have been extracted by the brain in the systemON$_{sham}$ condition where the gain was reversed.

It is generally accepted that the drop of VA measured in dynamic conditions in patients suffering from a BVL is due to a poorly functioning (or absent) VOR, which is generally considered the main vestibular mechanism involved in gaze stabilization. Initially, we wanted to quantify the artificially generated VOR during the VA task in dynamic conditions in order to demonstrate that any measured improvements would be due to the restoration of this reflex with our vestibular implant prototype. We attempted recording eye movements while we measured the VA in dynamic conditions using a fast 2D video- oculography system (EyeSeeCam VOG; Munich, Germany), but were not successful in achieving precise recordings. In order to avoid artifacts due to goggle slippage, the goggles had to be very tightly adjusted. This was too painful to patients after just a few minutes, not giving enough time to complete the task. Furthermore, the tightly fixed glasses also disrupted the visual abilities of patients, especially at near-threshold values. As a consequence, we decided not to record eye movements during VA measurements. However, in an attempt to better understand how the magnitude of the electrically evoked VOR influenced the VA results we decided to compare the latter with previously presented results of the artificial VOR measured in static conditions (Guinand et al., 2015). Surprisingly, we found no correlation between the magnitude of the evoked VOR and the observed improvements in the systemON$_{motion}$ condition. This could of course be due to the small sample size of the study. However, it could also suggest other vestibular

mechanisms could also be substantially contributing to gaze stabilization. A first hypothesis is that, by electrically delivering motion information to the vestibular nerve, other vestibular reflexes are also activated. Indeed, although it was not systematically documented in this study, during the static artificial VOR measurements we observed that in some cases sinusoidal head movements were evoked in parallel to eye movements. Moreover, these head movements were phase locked with the sinusoidal electrical stimulus. This strongly suggests that the vestibulo-collic and the vestibulo- spinal pathways were also activated during our experiments. This hypothesis is supported by observations of other research teams. For example, postural responses have been reported upon electrical stimulation of the ampullas (Phillips et al., 2013) and even by using motion modulated stimulation delivered by intracochlear electrodes of a regular cochlear implant (Cushing et al., 2012). More recently, direct activation of vestibular reflexes upon electrical stimulation delivered through the intracochlear array of the cochlear implant has also been demonstrated (Parkes et al., 2016).

Future research efforts will be devoted to a more comprehensive evaluation of vestibular function, well-beyond the VOR. For example, a matter of particular interest will be to better understand whether the activation of the vestibulo-collic pathway results from current spread to the otolithic organs, or whether the role of the semicircular canals in the control of posture has been underestimated. In addition, up to now all our experiments have been carried out while activating a single electrode at a time. Future experiments we will assess the simultaneous use of multiple vestibular electrodes (in contact with all three ampullary nerves) for integration of 3D angular motion information. This will imply the development of more complex stimulation parameters and strategies. Another important aspect of future developments will involve the refinement of the electrode design and of the surgical insertion techniques to optimize electrode positioning (i.e., selectivity of the stimulation), while preserving any pre-existing auditory and residual vestibular function. This is of crucial importance as the majority of patients with a BVL have normal or only mild hearing loss. In addition, to warrant successful translation of vestibular implants to the clinic, surgical procedures should be simplified and standardized as much as possible in order to become accessible to most of otologists. Finally, a unique aspect of the vestibular implant is that it is the first experimental setup that allows activating the vestibular system exclusively, without the unwanted contribution of other sensory modalities (e.g., vision, proprioception) that intervene in the complex activities mediated by balance. We expect thus that basic research studies with this device will open new doors increasing our fundamental knowledge on the physiology of the vestibular system and its interactions with extra-vestibular mechanisms.

Finally, it is worth mentioning that the promising results presented here were obtained with a first-of-its-kind, rudimentary vestibular implant, and during acute testing sessions. Indeed, it could be expected that both improved devices and

sufficient training (i.e., when patients have enough time to adapt and use the full potential of the artificial vestibular information), would result in improved performance and rehabilitation prospects. We are therefore convinced that the vestibular implant is an evolutionary device with an immense clinical and research potential. Further research and development in this field are thus justified and warranted.

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Final discussion and valorisation

Final discussion and valorisation

The success of the development of a medical device heavily depends on the proper criteria for patient selection. However, criteria can only be formulated by having validated insights in the real problems that patients encounter. Currently, many unresolved challenges are met when interpreting the standard diagnostic tests. It is imperative that the recently developed diagnostic criteria for bilateral vestibulopathy (BV) (Strupp et al., 2016) are complemented by deeper insights in these challenges. This will not only lead to better patient selection for a VI, but also to better effect evaluation (Chapter two).

In 2009 the VI-project was extended from Geneva to Maastricht, creating the Geneva-Maastricht team. All available information from previous research was used to proceed with experiments in humans (Chapter three). One of the first choices was to add the intralabyrinthine approach to the surgical techniques. This was previously not performed due to several reasons. Next to the risk of hearing loss, a main concern comprised the chance of not being able to elicit a response, as a result of "dying back" of the nerves after a long-standing loss of vestibular function. Previous intralabyrinthine approaches were only performed in animals in which a vestibular loss was recently induced by canal plugging or ototoxic medication, not addressing the effect of "dying back" of the nerves. By intraoperative intralabyrinthine stimulation of the vestibular system in a patient with a long-standing vestibular loss, it was shown that intralabyrinthine stimulation was at least feasible in a subset of patients with BV. It paved the way for the use of the intralabyrinthine approach for vestibular implantation in humans (Chapter four).

After showing the first results of a real vestibular prosthesis in humans (Perez Fornos et al., 2014), not included in this thesis), a total overview was desired about all the results obtained so far in the first 11 patients implanted with the vestibular implant prototype. Publishing these results provided more clarity and illustrated the feasibility of a VI, whilst at the same time showing that many challenges needed to be met in order to get a clinically useful device (Chapter five).

One of these challenges is the stimulation paradigm. Animal research has shown that gain, alignment and asymmetry of the response can be improved by optimizing the stimulation paradigm (Davidovics et al., 2012). However, some characteristics of the natural response are frequency dependent. Therefore, the natural frequency-dependency of the VOR is an aspect that could be taken into account with respect to the stimulation paradigm. If the response elicited by the VI shows other frequency-dependent characteristics than the natural vestibular system, the stimulation paradigm might have to be adjusted to compensate for this difference. Therefore, the frequency-dependency of the VI was tested in 7 implanted patients and compared to a group of age-matched healthy volunteers. It was shown that the VI closely mimicked

the frequency-dependency of the natural vestibular system in the tested frequency range (0.5 to 2Hz) (Chapter six).
Another factor to take into account is the residual natural vestibular function. Many patients suffering from BV (who might benefit from a VI) still have some residual "natural" vestibular function. This residual "natural" function could potentially interact with the "artificial" function of the VI in dynamic situations. Chapter seven demonstrated the presence of an interaction between the "natural" vestibular input and the "artificial" VI-input in the acute phase of stimulation. Whether this interaction still exists after the acute phase, has yet to be investigated in chronic stimulation trials. Nevertheless, the presence of this interaction is an important finding, since it might be taken into account during the initial phase of "fitting" of the VI. It could also be of benefit when trying to counteract vestibular asymmetry as occurring during disabling attacks of vertigo. If a fluctuating residual natural vestibular function would elicit an attack of vertigo, the VI could interact with it and might be able to "overrule" the residual natural function. This would result in the VI having control of the vertigo-attack and the patient feeling less vertiginous. The VI could then serve as an alternative therapeutic strategy in e.g. Meniere's disease. However, whether this interaction is beneficial or counterproductive in these situations, has not been determined yet. Next to this, many non-linearities were found in the eye movements resulting from VI stimulation. This initated the development of a new method of eye movement signal analysis. It implies that previous findings of VI experiments should be interpreted with care.
Animal research and the first experiments in humans mainly focused on the VOR. However, creating an optimal VOR-response with the VI, does not necessarily indicate a functional benefit for the patients. Other outcome parameters should be taken into account. One of these alternative parameters is the dynamic visual acuity, since it can be decreased in BV patients. For the first time in the world, a real functional benefit of the VI was demonstrated in a placebo-mode controlled trial: The dynamic visual acuity significantly increased by the VI (Chapter eight).

All things considered, a VI seems to be feasible as a therapeutic device for (at least) BV patients. However, many aspects should still be investigated or developed, before the VI can be considered as a clinically useful medical device. These aspects will be discussed below.

Surgical technique and electrode design

Regarding VI surgery and electrodes, the ultimate goal is to get the VI-electrodes as safe and simple as possible at the desired location of stimulation, whilst preserving inner ear function. For future investigations, this implies a more thorough exploration of the intra- as well as the extralabyrinthine approach and tailor-made electrodes

facilitating these approaches. Surgical techniques should become more standardized and accessible, while also taking into account “soft surgery” in order to preserve inner ear function. The electrodes should be designed in such a way that positioning is easy and without any significant damage to adjacent structures, while at the same time facilitating optimal stimulation with the possibility of e.g. reducing current spread. The Geneva-Maastricht team is currently working on optimization of surgical techniques with corresponding electrode designs.

Optimization of signal analysis

At this moment, most of the VI-research uses techniques for signal analysis with many “old-fashioned” pre-assumptions about the expected VOR-response. However, preliminary results showed a more complex VOR-response than expected previously. In order to measure the VOR-response as purely as possible, new techniques for signal analysis have been developed that do not force signals into expected patterns, but are more open to variability in time and the non-linearity of the response. The Geneva-Maastricht team is currently working on optimization of the signal analysis, in close cooperation with the faculty of physics of Tomsk State University, Russia.

Optimization of the stimulation paradigm and transfer function

After optimization of the signal analysis, the optimization of stimulation paradigm and transfer function can be realized. This is necessary to eventually provide the vestibular system with a VI-stimulation pattern that facilitates an output that mimics as closely as possible the output of the natural vestibular system for a given input. Challenges that will have to be met are e.g. current spread, different dynamic ranges for each electrode and the non-linearity of the VI-response. The stimulation paradigm and transfer function are currently investigated using a biophysical approach by the Geneva-Maastricht team in close cooperation with the faculty of physics of Tomsk State University, Russia.

Optimization of effect evaluation

The VI offers a whole new approach for stimulating the vestibular system. This implies that conventional methods of effect evaluation using e.g. the VOR, the vestibulo-collic reflex, posturography and dynamic visual acuity, might not be sufficient. However, in order to know what effects can be expected, it is important to first gain insights into the abnormalities that can be expected in BV. At this moment, sufficient knowledge about BV is lacking regarding e.g. perception, walking, cognition, patient expectations, health related costs and the relation between different testing parameters. After having this structurally analyzed, new methods of effect evaluation can be developed, that go “beyond” the traditional methods of effect evaluation. The Geneva-Maastricht

team is currently investigating patient expectations, health related costs and patient characteristics in patients with BV, aiming at the development of new methods of effect evaluation. This research is conducted in close cooperation with the Department of Clinical Epidemiology and Medical Technology Assessment of the University of Maastricht.

Development of criteria for vestibular implantation

Recently, diagnostic criteria have been developed for BV (Strupp et al., 2016). However, definite criteria for vestibular implantation have not yet been developed. The previously mentioned study of patient expectations and patient characteristics will also be used to support the development of these criteria. After having implanted BV patients in a trial with chronic stimulation, it could be considered to expand the implantation criteria to other diseases like unilateral vestibular hypofunction, attacks of vertigo (e.g. using the VI as a "vestibular pacemaker", if possible) and presbyvestibulopathy.

Development of rehabilitation strategies

After implantation, patients should get used to the VI as fast and safe as possible while maximizing the benefit. Just like cochlear implant recipients need to learn how to "hear" with the implant, VI recipients need to learn how to use the new vestibular information for image stabilization, balance and spatial orientation. However, how they should learn this, is currently an open question since "maintaining" balance is a multimodal task. This implies that the VI "adds" information to an already active system, instead of providing the sole input. Rehabilitation should imply integration of all the sensory systems involved and the use of the strong adaptive capacities of the brain. The content of rehabilitation will probably take shape during the chronic stimulation trials.

Optimizing biomechanical aspects

The first VI's were prototypes and consisted of research software, big batteries, big processors, etc. In order to become a medical device, the VI should be a small, lightweight and portable device with strong batteries and sensors firmly attached to the head. Ideal situation would be to have the most components of the VI in the external part, facilitating continuous updates without having to manipulate the implanted parts. This means that many biomechanical aspects should be optimized. The Geneve-Maastricht team is currently working on these aspects in close cooperation with Medel.

Development of a second prototype V(C)I

The above-mentioned topics are all necessary to eventually develop a second prototype VI suited for a more extended clinical trial with chronic stimulation. Since several research groups are currently addressing the topics, both the prototype and set-up of the new trial will probably consist of inventions from more than one research group. Medel and its research partners have already given the initial impetus to this trial.

This thesis illustrates that BV is a disease with an important impact on quality of life that imposes a socioeconomic burden on society. Since current treatments options are limited and with low yield, a more substantial treatment is needed. This thesis has shown the feasibility of a VI and it has paved the way for newly already initiated research projects. These projects will define more thoroughly all aspects necessary to have the VI as a clinically useful device. After that, hopefully in the near future, we will be able to provide a more substantial treatment for patients suffering from loss of vestibular function.

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Summary

Summary

Bilateral vestibulopathy (BV) probably represents a heterogeneous disorder with clinical heterogeneity, with and without vertigo. In spite of increasingly sophisticated electrophysiological testing, still many challenges are to be faced when establishing a diagnosis of BV. These challenges reflect its often difficult presentation and the lack of diagnostic standards regarding implementation and interpretation of vestibular tests. There is an urgent need for standardization of vestibular tests. This will result in more adequate diagnoses of BV, better patient selection for vestibular implantation and it will provide a basis for standardized effect evaluation of the vestibular implant **(Chapter two)**.

Early research on the vestibular implant in animals as well as humans showed important findings about the feasibility of a vestibular implant in humans. Firstly, electrical stimulation of a semicircular canal induced a nystagmus that corresponded to the plane of the canal that was innervated by the stimulated nerve branch. Secondly, the brain was also able to adapt to higher baseline stimulation, while still reacting on a dynamic component. Thirdly, the best responses were achieved by a combination of the optimal stimulus (stimulus profile, stimulus location, precompensation), complemented by central vestibular adaptation. It was hypothesized that the degree of response would probably vary between individuals, depending on pathology and their ability to adapt **(Chapter three)**.

These findings paved the way to further investigate the feasibility of the vestibular implant in humans, which started with exploration of a surgical approach: the intralabyrinthine (ampullar) approach. This surgical approach was tested during cochlear implantation in a 21-year old female patient, who had experienced bilateral vestibular areflexia and sensorineural hearing loss for almost 20 years. The approach was successfully performed and electrical stimulation of the ampullae evoked eye movements containing vectors congruent with the stimulated canals. As expected, the eye movements were influenced by the general anesthesia. Nevertheless, this was the first demonstration of ampullar stimulation in a human. It showed that the vestibulo-ocular reflex (VOR) could be evoked by ampullar stimulation, even when there has been no vestibular function for almost 20 years **(Chapter four)**.

After this experiment, the Geneva-Maastricht team implanted more than 11 BV patients with a custom-modified cochlear implant (Med-El, Innsbruck, Austria) with 1, 2 or 3 vestibular electrodes. In 5 patients the electrodes were put directly on the nerve (extralabyrinthine approach), and in the other patients the intralabyrinthine approach was used. The results of the first 11 patients were described. In all patients smooth, controlled eye movements were obtained, although both the electrical

dynamic range and the amplitude of the eye movements varied between patients. The axis of the response was consistent with the stimulated nerve branch in 17 out of the 24 tested electrodes. Next to this, diverse percepts were reported upon electrical stimulation (i.e. rotatory sensations, sound, tickling or pressure) with intensities increasing as the stimulation current increased. These findings showed that electrical stimulation is a safe and effective means to activate the vestibular system, even in a heterogeneous patient population with different etiologies and disease durations **(Chapter five)**.

To explore whether frequency-dependency might be taken into account in the stimulus processing strategies, the electrically evoked VOR (eVOR) elicited by the VI, was compared to the "natural" VOR. For this, 12 vestibular electrodes in 7 implanted patients were selected and electrically stimulated with a sinusoidal profile at frequencies of 0.5, 1 and 2Hz. The main characteristics of the obtained eVOR were evaluated and compared to the "natural" VOR measured in a group of age-matched healthy volunteers who were subjected to horizontal whole-body rotations with equivalent sinusoidal velocity profiles at the same frequencies. A strong and significant effect of frequency was observed in the total peak eye velocity of the eVOR. This effect was similar to that observed in the "natural" VOR. Other characteristics of the (e)VOR showed no significant frequency-dependent effect. It was therefore demonstrated that, at least at the specific (limited) frequency range tested, responses elicited by a vestibular implant closely mimicked the frequency-dependency of the "natural" vestibular system **(Chapter six)**.

Since BV patients can still have some residual "natural" function, this residual "natural" function might possibly interact with the "artificial" VI-response. The interaction between residual "natural" input and "artificial" VI-input was therefore investigated in 5 electrodes in 4 implanted patients. The residual "natural" input and "artificial" VI-input were separately measured first and then combined in conditions where both inputs would hypothetically collaborate and counteract each other.
Combining both inputs resulted in an interaction in which the characteristics of the resulting eye movement responses (gain, asymmetry, angle and/or phase) could significantly differ from those observed when responses were measured for each input separately. In the total eye response, inputs with a stronger vector magnitude were represented more than inputs with a lower vector magnitude, in a non-linear fashion. Next to this, eye movement responses often showed non-linearities in the conditions with "artificial" VI-input. All these findings implied that the brain was not capable of suppressing conflicting vestibular information in the acute phase of stimulation. This suggests that the VI could be of benefit when trying to counteract vestibular asymmetry as occurring during disabling attacks of vertigo. It also indicates the necessity of incorporating new methods of eye movement signal analysis and

optimized transfer functions for each electrode, unless the brain is able to optimally combine both sources of information in the long term **(Chapter seven)**.

At first, all research focused on parameters of the eVOR. However, to evaluate a functional benefit of the VI, the dynamic visual acuity (DVA) was evaluated in 6 implanted patients. The DVA was measured while standing, while walking on a treadmill without the VI, while walking on a treadmill with the VI turned on, and while walking on a treadmill with the VI providing aberrant motion information. The visual acuity was significantly better with the VI turned on, compared to the conditions while walking on the treadmill without VI and with the VI providing aberrant motion information. This demonstrated that the VI could significantly improve gaze stabilization by artificially (partially) restoring vestibular function. It was the first evidence of a functional benefit obtained by a VI in humans **(Chapter eight)**.

This thesis illustrates that a VI seems to be feasible as a therapeutic device for (at least) BV patients. However, many aspects should still be investigated or developed, before the VI can be considered as a clinically useful medical device.

Summary in Dutch – Nederlandse samenvatting

Summary in Dutch – Nederlandse samenvatting

Bilaterale vestibulopathie (BV) omvat waarschijnlijk een heterogeen ziektebeeld met verschillende klinische beelden, mét en zonder draaiduizeligheid. Ondanks dat er steeds meer geavanceerde elektrofysiologische testmethodes zijn, blijven er nog vele uitdagingen tijdens het stellen van de diagnose. Deze uitdagingen reflecteren de vaak moeilijke klachtenpresentatie en het gebrek aan diagnostische standaarden voor implementatie en interpretatie van vestibulaire testen. Er is daarom een sterke wens tot standaardisatie van vestibulaire testen. Dit zal hoogstwaarschijnlijk leiden tot meer correcte diagnoses en betere patiëntselectie voor vestibulaire implantatie. Het kan daarnaast zorgen voor een basis voor gestandaardiseerde effectevaluatie van het vestibulair implantaat **(Hoofdstuk twee)**.

Eerdere mens- en diergebonden onderzoeken naar het vestibulair implantaat resulteerden in belangrijke bevindingen ten aanzien van de haalbaarheid ervan in mensen. Ten eerste werd er gevonden dat het elektrische stimuleren van een semicirculair kanaal een nystagmus induceerde die overeenkwam met het gestimuleerde kanaal. Ten tweede bleken de hersenen te adapteren aan een hogere grondstimulatie, terwijl reactie op een dynamische component aanwezig bleef. Ten derde werden de beste responsen behaald door de combinatie van een optimale stimulus (stimulusprofiel, stimuluslocatie, precompensatie) en centraal vestibulaire adaptatie. Er werd verwacht dat de mate van respons waarschijnlijk individueel bepaald zou zijn, mogelijk afhankelijk van de pathologie en de mogelijkheid tot adaptatie **(Hoofdstuk drie)**.

Bovenstaande bevindingen boden perspectief om de haalbaarheid van het vestibulair implantaat in mensen verder te onderzoeken. Dit startte met de exploratie van de chirurgische benadering: de intralabyrinthaire (ampullaire) benadering. Deze chirurgische benadering werd getest tijdens cochleaire implantatie in een 21-jarige patiënte, die bijna 20 jaar klachten had van bilaterale vestibulaire areflexie en een perceptief gehoorverlies. De chirurgie werd succesvol uitgevoerd en elektrische stimulatie van de ampullae zorgde voor oogbewegingen met vectoren die overeenkwamen met de gestimuleerde kanalen. Zoals verwacht, werden de oogbewegingen wel beïnvloed door de narcose. Niettemin was dit het eerste bewijs van ampullaire stimulatie in een mens. Het werd gedemonstreerd dat de vestibulo-oculaire reflex (VOR) uitgelokt kon worden door ampullaire stimulatie, zelfs in dit geval waarbij er bijna 20 jaar geen vestibulaire functie meer aanwezig was geweest **(Hoofdstuk 4)**.

Na dit experiment heeft het Geneva-Maastricht team meer dan 11 BV-patiënten geïmplanteerd met een op maat aangepast cochleair implantaat (Med-El, Innsbruck,

Oostenrijk) met 1, 2 of 3 vestibulaire elektrodes. In 5 patiënten werden de elektrodes direct op de zenuw geplaatst (de extralabyrinthaire benadering) en in de andere patiënten werd de intralabyrinthaire benadering toegepast. De resultaten van de eerste 11 patiënten werden beschreven. In alle patiënten konden gladde, gecontroleerde oogbewegingen worden opgewekt. Zowel het dynamisch bereik als de amplitude van de oogbewegingen varieerden tussen patiënten. In 17 van de 24 geteste elektrodes bewogen de ogen in hetzelfde vlak als dat verwacht zou worden op basis van de gestimuleerde zenuwen. Tevens werden verschillende waarnemingen gerapporteerd tijdens elektrische stimulatie (bijv. draaisensaties, geluid, kietelend gevoel of druk). De intensiteit ervan nam toe bij toename van de stimulatiestroom. Deze bevindingen toonden aan dat elektrische stimulatie een veilige en effectieve manier is om het vestibulaire systeem te activeren, zelfs in een heterogene patiëntenpopulatie met verschillende oorzaken en ziekteduur **(Hoofdstuk vijf)**.

De door het vestibulair implantaat uitgelokte elektrische VOR (eVOR) werd vergeleken met de “natuurlijke” VOR, om te onderzoeken of er bij het afstellen van het VI rekening gehouden dient te worden met de frequentie-afhankelijkheid van de respons. Hiervoor werden 12 vestibulaire elektrodes in 7 geïmplanteerde patiënten geselecteerd. Deze elektrodes werden vervolgens elektrisch gestimuleerd met een sinusoïdaal profiel op 0.5, 1 en 2Hz. De belangrijkste karakteristieken van de verkregen eVOR werden geëvalueerd en vergeleken met de “natuurlijke” VOR die gemeten was in een groep gezonde vrijwilligers van ongeveer dezelfde leeftijd. De “natuurlijke” VOR in deze gezonde personen werd verkregen door het uitvoeren van draaistoeltesten met equivalente sinusoïdale profielen op dezelfde frequenties. Er was een sterk en significant effect van frequentie op de totale piekoogsnelheid van de eVOR. Dit effect was gelijk aan wat geobserveerd werd bij de “natuurlijke” VOR. Andere karakteristieken van de (e)VOR lieten geen significante frequentie-afhankelijkheid zien. Zo werd aangetoond dat, tenminste in dit specifieke (beperkte) frequentiespectrum, de respons uitgelokt door het VI ongeveer gelijk frequentie-afhankelijk gedrag vertoonde als de respons van het “natuurlijke” vestibulaire systeem **(Hoofdstuk zes)**.

Aangezien BV patiënten nog steeds enige residuale “natuurlijke” vestibulaire functie kunnen hebben, zou deze functie mogelijk een interactie aan kunnen gaan met de “kunstmatige” VI-respons. Daarnaast zou deze residuale “natuurlijke” functie nog steeds kunnen leiden tot invaliderende aanvallen van draaiduizeligheid. De interactie van de residuale “natuurlijke” input en “kunstmatige” VI-input werd daarom onderzocht in 5 elektrodes van 4 geïmplanteerde patiënten. De residuale “natuurlijke” input en “kunstmatige” VI-input werden eerst onafhankelijk van elkaar gemeten en daarna gecombineerd in condities waarbij ze elkaar hypothetisch zouden kunnen versterken of juist tegenwerken. Het combineren van beide inputs resulteerde in een

interactie waarbij de karakteristieken van de resulterende oogbewegingen (gain, asymmetrie, hoek en/of fase) significant konden verschillen van de karakteristieken die geobserveerd werden als iedere input apart werd gemeten. In de uiteindelijke oogbewegingen werden inputs met een sterkere vector magnitude meer gerepresenteerd dan inputs met een kleinere vector magnitude, op een non-lineaire wijze. Daarnaast waren er vaak non-lineariteiten zichtbaar in de oogbewegingen die uitgelokt werden in condities met "kunstmatige" VI-input. Al deze bevindingen hielden in dat de hersenen niet in staat waren om conflicterende vestibulaire informatie te onderdrukken in de acute fase van stimulatie. Dit suggereerde dus ook dat de VI mogelijk een rol zou kunnen betekenen bij het tegengaan van vestibulaire asymmetrie die aanwezig is tijdens invaliderende duizeligheidsaanvallen. Daarnaast is er een noodzaak om nieuwe methodes van signaalanalyse te incorporeren, evenals een geoptimaliseerde transferfunctie voor iedere elektrode, tenzij de hersenen in staat zijn om optimaal beide inputs te combineren op de lange termijn. **(Hoofdstuk zeven)**.

In het begin hadden alle onderzoeken zich gericht op de eVOR-parameters. Echter, om de invloed van het VI op de functionaliteit van patiënten te evalueren, werd de dynamische visus (DVA) onderzocht in 6 geïmplanteerde patiënten. De DVA werd gemeten tijdens stilstand, tijdens lopen op een loopband zonder het VI, tijdens lopen op een loopband met het VI aan, en tijdens lopen op een loopband waarbij afwijkende bewegingsinformatie werd gegeven door het VI. De DVA was significant beter met het VI aan, vergeleken met het lopen op de loopband zonder VI en vergeleken met de conditie waarbij het VI afwijkende bewegingsinformatie gaf. Dit demonstreerde dat beeldstabilisatie significant verbeterd kon worden door het VI, door middel van het (deels) herstellen van de vestibulaire functie. Dit was het eerste bewijs van een functionele verbetering door een VI in mensen **(Hoofdstuk acht)**.

Deze thesis illustreert dat een VI haalbaar lijkt als een therapeutisch middel voor (tenminste) BV patiënten. Echter, vele aspecten zullen nog onderzocht of ontwikkeld moeten worden, voordat het VI als een klinisch bruikbaar medisch apparaat overwogen kan worden.

List of publications

List of publications

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Curriculum vitae

Curriculum vitae

Raymond van de Berg, was born together with his twin brother Roger, on September 5th 1984 in Geldrop, The Netherlands. He graduated cum laude from Het Augustinianum in Eindhoven in 2002. From 2002 until 2008 he studied Medicine at Maastricht University with foreign internships in Aruba, The Philippines and South-Africa. Directly after graduation, he started his residency in Otorhinolaryngology and Head & Neck Surgery at Maastricht University Medical Center under the supervision of Prof. Dr. Bernd Kremer. Already from the beginning, the vestibular system drew his attention and in parallel to his residency, this PhD-project on the vestibular implant was initiated by Prof. Dr. Herman Kingma. His last year was partially spent at the Johns Hopkins Hospital in Baltimore, to gain more knowledge about vestibular disorders. He currently works as an ENT-surgeon at Maastricht University Medical Center, with a special interest in vestibular disorders and research projects on e.g. the vestibular implant, bilateral vestibulopathy, Ménière's disease, vestibular rehabilitation, video-head-impulse-testing and oculomotor signs in RETT-syndrome. He is also head of the vestibular laboratory and head of the Department of Audiology at Maastricht University Medical Center. Next to this, he is appointed as assistant professor at the Faculty of Physics at Tomsk State University in Russia.

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Dankwoord

Dankwoord

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Stellingen behorend bij het proefschrift

The Vestibular Implant:

Feasibility in humans

1. Standardization of vestibular testing is crucial to obtain more adequate diagnoses of bilateral vestibulopathy, and better patient selection for the vestibular implant. (This thesis)

2. Electrical stimulation is a safe and effective means to activate the vestibular system, even in a heterogeneous patient population with different etiologies and disease durations. (This thesis)

3. Responses elicited by a vestibular implant closely mimick the frequency-dependency of the “natural” vestibular system in a specific frequency range. (This thesis)

4. The brain is not capable of suppressing conflicting vestibular information in the acute phase of stimulation. (This thesis)

5. The vestibular implant induces non-linearities in the eye movement response. (This thesis)

6. The vestibular implant is able to significantly improve gaze stabilization by artificially (partially) restoring vestibular function. (This thesis)

7. The vestibular implant seems to be feasible as a therapeutic device for (at least) patients with bilateral vestibulopathy. (This thesis)

8. History taking in a vestibular patient is like surgery of the mind.

9. A big Thank You for quality officers! Unfortunately quality decreases again when the optimum number of officers involved is surpassed.

10. Medicine is not like the Dutch Railways…Ladies and Gentlemen.

Maastricht, 20 september 2018

Raymond van de Berg