Considerations for quantifying vestibular function

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Considerations for quantifying vestibular function

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Hereby I confirm that I have worked out the present doctoral thesis, which I submitted for consideration at Maastricht University for acquisition of a PhD degree in biophysics. The present doctoral thesis is not submitted in other scientific institutions for acquisition of a scientific degree.

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Abbreviations

All abbreviations are mentioned separately in their chapters.
Mostly used abbreviations are (in alphabetical order):

BV	bilateral vestibulopathy
DVA	dynamic visual acuity
fHIT	functional head impulse test
HIMP	head impulse paradigm
SHIMP	suppression head impulse paradigm
vHIT	video head impulse test
VI	vestibular implant
VOR	vestibulo-ocular reflex

Chapter I
General introduction

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Anatomy and physiology of the peripheral vestibular system

The vestibular system comprises two peripheral organs located in the inner ears (1). Each organ has five sensors: three semicircular canals detecting head rotational movements and two otolith organs detecting head translational movements and gravity (See *Figure 1*). The semicircular canals are the bony tubes filled with two liquids, perilymph and endolymph, which are separated by the epithelial membrane. Each canal has an ampulla, which is a widened part of the canal that contains the cupula, gelatinous body. This gelatinous body is deflected by the endolymph, which due-to the inertia moves to the opposite direction of the head rotational acceleration. Therefore, the cupula also deflects to the opposite direction of the head rotational acceleration. This deflection bends the hair bundles of the hair cells, which are embedded into the cupula. The hair cells act as mechano-receptors: bending the hair bundle (cilia) activates the hair cells leading to a change of the receptor potential. The changes in receptor potential modulate the spontaneous firing rate of the vestibular nerve via the synaptic transmission. The hair cells activate (increase the firing rate) only if they bend to the direction of the longest cilium, called the kinocilium. If the hair bundle deflects to the opposite of the kinocilium direction, the hair cell inhibits (reduce the firing rate). The change of receptor potential is larger upon deflections towards the kinocilium than to the opposite direction away from the kinocilium. In each cupula all hair bundles are oriented to the same side to make each semicircular canal very sensitive to a specific movement direction. For example, for the left horizontal semicircular canal head rotations to the left are strong excitatory, and head rotation to the right – mild inhibitory. For the right semicircular canal, it is opposite. This causes an asymmetric response for the same semicircular canal to opposite directions of the head movement.

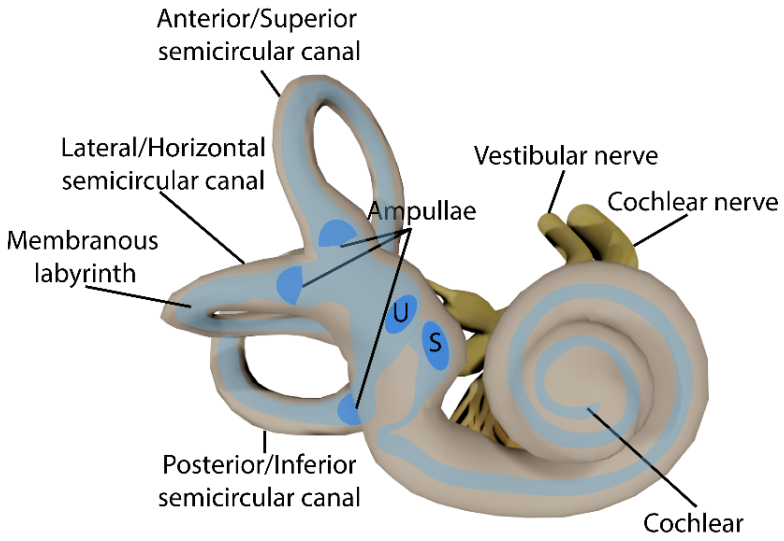

Figure 1. The human vestibular organ. U - utricle, S – saccule

The picture is rendered using a 3D model made at the University of Dundee (Scotland), which is available on https://sketchfab.com/3d-models/anatomy-of-the-inner-ear-f80bda64666c4b8aaac8f63b7b82a0a0

Two otolith organs, the utricule and saccule, detect head translational accelerations in all directions and tilts to the gravitational vector (2). The saccule is sensitive for gravity and translations in the vertical plane and the utricle is sensitive for gravity and translations in the horizontal plane. Both otoliths are composed of a gelatinous body with hair cells embedded on the bottom. On the top of the gelatinous body, small

crystals of calcium carbonate called otoconia, are located. When the head is displaced, the otoconia deflect the gelatinous body with the hair cells embedded in it, thereby activating the hair cells. These hair cells allow transmission of head motion information to the brain.

Considerations on vestibular testing

Vestibular hypofunction (also vestibulopathy, vestibular dysfunction, -hyporeflexia, -loss, -failure, -deficiency), i.e. a unilateral or a bilateral vestibulopathy, is a heterogeneous disorder of the peripheral and/or rarely central vestibular system leading typically to disabling symptoms like dizziness, imbalance, and/or oscillopsia (3–5). It affects up to 95 million adults in Europe and the USA (6). However, in many cases vestibular hypofunction is missed or misdiagnosed. One of the reasons is that the vestibular testing still faces many diagnostic challenges (7–12), which lead to unreliable and inconsistent values used by different laboratories for discriminating patients from the healthy population (13). Therefore, to improve the vestibular evaluation, it is imperative to standardize the existing methodology for the vestibular function tests. A short introduction on the current state of the vestibular laboratory testing is given below.

Video-oculography and electro-oculography

Nowadays, video-oculography (VOG) is used as a routine method in clinical practice to quantitatively measure eye movements, whereas electro-oculography (EOG) is rarely applied anymore (14). Using an infrared video camera, VOG detects eye movements by analyzing 2D images of the eye that are illuminated by infrared LEDs. The position of the pupil is calculated and used to track the horizontal and vertical eye movements, generally up to sample frequencies of 250 Hz or less [15]. Resolution and accuracy of VOG vary with image quality, but are generally <1° in 2D over a gaze range of a minimum of ±25° horizontal and ±20° vertical, as long as the pupil is fully visible for the camera. Detection of torsional eye movements is based on the detection of rotation of the iris structure around the pupil center. This technique often fails as the image of the iris varies with gaze due to its 3D structure. Another possible alternative is to use a contact lens with markers [16]. However, this method is not common in practice and its clinical value is still to be determined.

Electro-oculography (EOG) is based on detecting the corneo-retinal potential (15–17) using electrodes placed around the eyes. An EOG resolution in 2D of typically <1° can be obtained over a gaze range of ±30° horizontal and ±20° vertical (although linearity only holds up to an eccentric gaze of 15-20°). The most frequently used sample frequency is 50-250 Hz. Accuracy (detection of absolute eye position) is limited due to substantial drift that often occurs. Frequent recalibrations are required as corneo-retinal potentials and EOG amplitudes vary by a factor of 4-5 with low versus bright ambient light intensity. Above 100 Hz the signal-to-noise-ratio often decreases by an increasing contribution of other electrophysiological signals like EMG (18).

VOG and EOG systems both meet requirements for clinical use in terms of their accuracy and sensitivity of approximately 1°. There does not seem to be a “best method”, but VOG can be easily applied in clinical practice and is therefore most often used. The preferred method of choice depends on how clinicians and/or technicians weigh the pros and cons of each technique with respect to their own requirements and patient population.

The video-Head Impulse Test (vHIT or HIMP)

The vestibulo-ocular reflex (VOR) helps to keep the gaze stable during head movements. The vHIT is able to quantitatively assess the VOR of all six semicircular canals in the high-frequency domain and it can be used in acute, episodic and chronic vestibular syndromes (8,19,20). However, it does not purely test one vestibular organ: some contribution from the other side remains (8). vHIT is a much more sensitive and specific test than the clinical HIT (21). The commercially available vHIT-devices differ regarding patient comfort, accuracy of pupil detection, and methods for quantifying the VOR.

The accuracy of pupil detection can be affected by incorrect camera adjustment, poor calibration, blinking, eyelashes, narrow eyelids, poor illumination, mascara, spontaneous nystagmus, and goggle slippage. These factors can cause recording artifacts that might not be detected by the software and which could negatively influence the reliability of test outcomes (22–26). Training of examiners is therefore imperative, since it significantly reduces artifacts (27). The number of impulses required to achieve reliable results can be reduced to two in the case of artifact-free traces, which is especially important when testing very young children with relatively little attention (28). The VOR is quantified by calculating gain. VOR gain is the measure that illustrates to which extent eye movements (produced by the VOR) compensate for head movements. However, all commercially available devices use different gain calculation methods, which can lead to significant discrepancies in results (29). Two methods have been proposed to standardize gain calculation and to lower variability in results (30), but they are not (yet) routinely implemented in clinic. Gain is also influenced by head velocity (higher velocity, lower gain) (31), target distance (shorter distance, higher gain) (32)), and (in the case of goggles) a direction bias for the side on which the camera is placed (higher gains for the side with the camera (26)). It is therefore advised to standardize these variables as much as possible in clinic. If no normative data is available, absolute gain values below 0.8 can be considered pathological (33).

The vHIT is able to detect corrective saccades appearing during and after head impulses (covert and overt saccades respectively). An earlier timing (34,35) and a higher level of grouping (clustering regarding timing, quantified using the PR-score) of saccades might be indicative of compensation and might be correlated with lower handicap in patients with vestibular hypofunction (36–40). However, corrective saccades do not only reflect clinically relevant vestibular hypofunction or compensatory mechanisms: small saccades also appear in healthy subjects, especially with increasing age (41).

The Suppression Head Impulse Paradigm (SHIMP) was proposed to overcome the problem of covert saccades regarding gain calculation (42,43). SHIMP differs from vHIT with respect to the target: it moves along with the head. In this case, the presence of corrective saccades indicates the presence of vestibular function (42), while the absence of corrective saccades indicates impaired vestibular function (44). VOR gain with SHIMP is significantly lower than with vHIT, which might (partially) be explained by age and VOR inhibition strategies during SHIMP (45,46). SHIMPs significantly reduce covert saccades, but not all of them. Furthermore, vHIT alone seems to be sufficient for detecting bilateral vestibulopathy regardless of the presence of covert saccades.

Testing of Dynamic Visual Acuity

An impaired VOR (especially bilaterally) causes blurred vision during head movements. This can result in loss of DVA. The DVA loss is quantified by the difference in visual acuity in static and dynamic conditions,

which is measured using optotype charts or computerized DVA systems (9,47). The dynamic conditions can involve walking or active/passive head movements while sitting or standing. In case of impaired VOR, DVA loss is generally higher for passive head movements than for active head movements (48,49). Contradictory evidence exists regarding the influence of age on DVA: it is either weak or absent (50–52).

Recently, a new test for high-frequency DVA was proposed: the functional head impulse test (fHIT) (53–55). During fHIT, the test subject is placed in front of a computer screen and head impulses are applied in the tested plane. When head acceleration exceeds a predefined threshold, a Landolt ring optotype appears for a predefined short time on the screen. After the impulse, the subject is instructed to choose its orientation using a keyboard. The percentage of correct answers is used as the output of the test. The test has shown effectiveness when evaluating acute unilateral vestibulopathy (56). Although fHIT moderately correlates with oscillopsia severity, no correlation was observed between fHIT and the DVA test on a treadmill (57). These tests seem complementary and do not substitute for each other.

DVA is a functional outcome of all systems involved: VOR, the oculomotor system, and central processing of signals (57). For instance, internal feed-forward commands can mediate gaze (58), gait stabilization strategies can help to reduce head oscillations (59), and covert saccades improve DVA in patients with unilateral vestibulopathy (34,60). Therefore, DVA testing is mainly suited for evaluating the functional state of the vestibular system and compensation strategies, not for diagnosing peripheral vestibular deficits.

Caloric testing

Caloric testing is a widely used method to selectively assess vestibular function on each side in the low-frequency domain (~0.003Hz), using bithermal (30°C and 44°C) caloric irrigations with water (the preferred stimulus) or air (7,10,61) which is not recommended. To optimize stimulation, horizontal canals are aligned with the vertical plane by asking the test subject in a supine position to tilt the head 20°-30° (62). Irrigations of sufficient volume of water (>250ml) should last at least 30 seconds and can be performed in any order (63–65). For the sake of standardization, it is advised to use cold irrigation first on the right, followed by cold on the left, then warm on the right, and finally warm on the left. A five minute interval between the four successive irrigations have to be obeyed to avoid residual effects of the previous irrigation (66). The slow phase velocity (SPV) of the caloric nystagmus is measured for each irrigation. In symptomatic patients, the sum of the bithermal maximum peak SPV <6°/s can be considered a diagnostic criterion for bilateral vestibulopathy and the sum of bithermal maximum peak SPV on each side between 6 and 25°/s for presbyvestibulopathy (when also age ≥60 years) (3). The upper limits for both vestibular asymmetry and directional preponderance can be set at 20% when no normative data is available (63,67). Poor attention, poor alertness, visual suppression, and unreliable eye movement detection often lead to false-positive findings of vestibular hypofunction (7).

Complete vestibular areflexia cannot be identified using ice water calorics, since the test mostly only evaluates low-frequency horizontal canal function (68–70). Moreover, ice water calorics itself might induce an irrelevant aspecific latent spontaneous nystagmus in a non-specific way (7).

Rotatory chair testing

Rotatory chair tests are generally used to assess horizontal semicircular canal function in the low and middle frequency domains. Two types of tests are mainly performed: the Torsion Swing Test (TST) and the Velocity Step Test (VST).

The TST is divided into the Sinusoidal Harmonic Acceleration Test (SHAT), which involves a single frequency sinusoidal stimulus, and the Pseudo-Random Rotation Test (PRRT), which involves sinusoidal stimuli with different frequencies. VST uses a slow acceleration (e.g. ≤ 2°/s^2) to reach a constant velocity (often 100°/s) followed by an abrupt deceleration (e.g. 200°/s^2). The VST mainly tests the excited canal, though a contribution of the contralateral canal to the total response still remains (71). The VST is believed to be closer to the frequency spectrum of most natural head movements than TST (7,11,72). Eyes should be open during testing in complete darkness, since eye closure (tactile feedback and different mental setting) and vision (by fixation supression) reduce the VOR response (73).

The outputs for SHAT are gain (ratio of slow phase eye velocity to chair velocity), phase (time relation between eye and chair velocities), and directional preponderance (asymmetry in magnitude/gain for left and right rotations), whilst for VST the time constant (time for nystagmus to decay to 37% of its peak magnitude) and gain are most relevant (11). Since gain is frequency-dependent, each frequency tested by SHAT or PRRT has its own normative values (74–76). Phase and time constant are very stable parameters: no large inter-laboratory differences are observed (77). A reduced gain and/or time constant reflect a unilateral or bilateral vestibulopathy, attention deficit, or visual suppression. A high gain and/or long time constant indicate hypersensitivity (anxiety and or hyperventilation during the test, or central pathology leading to disinhibition) (78,79). In addition, the product of gain and time constant seems to better reflect the impairment of the vestibular system than gain and time constant alone (80). Abnormalities of phase and time constant can point to peripheral (e.g. bilateral vestibulopathy) and/or central vestibular disorders. The presence of a directional preponderance indicates a dynamic VOR asymmetry. This is often seen in uncompensated peripheral vestibular disorders and central vestibular disorders and provides insights into central processing of vestibular input from both labyrinths (7,11,87,72,75,81–86).

Vestibular evoked myogenic potentials

Vestibular evoked myogenic potentials (VEMP) are believed to reflect the otolith function (12,88). Air-conducted sound or bone-conducted vibration of the skull induces otolith vestibular responses, resulting in VEMP, which can be recorded using electromyography. Two types of VEMP are currently measured: cervical VEMP (cVEMP) and ocular VEMP (oVEMP). cVEMP mainly evaluate saccular function by measuring the inhibitory response from the ipsilateral sternocleidomastoid muscle. Therefore, the muscle should be contracted during the test. However, differences in muscle contraction can lead to inter- and intrasubject variabilities in response, hindering thorough evaluation (89–92). Multiple methods have been proposed that effectively reduce variability, although none of them are (yet) widely applied in clinical practice (91,92). oVEMP mainly evaluates utricular function by measuring the excitatory response from the contralateral inferior oblique extra-ocular muscle. Standardized upward gaze is necessary to bring the eye muscles in close contact with the electrodes placed below the eyes (12,88). Regarding stimuli, air-conducted sound (cVEMP) and bone-conducted vibration (oVEMP) are the preferred stimuli to detect vestibular hypofunction, although air-conducted sound is preferred to detect vestibular hyperfunction

(e.g., superior semicircular canal dehiscence syndrome). For air-conduction, obtained results should be corrected for the present air-bone gap in cases with ipsilateral conductive hearing loss (93). The air-conducted and bone-conducted stimuli mostly involve 500 Hz stimuli presented at a rate of 5 Hz to obtain optimal responses, although VEMP can be tested at different frequencies to obtain more insights into specific disease patterns (94) (e.g., testing a range from 250-1000 Hz). Furthermore, increasing the stimulation rate from 5 to 13 Hz has been shown to produce reliable cVEMP thresholds, while decreasing testing time and subject discomfort (92).

Electromyographic responses of VEMP include two peaks of vestibular origin, which appear at approximately 13 and 23 msec in cVEMP, and at approximately 10 and 15 msec in oVEMP. Peaks appearing later in time have mixed and/or different origins including vestibular, stretch reflex and cochlear (95,96). Outcome parameters used for VEMP are the presence of the response, the threshold (in dB), peak-to-peak amplitude (µV), peak latency (ms), and interaural asymmetry ratio. The testing paradigm and interpretation of VEMP are not yet standardized (97–100). For correct interpretation, it is strongly advised to obtain age-matched normative data (13), since with age the amplitudes and response rates decline (101). This implies that absent responses also appear in non-symptomatic healthy individuals, especially above the age of 60 years old (102). The role of VEMP in clinical practice has been investigated extensively regarding diagnostics, prognosis, and monitoring of vestibular disorders (103,104).

The most important clinical application of the VEMP is the syndromes of the third mobile window, including superior canal dehiscence syndrome (SCDS, see below) (104–106). The relevance of VEMP in Menière's disease, unilateral and bilateral vestibulopathy, vestibular migraine, BPPV, and auditory neuropathy is very limited or not relevant (102,107–114). In SCDS, VEMP amplitudes are increased and VEMP thresholds are lowered on the affected side(s), as a result of a third mobile window (115). To diagnose SCDS, using oVEMP amplitudes higher than 16.7 µV as a cut-off point results in a sensitivity of 100% and a specificity of 89% (116). Regarding cVEMP thresholds, 2000 Hz tone burst stimuli show the best diagnostic accuracy, with sensitivities equal to or higher than 92% and a specificity of 100% (117). Taking into account all the existing evidence about the use of VEMP to diagnose SCDS, oVEMP seems to be more sensitive and specific than cVEMP (106).

Perceptual threshold testing

Self-motion perception was first measured by Mach in the 19th century (118). Currently used methods to measure self-motion perceptual thresholds involve devices such as hydraulic or electric moving platforms (119,120) or sleds (121). To test self-motion perceptual thresholds, the subject is seated on a chair mounted on the platform or sled. Visual, auditory and somatosensory input are decreased as much as possible by, e.g., testing in darkness, wearing headphones, and covering skin surfaces (122). The platform or sled then accelerates into the tested plane of motion, with the desired stimulus parameters (magnitude, frequency, etc.). After each stimulus, the subject has to indicate whether the movement was perceived. The main outcome parameter is the self-motion perceptual threshold representing the minimal value of a physical stimulus that can still be perceived (123,124). There are two types of perceptual thresholds: detection thresholds (motion is perceived: yes/no), and recognition thresholds (type and direction of motion).

In healthy subjects, self-motion perceptual thresholds are higher than horizontal VOR-thresholds, indicating a higher sensitivity of the brainstem than vestibulothalamic pathways (125). Furthermore, self-motion perceptual thresholds increase after the age of 40 (119,120), are frequency-dependent (lower thresholds at higher frequencies) (122), decrease with visual input (126), depend on stimulus profile (127,128) and some thresholds might be affected by vestibular disorders like Menière's disease (higher thresholds) and vestibular migraine (lower thresholds) (129–131). The peripheral vestibular system strongly contributes to self-motion perceptual thresholds (especially rotations), as shown by significantly higher thresholds in patients with bilateral vestibulopathy compared to a control group (131–133). One of the disadvantages of testing self-motion perception is the substantial time needed to complete testing for one subject (several hours). Recently, a faster method to determine self-motion perceptual thresholds was proposed, which facilitates testing of 12 motion types within one hour. The clinical value of tests for vestibular perception is not yet fully determined. However, since they can be of direct functional relevance, they might develop in the future into the "speech audiogram" for vestibular disorders (7,119).

General guidance for detecting vestibular hypofunction

In order to reliably detect vestibular hypofunction, normative laboratory values should be obtained for each test (if possible) and technicians should be trained (13). When vestibular hypofunction is suspected, it might be recommended to start with the vHIT due to its low burden for the test subject. If vHIT results are abnormal, no other vestibular testing is necessary. However, in case of normal vHIT results, performing caloric testing might be advisable, since caloric testing seems to be more sensitive than the vHIT in detecting vestibular hypofunction in some vestibular disorders, in particular Menière's disease (134–137). Furthermore, a dissociation between caloric testing and the vHIT might be present, especially in cases with endolymphatic hydrops due to altered mechanics of the inner ear (138–141). In case of bilateral vestibulopathy, rotatory chair testing can be added to increase specificity of testing (not sensitivity) (78,142) and to help determine residual vestibular function (80), since the responses to rotatory chair testing are often better preserved than the responses to vHIT or caloric stimulation (142). Dynamic visual acuity testing is recommended for evaluation of the functional state of the vestibular system as well as compensatory processes occurring over time. VEMP is currently only advised for detecting superior canal dehiscence syndrome.

Definition of the problems

As described, the current vestibular test battery mainly involves tests of the VOR. One of the most frequently used tests is vHIT (8). The vHIT stimulus involves head movements, whose variability might influence test outcomes. However, not much is known about the influence of head movement variability on vHIT results. In addition, different data analysis methods are used by different vHIT systems. This might affect test outcomes. This implies that different vestibular laboratories use different methods of data collection and analysis. Such variation might cause significant discrepancies in test results.

To evaluate the functional state of the vestibular system, DVA tests are usually performed either while walking or sitting (51,143). However, age might affect DVA outcomes and knowledge about this effect is scarce in literature.

Considerations on vestibular implant testing

The vestibular implant

There is no clinically available therapeutic option to restore the vestibular function. Fortunately, a novel promising treatment, the vestibular implant (VI), was recently proposed and successfully validated (144). The concept of the VI is similar to the cochlear implant: it converts head movement information into a modulated electrical signal and delivers it to the vestibular nerve afferents via the electrodes (145). The electrodes are inserted into the ampullae of the semicircular canals or the electrodes are positioned near the vestibular nerve afferents (146). Thereby, the VI can replace (partially) the original vestibular organ like the cochlear implant replaces the hearing organ. The VI is believed to significantly improve quality of life of patients suffering from vestibular hypofunction.

Definition of the problems

The VOR is used to measure the effect of the vestibular implant. There are different signal analysis methods for the analysis of the VOR response, which are extensively used (147,148). However, the influence of different analysis methods on VOR outcomes, remains unknown. Furthermore, dynamic visual acuity and VOR are closely related, but not all patients can perform DVA testing while walking. The "functional Head Impulse Test" is able to measure dynamic visual acuity while sitting on a chair, using head impulses.

The aims of this thesis

The aims of this thesis were to complement the existing knowledge of the influence of different methodological and technical aspects on vHIT and DVA testing, to determine the effect of different analysis methods on VOR outcomes when using the VI, and to determine the effect of the VI on functional head impulse test results.

Objectives of the present work

- To investigate the influence of different head movement paradigms on vHIT outcomes (chapter II);
- To investigate the influence of using different commercially available vHIT systems, on vHIT outcomes in patients with bilateral vestibulopathy (chapter III).
- To investigate the influence of age on DVA outcomes, when tested DVA on a treadmill in patients with bilateral vestibulopathy and healthy subjects (chapter IV);
- To investigate the influence of using different signal analysis methods for evaluation of the VOR in VI patients and healthy subjects (chapter V).
- To investigate the effect of the electrically evoked VOR on functional head impulse test outcomes in a patient with bilateral vestibulopathy (chapter VI);

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Chapter II

The effect of different head movement paradigms on vestibulo-ocular reflex gain and saccadic eye responses in the suppression head impulse test in healthy adult volunteers

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Abstract

Objective: To identify differences in Vestibulo-Ocular Reflex gain (VOR gain) and saccadic response in the Suppression Head Impulse Paradigm (SHIMP) between predictable and less predictable head movements, in a group of healthy subjects. It was hypothesized that higher prediction could lead to a lower VOR gain, a shorter saccadic latency, and higher grouping of saccades.

Methods: Sixty-two healthy subjects were tested using the video Head Impulse Test and SHIMPs in four conditions: active and passive head movements for both inward and outward directions. VOR gain, latency of the first saccade, and the level of saccade grouping (PR-score) were compared among conditions. Inward and active head movements were considered to be more predictable than outward and passive head movements.

Results: After validation, results of 57 tested subjects were analyzed. Mean VOR gain was significantly lower for inward passive compared to outward passive head impulses ($p < 0.001$), and it was higher for active compared to passive head impulses (both inward and outward) ($p \leq 0.024$). Mean latency of the first saccade was significantly shorter for inward active compared to inward passive ($p \leq 0.001$) and for inward passive compared to outward passive head impulses ($p = 0.012$). Mean PR-score was only significantly higher in active outward than in active inward head impulses ($p = 0.004$).

Conclusion: For SHIMP, a higher predictability in head movements lowered gain only in passive impulses, and shortened latencies of compensatory saccades overall. For active impulses, gain calculation was affected by short-latency compensatory saccades, hindering reliable comparison with gains of passive impulses. Predictability did not substantially influence grouping of compensatory saccades.

1. Introduction

The peripheral vestibular system is the part of the inner ear and it includes three semicircular canals and two otolith organs. The semicircular canals detect 3D head rotations and induce eye movements in the opposite direction of head rotation. This is the angular Vestibular Ocular Reflex (VOR) (1). The VOR enables gaze stabilization during head movements. In case of reduced or absent function of the semicircular canals, the VOR is affected, which might cause oscillopsia, a symptom of blurred vision during head movements (2).

The function of all three semicircular canals can be assessed in the high frequency domain using the video Head Impulse Test (vHIT) (3). During this test, while the subject is fixating a visual target, an examiner rotates the subject's head with a brisk, small amplitude, and high angular velocity. Such a head turn delivered by the examiner is called a "head impulse". The head and eye movements are then recorded simultaneously by a device, which is either a pair of goggles mounted with a high-speed infrared camera or only a remote camera fixated in front of the subject. In the first case, a camera mounted on a goggle frame detects eye movements, while gyroscopes positioned on the same frame record head movements. In the second case, both eye and head movements are derived from images recorded by the camera (4). The ratio of eye to head angular velocity, called gain, is used as a parameter to assess the VOR. In healthy subjects this ratio is close to 1.

Two different testing paradigms exist in vHIT: the Head Impulse Paradigm (HIMP) and the Suppression Head Impulse Paradigm (SHIMP). They differ with respect to the target of fixation. In HIMP, the target is fixated with respect to the earth at a distance of 1.5 – 2 meters from the test subject (3). In SHIMP, the target is projected on a wall in front of the subject and it moves synchronously with the head of the test subject (5).

In HIMP healthy subjects are able to keep their gaze on the target during the head impulse due to the VOR. Patients with an impaired VOR are not able to keep their eyes on the target, and have to produce fast eye movements to reposition the eyes on the target: the catch-up saccades. In contrast to HIMP, healthy subjects in SHIMP have to produce saccades since the VOR drives the eyes in the opposite direction of the head impulse, while the target is moving synchronously with the head. Patients with an absent VOR do not have to produce saccades during SHIMP, since their eyes are already moving along with the head during the head impulse, keeping them on the target. Both paradigms are able to indicate loss of semicircular canal function (3,5), although SHIMP might better indicate residual vestibular function (6) and might more reliably facilitate gain calculation in patients with severe loss of vestibular function. Since in SHIMP physiological saccadic eye movements appear in healthy subjects (5), SHIMP is the paradigm of choice in investigating saccadic eye responses during head impulses in healthy subjects.

The head impulse itself can be performed in different ways, which might have an effect on the predictability of the vHIT. These head impulse variations mainly include differences in direction (inward versus outward direction) and type of movements, which are either delivered by the examiner (passive) or produced by test subjects themselves (active). Since subjects know the direction of inward head movements, this makes inward impulses more predictable than outward impulses (7). Since subjects know both timing and direction of active head impulses, this makes active impulses more predictable than passive head impulses (8).

Although the consequences of different head impulses for outcome measures in vHIT have not been well established, recent studies have reported effects of predictability on gain values and saccadic eye responses. Conflicting evidence exists about the effect of predictability on VOR gain. VOR gain was found to be decreased in inward, more predictable head movements in HIMP. This could involve impulses to both directions, or only to the contralesional side in patients with unilateral vestibulopathy (7,9,10). However, another study did not find any difference between passive in- and outward head impulses in healthy subjects (11).

Regarding active, more predictable head movements, VOR gain increased in patients with unilateral vestibulopathy (8,12) but remained unchanged in healthy subjects (12), compared to passive head movements. Saccade latency was shorter in more predictable passive inward rather than in passive outward head impulses in both HIMP and SHIMP (8,13,14). Saccades became more grouped in patients with unilateral vestibulopathy after training with active head impulses in HIMP (15), but it was not determined whether predictability played a significant role. The effects of predictability on grouping of saccades in healthy subjects is not yet known.

The aim of this study was to identify differences in VOR gain and saccades in SHIMP between predictable and less predictable head movements in a group of healthy subjects. It was assumed that inward and active head movements could lead to higher prediction. Based on the previous studies it was hypothesized that this higher degree of predictability could lead to a decrease in VOR gain values, a shorter saccadic latency, and higher grouping of saccades (7–9,13–15). This hypothesis might imply that when SHIMP is applied in a predictable way (inward and/or active head impulses), specific measures should be taken to correct for the change in eye movement responses.

2. Material and Methods

2. 1 Study population

This prospective study was performed in healthy subjects in Maastricht University Medical Centre+ (MUMC+). The study lasted from October 2020 until April 2021. Subjects between 18 and 80 years old were included. Subjects were excluded if they met at least one of the following criteria: inability to see the point of fixation on the wall, inability to understand the examiner's instructions, severe physiological nystagmus, neck pathology or limited neck mobility, history of vestibular or neurological impairment or inner ear surgery, posture or gait abnormalities, severe hearing problems, prior use of alcohol at least 24 hours before the study or use of any tranquilizers, sedatives, or other vestibular suppressants at least 48 hours before the study. A questionnaire was used to screen for the abovementioned criteria.

2.2 Experimental setup and preparations

Examinations were performed using the ICS Impulse device (Natus, Taastrup, Denmark) with one camera focused on the pupil of the right eye. Each head impulse was applied by the same trained right-handed examiner (BV), and according to a previously published strict experimental setup (16,17). The test subject was seated on a chair at a distance of 2 meters from a wall. For HIMP, the target was fixated on this wall. During SHIMP, the target was projected on this wall by a head-mounted laser. In both cases the target was at the level of the subject's eyes. The room was well lit to ensure a small pupil size required for an accurate pupil detection by the vHIT system. Shadows or light reflections onto the pupil were minimized

(17). The head band of the goggles was tightly strapped. After fixating the goggles, the rim of the goggles was adjusted so the eyelids were held back. The eye position was calibrated using the ICS impulse two-point calibration (18). After successful calibration the subject was instructed not to touch the strap, goggles, face, and head (17).

2.3 Study design

The protocol started in each participant with a HIMP session, to ensure an adequate functioning of the lateral semicircular canals. HIMP testing involved only passive outward horizontal impulses. Immediately after the HIMP, the SHIMP was performed using four conditions with different head movement patterns based on the previously described SHIMP protocol (5): passive head movements directed from the midline towards the side with gaze ended lateral (passive outward impulses); passive head movements directed from the side towards the midline with gaze ended central (passive inward impulses); active head movements directed from the midline towards the side with gaze ended lateral (active outward impulses); active head movements directed from the side towards the midline with gaze ended central (active inward impulses). In order to control possible learning effects, the order of SHIMP conditions was randomized using the Latin square design (19). A summary of the test conditions is presented in *Table 1*.

Table 1. The conditions of the HIMP and SHIMP vHIT procedures

	Head direction	
Movement type	*Inward*	*Outward*
Active	SHIMP	SHIMP
Passive	SHIMP	HIMP and SHIMP

2.4 vHIT procedure

Subjects were instructed to keep their eyes wide open, fixate on the target, and to not blink during testing. Before start of the official testing, slow horizontal sinusoidal head movements were given in order to assess neck stiffness and to give final instructions. In case of significant neck muscle tension during head impulses the subject was excluded from the study. After the first six HIMP impulses, traces were analyzed in order to check for possible calibration problems or distinct artifacts. If no calibration problems or artifacts were observed, the official testing started.

During passive head impulses (HIMP and SHIMP) the examiner stood behind the subject with both hands-on top of the head, holding it firmly without touching the strap or goggles. A head pitch between 0° and 15° downwards was maintained. The head impulses comprised fast (peak velocity >120°/s) horizontal rotational head movements with a small amplitude (±15°), unpredictable in timing and direction (only for outward). After each impulse the participant's head was slowly moved back to the starting position by the examiner. Active head impulses (only SHIMP) were performed by the subjects themselves. They were asked to make rapid horizontal head rotations with the same velocity and amplitude as passive head impulses (8). A minimum of 10 impulses accepted by the device software were delivered to each side in each test condition. After every eight impulses a small break was planned, so the subject could blink and relax for a short moment. The examiner repeated the instructions after each break to ensure optimal compliance.

2.5 Data cleaning

Head and eye velocity traces were exported and further processed using a custom-made software written in Python v.3.7.

The traces were automatically removed by custom-made software when (20,21): head impulse bounce was more that 50% of the peak head velocity; head velocity never crossed zero after peak head velocity; head velocity was lower than 120 °/s; mean head velocity calculated in the interval of 80 ms prior and 120 ms after peak head velocity was not in the range of the mean ± 3SD calculated for these means per subject, side, and test condition. After this procedure, the traces were manually inspected and removed based on consensus among three authors (RB, BV, DS) if one of the following artifacts were present: the eye leaded the head; multiple head velocity peaks; an eye movement in the opposite direction of the expected vestibulo-ocular reflex; oscillations not qualified as saccades; the head velocity curve was not bell-shaped (4,20,21).

It should be noted that 120 °/s was chosen as the minimum peak head velocity. This (relatively) lower velocity allowed to collect enough data, since some subjects had difficulty to consistently reach high peak head velocities. This velocity has shown to be adequate for reliably testing VOR gain in children and adolescents, in which reaching high head velocities might also not always be feasible (22).

2.6 Data analysis

The onset of head movement was defined at the point of 60 ms before peak head acceleration. The offset of head movement was defined at the point where head velocity returned to zero. Timing of the peak head velocity was calculated related to the onset of the head movement.

VOR gain was used as the primary outcome measure. VOR gain for HIMP and SHIMP was calculated by the custom-made software (4) using the area under the curve method within the interval between head onset and offset (23). Both eye and head traces were desaccaded first, before VOR gain was calculated. No interpolation was applied. Only data of subjects with mean gain values in HIMP $\geq$ 0.8 were used for the analysis (24).

Latency of the first saccade and the degree of grouping regarding timing (global PR-score, further in the text PR-score (25)) of all saccades were used as secondary outcome measures. The PR denomination does not have any mathematical or scientific significance (25). A custom-made algorithm was applied to extract saccades in SHIMP with as much accuracy as possible (4). Every saccade was verified by visual inspection by two of the authors (BV and DS). Saccades were included when 1) they occurred after head impulse onset, and 2) they had a magnitude of more than 60 °/s, and 3) their peak velocity was recorded. Erroneously detected saccades were manually excluded. Latency (in milliseconds) and the degree of grouping (PR-score) of the included saccades were extracted from the first 10 artifact free traces. Saccade latency was related to the onset of the head impulse (4,14). Only latency of the first saccade of each impulse was determined. The PR-score was calculated using the method originally implemented in the MATLAB open-source script named HITCal (25). For short, the PR-score is the weighted arithmetic mean of the variation coefficients of the first and second order saccades with the weights of 0.8 and 0.2 respectively. Two corrections are applied: the PR-score value is limited to 100 and in case when the PR-

score is over 35, the weight for the variation coefficient of the second order saccades is reduced in the arithmetic mean inversely to their number (25).

2.7 Statistical analysis of peak head velocities

Mean peak head velocity was calculated per subject and test condition. In order to account for a possible effect of head velocity on gain differences, two analyses were performed. First, means of the mean peak head velocities were compared in each pair of the test conditions using the paired T-test. Secondly, for each significant difference (separately for each side), a linear regression model was fitted with the difference of mean gain as the dependent variable and the difference of mean peak head velocity as the independent variable. These differences were calculated as follows: for active and passive head impulses they were calculated as outward value minus inward value; for outward and inward head impulses - passive value minus active value. The α-level was set on 0.05. All p-values were Bonferroni corrected for multiple comparisons.

2.8 Statistical analysis of main outcomes

Mean age with a standard deviation was calculated for the tested group. Mean of the outcome measures (for HIMP and SHIMP: gain, only for SHIMP: latency of the first saccade and PR-score) were calculated per subject for each side and test condition. Mean with a 95% confidence interval was calculated for the means of the outcome measures.

Since all subjects produced at least one saccade in all SHIMP impulses, there was no missing data regarding latencies of the first saccade and PR-score. To analyze the effect of head movement type (active, passive), head direction (inward, outward), and side (left, right) on each outcome measure, three three-way repeated measures ANOVAs (RANOVA) were fitted. Movement type (active, passive), head direction (inward, outward), and side (left, right) were set as the two-level within-subject factors including their two- and three-way interactions. The corresponding outcome measure (gain, latency, PR-score) was set as the dependent variable. In case of statistical significance of the two-way interaction, two-way RANOVAs were fitted per each unique level of the corresponding factors. If in this model a two-way interaction was significant, the paired T-test was used to evaluate pairwise comparisons between levels of the corresponding factors. The α-level was set on 0.05. The p-values were Bonferroni corrected for multiple comparisons

2.8.1 Preliminary statistical results for main outcome measures

For the three-way RANOVA with gain as the dependent variable a two-way interaction between side and movement type was significant ($F(1,56) = 4.38$, $p = 0.041$) and a two-way interaction between movement type and head direction was significant ($F(1,56) = 63.49$, $p < 0.001$). Therefore, six two-way RANOVAs were fitted.

For the three-way RANOVA with latency as the dependent variable a two-way interaction between side and movement type was significant ($F(1,56) = 5.43$, $p = 0.023$) and a two-way interaction between side and head direction was significant ($F(1,56) = 6.10$, $p = 0.017$). Therefore, six two-way RANOVAs were fitted.

For the three-way RANOVA with PR-score as the dependent variable a two-way interaction between movement type and head direction was significant ($F(1,56) = 7.08$, $p = 0.01$). Therefore, four two-way RANOVAs were fitted.

2.8.2 Additional statistical analysis of gain calculated by the device software

Gain values for each impulse were exported from the ICS Impulse software (vHIT software), which calculates gain using the same algorithm as the custom-made software (26). Mean gain values derived by both programs were compared per side and test condition using the paired T-test. The α-level was set on 0.05. The p-values were Bonferroni corrected for multiple comparisons. All statistical analyses were performed in R v.4.0.3 (R Foundation for Statistical Computing, Vienna, Austria) and SPSS Statistics v27 (SPSS Inc., Chicago, Ill., USA).

2.9 Ethical considerations

This study was performed in accordance with the guidelines outlined by Dutch legislation. According to the Medical Research Involving Human Subjects Act (WMO) ethical approval was not required, since the purpose of this study was to validate our own system and to obtain the normative values. Written informed consent for participation and publication of these results was obtained from all subjects.

3. Results

3.1 Characteristics of healthy volunteers

Sixty-two healthy subjects were recruited, whose characteristics are presented in *Table 2*. Five subjects were excluded: two subjects were excluded due to pupil detection problems, one subject was excluded due to inadequate neck relaxation, which compromised the collection of appropriate head impulses, and two subjects were excluded due to less than 10 valid impulses per side. In total, vHIT data of 57 subjects were included, containing 10.440 impulses, of which 9.983 (96%) were free of artifacts. Since for each subject the first 10 artifact-free traces of each side per condition were included in the analysis, a total of 5.700 impulses were used for statistical analysis. All test subjects showed a mean VOR gain ≥ 0.8 when tested with passive outward HIMPs (*Table 2*). An example of horizontal SHIMP vHIT traces for all tested conditions in one subject, is presented in *Figure 1*.

Table 2. Characteristics of the study population

N	57
Male	26
Female	31
Mean age (years)	26 ± 3
Head Impulse Paradigm mean VOR gain (Left)	0.92 ± 0.07
Head Impulse Paradigm mean VOR gain (Right)	0.99 ± 0.08

Age in years ± standard deviation.
VOR gain ± standard deviation.
VOR = Vestibular Ocular Reflex
Head Impulse Paradigm VOR gain is calculated for passive outward head impulses

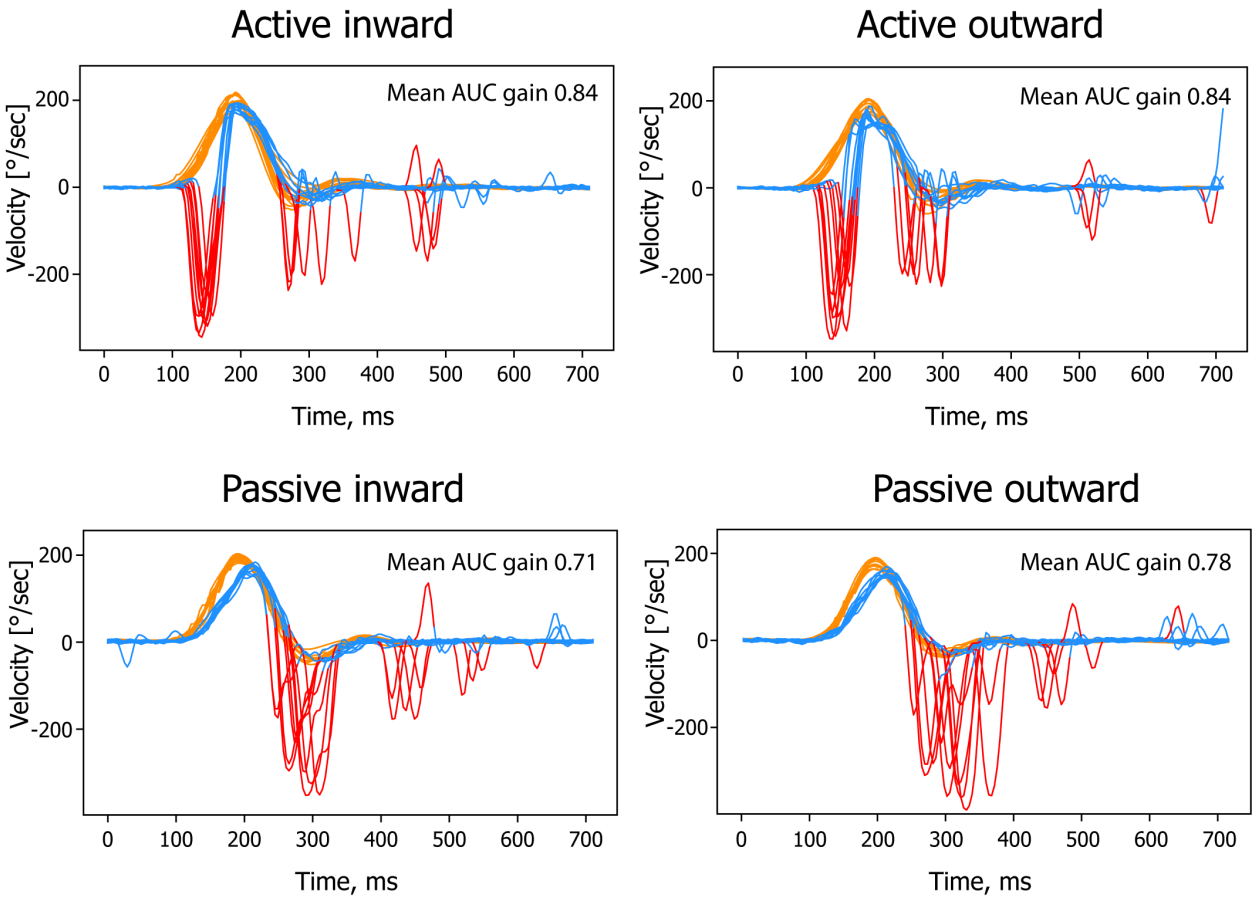

Figure 1. An example of SHIMP vHIT traces for all tested conditions (left side) in one test subject

3.2 VOR gain, latency of the first saccade, and global PR-score in SHIMP conditions

For each tested SHIMP condition, means of VOR gain, latency, and PR-score are presented in *Figure 2*and *Table 3*.

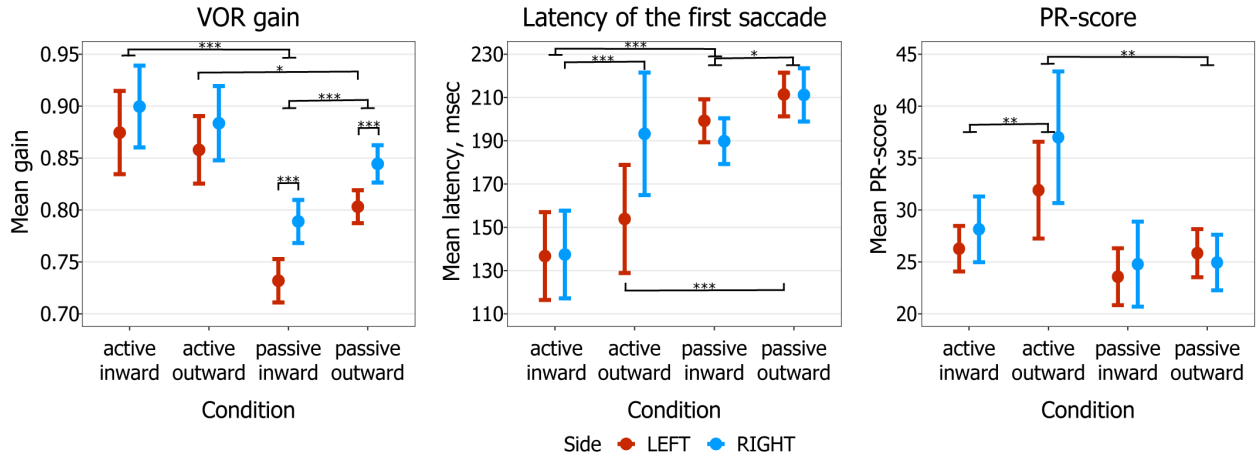

*Figure 2. SHIMP mean values with corresponding 95% confidence intervals, calculated for mean VOR gain, mean latency of the first saccade, and mean PR-score. * = p < 0.5, ** = p < 0.01, *** = p < 0.001*

3.2.1 VOR gain

Regarding movement type, mean gain was significantly higher in active than in passive head impulses in inward direction ($p < 0.001$) The same effect was observed in outward direction, but only for the left side ($p = 0.024$). Regarding head direction, mean gain was significantly higher in outward than in inward passive head impulses, regardless of side ($p < 0.001$). No significant difference was observed between inward and outward active head impulses. Regarding side, mean gain was significantly higher to the right than to the left in passive inward and outward head impulses ($p < 0.001$).

Table 3. Mean gain, mean latency of the first saccade, and mean PR-score with corresponding standard deviation (SD) and 95% confidence intervals (CI) for each combination of movement type, head direction, and side. Mean latency is in milliseconds

			Gain			**Latency, ms**			**PR-score**		
Movement type	Head direction	Side	Mean	SD	95% CI	Mean	SD	95% CI	Mean	SD	95% CI
Active	Inward	LEFT	0.87	0.15	(0.83, 0.91)	137	75	(116, 157)	26	8	(24,28)
Active	Inward	RIGHT	0.90	0.15	(0.86, 0.94)	137	76	(117, 158)	28	12	(25,31)
Active	Outward	LEFT	0.86	0.12	(0.83, 0.89)	154	94	(129, 179)	32	18	(27,37)
Active	Outward	RIGHT	0.88	0.14	(0.85, 0.92)	193	107	(165, 221)	37	24	(31,43)
Passive	Inward	LEFT	0.73	0.08	(0.71, 0.75)	199	37	(189, 209)	24	10	(21,26)
Passive	Inward	RIGHT	0.79	0.08	(0.77, 0.81)	190	40	(179, 200)	25	15	(21,29)
Passive	Outward	LEFT	0.80	0.06	(0.79, 0.82)	211	38	(201, 221)	26	9	(24,28)
Passive	Outward	RIGHT	0.84	0.07	(0.83, 0.86)	211	46	(199, 223)	25	10	(22,28)

3.2.2 Latency of the first saccade

Regarding movement type, mean latency of the first saccade was significantly shorter in inward active than in inward passive head impulses, regardless of side ($p < 0.001$). The same effect was observed in outward direction, but only for the left side ($p < 0.001$). Regarding head direction, mean latency was significantly shorter in passive inward than in passive outward head impulses, regardless of side ($p = 0.012$). The same effect was observed in active head impulses, but only for the right side ($p < 0.001$). Regarding side, mean latency was only significantly different between active outward left and right head impulses (lower in left, $p = 0.006$), but this effect became insignificant after the Bonferroni corrections ($p = 0.144$).

3.2.3 PR-score

A significant difference in mean PR-score between active and passive head impulses was only observed in outward impulses, where it was higher in active head impulses regardless of side ($p = 0.004$). Furthermore, regarding head direction, mean PR-score was only significantly higher in active outward than in active inward impulses, regardless of side ($p = 0.004$). No significant differences were observed between sides in all tested conditions.

3.3 Factors that could influence main outcome measures

3.3.1 Differences in head velocities between tested conditions

Mean peak head velocities and their latencies of each SHIMP condition, are shown in *Table 4* of *the Supplementary Materials*. The maximum difference in mean peak head velocities between conditions was 41 deg/s (active inward impulses to the left versus passive outward impulses to the left). Mean peak head velocities were significantly lower for outward (both passive and active) and passive (both inward and outward) head impulses regardless side ($p \leq 0.009$). Eight linear models were fitted to assess the influence of the difference in mean peak head velocity on the difference in mean gain (outward minus inward and passive minus active, one per side). No significant effect was found in any pairs of the test conditions ($p \geq 0.32$).

3.3.2 Difference in VOR gain calculation between the custom-made software and vHIT device

Mean VOR gain values significantly differed in all SHIMP conditions between the custom-made software and the vHIT device ($p < 0.001$). The vHIT software calculated lower VOR gains in all test conditions (both sides), with the lowest values in active inward head impulses (*Figure 4*, *Supplementary Materials*).

4. Discussion

This study compared VOR outcome measures of SHIMP between less predictable head movements (passive and outward) and more predictable head movements (active and inward). It was shown that in more predictable inward impulses gain was lower than in outward impulses, but only for the passive head movements. The latency of the first compensatory saccades was shortened in all more predictable conditions. No significant influence of predictability was observed on grouping of the saccades.

The more predictable inward passive head movements demonstrated lower VOR gains compared to the less predictable outward passive head impulses. This is congruent with the hypothesis and with previous literature (7,9). Possible contributing factors are decreased alertness, less contraction of cervical muscles, and better VOR suppression due to the predictability during inwards head impulses, leading to lower VOR gains (5–7,9,27–30). Predictability was also found to decrease the translational VOR gain (31). Although head velocities differed between test conditions in this study, it is less likely that these different head velocities contributed to the different VOR gains found in inward passive and outward passive impulses. After all, the variation in mean peak head velocities between passive inward and outward head impulses was little (10 deg/sec for both sides), and statistical analysis demonstrated no effect of head velocity difference on VOR gain difference (32). Therefore, this study seems to support that higher predictability of head impulses leads to a lower VOR gain in SHIMP. Nevertheless, this VOR gain difference is relatively small (< 0.1) and might not have any clinical consequences (7).

However, in contrast to the hypothesis suggested earlier, SHIMP VOR gain was significantly higher in the more predictable active head impulses than in the less predictable passive head impulses. This was previously also described in HIMP (8). Nevertheless, this does not directly imply that predictability leads to a higher gain in active SHIMP head impulses. After all, when comparing active head impulses with passive head impulses in SHIMP, gain calculation using the “area under the curve method” is compromised by early saccades that mainly occur during active head impulses. This results in a less reliable comparison

between active and passive head impulses. Background of this phenomenon is that during active head impulses 35% of the subjects in this study produced large (400 deg/sec) saccades before the mean timing of peak head velocity, while during passive head impulses saccades were predominantly produced after mean peak head velocity timing. Since saccades were eliminated from the traces without interpolation, gain for active head impulses was often based on the descending phase of the VOR curve (see *Figure 1* and *Figure 3*), and gain for passive head impulses was often based on the ascending phase of the VOR curve (33). Gain calculated from the ascending phase of the VOR curve is expected to be lower than gain calculated from the descending phase of the VOR curve due to the fact that the VOR is physiologically delayed by on average 8-9 milliseconds (see *Figure 3*a). Therefore, it cannot be reliably stated that active head movements demonstrate a higher gain related to predictability: the gain calculation method might also play a significant role (33,34). Given the influence of early saccades on gain calculation, attention should be paid when comparing gain between active and passive head movements in future studies. These early saccades do not only affect gain calculated by the area under the curve method, but also other methods like instantaneous or regression gain. A possible solution to calculate and compare VOR gains, could be to only include time points which are present in all impulses, after the desaccading process. This needs to be investigated in future trials.

Furthermore, higher mean peak head velocities were accompanied by higher mean gains in active head impulses. This is in contrast to previous studies, in which lower VOR gains were found with increasing head velocities in healthy subjects (HIMP, outward passive head impulses) (35–37). Again, this might be related to the influence of using ascending and descending phases during gain calculation.

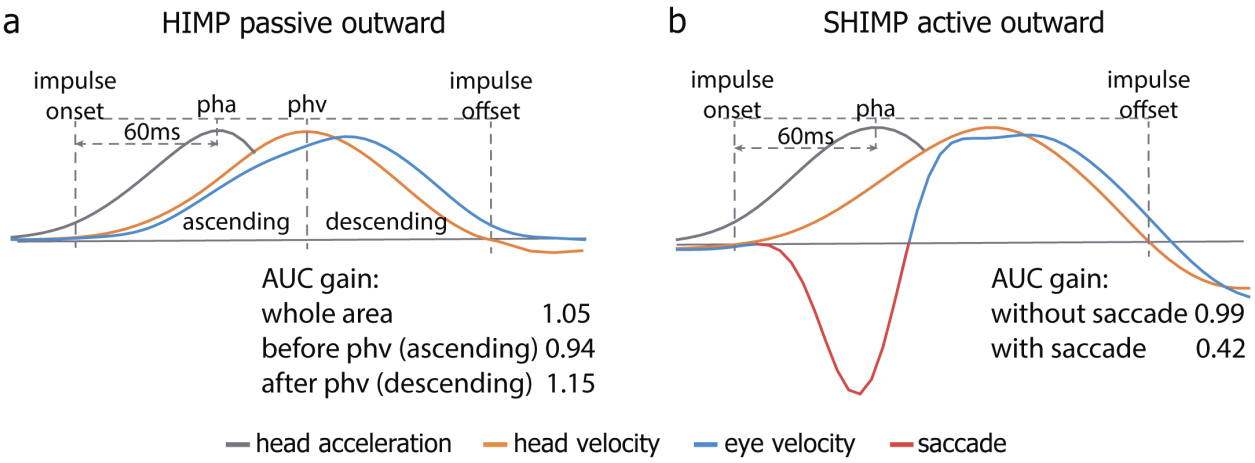

Figure 3. A schematic overview of the Area Under the Curve (AUC) gain calculation method and its vulnerability to calculating gain from the ascending versus descending phase (3a), and the presence of an early saccade (3b). Due to the physiological delay of the VOR, the AUC of the ascending phase of the eye response is lower than that of the descending phase, leading to an inherent lower gain calculated by the AUC method (3a). Not detecting the early saccade (red part of the eye velocity trace, 3b) by the vHIT system, leads to a lower gain since the AUC of the saccade is subtracted from the remaining eye response (blue part of the trace, 3b). Legend: pha = peak head acceleration; phv = peak head velocity

SHIMP VOR gain values calculated by the vHIT software were significantly lower than those calculated by the custom-made software, although low VOR gains were not expected in this healthy population (HIMP gain > 0.8). This finding highlights the fact that VOR gain outcomes are very sensitive to pre-processing. Since both calculation methods are based on the same area under the curve method using the same interval, differences in gain values were most likely related to the desaccading process. Erroneously including an early saccade in the gain calculation process leads to a lower gain since its area under the curve is subtracted from that of the VOR (see *Figure 3*b). Although in some vHIT systems the minimal latency of saccades can be defined to detect saccades, one still need to be very cautious when letting the default software automatically process the traces. Manual inspection is still required.

Regarding the gain asymmetry observed in passive head impulses between sides, probably the main factor that could contribute to this finding is the side on which the camera was placed (right side) (35–40). In active head impulses no significant difference was demonstrated between sides. A higher degree of predictability might mask this asymmetry.

The latency of the first saccade was shorter in the more predictable head movements, like in active inward head impulses when compared to passive inward head impulses, and in passive inward head impulses when compared to passive outward head impulses. Early saccades in voluntary head movements are well known in literature: for example, subjects produce earlier saccades if they are informed about the direction of the next impulse (14). Early saccades are thought to have a central and cervical-reflex origin (41–46). Their aim is to shift gaze towards the visual target and are usually followed and complemented by the VOR and smaller corrective saccades (8,13). In case of a deficient VOR, they can facilitate improvement of dynamic visual acuity (47,48). It should be noted that early saccades can precede head movements (42). In this study, this was also found in six subjects during inward and outward active head impulses. Such early saccades can be “invisible” for the vHIT software, since saccade detection often only starts at least after the head impulse onset (18,49). This phenomenon should therefore be taken into account during the gain calculation process of active head impulses.

The present study did not find any significant differences in the level of saccade grouping among different head movement paradigms, except for a significantly higher PR-score in active outward head impulses. This could mean that although subjects produced earlier saccades in case of active and inward impulses, the saccades were grouped approximately at the same level. However, this does rule out the effect of the predictability on saccade grouping. Further studies of the influence of predictability on saccade grouping in healthy subjects are required.

Limitations of the study

Main limitation of this study is significantly hindered comparison of the gain values between active and passive head movements. In addition, the effect of age on consequences of predictability of head movements in SHIMP could not be determined due-to relatively small age structure. However, this is less likely of relevance since the gain is known to be stable until at least 70 years (36). Furthermore, as a result of study design (using SHIMP in order to be able to study saccadic responses in healthy subjects) not all head movement paradigms were tested in HIMP. It therefore cannot be determined whether these findings in SHIMP can be generalized to HIMP.

5. Conclusion

For SHIMP, a higher predictability in head movements lowered gain only in passive impulses, and shortened latencies of compensatory saccades overall. For active impulses, gain calculation was affected by short-latency compensatory saccades, hindering reliable comparison with gains of passive impulses. Predictability did not substantially influence grouping of compensatory saccades.

Author contributions

All authors participated in the design of the experimental protocol and analysis. BV, LvS, and TD carried out the experiment. AMLJ, BV, and DS performed the statistical analysis. DS and BV made the software for analysis. DS, BV, and RvdB wrote the manuscript. MP, LvS, NG, AP, VR, and HK critically revised the manuscript.

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Supplementary material

Table 4. Mean peak head velocities and their timings calculated for each SHIMP condition

Movement type	Head direction	Side	Peak head velocity, deg/s				Timing, msec			
			Mean	SD	Median	1st|2nd quartiles	Mean	SD	Median	1|2nd quartiles
Active	Inward	LEFT	208	13	205	176|237	104	13	102	96|110
Active	Inward	RIGHT	196	13	192	167|222	106	13	106	98|114
Active	Outward	LEFT	188	14	183	157|214	105	14	102	96|111
Active	Outward	RIGHT	190	14	188	160|216	105	14	102	98|110
Passive	Inward	LEFT	176	13	177	161|190	107	13	107	98|115
Passive	Inward	RIGHT	186	11	187	170|202	102	11	102	94|110
Passive	Outward	LEFT	167	13	166	153|180	105	13	102	97|114
Passive	Outward	RIGHT	176	11	174	160|192	103	11	102	98|110

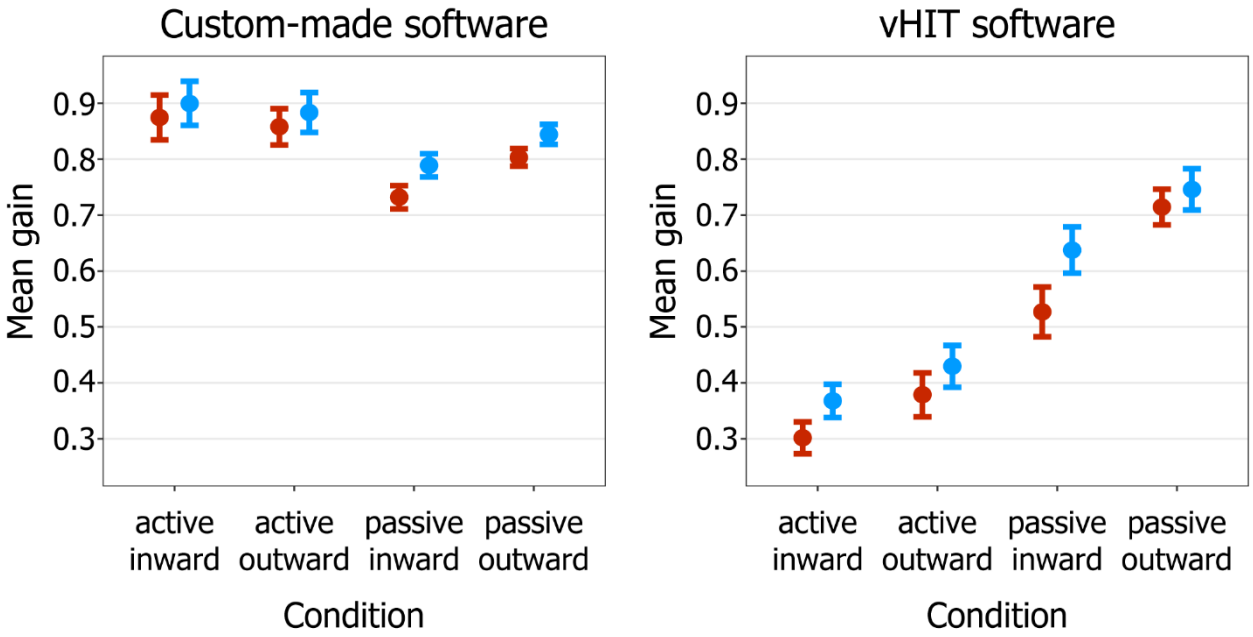

Figure 4. SHIMP mean VOR gains with corresponding 95% confidence intervals, as calculated by the custom-made software (modified from Figure 2) and the vHIT device software

Chapter III

Comparison of three video head impulse test systems for the diagnosis of bilateral vestibulopathy

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Abstract

Introduction: A horizontal vestibulo-ocular reflex gain (VOR gain) of < 0.6, measured by the video head impulse test (vHIT), is one of the diagnostic criteria for bilateral vestibulopathy (BV) according to the Bárány Society. Several vHIT systems are commercially available, each with different techniques of tracking head and eye movements and different methods of gain calculation. This study compared three different vHIT systems in patients diagnosed with BV.

Methods: This study comprised 46 BV patients (diagnosed according to the Bárány criteria), tested with three commercial vHIT systems (Interacoustics, Otometrics and Synapsys) in random order. Main outcome parameter was VOR gain as calculated by the system, and the agreement on BV diagnosis (VOR gain < 0.6) between the vHIT systems. Peak head velocities, the order effect and covert saccades were analyzed separately, to determine whether these parameters could have influenced differences in outcome between vHIT systems.

Results: VOR gain in the Synapsys system differed significantly from VOR gain in the other two systems [$F(1.256, 33.916) = 35.681$, $p < 0.000$]. The vHIT systems agreed in 83% of the patients on the BV diagnosis. Peak head velocities, the order effect and covert saccades were not likely to have influenced the above-mentioned results.

Conclusion: To conclude, using different vHIT systems in the same BV patient can lead to clinically significant differences in VOR gain, when using a cut-off value of 0.6. This might hinder proper diagnosis of BV patients. It would, therefore, be preferred that vHIT systems are standardized regarding eye and head tracking methods, and VOR gain calculation algorithms. Until then, it is advised to not only take the VOR gain in consideration when assessing a vHIT trial, but also look at the raw traces and the compensatory saccades.

Introduction

Bilateral Vestibulopathy (BV) is a heterogeneous chronic condition in which the vestibular function is severely impaired or absent in both ears (1). A greatly reduced or absent vestibulo-ocular reflex (VOR) is a clinically useful marker of BV, among other symptoms (2). To quantify the VOR function in all planes of the semicircular canals, the video head impulse test (vHIT) is widely used (3). The vestibulo-ocular reflex gain (VOR gain) is considered to be the main outcome parameter of the vHIT. VOR gain represents the correlation between eye and head velocity, and can be calculated in various ways. For example, VOR gain can be calculated as the ratio between eye and head velocity at a certain point in time, at peak head velocity, or throughout the whole head movement (i.e. the area under the curve gain) (4–6). VOR gain should be close to 1.0 in healthy subjects (7). Therefore, a decreased VOR function should result in a decreased VOR gain. Moreover, a horizontal angular VOR gain of < 0.6 on both sides, as measured by the vHIT, is one of the diagnostic criteria for BV according to the Bárànу Society (8).

BV patients can also show catch-up saccades during the vHIT. These saccades are a compensation mechanism for the retinal slip during head movements, and can occur during or shortly after a head impulse ("covert" saccades and "overt" saccades respectively). As an adaptation effect, the latency of the catch-up saccades can decrease and therefore the number of covert saccades can increase (9). These covert saccades could influence VOR gain calculations, especially when area under the curve gain calculation is used.

Several vHIT systems are commercially available, each with different methods of gain calculation and different techniques of tracking eye and head movements. Small study populations show significant differences in VOR gain between different vHIT systems within healthy subjects and patients. Despite these differences in VOR gain, all systems identified vestibular deficits similarly (5,6). It is unknown what the effect of using different vHIT systems is on the VOR gain in subjects with severely impaired vestibular function on both ears. In case the use of different vHIT systems would result in different clinical diagnoses within the same patient (e.g. classifying a patient "yes" or "no" with BV), it might be necessary to standardize systems regarding VOR gain calculation algorithms and eye and head tracking methods.

Objective of this study was to compare three commercial vHIT systems (Interacoustics, Otometrics, and Synapsys) in a large group of BV patients. Main outcome parameters were horizontal VOR gain as calculated by the system, and the agreement between the systems on identifying BV according to the diagnostic criteria (horizontal VOR gain < 0.6). Since there are technological differences inherent to the vHIT systems (i.e. different VOR gain calculation algorithms and different head and eye tracking), it was hypothesized that different vHIT systems could lead to clinically relevant differences in vHIT outcome within the same BV patient.

Methods

Study population

This study comprised 46 patients diagnosed with BV at the Division of Balance Disorders at Maastricht University Hospital, based on the diagnostic criteria for BV from the Bárány Society (8). Since VOR gain obtained by vHIT was used as an outcome parameter in this study, this criterium was removed from the inclusion criteria. Patients diagnosed with BV solely based on vHIT outcomes were, therefore, not part of

this study population. Inclusion criteria comprised (1) reduced caloric response (sum of bithermal maximum peak slow phase eye velocities of < 6°/s on each side), (2) and/or reduced horizontal angular VOR gain < 0.1 on rotatory chair and a phase lead > 68°. Exclusion criteria comprised being unable to stop vestibular suppressants for 1 week (cinnarizine and all psychiatric medication), and the inability to undergo one of the vestibular examinations.

Testing protocol

1. Experimental setup (7)

One trained examiner (FL) performed all vHIT's. A fixed distance of two meters from the back of the chair to the point of fixation was ensured [10]. Patients were seated on a static chair, to prevent upper body movement during head impulses. The room was well lit, to ensure a small pupil in every patient. Patients fixated on a green (532-nm) 1-mw laser dot projected on a large full visual field black (or white) painted wall. This facilitated a wider range for measuring the eye movements. At the same time, it minimized the change of artefacts due to light reflections onto the pupil. The fixating point was adjusted to the eye level of every patient. Each test started with calibration of the system. The examiner assessed the quality of the calibration and determined whether the process needed to be repeated. The examiner stood behind the patient, holding the head firmly during head impulses. Patients were instructed to relax their neck, keep their eyes wide open and fixate on the target in front of them. The examiner continuously repeated these instructions to facilitate optimal awareness of the patient. The head impulses comprised fast horizontal rotational head movements (> 120°/s) with a low amplitude, unpredictable in timing and direction. Only outward impulses were given (10).

The camera of the Interacoustics and Otometrics systems is head fixed and is integrated in a pair of goggles. There- fore, before start of testing, goggle movement was minimized by tightly fastening the strap of the goggles around the patients' head. The camera was always set on the right eye and focused on the pupil while the patient looked at the point of fixation with eyes wide open. In case the eyelids were in front of the pupil, the examiner adjusted the rim of the goggles so they would hold the eyelids back. After calibration, the patient was instructed to not touch (the strap of) the goggles, their face and/or their hair. The camera of the Synapsys system is space fixed, and therefore, no goggles were used. The camera that measured eye and head movements was placed in front of the patient. Eye movements from both eyes were measured (*Figure 1*).

2. vHIT systems

Three different vHIT systems were used in this study: EyeSeeCam (Interacoustics VOG; Munich, Germany), ICS Impulse (GN Otometrics; Taastrup, Denmark), and Ulmer (Synapsys, Marseille, France). Each patient sequentially underwent the horizontal vHIT with the different vHIT systems. The Synapsys system was not used in 17 patients, and the Interacoustics system was not used in one patient, due to the unavailability of the systems at the time of testing. The order of testing of the different vHIT systems was randomized by draw.

3. VOR gain calculation by the different vHIT systems

VOR gain, as calculated by the systems, was used as main outcome parameter. The three systems calculate VOR gain differently. Interacoustics uses instantaneous gain; it divides eye and head velocity at a certain point in time (small window around 60 ms) after onset of the head movement (11). Otometrics calculates VOR gain as the ratio of the area under the eye velocity and head velocity curve (from 60 ms before peak head acceleration to the last value of 0°/s as the head returns to rest). If needed, the eye movement is desaccaded by the system before the VOR gain is calculated. The Synapsys system calculates the VOR gain over the period from 40 ms before to 80 ms after peak head acceleration for each impulse. In case of a covert saccade, the 80-ms window is reduced, and stops at time of onset of the covert saccade (12). However, the method of gain calculation used by the Synapsys system was unknown to this research group, despite multiple efforts to obtain more information from the manufacturer.

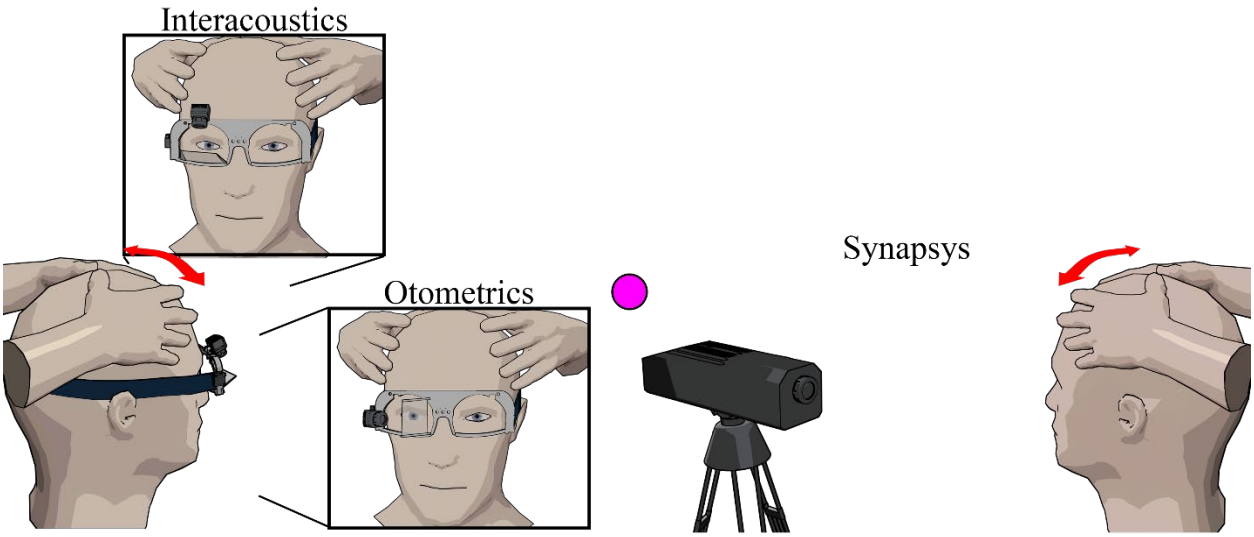

Figure 1. Animations of the three vHIT systems used in this study. The Interacoustics and Otometrics vHIT systems both consist of a pair of goggles with a build-in eye and head movement tracking system. The Synapsys vHIT system comprises a space-fixed camera placed in front of the patient

4. Covert saccades

Covert saccades might influence VOR gain (calculation). Therefore, covert saccades in this study population were analyzed separately to assess whether they differed between tests (as an adaptation effect) in this BV population when repeatedly tested. The frequency of occurrence of covert saccades, and the latency of the first covert saccade of a trace were analyzed.

5. Extracting data

To extract saccades, head and eye velocity (Interacoustics and Otometrics) and position (Synapsys) traces were exported and processed using Wolfram Mathematica 11.3 (Wolfram Research, Champaign, IL, USA). Only traces that were accepted by the systems were exported.

6. Pre-processing data

Synapsys measures both eyes during vHIT, but in this study, it was chosen to only use traces from the right eye, to better facilitate comparison with Interacoustics and Otometrics, which only register data from the right eye. In case of missing values from the right eye, data from the left eye were used. Because of the lower resolution of the Synapsys camera (100 Hz), the original eye and head position data were resampled to 250 Hz using linear interpolation. By differentiating these eye and head position traces, the velocity traces were calculated for eye and head movements recorded with the Synapsys system. Eye and head velocity traces from Interacoustics and Otometrics were directly extracted from the system itself. Eye and head position data for these two systems were calculated using numerical integration. Head and eye acceleration data were calculated for all three systems by differentiating the eye and head velocity signal.

7. Cleaning data

To establish artefact-free traces for analysis, traces were removed when (1) peak head velocity was < 120°/s, or (2) the head velocity trace contained a bounce at the end of the impulse of > 50% of peak head velocity, or (3) head velocity never crossed zero after peak head velocity (within the recorded time frame), or (4) the head velocity trace contained missing values, or (5) the shape of the head velocity trace implied an inadequate head impulse, assessed by visual inspection and consensus between three authors (RB, DS, TD), or (6) when the mean head velocity of the interval of 80 ms prior and 120 ms after a peak head velocity was not in the range of ± 3 SD of the set of mean head velocities calculated in the same interval in all traces of one patient (4,13,14).

8. Saccade detection

A custom-made algorithm was developed in Mathematica, and applied to extract saccades from the eye traces. To increase accuracy, every saccade was verified by visual inspection in the eye and head velocity and position traces. Two authors needed to achieve consensus (TD, DS) before a saccade was approved. Head impulse onset was specified as head velocity exceeding 10°/s, head impulse offset was

Journal defined as head velocity crossing 0°/s. Onset of a saccade was marked as the point where eye velocity crossed 0°/s or eye acceleration reached 2000°/s^2. Saccades were included when (1) they occurred after peak head velocity, and (2) had a magnitude of more than 60°/s, and (3) peak velocity of the saccade was recorded, and (4) occurred at least in two traces around the same location within the same trial and patient. A saccade was classified as covert when onset occurred before head velocity crossed zero, and as overt when onset occurred after head velocity crossed zero.

9. Saccade analysis: defining frequency and latency

In this study, the first covert saccades of the first seven artefact-free traces were used for analysis (15). The frequency and latency of the covert saccades were extracted from the original eye velocities in the Interacoustics and Otometrics system, and from the calculated eye velocities in the Synapsys system. The frequency of occurrence of a covert sac- cade was first registered as a binary outcome (Yes/No) for every trace separately. From these data, a ratio per patient was calculated (in percentage). Latency (in milliseconds) was registered as the onset of the covert saccade, and was normalized to the start of the head impulse (16).

Statistical analysis

Data were analyzed using SPSS Statistics 24 for Windows and R (v.3.5.2.). The α-value was set on $p < 0.05$. In case of multiple comparisons, the Bonferroni correction was applied. When no interaction was found between leftwards and rightwards head impulses, the direction of the impulse was removed from the statistical model and both sides were analyzed together.

1. Statistical analysis of VOR gain and agreement of vHIT systems regarding BV diagnosis

A repeated-measures ANOVA was used to compare mean VOR gain between the three systems. A VOR gain of < 0.6 was classified as "bilateral vestibulopathy", a VOR gain of ≥ 0.6 was classified as "no bilateral vestibulopathy" (8). In case the vHIT systems showed a discrepancy in classifying BV, it was classified as "no agreement".

2. Statistical analysis of VOR gain and repetitive testing (the order effect)

To evaluate the order effect, a repeated-measures ANOVA was used to compare mean VOR gain between the first and the last executed vHIT trial (regardless of the vHIT system).

3. Statistical analysis of peak head velocity

Peak head velocities (extracted from the raw traces of the vHIT systems) of all traces of all patients were combined per vHIT system. Median peak head velocities were compared between vHIT systems using a Mann–Whitney U test. In patients with "no agreement" between systems, peak head velocities were analyzed separately within the BV patient. Median peak head velocities of those particular trials were compared between vHIT systems using a Mann–Whitney U test.

4. Statistical analysis of saccades

The frequency of occurrence of covert saccades was compared between the first and the last executed vHIT trial (regardless of the vHIT system) using a generalized linear mixed-effects model. Additionally, the latency of the first covert saccade was compared between the first and the last executed vHIT trial (regardless of the vHIT system) with a paired T test. Patients with missing values (no saccades) were not included in this last analysis.

Results

1. Patient characteristics

In total, 46 BV patients were included: 23 males and 23 females. Mean age was 59 years (standard deviation 11 years). Definite and probable etiologies comprised: ototoxic effects of antibiotics (n = 8) or chemotherapy (n = 1), post-infectious due to Lyme disease (n = 1), Hashimoto's thyroiditis (n = 1), Herpes infection (n = 1), meningitis (n = 2), inherited, e.g. by DFNA9 gene mutation (n = 7), bilateral Menière's disease (n = 3), autoimmune disease (n = 1). In 21 patients, no etiology could be determined (idiopathic).

All three vHIT systems were able to capture the same type of eye movement responses to head impulses. This is illustrated in *Figure 2*, which presents the raw data of one BV patient (patient 21), selected as a representative sample of the whole study population. Further details of vHIT characteristics (VOR gain, peak head velocity, timing of saccades) of all tested patients will be discussed below.

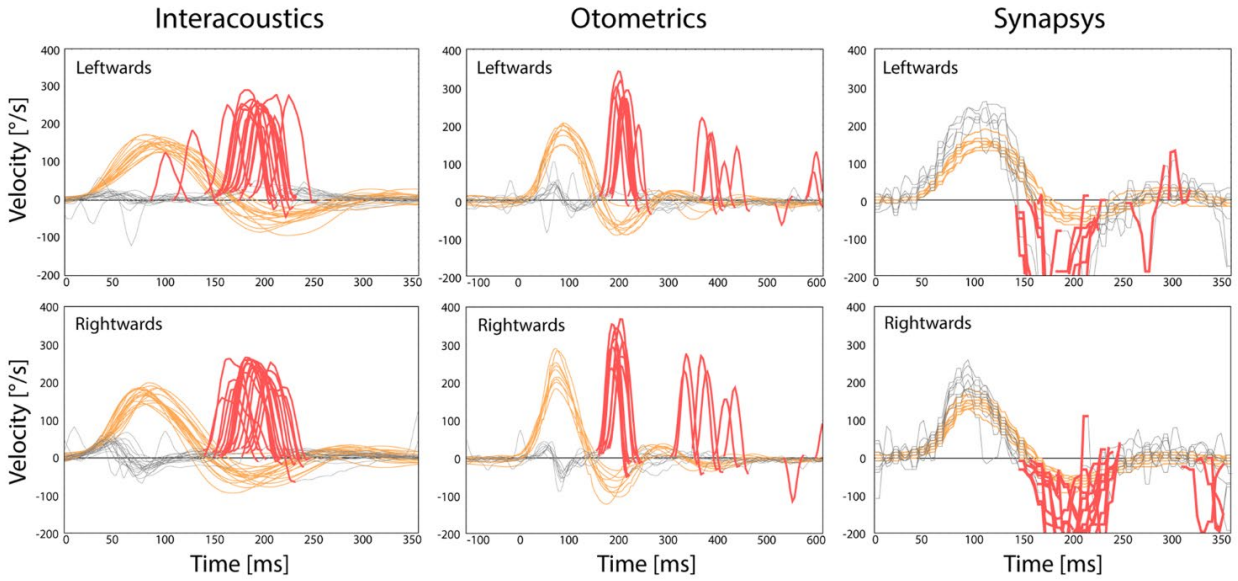

Figure 2. Raw eye and head movement data of one BV patient (patient 21), obtained by three different vHIT systems during three consecutive vHIT trials. Grey dotted lines represent eye movements, orange lines represent head movements, red lines represent saccades. Note that eye movements obtained with the Synapsys system have a different graphical representation. This is based on the fact that a space- fixed camera with a lower sampling rate was used, instead of a head- fixed camera

2. VOR gain and agreement of vHIT systems regarding BV diagnosis

Figure 3 illustrates that different VOR gains were obtained by different vHIT systems, within the same BV patients. There was a statistically significant difference between the three systems in VOR gains [$F(1.256, 33.916) = 35.681$, $p < 0.000$]. VOR gains obtained with the Synapsys system differed significantly from VOR gains obtained with the other two systems. No statistically significant difference was found in VOR gains between the Interacoustics and Otometrics system. Mean VOR gains of all patients were 0.33, 0.35 and 0.10 for Interacoustics, Otometrics and Synapsys system, respectively.

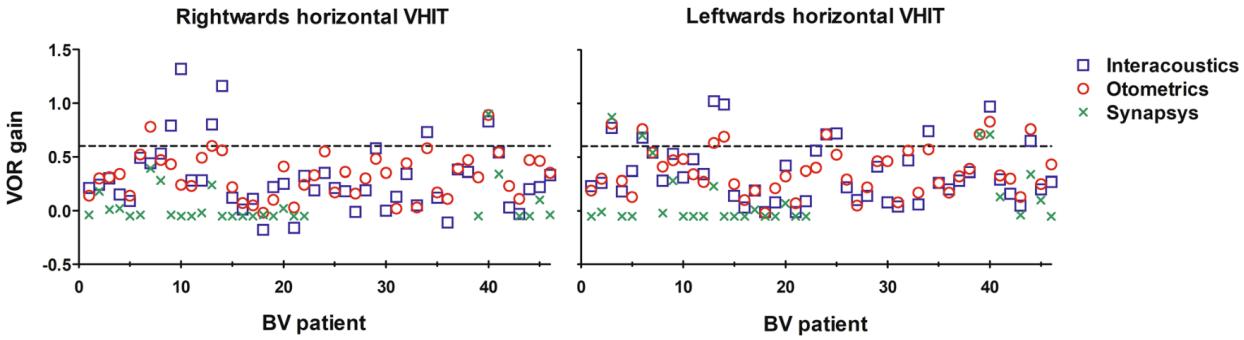

Figure 3. VOR gains for leftwards and rightwards horizontal vHIT separately, as tested with the different vHIT systems. Every symbol represents the VOR gain of one vHIT trial in one patient obtained with one vHIT system. The horizontal line at a VOR gain of 0.6 represents the cut-off value according to the BV criteria of

the Bárànу society. (8) *VOR gain in the Synapsys system differed significantly from VOR gain in the other two systems. No statistically significant difference was found in VOR gain between the Interacoustics and Otometrics system*

The vHIT systems agreed in 83% of the 46 patients on the BV diagnosis ("bilateral vestibulopathy" or "no bilateral vestibulopathy") according to the criteria of the Bárány Society (8). In eight patients (17%), no agreement was found (*Table 1*). These eight patients were diagnosed with BV resulting from various etiologies: ototoxic effects of gentamicin (n = 1) and chemotherapy (n = 1), bilateral Menière's disease (n = 1), post-infectious due to Lyme's disease, (n = 1) inherited (n = 1), and idiopathic (n = 3). In the 28 patients tested with all three vHIT systems, the percentage of agreement between the vHIT systems was 79% (68% BV, 11% no BV), and in 21% there was no agreement. The mean VOR gains obtained in these 28 patients were 0.36, 0.36 and 0.09 for Interacoustics, Otometrics and Synapsys respectively.

Table 1. Agreement of the vHIT systems regarding BV diagnosis, based on the VOR gain as calculated by the vHIT system. Horizontal VOR gain of < 0.6 was classified as "bilateral vestibulopathy", a VOR gain of ≥ 0.6 was classified as "no bilateral vestibulopathy". In case the vHIT systems showed a discrepancy in diagnosis of BV, the patient was classified as "no agreement". In 80% of the BV patients, all three vHIT systems diagnosed "bilateral vestibulopathy". In 20% no agreement on the diagnosis was found between the three vHIT systems within the same BV patient

Diagnosis according to vHIT results	**Number of patients**	**[%]**
Bilateral vestibulopathy	35	70
No bilateral vestibulopathy	5	10
No agreement	10	20

3. VOR gain and repetitive testing

No order effect was present, since no difference in VOR gain was found between the first and the last vHIT trials, regard- less of the system used for vHIT.

4. Peak head velocity

For every vHIT system, median peak head velocities with their interquartile range of all traces together from all patients are presented in *Table 2*. A significant difference in the velocity of the head impulses between the three systems was found ($p < 0.001$). Regarding the Synapsys system, significantly lower median peak head velocities (maximum 43°/s lower) and VOR gains (maximum 0.37 lower) were present than in the other two systems. Interacoustics and Otometrics did not significantly differ regarding VOR gain, only regarding median peak head velocity (maximum 11°/s).

Table 2. Median peak head velocities (with their first (Q1) and third quartile (Q3)) and median VOR gain (as calculated by the vHIT system) for rightwards and leftwards horizontal head impulses. There was a statistically significant difference in peak head velocities between the three systems. Both peak head velocity and VOR gain were lower in Synapsys than in the other two systems

	Rightwards horizontal vHIT			**Leftwards horizontal vHIT**		
vHIT system	**Peak head velocity**	**Q1 | Q3**	**VOR gain**	**Peak head velocity**	**Q1 | Q3**	**VOR gain**
Interacoustics	209	184 | 231	0.25	199	176 | 218	0.28
Otometrics	216	194 | 242	0.34	209	186 | 231	0.34
Synapsys	181	156 | 205	-0.04	166	135 | 194	-0.05

Peak head velocities were separately analyzed in the eight patients with "no agreement" on the diagnosis of BV according to the vHIT systems (*Figure 3*). In one out of the eight patients, the median peak head velocity of the given head impulses was significantly higher in the system with the lower VOR gain. This patient showed in the Interacoustics system a VOR gain of 0.74 with median peak head velocity of 196°/s (leftwards impulses) and a VOR gain of 0.73 with median peak head velocity of 214°/s (rightwards impulses), versus a VOR gain of 0.57 with median peak head velocity of 265°/s (leftwards impulses) and a VOR gain of 0.58 with median peak head velocity of 255°/s (rightwards impulses) in the Otometrics system.

In the other seven patients, no statistically significant difference in peak head velocities between vHIT systems was found, or the system with significantly higher (or lower) peak head velocities also measured higher (or lower, respectively) VOR gains in that patient (17).

5. Frequency and latency of covert saccades

According to the strict methods as described above, frequency of covert saccades could be analyzed in 34 patients, and latency of covert saccades in 20 patients. In this study, no statistically significant difference in the frequency of occurrence of covert saccades and in the latency of the first appearing covert saccade was found between the first and the last vHIT trials, regardless of the system (*Figure 4*).

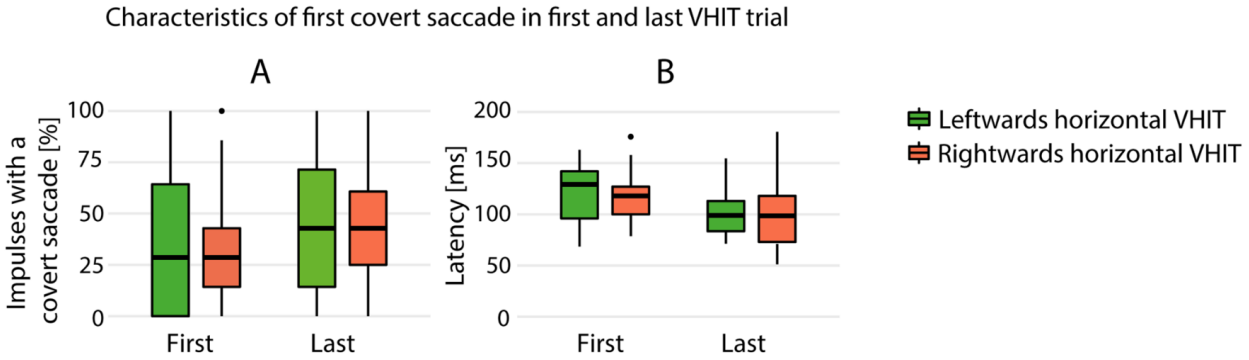

Figure 4. Characteristics of the first appearing covert saccade from the first seven artefact free traces of all patients together. A. The frequency of covert saccades (percentage of impulses with at least one covert saccade) in the first and last vHIT trial. B. Latency of the first covert saccade (the moment of onset of the saccade in milliseconds, start of head impulse is 0ms) in the first and last vHIT trial. No statistically significant difference was found within the characteristics between the first and the last vHIT trial regardless of the vHIT system (Interacoustics, Otometrics or Synapsys)

Discussion

This study compared the VOR gains obtained with three commercially available vHIT systems (Interacoustics, Oto- metrics and Synapsys) in a large group of BV patients. In 83% of the patients the vHIT systems agreed on the diagnoses of BV, when using a cut-off horizontal VOR gain of < 0.6 (8). Additionally, while VOR gains did not significantly differ between the Interacoustics and Otometrics system, they both significantly differed from VOR gains obtained with the Synapsys system.

The fact that agreement between vHIT systems on BV diagnosis was present in 83% of the cases implies that in 17%, no agreement was present. This is suboptimal for diagnostic devices used in clinical setting. It would be preferred to further investigate the origin of these differences in outcome between vHIT systems, to improve the diagnostic pathway in BV patients. The origin might have (partially) resulted from inherent differences in the vHIT systems themselves, e.g. differences in eye and head tracking, and/ or VOR gain calculation. This has been described before in healthy subjects, but this is the first study that shows the possible significant impact on the diagnosis of BV (5,6). It has been hypothesized that mainly the differences in VOR gain calculation algorithm are responsible for the VOR gain differences (van der Lans, manuscript in preparation). After all, especially in BV patients, the transfer function of the VOR is often not linear, and the appearance of covert saccades might interfere with VOR gain calculation. This implies that VOR gain outcomes are very sensitive to pre-processing (e.g. desaccading) and interpretation of the traces by the VOR gain calculation algorithm. To overcome some of these challenges, the Suppression Head Impulse Test (SHIMP) was proposed, that might decrease the amount of covert saccades and better show the residual vestibular function (18,19). However, this paradigm still depends on the VOR gain calculation algorithm, and its clinical relevance in BV is yet to be determined (van Dooren, manuscript in preparation). Generally, it seems therefore necessary that vHIT systems are standardized regarding eye and head tracking methods and VOR gain calculation algorithms, to improve proper diagnosis of BV. If this is not possible, it could be investigated whether vHIT system-specific cut-off values to diagnose BV are a possibility to increase agreement between vHIT systems. Nevertheless, it remains important to not only assess VOR gain, but also the raw traces and compensatory saccades. In addition, BV is diagnosed using a combination of symptoms and several vestibular tests (caloric test, rotatory chair test, vHIT). Since these vestibular tests are complementary, only performing vHIT might not be enough to rule out BV (8,20).

In this BV population, outcomes of the Synapsys system differed significantly from the other two vHIT systems: Synapsys showed a lower VOR gain than Interacoustics and Otometrics (*Figure 3*). This could (partially) be explained by differences in gain calculation algorithms, different eye- and head tracking methods (Synapsys uses a space-fixed camera, the other two systems use a camera fixed to a pair of goggles), or differences in sampling frequency (Synapsys uses a lower sampling frequency of 100 Hz, compared to 220 Hz and 245 Hz for Interacoustics and Otometrics, respectively). Furthermore, during visual inspection the Synapsys system showed less smooth eye velocity traces, and more missing values than Interacoustics and Otometrics (*Figure 2*). However, when the Synapsys system considered a patient "no BV" (VOR gain ≥ 0.6), this was always in agreement with both of the other two systems. Nevertheless, the other way around ("BV" with Synapsys and "no BV" in the other two systems) also occurred. It is unknown whether this was a systematic mistake of the Synapsys system, or whether Synapsys was the only system that was able to best detect BV in the high-frequency range of this population. This question was beyond the scope of this article, but could be addressed in the future.

When observing differences in VOR gains between different vHIT systems and vHIT trials, it is very important to first rule out measurement artefacts, like clinically relevant differences in peak head velocities, the order effect, and differences in frequency and latency of covert saccades that could influence the VOR gain calculations (5,14,20). Regarding differences in peak head velocities, a higher peak head velocity might result in lower VOR (17). However, in contrast to these findings, the system with significantly lower median peak head velocities during vHIT trials (Synapsys), also showed the lowest VOR

gains in this study. Therefore, it is very unlikely that differences in peak head velocity between Synapsys and the other vHIT systems might have caused most of the VOR gain differences between vHIT systems in this study. The statistically significant difference in median peak head velocities between vHIT trials of Interacoustics and Otometrics was only small (11°/s difference), and, therefore, probably not influenced the (not significant) VOR gain differences between the two systems (17). Regarding the order effect and the frequency and latency of covert saccades, VOR gains and covert saccades did not show differences in this BV population with repetitive testing. This is in agreement with previous studies on healthy subjects and patients with vestibular dysfunction (7,21). Therefore, it can be concluded that it is very unlikely that measurement artefacts like the order effect or covert saccades could explain the significant differences in VOR gains found between the three vHIT systems in this study.

Limitations

In patients with low VOR gains, biphasic eye movement artefacts can occur at the beginning of head impulses, when using a head-mounted vHIT system (e.g. *Figure 2*, eye movements obtained during rightward impulses with Interacoustics and Otometrics system). This might lead to erroneous higher VOR gains, especially when using the instantaneous gain calculation method (Interacoustics) compared to the area under the curve gain calculation method (Otometrics) (14). This type of artefact was not specifically addressed in this study. Since VOR gains obtained with the Interacoustics and Otometrics systems did not significantly differ in this study, comparison of these two systems was most likely not compromised by this artefact. However, it cannot be ruled out that this artefact might (partially) explain some of the relatively lower VOR gains in the Synapsys system.

Conclusion

To conclude, using different vHIT systems in the same BV patient can lead to clinically significant differences in VOR gain, when using a cut-off value of 0.6. This might hinder proper diagnosis of BV patients. It would, therefore, be preferred that vHIT systems are standardized regarding eye and head tracking methods, and VOR gain calculation algorithms. Until then, it is advised to not only take the VOR gain in consideration when assessing a vHIT trial, but also look at the raw traces and the compensatory saccades.

Author contributions

Design of the work: HK, RB. Acquisition: FL. Analysis: TD, DS, BV, AJ. Interpretation: TD, NG, AP, VV, HK, RB. Revising the work: TD, DS, FL, AJ, NG, AP, VV, HK, RB. Final approval of the version to be published: TD, DS, FL, BV, AJ, NG, AP, VV, HK, RB. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: TD, DS, FL, BV, AJ, NG, AP, VV, HK, RB.

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Chapter IV

Bilateral vestibulopathy and age: experimental considerations for testing dynamic visual acuity on a treadmill

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Abstract

Introduction: Bilateral vestibulopathy (BVP) can affect visual acuity in dynamic conditions, like walking. This can be assessed by testing Dynamic Visual Acuity (DVA) on a treadmill at different walking speeds. Apart from BVP, age itself might influence DVA and the ability to complete the test. The objective of this study was to investigate whether DVA tested while walking, and the drop-out rate (the inability to complete all walking speeds of the test) are significantly influenced by age in BVP-patients and healthy subjects.

Methods: Forty-four BVP-patients (20 male, mean age 59 years) and 63 healthy subjects (27 male, mean age 46 years) performed the DVA test on a treadmill at 0 (static condition), 2, 4 and 6 km/h (dynamic conditions). The dynamic visual acuity loss was calculated as the difference between visual acuity in the static condition and visual acuity in each walking condition. The dependency of the drop-out rate and dynamic visual acuity loss on BVP and age was investigated at all walking speeds, as well as the dependency of dynamic visual acuity loss on speed.

Results: Age and BVP significantly increased the drop-out rate ($p \leq 0.038$). A significantly higher dynamic visual acuity loss was found at all speeds in BVP-patients compared to healthy subjects ($p < 0.001$). Age showed no effect on dynamic visual acuity loss in both groups. In BVP-patients, increasing walking speeds resulted in higher dynamic visual acuity loss ($p \leq 0.036$).

Conclusion: DVA tested while walking on a treadmill, is one of the few "close to reality" functional outcome measures of vestibular function in the vertical plane. It is able to demonstrate significant loss of DVA in bilateral vestibulopathy patients. However, since bilateral vestibulopathy and age significantly increase the drop-out rate at faster walking speeds, it is recommended to use age-matched controls. Furthermore, it could be considered to use an individual "preferred" walking speed and to limit maximum walking speed in older subjects when testing DVA on a treadmill.

Introduction

The vestibular system has two sets of peripheral organs that detect head accelerations and tilt. One of their main functions is to facilitate gaze stabilization. This is made possible to a large extent by a reflex from the vestibular organs to the eyes, called the vestibulo-ocular reflex (VOR) (1). The VOR generates eye movements in the opposite direction of the head movements, stabilizing the eyes in space during head movements. As a result, the image of the environment remains stable on the retina while in movement.

In bilateral vestibulopathy (BVP), the vestibular function is reduced or absent on both sides (2). This is a heterogeneous disorder in which the VOR, among other vestibular functions, is impaired (3). It can lead to insufficient gaze stabilization, resulting in "blurred" vision during head movements, also known as "oscillopsia". Oscillopsia is, next to imbalance, one of the main symptoms of BVP (2,4–6). BVP also has a strong negative impact on quality of life and social participation; many BVP-patients suffer from a constant psychological burden caused by fear of falling, decreased activity levels, and social isolation (2,4,5).

One way to quantify the functional outcome of gaze stabilization, is to test Dynamic Visual Acuity (DVA). DVA reflects the ability of the eyes to distinguish fine details in static objects during head movements (7). DVA is often tested by comparing the visual acuity in a static condition (i.e. without head movements) to the visual acuity in a dynamic condition (i.e. with head movements). The loss of visual acuity in dynamic conditions (DVAL) is mostly used as outcome measure. Apart from being a functional outcome of the VOR, it also reflects the function of the visual, oculomotor, and vestibular system. That is why not all BVP-patients suffer from oscillopsia: other systems might compensate for the loss of VOR, such as otolith outputs (8,9), automatic spinal locomotor programs (10), or compensatory walking strategies, e.g. reduction of walking speed or stride length (11). The DVA can be tested in several ways, varying from passive head movements in an office chair, to walking on a treadmill (12–14). For the latter, Guinand et al.(12) demonstrated a rise in test sensitivity for BVP with increasing locomotor speed: from 76% at 2km/h to 97% when combining 2,4, and 6 km/h.

It was previously reported that depending on the test protocol, up to 22% of BVP-patients were not able to complete the DVA test on a treadmill (drop-out), since they could not walk at the test speeds (12). This increase in drop-out rate might have important implications when DVA while walking is considered as an outcome measure for therapeutic interventions, such as a vestibular implant (15). However, age on its own, or in combination with BVP, has not yet been taken into account in previous studies, despite evidence of age related differences in gait variability and stability among healthy adults (16–19). Furthermore, age might also influence DVA. For example, it has recently been demonstrated that DVA during self-generated side to side head movements remains stable in healthy individuals aged 3 to 49 years, but starts to decline at the age of 50 (20). Therefore, age might significantly impact the feasibility of the DVA test on a treadmill. This might be important when investigating DVA in BVP, since BVP is more often seen at older ages: most patients are between 50-70 years old (21).

The objective of this study was to investigate the effects of BVP and age when testing DVA on a treadmill. For this, DVA's of BVP-patients and healthy subjects were evaluated on a treadmill at different speeds. It was hypothesized that BVP and age could significantly influence the drop-out rate and DVA, which might decrease the feasibility of the test in the BVP population.

Methods

Participants

Participants were recruited at a tertiary referral center (Maastricht UMC+) between June 2016 and December 2018. Inclusion criteria for BVP-patients were in accordance with the Diagnostic criteria Consensus document of the Classification Committee of the Bárány Society (22): a horizontal angular VOR gain on both sides <0.6 (angular head velocity 150–300◦/s) and/or summated slow phase velocity of nystagmus of less than 6°/s on each side during bithermal caloric tests (30 and 44°C, 300ml in 30 seconds) and/or a horizontal angular VOR gain <0.1 upon sinusoidal stimulation on a rotatory chair (0.1 Hz, Vmax=50◦/sec) and/or a phase lead >68 degrees (time constant of <5 seconds). In addition, patients needed to be older than 18 years old. Patients unable to stop medication against anxiety or depression one week before testing, were excluded from the study, as well as those suffering from peripheral neuropathy of the lower extremities.

Healthy subjects were recruited via posters in the hospital and among families and friends of the researchers. A questionnaire was used to rule out, as much as possible, any deficits or diseases that could influence the vestibular system. It comprised the following topics: previous medical history (including otorhinolaryngological, neurological, ophthalmological); use of any medication; known balance problems, recent neck trauma or dizziness in the past six months.

All participants were excluded from the study if they were unable to walk on the treadmill at 2 km/h or had a vision of -4.0 Diopter or lower (without correction), in which they could not read the first line of the optotypes on the computer screen. In some cases, BVP-patients were allowed to hold handrails of the treadmill to prevent falling (10 BVP-patients). The use of alcohol or other stimulants was forbidden in the 24 hours before examination.

Evaluating age effect on the vestibular function in BVP-patients

The potential effect of age on vestibular function in BVP-patients (which could affect drop-out rate and DVA) was assessed using outcomes from two tests: the video Head Impulse Test (vHIT, ICS Impulse, GN Otometrics; Taastrup, Denmark) and the caloric test using bithermal (30° and 40° Celcius) irrigations of water. vHIT gains were calculated for the leftward and rightward directions in the lateral plane, and for the upward and downward directions in right anterior – left posterior and left anterior – right posterior planes. The sum of bithermal maximum peak slow phase velocities (SPV) of the nystagmus was used as outcome measure of the caloric test, calculated separately for each side.

Testing DVA on a treadmill

Sloan optotypes (C, D, H, K, N, O, R, S, V and Z) projected on a computer screen were used to test visual acuity. The computer screen was placed at eye level and at 2.8m from the subject. A Sloan letter was presented on a computer screen (LG 24bk55 24’’), using a custom program written in Matlab R2010a (The Mathworks, Natick, MA, USA). The program randomly showed five letters in a single-letter sequence at one logarithm of the Minimum Angle of Resolution (logMAR). If a minimum of two out of five letters were correctly recognized, the letter size decreased by 0.1 logMAR and five new letters were shown, one after another. If less than two out of five letters were recognized, the procedure was stopped.

The visual acuity of all BVP-patients and healthy subjects was tested in two conditions: static and dynamic. Static visual acuity was measured when the subject was standing still on the treadmill (1210 model, SportsArt, Inc., Tainan, Taiwan). Visual acuity in dynamic conditions was measured while walking on the treadmill at different speeds (2, 4, 6 km/h, non-randomized). The study procedure ended either when all walking speeds were completed, or when subjects could not walk at a higher speed. If subjects were not able to complete the test at a specific walking speed, they were considered as a "drop-out" for that walking speed. To ensure the subject's safety, a safety string was clipped to the subject's waist that was connected to the emergency brake of the treadmill.

Data analysis and statistics

Visual acuity in static and dynamic conditions was calculated as: $LogMAR = 0.1 + LogMAR_x - 0.02 \cdot y$ (23), where "*x*" was defined as the last optotype line in which two or more letters were read correctly and "y" was defined as the number of correctly read letters at that line.

DVAL was defined as the difference between visual acuity in the static condition and the dynamic conditions. Note that a negative DVAL indicates poorer vision in the tested dynamic condition compared to the static condition. Descriptive statistics were made for age and DVAL. The independent sample t-test was used to compare mean age between groups.

To evaluate whether holding the treadmill handrails affected DVAL, an independent t-test was used to assess whether a difference in mean DVAL existed between patients who held the treadmill handrails and patients who did not hold the treadmill handrails. Obtained p-values were Bonferroni corrected.

The potential effect of age on vestibular function in BVP-patients was analyzed using linear regression analyses. Each model contained age as an independent variable and the corresponding outcome (gain or SPV) as a dependent variable.

Since drop-out at the speed of 4 and 6 km/h was perfectly correlated (e.g. drop-out at 4 km/h excluded successful completion of the test at 6 km/h), multilevel logistic regression of drop-out (yes or no) on speed, age and group (BVP-patients or healthy subjects) failed (multicollinearity). Therefore, a new dependent variable reflecting the missing pattern was formed using the following criteria: pattern 1 – no drop-out at all speeds, pattern 2 – drop-out at 6 km/h, and pattern 3 – drop-out at 4 and 6 km/h. Then multinomial logistic regression was performed to determine the dependency of drop-out on group and age.

To analyze the effect of age and speed on DVAL, while accounting for the dependence among measurements of the same participant, a linear-mixed effects model was applied. Initially, age, group, speed, and all their two-way interactions were included as fixed factors. Then, the non-significant interactions were removed by backward selection. Finally, age, group, speed and group by speed interaction were left in the model. Pairwise comparisons were made per group to compare DVAL at 2, 4, and 6km/h. Pairwise comparisons were also made per speed to compare DVAL in BVP-patients and healthy subjects. The significance level, alpha, was set to 0.05. In case of multiple comparisons, p-values were Bonferroni corrected. Data were analyzed in R (v.3.5.2) and SPSS (v.25).

Ethical considerations

This study was in accordance with the Declaration of Helsinki (amended version 2013) Approval was obtained by the ethical committees of Maastricht University Medical Centre (NL52768.068.15 / METC 151027). All participants provided written informed consent prior to the study.

Results

Participants

Forty-four BVP-patients (20 male, mean age 59 years, standard deviation 11 years) and 63 healthy subjects (27 male, mean age 46 years, standard deviation 20 years) were included in this study. Although mean age was significantly higher in BVP-patients ($p<0.001$), ages of 60% of the healthy subjects were equally distributed within the age range of the tested BVP-patients (41-83 years). Age characteristics of both groups are presented in *Table 1*. Etiologies of BVP comprised: gentamicin treatment (n=5), vancomycin (n=1), amikacin (n=1), chemotherapy (n=1), Herpes infection (n=1), meningitis (n=3), Hashimoto's disease (n=1), renal failure (n=1), Meniere's Disease (n=4), sequential acute unilateral vestibulopathy (n=1), and genetic (n=5). The etiology remained idiopathic in 20 subjects. In BVP-patients no significant age effect was found on the outcomes of the vHIT and caloric test ($p\geq0.161$).

Table 1. Age characteristics of the tested groups. The number of participants is shown per age group for both BVP-patients and healthy subjects

	Age group (years)					
	19-30	31-40	41-50	51-60	61-70	71-83
BVP-patients	1	0	9	14	16	4
Healthy subjects	23	2	10	10	10	8

Drop-out

Not all BVP-patients and healthy subjects were able to complete the DVA test at each walking speed, which resulted in dropping-out. The drop-out rate per group, walking speed, and age decade is presented in *Figure 1*. Age significantly increased the odds of dropping-out at 6 km/h (odds ratio=1.12, $p<0.001$), and both age and BVP increased the odds of dropping-out at 4 km/h, and consequently at 6 km/h (Age: odds ratio=1.15, $p=0.008$; BVP: odds ratio=12.40, $p=0.038$).

Dynamic Visual Acuity Loss

DVAL was significantly lower in BVP-patients at all walking speeds ($p<0.001$) (*Figure 2*). Neither age ($p=0.399$) nor speed ($p\geq0.258$) had a significant effect on DVAL in the group of healthy subjects. In the group of BVP-patients only speed ($p\leq0.036$) significantly influenced DVAL: it decreased with an increase of speed. There were no significant differences in DVAL across speeds in patients who did and did not hold the treadmill handrails ($p\geq0.29$).

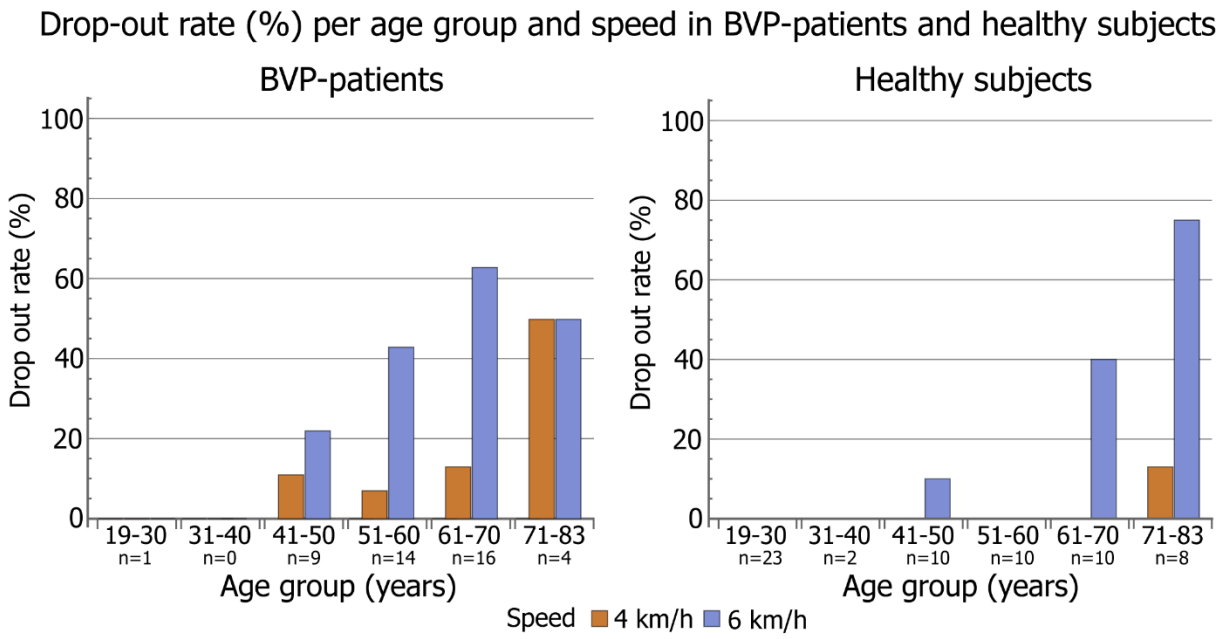

Figure 1. Drop-out rate (%) in BVP-patients (left) and healthy subjects (right) per age group and speed

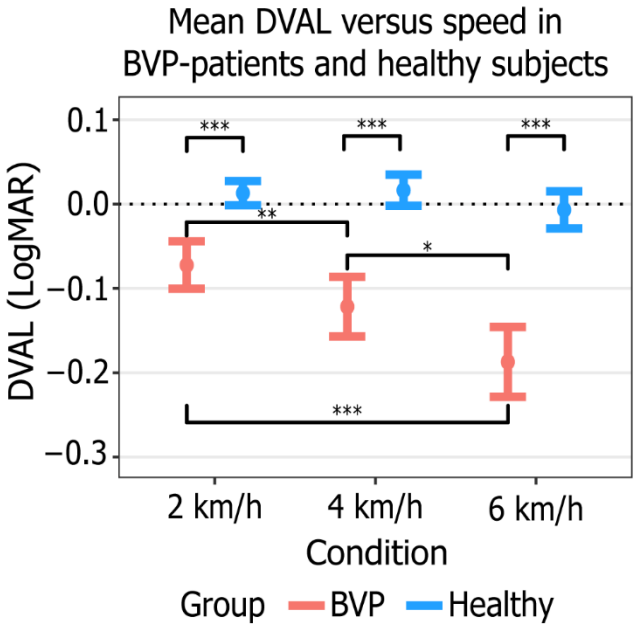

Figure 2. Mean DVAL versus speed in BVP-patients (red) and healthy subjects (blue). DVAL was calculated as the decline in logMAR between VA_{static} and $VA_{dynamic}$. Therefore, a negative DVAL value indicates poorer vision while walking on the treadmill, compared to standing still. Error bars represent 95% confidence interval. Three asterisks (***) indicate p<0.001, two asterisks (**) indicate p<0.01, one asterisk (*) indicates p<0.05

Discussion

This study investigated the drop-out rate and DVA of BVP-patients and healthy subjects. BVP and age were hypothesized to significantly influence the drop-out rate and DVA obtained in both groups. It was demonstrated that both BVP and age, significantly increased the drop-out rate in both groups at the speed of 4km/h or higher. Regarding DVA, only BVP (not age), significantly decreased DVA in the subjects who were able to walk on the treadmill. Furthermore, DVA significantly decreased with higher walking speeds only in BVP patients. To our knowledge, this study has the largest group of BVP patients in which the influence of BVP and age on the drop-out rate and DVA was tested on a treadmill (12,14).

A higher drop-out rate in both BVP patients and healthy subjects with increasing age and walking speed could be explained by an age-related multisensory decline of the systems involved in maintaining posture and gait (24–26). In the group of healthy subjects, this might also include presbyvestibulopathy: an age-related decline of the vestibular function (27). Since BVP mostly occurs at older ages, and BVP-patients are often unable to walk at speeds higher than 5 km/h (21,26,28), it might be questioned whether testing DVA at fixed speeds on a treadmill would be a reasonable outcome measure for vestibular rehabilitation of BVP-patients in a research setting. However, testing DVA while walking is only one of the few "close to reality" functional outcome measures of vestibular function in the vertical plane (12). It could therefore be proposed to individually adjust the walking speed for each patient, using their "preferred" walking speed. In older subjects on group level, the preferred walking speed range would probably be between 2 km/h and (below) 6 km/h. After all, mean DVA is already significantly reduced at 2km/h (12), the self-selected walking speed for patients with vestibular dysfunction is about 3km/h (29,30), and at 6km/h both healthy subjects and BVP patients above 40 years old show a significantly increased drop-out rate. The use of a preferred walking speed was already successfully demonstrated in BVP-patients fitted with a prototype vestibular implant (31). Nevertheless, other possible functional outcome measures could also be hypothesized which do not involve walking. For instance, testing DVA with actively generated head movements while sitting on a chair (20) or the functional head impulse test (32). However, it should be taken into account that each specific way of testing DVA examines (to a certain extent) different parts, sensitivities and mechanisms of the vestibular system: e.g. the semicircular canals, otolith organs, low- and high-frequency sensitivity, and compensatory strategies. This has already been revealed by the lack of correlation between outcomes of the DVA test on a treadmill, and the functional head impulse test (33).

Conflicting evidence exists regarding the effect of age on DVA when tested on a treadmill in healthy subjects. One previous study described a significant age effect on DVA at only 4km/h (not at 3, 6, and 9 km/h) (14), while another study found a significant age effect at 4 and 6 km/h (12). The present study did not find any effect of age on DVA. This might partially be explained by different inclusion criteria used for the group of healthy subjects; Verbecque et al.(14) used a questionnaire and age-specific static balance testing, Guinand et al.(12) used the Video Head Impulse Test, and this study used a questionnaire to rule out (as much as possible) any deficits or diseases that could influence the vestibular system. Furthermore, the different statistical analyses and testing paradigms, including the used optotype charts and DVA cut-off values, could contribute to the conflicting evidence. Nevertheless, the findings of this study do not rule out any age effect, since the DVA in the group of subjects who dropped-out, remains unknown. Furthermore, DVA tested during self-generated side to side head movements significantly declines from

the age of 50 (20). Therefore, taking the drop-out rate and the evidence regarding age effect into account, it would be recommended to use age-matched controls when testing DVA in research settings and to limit maximum walking speed for older subjects (e.g. below 6km/h).

BVP-patients showed, on group level, worse DVA than healthy subjects at all walking speeds. This finding is congruent with previously described results (12). In addition to impaired vestibular function, this DVA decrease might (partially) be induced by attention deficits (34) or the inability to correctly perform dual-tasks, which can be present in BVP-patients (35). However, DVA overlapped between BVP-patients and age-matched controls. This can be explained by multiple factors. First, the DVA is a functional outcome of a multisensory system. Input from the visual, vestibular and oculomotor systems is centrally processed, which facilitates adaptation and compensation mechanisms. An example of such a compensation mechanism is minimizing head movements to improve gaze stabilization. Secondly, DVA can be trained. It has been shown that vestibular rehabilitation exercises facilitate the recovery of gaze during head movements in BVP-patients (36). Furthermore, in patients with unilateral peripheral vestibulopathy, covert saccades can improve DVA (37,38). Thirdly, during the DVA test on a treadmill, (partially) active movements are made. These active movements are less useful in discriminating between BVP-patients and healthy subjects, as compared to passive movements (13,39). In addition, during stereotyped locomotion, feed-forward signals from an efference copy of the locomotor commands suppress the VOR in the vertical plane, which can mediate gaze stabilization (40). Finally, walking speed affects gait parameters in BVP-patients (26). All these factors imply that the DVA test on a treadmill should mainly be used to evaluate the functional status of the vestibular system.

Limitations of the study

In contrast to previous studies (12,14) only a questionnaire was used to determine whether a subject was healthy or not. None of the vestibular tests like the Video Head Impulse Test or caloric test were performed in healthy subjects. It cannot be ruled out that results of the healthy subjects might have been influenced by factors like presbyvestibulopathy or asymptomatic vestibulopathies. This could mainly imply that the effects of BVP on drop-out and DVA found in this study, might be underestimated. Height of the participants was not measured, which could affect stride length and therefore head movement amplitude and, consequently, DVA. Furthermore, statistical power in the highest age groups was small due to the high drop-out rate. It can therefore only be stated that DVA was not significantly influenced by age in BVP-patients and healthy subjects who were able to walk at the tested speeds. The DVA of subjects who were unable to walk could not be determined using the treadmill test.

Conclusion

DVA tested while walking on a treadmill, is one of the few “close to reality” functional outcome measures of vestibular function in the vertical plane. It is able to demonstrate significant loss of DVA in bilateral vestibulopathy patients. However, since bilateral vestibulopathy and age significantly increase the drop-out rate at faster walking speeds, it is recommended to use age-matched controls. Furthermore, it could be considered to use an individual “preferred” walking speed and to limit maximum walking speed in older subjects when testing DVA on a treadmill.

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Chapter V
Optimised signal analysis to quantify the non-linear behavior of the electrically evoked vestibulo-ocular reflex in patients with a vestibular implant

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Abstract

Introduction: Different eye movement analysis algorithms are used in vestibular implant research to quantify the electrically evoked vestibulo-ocular reflex (eVOR). Often standard techniques are used as applied for quantification of the natural VOR in healthy subjects and patients with vestibular loss. However, in previous research we observed that the morphology of the VOR and eVOR may differ substantially. In this study we investigated if the analysis techniques for eVOR need to be adapted to optimise a truthful quantification of the eVOR (VOR gain, orientation of the VOR axis, asymmetry, and phase shift).

Methods: "Natural" VOR responses were obtained in six age-matched healthy subjects and eVOR responses were obtained in eight bilateral vestibulopathy patients fitted with a vestibular implant. Three conditions were tested: "nVOR" 1 Hz sinusoidal whole-body rotations of healthy subjects in a rotatory chair; "eVOR" 1 Hz sinusoidal electrical vestibular implant stimulation without whole-body rotations in bilateral vestibulopathy patients, and "dVOR" 1 Hz sinusoidal whole body rotations in bilateral vestibular patients using the chair mounted gyroscope output to drive the electrical vestibular implant stimulation (therefore also in sync 1 Hz sinusoidal). VOR outcomes were determined from the obtained VOR responses, using three different eye movement analysis paradigms: 1) peak eye velocity detection using the raw eye traces; 2) peak eye velocity detection using full-cycle sine fitting of eye traces; 3) peak eye velocity detection using half-cycle sine fitting of eye traces.

Results: The type of eye movement analysis algorithm significantly influenced VOR outcomes, especially regarding the VOR gain and asymmetry of the eVOR in bilateral vestibulopathy patients fitted with a vestibular implant. Full-cycle fitting lowered VOR gain in the eVOR condition (mean difference: 0.14 ± 0.06 CI95%, p = 0.018). Half-cycle fitting lowered VOR gain in the dVOR condition (mean difference: 0.08 ± 0.04 CI95%, p = 0.009). In the eVOR condition half-cycle fitting was able to demonstrate the asymmetry between the excitatory and inhibitory phases of stimulation in comparison with the full-cycle fitting (mean difference: 0.19 ± 0.12CI95%, p = 0.024). VOR axis and phase shift did not differ significantly between eye movement analysis algorithms. In healthy subjects no clinically significant effect of eye movement analysis algorithms on VOR outcomes was observed.

Conclusion: For the analysis of the eVOR, the excitatory and inhibitory phases of stimulation should be analyzed separately due to the inherent asymmetry of the electrically evoked VOR. A half-cycle fitting method can be used as a more accurate alternative for the analysis of the full cycle traces.

Introduction

Bilateral vestibulopathy can lead to a bilaterally reduced or absent function of the vestibular organs, often, among others, resulting in a loss of visual acuity during head motions and severely impaired imbalance. Current treatment options for this disabling disease (1) are scarce and results are limited (2). A promising non-invasive treatment by a balancebelt has recently be introduced and improves balance significantly, but seems to offer no solution for the reduced dynamic visual acuity (3). However, another promising but invasive treatment, the vestibular implant (VI), has been proposed over the last years and feasibility was demonstrated (4–7). The concept of the VI is to convert head movement information into a modulated electrical signal and deliver it to the vestibular nerve afferents via implanted electrodes (8). In order to objectively validate the contribution of the vestibular implant, the vestibulo-ocular reflex (VOR) is detected by Video-Oculography (VOG) and quantified (9–11). In healthy subjects this reflex moves the eyes in the direction opposite to the head movement, thereby keeping gaze stable. In patients with bilateral vestibulopathy, the VOR is severely reduced or absent, which is generally believed to result in blurred vision during head movements (12). It has been demonstrated that the VI is an effective way to electrically evoke the VOR (eVOR), replacing the physiological signal of the non-functional vestibular system (10,11). However, at head impulses with high head peak velocities (> 100 °/sec) a single healthy vestibular organ has an asymmetric response to different head movement directions (2nd Law of Ewald), with better gain in the excitatory direction (motion towards the stimulated ear) than in the inhibitory direction (motion away from the stimulated ear) (13). Therefore, contribution from both symmetrically orientated vestibular organs is required at higher head peak velocities to produce symmetric responses in all head movement directions. Current VI trials involve unilateral implantation/stimulation, thus mimicking the “asymmetrical” unilateral vestibular function (14). Consequently, one can expect the electrically evoked VOR to also show this asymmetry with higher gains for the excitatory stimulation.

Main outcome measures to assess the eVOR are (10,11): VOR gain (the ratio of eye velocity to head velocity), VOR asymmetry (ratio of VOR gain during excitation and VOR gain during inhibition), VOR axis in 2D (eye movement direction with respect to the horizontal eye velocity), and phase shift (the lag or lead of the eye response relative to the stimulus). However, derivation of these outcomes from the raw eye movement traces is hindered mainly by non-linearity of the eVOR response and artefacts appearing during pupil detection with an eye tracking and recording system (10). Therefore, adapted eye movement analysis algorithms have to be applied for a more accurate evaluation of the eVOR responses.

For conditions with VI stimulation using sinusoidally modulated electrical signals, different eye movement analysis algorithms were previously used in VI-research: 1) peak eye velocity detection using the raw eye traces without assuming a sinusoidal (linear) response; 2) peak eye velocity detection using full-cycle sine fitting of eye traces; 3) peak eye velocity detection using half-cycle sine fitting of eye traces (10,11). The advantage of raw eye trace analysis is the fact that no assumptions are made about the “true” shape of the eVOR response. In case of full-cycle and half-cycle sine fitting, the raw eye traces are fitted a sine curve (11), which facilitates analysis of small and noisy responses. Although all three type of algorithms allowed the demonstration of the possibility to restore the VOR with a VI (10,11), it remains to be determined how the different analysis algorithms affect the objective eVOR outcome measures (gain, asymmetry, VOR axis and phase shift). This issue is important to appropriately compare VOR outcome measures between studies and research groups.

The aim of this study was to investigate the influence of the three previously used eye movement analysis algorithms on the main VOR outcome measures (VOR gain, VOR axis, asymmetry, and phase shift).

Material and methods

Study design

Eye movement traces of electrically evoked VOR responses obtained in bilateral vestibulopathy patients fitted with a VI and traces of "natural" VOR responses obtained in healthy subjects were analysed in this study. These eye movement traces have been already presented in previous studies (10,11). Three different eye movement analysis algorithms (peak eye velocity detection using 1) the raw eye traces; 2) full-cycle sine fitting of eye traces, and 3) half-cycle sine fitting of eye traces; see below) were used to determine the main VOR outcome measures (gain, asymmetry, VOR axis, and phase shift). Results of these outcome measures were then compared.

Test conditions and eye movement recording

Eye movements were recorded during sinusoidal horizontal whole-body rotations elicited by a rotatory chair, at a frequency of 1Hz and with a peak angular velocity of 30 deg/s. All trials were conducted in complete darkness and lasted 60 seconds starting and ending abruptly. Eye movements of the dominant eye were recorded using the EyeSeeCam system (EyeSeeTec, Munich, Germany) equipped with infra-red camera with a frame rate of 220Hz. Experiments were conducted on healthy volunteers (nVOR) and on VI patients. Eye movements of VI patients were recorded in two different conditions: (1) a "static" condition while the patient was sitting on a fixed chair (not moving - eVOR) and (2) a "dynamic" condition where the patient was sitting in the rotatory chair and thus experiencing whole body rotations (dVOR). During these two conditions, VI patients were receiving electrical signals on one of the implanted vestibular electrodes (see below for details on the electrical stimulation paradigm). In both cases, the electrical stimulation was modulated by the angular velocity of the chair, captured with a motion sensor fixed on it.

Test subjects

Six healthy subjects with no history for vestibular disorders, three males and three females, with no vestibular symptoms and no prior history of vestibular disorders were included. Their mean age was 63 ± 4 SD years. Data from eight VI patients was available for the analysis in the eVOR condition. Data from five VI patients was available for the analysis of eye movements in the dVOR condition. All patients were implanted on one ear with a VI prototype (MED-EL, Innsbruck, Austria) (10,11,15). Detailed characteristics of the healthy subjects and the VI patients are presented in *Table 1*. An example of raw eye velocity traces of three tested subjects is presented in *Figure 1*. All traces are shown in *Supplementary Figure 1*.

Table 1. Characteristics of the healthy subjects (HL) and the VI patients including electrical stimulation parameters and the test condition. (BV = bilateral vestibulopathy, AM = amplitude modulation, LAN – lateral ampullary nerve, SAN – superior ampullary nerve, PAN – posterior ampullary nerve)

Tested subject	Sex	Age, years	Aetiology	Surgical approach (16)	Stimulated electrode	Side of implantation	Baseline and modulation amplitude, μA	Test conditions
HL1	F	62	-	-	-	-	-	nVOR
HL2	F	60	-	-	-	-	-	nVOR
HL3	M	62	-	-	-	-	-	nVOR
HL4	F	69	-	-	-	-	-	nVOR
HL5	M	59	-	-	-	-	-	nVOR
HL6	M	66	-	-	-	-	-	nVOR
BV1	F	67	DFNA-9	Intra-labyrinthine	LAN	Left	325 ± 75	eVOR
BV2	M	71	Menière's Disease	Extra-labyrinthine	PAN	Left	250 ± 40	eVOR
BV3	M	46	Idiopathic	Extra-labyrinthine	PAN	Left	350 ± 100	eVOR, dVOR
BV4	M	53	Trauma	Intra-labyrinthine	SAN	Right	350 ± 50	eVOR
BV5	F	67	Trauma	Intra-labyrinthine	LAN	Left	250 ± 30	eVOR, dVOR
BV6	F	48	Meningitis	Intra-labyrinthine	PAN	Right	150 ± 50	eVOR, dVOR
BV7	M	67	DFNA-9	Intra-labyrinthine	LAN	Left	120 ± 60	eVOR, dVOR
BV8	M	53	Trauma	Intra-labyrinthine	SAN	Right	350 ± 125	eVOR, dVOR

Electrical stimulation

The detailed explanation of the implantation procedure and the determination of the stimulation parameters can be found in the previous publications (8,16). In short, constant amplitude stimulation was provided in order to restore a baseline "spontaneous" firing rate that could then be up- and down-modulated to encode excitatory and inhibitory stimulation as described in previous studies (8). This supraphysiological baseline electrical stimulation consisted of biphasic, cathodic first, symmetric, charge-balanced electrical pulses with a phase duration of 200 μs and presented at a rate of 400 pulses per second. An adaptation time of at least 30 minutes before rotation trials was ensured in order to allow for dissipation of vestibular symptoms like vertigo and nystagmus related to the sudden restoration of unilateral vestibular function (11). In the eVOR condition the patients sat in an immobile chair. In the dVOR condition the patients sat in the rotatory chair. In both conditions a gyroscope (LYPR540AH; ST Micro-electronics; Geneva, Switzerland) was fixed on the rotatory chair and captured only horizontal (yaw) rotations of the chair, which had a sinusoidal profile with a frequency of 1 Hz and a peak velocity of 30deg/s (10). The gyroscope signal was used to modulate the amplitude of the baseline stimulation. In other words, in both eVOR and dVOR conditions, current amplitude was increased when the chair was moving to the side of implantation (excitatory phase). In the opposite direction current amplitude was decreased (inhibitory phase). Only one electrode was stimulated at a time for each patient in each test condition (see *Table 1*).

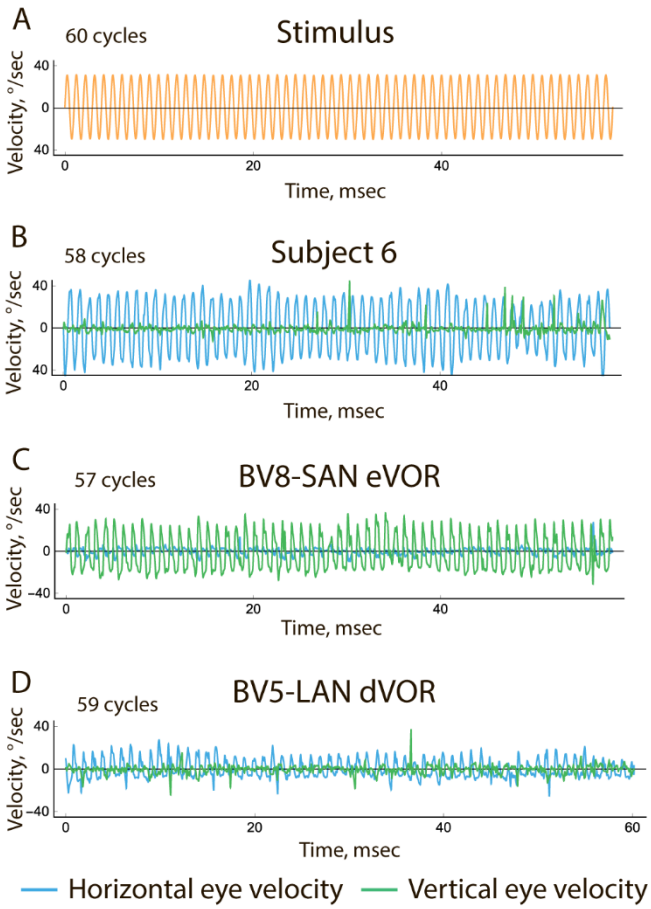

Figure 1. Examples of the stimulus trace (A, rotatory chair horizontal velocity), raw eye velocity traces of one healthy subject undergoing whole-body rotations (B, nVOR) and two bilateral vestibulopathy patients (BV) fitted with a vestibular implant in the eVOR (C, subject sitting static on an immobile chair) and dVOR (D, subject sitting in the rotatory chair) conditions. (LAN = lateral ampullary nerve electrode, SAN = superior ampullary nerve electrode)

Data preparation

The eye tracking system used for this study generated data files with raw horizontal and vertical eye position traces which were imported in Matlab 2018b (The Mathworks, Natick, MA, USA). Horizontal and vertical eye position were first smoothed using a 11th order Sawitzky-Golay filter and then with a 11th order median filter. Velocity traces were calculated from the smoothed positional traces using two-point numerical differentiation. Velocities of more than 600°/s were considered a blink, saccade, or a quick phase of nystagmus and removed. Gaps were interpolated using piecewise cubic Hermite interpolation. Then the traces were imported in Wolfram Mathematica 11 (Wolfram Research, Champaign, IL, USA) (10) for splitting the traces into cycles, calculation of the total eye and head velocities, data cleaning, fitting the sine curves, and calculation of the main outcome measures.

Splitting into full-cycles

The rotatory chair velocity was used as the stimulus signal (see *Figure 1A*). Horizontal and vertical eye and head velocities were split into cycles (further full-cycles) based on the stimulus signal. The number of available full-cycles in each tested subject is presented in *Supplementary Figure 1*.

Total velocities

The total velocities for each raw and fitted full-cycle were calculated as the magnitude of the vector with coordinates equal to the horizontal and vertical velocities (see *Figure 2b*).

Data cleaning

To automatically remove remaining blinks and small saccades for each total eye velocity trace, an interval of the mean maximum total eye velocity ± 1.96 of standard deviation was calculated. Total eye velocity full-cycle with the maximum value not within this interval were detected and removed. The same full-cycles were removed from the stimulus, total head velocity, and the horizontal and vertical eye and head movement traces.

Splitting into half-cycles

Then each remaining full-cycle of stimulus and eye and head velocity was split into two half-cycles by the point where the stimulus signal crossed zero (see *Figure 1A*).

Fitting the since curve

Each full-cycle and half-cycle of horizontal and vertical eye velocity traces were fitted with a sine (*NonlinearModelFit*, Wolfram Mathematica). The amplitude and the initial phase were set as hyperparameters (see *A* and φ_0 *Figure 2a*). The linear frequency of the fitted sine (see *f* in *Figure 2a*) was the dominant frequency in the Fourier spectrum calculated for the corresponding full-cycle of the eye velocity.

Classifying the half-cycles

For the healthy subjects all half-cycles were classified as rightward or leftward depending on the direction of rotation. For VI patients, each half-cycle of the stimulus was classified as either excitatory or inhibitory. The excitatory phase was determined when the rotation was to the side of implantation and the inhibitory phase – rotation to the opposite side (see *Material and methods: Electrical stimulation*).

Finding the peak total velocities

For the raw and fitted traces (full- and half-cycle fitting) peak values of the eye and head total velocities were found as the maximum value. Each peak was classified as either excitatory or inhibitory (see *Figure 2c*).

Calculation of outcome measures

For the healthy subjects and for the VI patients in the dVOR condition, the VOR gain was calculated as the ratio of the peak total eye velocity to the peak total head velocity, separately for each trace (raw, full-cycle fitting, and half-cycle fitting). In the eVOR condition, the VOR gain was calculated as the ratio of the

peak total eye velocity to the hypothetical peak head velocity equal to 30 deg/sec, also separately for each trace.

Orientation of eye VOR axis relatively to the horizontal plane was calculated as the angle between the total eye velocity vector and the horizontal plane. The angle was found as the arctangent of the ratio between the corresponding vertical and horizontal eye velocities (see *Figure 2a*). The angle was presented in the range of [0; 360] degrees (see angles α and β in *Table 2d: VOR axis*). Since the direction of the response varied depending on the stimulated electrode in the VI patients, the mean absolute differences of angles between directions of stimulation for healthy subjects or phases of stimulation for the patients were calculated in order to facilitate visual comparison between patients and healthy subjects (see the angle γ in *Figure 2d: VOR axis*).

Asymmetry was calculated as (rightward gain – leftward gain)/(rightward gain + leftward gain) for the healthy subjects and as (excitatory gain – inhibitory gain)/(excitatory gain + inhibitory gain) (10) for the eVOR and dVOR condition in VI patients.

The phase-shift between the horizontal eye and head velocities was calculated only for the healthy subjects and the dVOR condition in VI patients using the Spearman's correlation (10). The phase shift was calculated for the raw traces, full-cycle fitted traces, and the cycles reconstructed from the half-cycle fitted traces. The position of the maximum correlation value was the phase shift. Since some full-cycles could have a phase shift in the range of either [-180:0] degree (eye lead) or [0:180] degree (eye lag), calculation of descriptive statistics (mean, median etc.) was significantly hindered. For this, taking into account that the phase shift of the normal and electrically evoked VOR has values close to 180 (or -180) degrees (10), the obtained positive values were subtracted from 180, and the obtained negative values from -180. This procedure distributed the values around 0, which in this study corresponded to the phase shift of 180 degree for positive values (phase lead), and to -180 degree for negative values (phase lag) (see the ϕ in *Figure 2d: Phase shift*).

In order to estimate how well the fitted signals, repeat the raw traces, an additional metric called "error of fitting" was calculated for each half-cycle as the sum of the squared differences between the raw and fitted total eye velocities. To facilitate the comparison of the error between conditions, VOR-responses of each half-cycle of the raw and fitted total eye velocity were normalized to the maximum value of the corresponding raw total eye velocity.

Statistics

Firstly, median values for VOR gain, angle of the VOR axis, asymmetry, recalculated phase shift, and error of fitting were calculated per tested subject, phase of stimulation, and eye movement analysis. The medians for the angle of the VOR axis were calculated using circular statistics (17). Note, to improve readability, the word 'median' for these median values will not anymore be included in the descriptions.
Secondly, two-way repeated measures analysis of variance (RANOVA) was used to analyse the effect of eye movement analysis algorithm and stimulation phase on mean VOR gain and mean error of fitting across subjects, in each condition separately. In each model, eye movement analysis algorithm (raw, full-cycle, and half-cycle) and stimulation phase (excitatory and inhibitory) with their two-way interaction were set as the within-subject factors, VOR gain or error of fitting was set as the independent variable. For asymmetry and phase shift one-way RANOVAs were calculated per condition. Eye movement analysis

algorithm was set as the within-subject factor and asymmetry or phase shift was set as the dependent variable.

If the interaction effect in the two-way RANOVAs was significant, additional one-way RANOVAs were fitted per each level of stimulation phase. In these models, eye movement analysis algorithm was set as the main factor. Then, if the main factor in these models was significant, the paired t-test was used to compare means of dependent variables between its levels, three comparisons per each level of stimulation phase. The paired t-test was also used to compare means of dependent variables between levels of stimulation phase in each level of eye movement analysis algorithm. In case of insignificance of the interaction effect or in one-way RANOVAs the paired t-test was used for pairwise comparisons in each level of significant main factor.

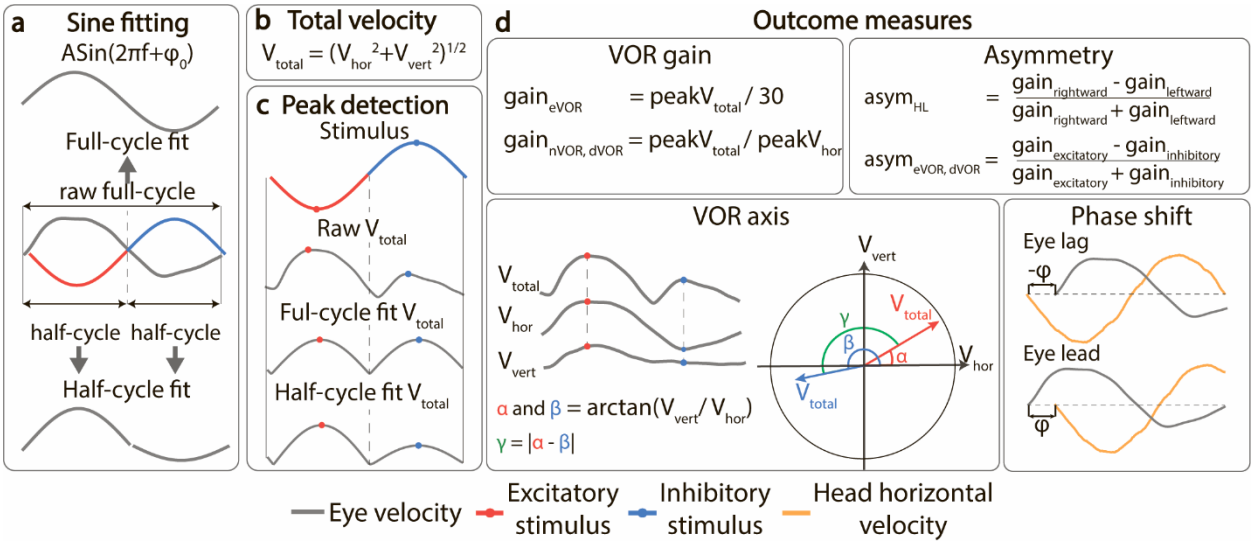

Figure 2a-d. Visualization of the main steps of the analysis: a) fitting the sine curve to the full-cycle, as well as to each half-cycle separately (A= amplitude, f = linear frequency, φ_0 = initial phase); b) calculation of the total eye velocity as the magnitude the vector with coordinates equal to the horizontal and vertical eye velocities; c) detection of the peak stimulus and peak total eye velocity in each half-cycle in all traces; d) calculation of the main outcome measures: VOR gain, asymmetry, angle for the VOR axis, and phase shift. For the angle, the position of the peak total eye velocity is used to extract corresponding horizontal and vertical eye velocities. Red and blue lines represent excitatory and inhibitory phases of stimulation respectively (α and β = angles of the excitatory and inhibitory phases of stimulation respectively, γ = absolute angle between the direction of the excitatory and inhibitory total eye velocities, nVOR = whole-body rotation in healthy subjects, eVOR = electrical stimulation in VI patients without whole-body rotations; dVOR = electrical stimulation in VI patients with whole-body rotations, V = eye velocity, hor = horizontal, vert = vertical, arctan = arctangent)

Due to the circular nature of the angular values related to VOR axis calculation, the analysis was split into inhibitory and excitatory phases in each testing condition. For each level one-way RANOVAs were calculated. Eye movement analysis algorithm was set as the within-subject factor and VOR axis was set as the dependent variable. In case of significance of the factor in one of the models, the paired t-test was used to evaluate the pairwise comparisons between its levels.

The alpha level was set to 0.05. All p-values were Bonferroni corrected (18). All statistical analyses were done in R (v.3.5.2).

Ethical statement

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

Data cleaning

In the healthy subjects, a total of 347 full-cycles were collected, from which 11 (3,2%) were removed. In the eVOR condition 441 full-cycles were collected, from which 19 (4,3%) were removed. In the dVOR condition 349 full-cycles were collected, from which 14 (4,0%) were removed. An example of the fitting of one cycle in each test condition is shown in *Figure 3*.

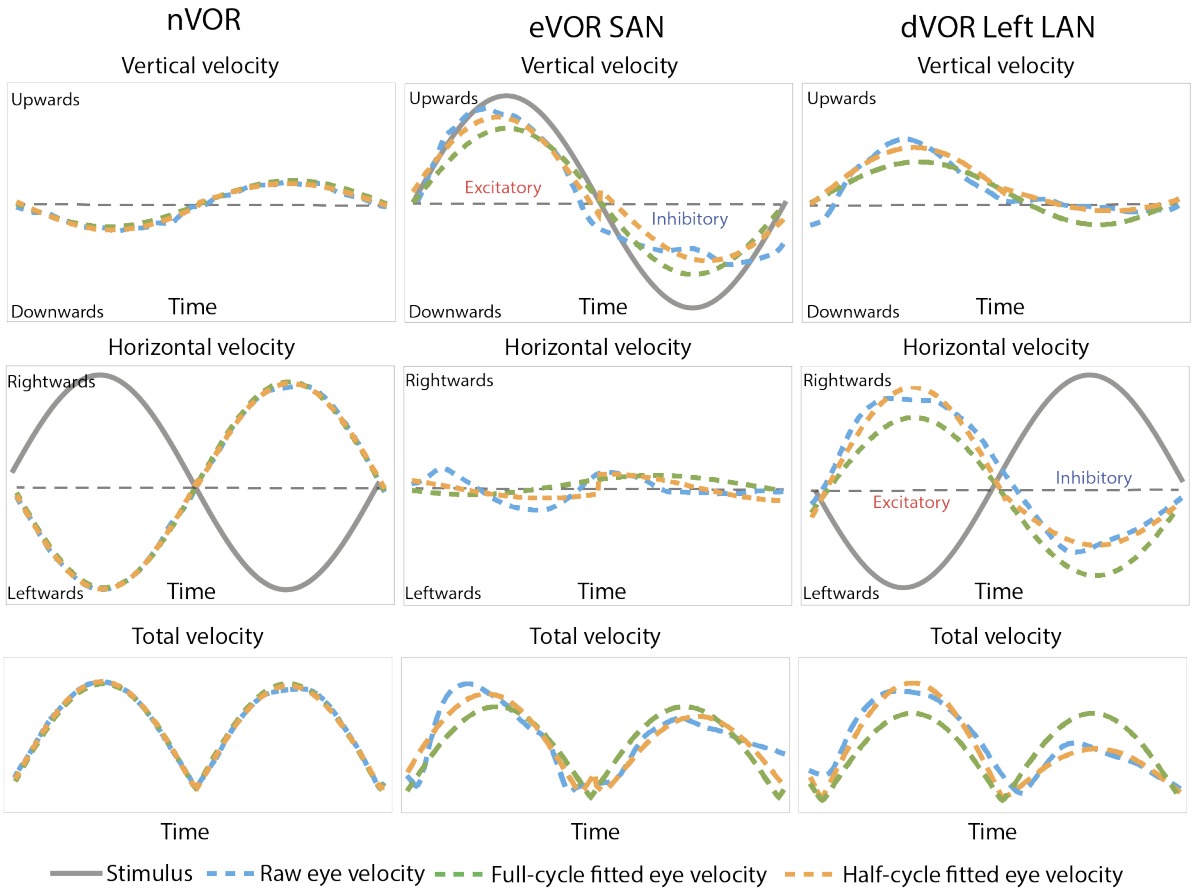

Figure 3. A one-cycle example of the raw, full-cycle fitted, and half-cycle fitted, VOR response in a healthy subject undergoing whole-body rotations (nVOR) and in two VI patients in two different conditions (eVOR = electrical stimulation in VI patients without whole-body rotations; dVOR = electrical stimulation in VI patients with whole-body rotations). For the VI patients the excitatory phase of stimulation corresponded

to the whole-body rotation to the side of implantation (SAN = superior ampullary nerve electrode, LAN = lateral ampullary nerve electrode)

VOR gain

The mean VOR gain values for each condition, stimulation phase, and eye movement analysis algorithm are presented in *Figure 4*.

In the healthy subjects the mean VOR gain obtained by analysis of the raw traces was significantly higher than the mean VOR gain obtained with full-cycle fitting (mean difference: 0.04 ± 0.02 $CI_{95\%}$, p = 0.008) and half-cycle fitting (mean difference: 0.03 ± 0.01 $CI_{95\%}$, p < 0.001) regardless of the direction. No differences were found between full-cycle and half-cycle fitting. The mean VOR gain was higher for the rightward head movements regardless of the type eye movement analysis algorithm (raw traces or half-cycle fitting) (mean difference: 0.06 ± 0.02 $CI_{95\%}$, p < 0.001).

In the eVOR condition, but only for the excitatory phase of stimulation, the mean VOR gain was higher in the analysis of the raw traces compared to full-cycle fitting (mean difference: 0.14 ± 0.06 $CI_{95\%}$, p = 0.018). For half-cycle fitting this difference was not statistically significant after Bonferroni correction (mean difference: 0.08 ± 0.05 $CI_{95\%}$, before correction p = 0.004, after correction p = 0.053). The mean VOR gain was lower when using full-cycle fitting compared to half-cycle fitting for the excitatory phase (mean difference: -0.06 ± 0.03 $CI_{95\%}$, p = 0.046). The mean VOR gain was higher for the excitatory phase compared to the inhibitory phase when using analysis of the raw traces (mean difference: 0.14 ± 0.09 $CI_{95\%}$, p = 0.027) and half-cycle fitting (mean difference: 0.08 ± 0.05 $CI_{95\%}$, p = 0.019).

For the dVOR condition the mean VOR gain obtained by analysis of the raw traces was significantly higher than the mean VOR gain obtained with half-cycle fitting, regardless of the stimulation phase (mean difference: 0.08 ± 0.04 $CI_{95\%}$, p = 0.009). The mean difference between the analysis of the raw traces and full-cycle fitting became insignificant after the Bonferroni correction (mean difference: 0.1 ± 0.09 $CI_{95\%}$, before correction p = 0.029, after correction p = 0.118). The same was with the mean difference between full-cycle and half-cycle fitting (mean difference: -0.02 ± 0.04 $CI_{95\%}$, before correction p = 0.029, after correction p = 0.116). The mean VOR gain was higher for the excitatory phases regardless of the eye movement analysis algorithm (raw traces or half-cycle fitting) (mean difference: 0.14 ± 0.06$CI_{95\%}$, p = 0.003).

Asymmetry

Mean asymmetry between directions of stimulation (right and left) for healthy subjects or phases of stimulation (excitatory and inhibitory) for patients are presented in *Figure 4*. In the healthy subjects no significant effect of the type of fitting on the mean asymmetry was found. In the eVOR condition the mean asymmetry differed between the raw and full-cycle fitted traces (mean difference: 0.21 ± 0.11$CI_{95\%}$, p = 0.011), as well between the half-cycle and full-cycle fitted traces (mean difference: 0.19 ± 0.12$CI_{95\%}$, p = 0.024). In the dVOR condition the mean asymmetry of the half-cycle fitted traces was higher than of the full-cycle fitted traces (mean difference: 0.11 ± 0.06$CI_{95\%}$, p = 0.016).

VOR axis

The absolute VOR axis angle between stimulation phases (see the angle γ in *Figure 2d: VOR axis*) is shown in *Figure 4*. No significant differences in the mean VOR axis angle of eye movement responses were found between all three types of eye movement analysis algorithms, neither in the healthy subjects nor in the VI patients.

Phase shift

Mean phase shifts calculated for the healthy subjects and dVOR condition per type of fitting are demonstrated in *Figure 4*. No significant differences in the mean phase shift were found between all three types of eye movement analysis algorithms, neither in the healthy subjects nor in the dVOR condition.

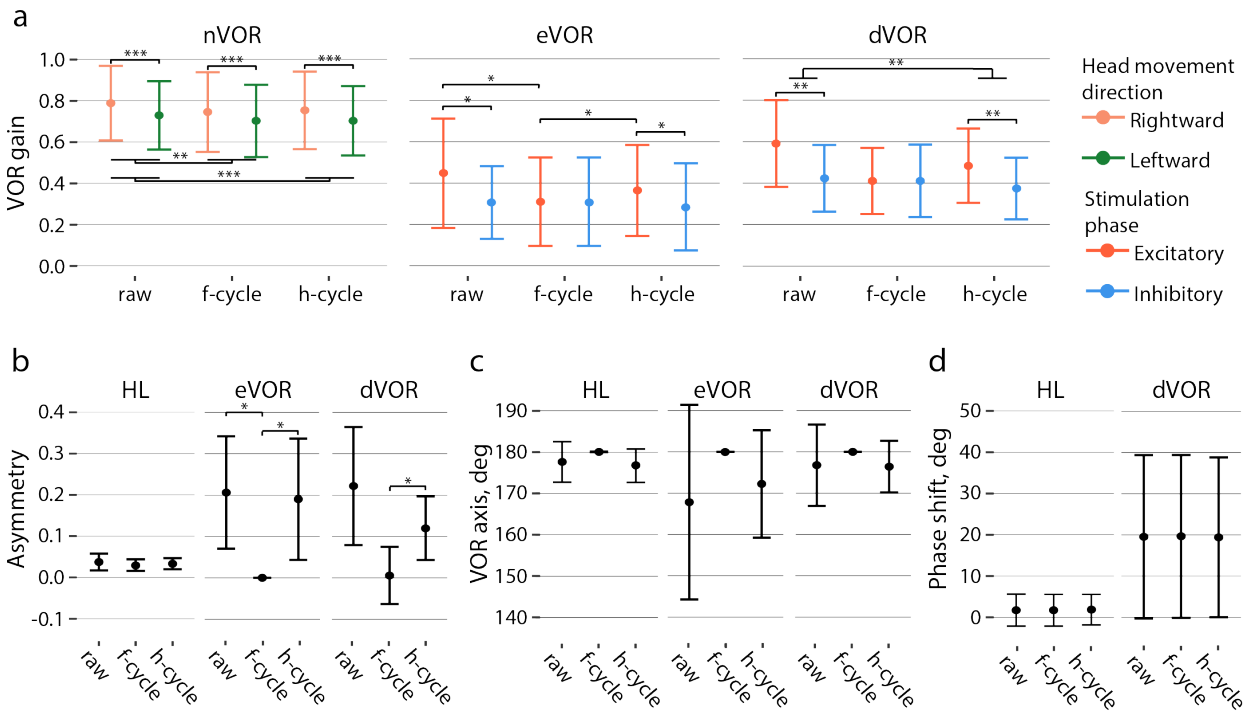

*Figure 4. Mean ± standard deviation of the VOR gain across subjects (a), asymmetry(b), angle of the VOR axis (c), and phase shift (d) calculated between the values obtained when using analysis of the raw traces, full-cycle fitting (f-cycle), and half-cycle fitting (h-cycle) fitted traces (nVOR = whole-body rotation in healthy subjects, eVOR = electrical stimulation in VI patients without whole-body rotations; dVOR = electrical stimulation in VI patients with whole-body rotations, *** = p<0.001, ** = p<0.01, * = p≤0.5)*

Error of fitting

The mean error of fitting calculated for each type of fitting (full-cycle and half-cycle) per tested condition and stimulation phase are presented in *Table 2*. In all conditions (nVOR, eVOR, and dVOR) the mean error of fitting was significantly higher in full-cycle fitting compared with half-cycle fitting, regardless of the stimulation phase (mean difference: 0.45 ± 0.23 $CI_{95\%}$, p = 0.002). Only in the eVOR condition, for both

full-cycle and half-cycle fitting, the mean error of fitting was significantly lower for the excitatory phases than the inhibitory phases (mean difference: -1.53 ± 0.83 $CI_{95\%}$, p = 0.003).

Table 2. Mean error of fitting ± standard deviation (sd) per type of fitting, test condition, and stimulation phase (nVOR = whole-body rotation in healthy subjects, eVOR = electrical stimulation in VI patients without whole-body rotations; dVOR = electrical stimulation in VI patients with whole-body rotations)

Condition	**Stimulation phase**	**Mean error of fitting ± sd**	
		Full-cycle fitting	*Half-cycle fitting*
nVOR	Rightward	0.72 ± 0.39	0.31 ± 0.12
	Leftward	0.86 ± 0.57	0.37 ± 0.15
eVOR	Excitatory	5.42 ± 2.79	2.71 ± 1.73
	Inhibitory	7.29 ± 3.11	3.91 ± 1.88
dVOR	Excitatory	4.34 ± 1.47	2.23 ± 0.93
	Inhibitory	7.32 ± 3.79	3.47 ± 2.03

Discussion

This study aimed at comparing the VOR outcomes between three different eye movement analysis algorithms which are used to investigate the natural and electrically evoked VOR. It was demonstrated that the type of eye movement analysis algorithm significantly influenced VOR outcomes, especially regarding VOR gain and asymmetry of the electrically evoked VOR in bilateral vestibulopathy patients fitted with a vestibular implant. VOR outcomes of the natural VOR obtained in healthy subjects were less affected by the type of eye movement analysis algorithm due to the use of low velocity stimulus, lower variability, and to the symmetry of the healthy VOR response.

VOR outcomes of the electrically evoked VOR were more affected by eye movement analysis algorithm than those of the natural VOR. This mainly resulted from the fact that the electrically evoked VOR is asymmetric, which was demonstrated in the present study by the significantly higher than zero asymmetry values, in both conditions (see *Figure 3*). This asymmetry was also previously described in other vestibular implant studies (10,11). The asymmetric VOR response to high velocity head movements is a characteristic of healthy unilateral vestibular function (13). Therefore, symmetrical VOR responses can only be achieved with two healthy vestibular organs since one ear is always better for encoding excitatory stimulations (e.g., directions of motion). However, due-to the use of small velocity stimuli (30 deg/sec), the asymmetry found in the present study might have another origin that in case of the healthy vestibular system. The origin might be related to e.g. the applied transfer function of the vestibular implant (linear transfer function), the level of baseline stimulation and/or the definition of the lowest threshold for stimulation (perception instead of VOR response).

In case of unilateral implantation as used in the present study, the asymmetry caused full-cycle fitting to show the highest mean errors of fitting. These values were almost 6-10 times higher in the electrically evoked VOR compared to the natural VOR, and almost twice as high compared to half-cycle fitting in all tested conditions. This could be explained as follows: since corresponding points of excitatory phase of stimulation have higher values than points of the inhibitory phase of stimulation, the sine curve always tends to take the intermediate position. Therefore, it underestimates the excitatory part of the response and overestimates the inhibitory part of the response. As a result, the full-cycle method significantly decreased the VOR gain values in the excitatory phase of stimulation. In the inhibitory phase of

stimulation, one could expect the higher VOR gain values. However, this was not statistically proven in the present study due-to small mean differences (see *Figure 4* and Supplementary *Table 3*), which were not detectable with the given sample size and, consequently, with the power of the used tests. These smaller differences might imply that the inhibitory phase had significant influence on the sine curve 'dragging' its amplitudes more to its values. The reason of this might be that the shape of the response to the expiatory phase was narrower that one to the inhibitory phase of stimulation (for example see *Figure 1*). It should be noted that the half-cycle method also tended to decrease the VOR gain in the excitatory phase of stimulation. This could be explained using the above assumption: since the raw VOR response to the excitatory phase of stimulation often had a prominently narrower shape than the purely sinusoidal response would have (see *Figure 1: eVOR SAN*), one can assume that the half-cycle method flattened the top of the shape, thereby decreasing the maximum value. This again was not the case in the response to the inhibitory phase, where the shape was more flattened. However, the full-cycle method decreased VOR gain 1.75 times more than half-cycle method. The latter only decreased VOR gain with approximately 0.3 – 0.13. Although this difference was statistically significant, it might not be considered clinically relevant if the following is true: if with an increase of the response the shape of the trace becomes closer to the sine curve (see *Supplementary Figure 1*) and also using the results obtained in the healthy subjects, it might be expected that the VOR gain differences between analysis algorithms will decrease with an increase of the VOR response. For this, more data might be needed than currently available in vestibular implant research.

No significant differences were found between analysis algorithms regarding eye movement angle and phase shift. This implies that the shape of the fitted signals was still close enough to the raw trace, to not significantly disturb VOR axis angle and phase analyses when using full-cycle or half-cycle fitting. Big variance of the phase shift could be caused by inclusion in the sample patients with small non-linear responses.

Considering the findings of this study, which illustrate that the asymmetry and morphology of the electrically evoked VOR response should be taking into account in the analysis, it would be advised to investigate each phase of the VOR response separately in vestibular implant research. This should be done at least before long term adaptation when the asymmetry is prominent. Therefore, in addition to the analysis of raw traces, half-cycle fitting is also a useful eye movement analysis algorithm for vestibular implant research. It can speed up time required for analysis, but it might come at the expense of a (possibly) not clinically relevant decrease in VOR gain. In the other hand, the full-cycle method still might be useful in case of functional rehabilitation studies. Patients with unilateral vestibulopathy have rare cases of oscillopsia, blurred vision during head movements, due-to compensatory strategies (e.g. refixation saccades) to overcome the deficiency in VOR (19,20). Therefore, one intermediate (between phases of stimulation) value of VOR gain calculated by the full-cycle method and accompanied by the dynamic visual acuity score might be still sufficient to retrace rehabilitation effect of the VI. This could simplify the analysis even more in comparing with the half-cycle method.

Limitations of the study

The main drawback of the study is the small sample size in all three test conditions. Unfortunately, only few patients have been implanted with a VI worldwide, limiting the current potential sample size. Consequently, although variability of the response within each subject was reduced by calculating median

values from relatively large number of cycles, the statistical tests used in the study possess low power. Therefore, this study does not rule out any small differences between raw and fitted values, which were classified insignificant in the present study, as well as the effect of the response magnitude on them.

Conclusion

For the analysis of the electrically evoked VOR, the excitatory and inhibitory phases of stimulation should be analysed separately due to the inherent asymmetry of the electrically evoked VOR. The half-cycle fitting method can be used as an alternative to the analysis of raw traces, but errors can be expected when the morphology of the half cycle differs substantially from a half-sinus.

Author contribution

AP-F, NG, MR, SC, RvdB and HK planned and conducted the experiment. DS and MP made the data processing and statistical analysis. DS and RvdB wrote the manuscript. All authors contributed to its editing.

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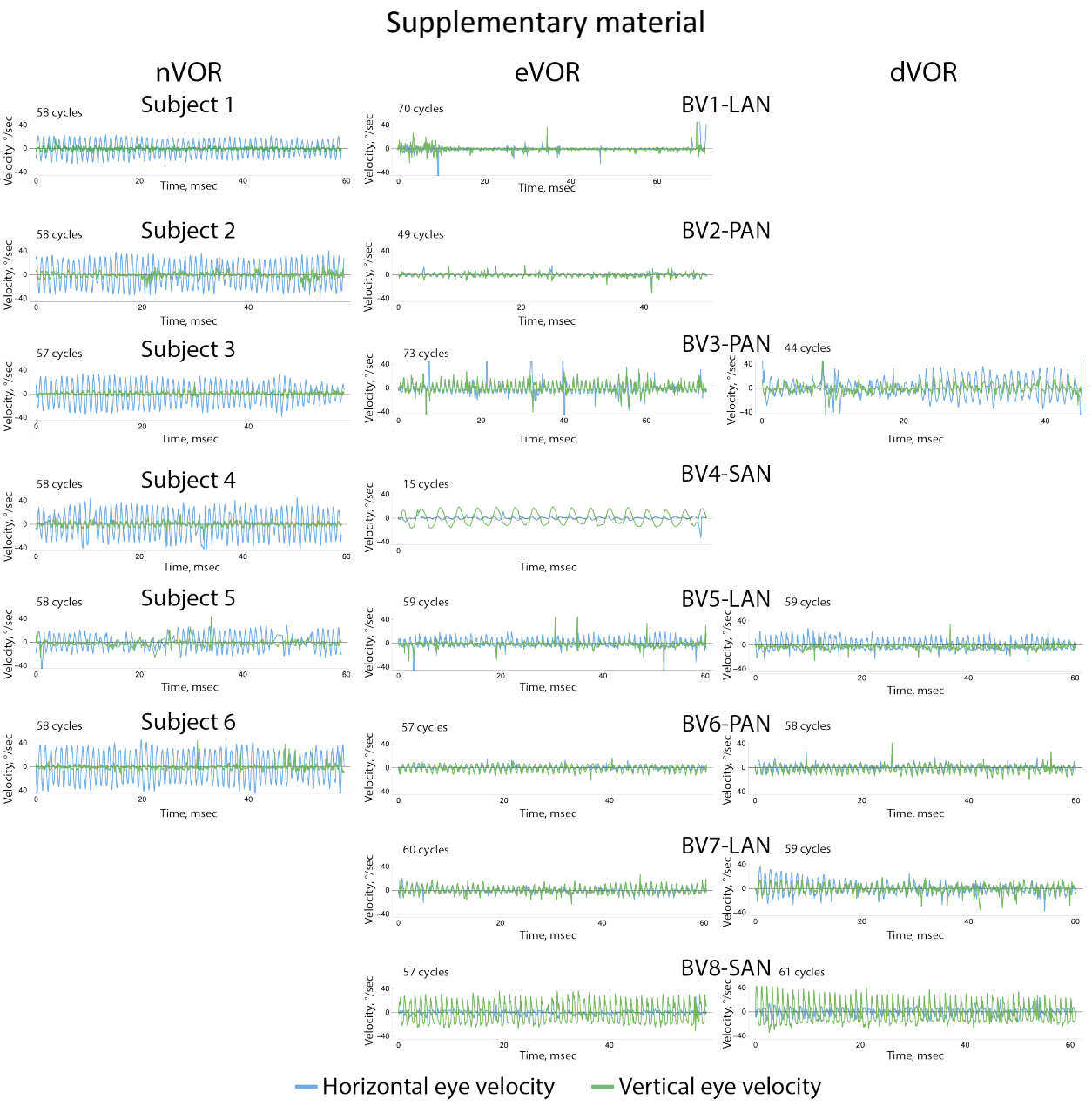

Figure 1. Raw eye velocity traces of the healthy subjects undergoing whole-body rotations (nVOR) and the bilateral vestibulopathy patients (BV) fitted with a vestibular implant. (LAN = lateral ampullary nerve electrode, SAN = superior ampullary nerve electrode, PAN = superior ampullary nerve electrode, cycles represent cycles of stimulation, cycles mean cycles of the sinusoidal stimulation available for the analysis)

Table 1. Median gain, error of fitting, and VOR axis angle per subject, test condition, stimulation phase, and analysis algorithm

Subject	Condition	Stimulation phase	Gain			Error		Angle		
			Raw	F-cycle	H-cycle	F-cycle	H-cycle	Raw	F-cycle	H-cycle
HL1	nVOR	Excitatory	0.60	0.54	0.56	0.55	0.32	-39	-16	-30
		Inhibitory	0.55	0.54	0.54	0.64	0.42	209	164	187
HL2	nVOR	Excitatory	1.00	0.95	0.96	0.58	0.28	235	227	228
		Inhibitory	0.95	0.89	0.90	0.72	0.25	55	47	54
HL3	nVOR	Excitatory	0.75	0.73	0.72	0.29	0.14	10	6	10
		Inhibitory	0.72	0.70	0.70	0.31	0.18	182	188	184
HL4	nVOR	Excitatory	0.92	0.87	0.89	0.90	0.32	52	43	49
		Inhibitory	0.82	0.80	0.78	0.82	0.34	216	223	217
HL5	nVOR	Excitatory	0.56	0.49	0.51	1.42	0.52	-9	-8	-5
		Inhibitory	0.53	0.45	0.47	1.98	0.60	173	172	171
HL6	nVOR	Excitatory	0.90	0.89	0.89	0.62	0.29	-3	-5	0
		Inhibitory	0.82	0.84	0.83	0.71	0.42	190	175	175
BV1	eVOR	Excitatory	0.09	0.04	0.05	10.53	6.37	243	240	242
		Inhibitory	0.08	0.04	0.04	9.10	6.68	52	60	62
BV2	eVOR	Excitatory	0.17	0.11	0.13	7.18	1.92	251	255	253
		Inhibitory	0.15	0.11	0.10	9.39	4.55	78	75	76
BV3	eVOR	Excitatory	0.56	0.37	0.45	4.57	2.61	57	60	60
		Inhibitory	0.37	0.37	0.35	6.71	3.51	237	240	232
BV4	eVOR	Excitatory	0.57	0.49	0.53	1.72	0.88	90	94	93
		Inhibitory	0.45	0.49	0.46	2.39	1.28	-87	-86	-86
BV5	eVOR	Excitatory	0.49	0.25	0.36	7.05	3.95	89	95	95
		Inhibitory	0.24	0.25	0.18	11.78	4.77	-87	-85	-88
BV6	eVOR	Excitatory	0.34	0.25	0.29	2.72	1.41	184	183	183
		Inhibitory	0.24	0.25	0.23	3.86	1.18	2	2	3
BV7	eVOR	Excitatory	0.42	0.27	0.36	5.00	2.14	185	186	185
		Inhibitory	0.30	0.27	0.23	8.89	5.10	5	6	5
BV8	eVOR	Excitatory	0.94	0.71	0.75	4.60	2.42	179	178	180
		Inhibitory	0.63	0.71	0.69	6.23	4.20	0	-2	-2
BV3	dVOR	Excitatory	0.80	0.62	0.71	2.71	1.11	26	24	27
		Inhibitory	0.61	0.54	0.51	4.04	1.85	191	204	194
BV5	dVOR	Excitatory	0.47	0.31	0.38	5.31	2.50	101	102	101
		Inhibitory	0.25	0.26	0.24	11.46	5.91	-83	-78	-81
BV6	dVOR	Excitatory	0.36	0.26	0.30	2.92	1.58	190	184	189
		Inhibitory	0.26	0.26	0.22	3.44	1.38	-2	4	-1
BV7	dVOR	Excitatory	0.50	0.32	0.39	6.05	3.52	184	184	184
		Inhibitory	0.47	0.35	0.36	6.62	2.96	5	4	5
BV8	dVOR	Excitatory	0.83	0.54	0.65	4.73	2.43	180	178	181
		Inhibitory	0.53	0.65	0.55	11.05	5.26	-4	-2	-4

Table 2. Median asymmetry and phase shift per subject, test condition, and analysis algorithm

Subject	Condition	Asymmetry			Phase shift		
		Raw	F-cycle	H-cycle	Raw	F-cycle	H-cycle
HL1	nVOR	0.05	0.01	0.03	8	8	8
HL2	nVOR	0.01	0.05	0.01	3	3	3
HL3	nVOR	0.02	0.03	0.03	2	2	2
HL4	nVOR	0.05	0.04	0.04	2	2	2
HL5	nVOR	0.06	0.03	0.05	-2	-2	-1
HL6	nVOR	0.04	0.02	0.04	-3	-3	-3
BV1	eVOR	0.07	0	0.16	-	-	-
BV2	eVOR	0.21	0	0.27	-	-	-
BV3	eVOR	0.16	0	0.12	-	-	-

BV4	eVOR	0.13	0	0.09	-	-	-
BV5	eVOR	0.52	0	0.51	-	-	-
BV6	eVOR	0.18	0	0.12	-	-	-
BV7	eVOR	0.17	0	0.21	-	-	-
BV8	eVOR	0.23	0	0.05	-	-	-
BV3	dVOR	0.11	0.06	0.13	16	17	17
BV5	dVOR	0.41	0.08	0.24	5	6	5
BV6	dVOR	0.18	0.02	0.12	11	10	10
BV7	dVOR	0.08	-0.05	0.03	12	12	12

Table 3. Mean gain and error ± standard deviation (sd) per test condition, stimulation phase, and analysis algorithm

Condition	Stimulation phase	Mean gain ± sd			Mean error ± sd	
		Raw	Cycle	Half-cycle	Cycle	Half-cycle
Healthy	Rightward	0.79 ± 0.18	0.74 ± 0.19	0.75 ± 0.19	0.72 ± 0.39	0.31 ± 0.12
	Leftward	0.73 ± 0.17	0.70 ± 0.18	0.70 ± 0.17	0.86 ± 0.57	0.37 ± 0.15
eVOR	Excitatory	0.45 ± 0.26	0.31 ± 0.21	0.36 ± 0.22	5.42 ± 2.79	2.71 ± 1.73
	Inhibitory	0.31 ± 0.18	0.31 ± 0.21	0.29 ± 0.21	7.29 ± 3.11	3.91 ± 1.88
dVOR	Excitatory	0.59 ± 0.21	0.41 ± 0.16	0.48 ± 0.18	4.34 ± 1.47	2.23 ± 0.93
	Inhibitory	0.42 ± 0.16	0.41 ± 0.17	0.37 ± 0.15	7.32 ± 3.79	3.47 ± 2.03

Table 4. Mean asymmetry, mean absolute differences of angles, and mean phase shift with their standard deviation (sd) calculated per stimulation condition and type of fitting. Mean asymmetry and mean differences of VOR axis angles were calculated between directions of stimulation (right and left) for healthy subjects or phases of stimulation (excitatory and inhibitory) for VI patients for each type of fitting. The values of angles are in the range of [0:360] degrees. The values of the phase shift correspond to the phase shift as if the eye response has been already shifted by 180 or -180 degrees and they are in the range of [-180;180]

Condition	Mean asymmetry ± sd			Mean angle difference ± sd, deg			Mean phase ± sd, deg		
	Raw	Cycle	Half-cycle	Raw	Cycle	Half-cycle	Raw	Cycle	Half-cycle
Healthy	0.04 ± 0.02	0.03 ± 0.01	0.03 ± 0.01	178 ± 5	180 ± 0	177 ± 4	2 ± 4	2 ± 4	2 ± 4
eVOR	0.21 ± 0.14	0 ± 0	0.19 ± 0.15	167 ± 2	180 ± 0	172 ± 1	-	-	-
dVOR	0.22 ± 0.14	0.01 ± 0.07	0.12 ± 0.08	176 ± 10	180 ± 0	176 ± 6	20 ± 20	20 ± 20	19 ± 19

Chapter VI

Restoring the High-Frequency Dynamic Visual Acuity with a Vestibular Implant Prototype in Humans

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Abstract

Introduction: The vestibular implant could become a clinically useful device in the near future. This study investigated the feasibility of restoring the high-frequency dynamic visual acuity (DVA) with a vestibular implant, using the functional Head Impulse Test (fHIT).

*Methods***:** A 72-years old female with bilateral vestibulopathy and fitted with a modified cochlear implant incorporating three vestibular electrodes (MED-EL, Innsbruck, Austria), was available for this study. Electrical stimulation was delivered with the electrode close to the lateral ampullary nerve in the left ear. The high-frequency DVA in the horizontal plane was tested with the fHIT. After training, the patient underwent six trials of the fHIT, each with a different setting of the vestibular implant: 1) System OFF before stimulation; 2) System ON, baseline stimulation; 3) System ON, reversed stimulation; 4) System ON, positive stimulation; 5) System OFF, without delay after stimulation offset 4; 6) System OFF, 25 minutes delay after stimulation offset. The percentage of correct fHIT scores for right and left head impulses were compared between trials.

Results: Vestibular implant stimulation improved the high-frequency DVA compared to no stimulation. This improvement was significant for "System ON, baseline stimulation" ($p = 0.02$) and "System ON, positive stimulation" ($p < 0.001$). fHIT scores changed from 19-44% (no stimulation) to maximum 75-94% (System ON, positive stimulation).

Conclusion: The vestibular implant seems capable of improving the high-frequency DVA. This functional benefit of the vestibular implant illustrates again the feasibility of this device for clinical use in the near future.

Introduction

One of the major functions of the vestibular organs is to facilitate visual acuity in dynamic situations (DVA). During abrupt head rotations, the semicircular canals in the vestibular system detect acceleration and induce an ocular reflex that generates compensatory eye movements: the vestibulo-ocular reflex (VOR). This mechanism allows the visual environment to remain stable on the retina (gaze stabilization), and therefore visual acuity during dynamically changing conditions is consequently preserved. Unfortunately, the VOR is often impaired in case of bilaterally reduced (or absence of) vestibular function, a condition called "bilateral vestibulopathy". This results in loss of DVA. Therefore, patients with bilateral vestibulopathy frequently complain of oscillopsia: the illusory movement of the visual environment.

The video Head Impulse Test (vHIT) is a clinical test frequently used to evaluate semicircular canal function (1,2). The vHIT evaluates vestibular function using gain and evaluation of the presence/absence of compensatory saccades. However, it does not directly measure the DVA. A method to measure the latter in "close-to-reality" conditions was previously described: the DVA test on a treadmill (3). This method mainly involves head movements in the vertical plane at relatively low velocities (maximum peak 30°/sec) and at a relatively low frequency (approximately 2Hz). A new complementary test involving fast and high-frequency head movements was recently proposed: the functional Head Impulse Test (fHIT) (4,5). In this test, patients undergo head impulses at high velocities to the right and left and have to identify optotype letters (Landolt C rings) that appear briefly during these impulses. The percentage of correctly identified optotypes is calculated for head impulses to each side. These results are considered to reflect the high-frequency DVA in the selectively tested plane. The fHIT and video Head Impulse Test (vHIT) have shown to be complementary in detecting vestibular dysfunction in patients during the acute phase of acute unilateral vestibulopathy. Furthermore it was demonstrated that the fHIT is able to detect compensation phenomena that appear in vestibular neuritis patients during the acute phase and after three months (6). Therefore, the fHIT might be a useful tool for evaluating outcomes of vestibular rehabilitation.

At this moment, no definite therapeutic option is yet clinically available for bilateral vestibulopathy. However, in the last years the feasibility of a possible treatment has been demonstrated: the vestibular implant (VI). The VI, in concept similar to the cochlear implant, attempts to restore head-motion sensitivity by capturing motion and delivering it as electrical current pulses to vestibular afferents. Vestibular afferents are stimulated via surgically implanted electrodes in the vestibular system (7–10). A functional benefit of the VI was already demonstrated by restoring the dynamic visual acuity during walking (11). The goal of this case study was to investigate the feasibility of restoring high-frequency DVA with a prototype vestibular implant, using the fHIT.

Materials and methods

Patient and Vestibular Implant

A 72-years old female with bilateral vestibulopathy and fitted with a modified cochlear implant on the left side, was available for this study. The patient fulfilled the previously reported inclusion criteria (8–10). In this specific case, the sum of the maximal peak velocities of the slow phase caloric-induced nystagmus for stimulation with warm and cold water was 1.7°/s and 2.2°/s in left and right ears respectively, vHIT gains were below 0.3 for all six semicircular canals, and cervical vestibular evoked myogenic potential responses were absent in both ears. The implanted prototype incorporated three vestibular electrodes (MED-EL,

Austria), an external processor, and a 3D gyroscope (LYPR540AH; ST Micro-electronics; Geneva, Switzerland). Head movements were captured by the gyroscope and converted into electrical signals by the processor. Electrodes delivered these signals to the vestibular afferents. The electrodes were implanted in the semicircular canals (intralabyrinthine approach (7)), in the vicinity of the lateral ampullary nerve, superior ampullary nerve, and posterior ampullary nerve.

Electrical stimulation

The lateral ampullary nerve electrode (in the lateral semicircular canal) was selected for this study, since the fHIT involved head movements in the horizontal plane. The electrode delivered a stimulus consisting of biphasic, cathodic-first, charge-balanced electrical pulses with a rate of 400 pulses per second (pps) and a phase duration of 200 μsec. The lowest current level was determined by slowly increasing the current by 10- to 25-μA, until 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'). Current was increased again until pain or facial nerve stimulation occurred. This level was considered the upper comfortable level for stimulation. The current interval from the lowest to upper comfortable level formed the dynamic range for stimulation in this patient (150 - 350 μA). Baseline of stimulation was set at 250 μA, which corresponded to the middle of the dynamic range. This supraphysiological baseline has shown to be effective for generating bidirectional eye movements when using a unilateral prosthesis (9). Experiments with the VI started after the patient was in the adapted state with baseline stimulation (e.g. when no more spontaneous nystagmus was present). Then the experimental trials with the VI started, where electrical stimuli were modulated in amplitude using the signal of the VI-gyroscope (yaw axis) which was strapped to the head of the patient with a head band. A linear transfer function was used to code the depth of current amplitude modulation, using the formula $I = g_z\omega_z$ + *baseline*, where *I = current (μA)*, g_z *= gain (μA/◦/sec)*, ***ω =*** *head angular velocity (◦/sec),* and **z** referred to the projection on the longitudinal axis. Gain g_z was set at 3 μA/◦/sec. Two types of stimulation were used: positive stimulation (positive gain), and reversed (negative gain). With positive stimulation, head motion was encoded correctly, i.e. the VI in the left ear facilitated upward modulation during head impulses to the left, and downward modulation during impulses to the right. This is how the VI should work in daily life. With negative modulation, motion information was reversed: the VI in the left ear facilitated downward modulation during head impulses to the left, and upward modulation during head impulses to the right (12). For safety reasons, modulation never exceeded the upper comfortable level, despite the high head velocities.

fHIT

The fHIT (BEON Solutions, Zero Branco, Italy) was performed by a trained examiner (FL) in a controlled laboratory setting. The patient was continuously instructed to stay alert, and to blink as little as possible. The patient was positioned in front of a computer screen (Sony SDM P232W 23'') at a distance of 1.5 m. Landolt optotype rings were displayed on the screen, to determine static visual acuity following the procedure described by Colagiorgio et al. 2013 (13). The obtained static visual acuity (LogMAR 0.7) was then used to set letter size in the experimental trials. Each fHIT trial consisted of 32 horizontal head impulses (16 to each side). Head motion was captured by a gyroscope connected to the fHIT via Bluetooth, which was tightly strapped to the head by a head band (see *Figure 1*). Therefore, in total two gyroscopes were strapped on the patient's head: the gyroscope of the fHIT, and the gyroscope of the VI. At the beginning of each trial a fixation target was shown at the center of the screen, and 80 msec after head

velocity exceeded 10 ◦/sec, a Landolt ring appeared at the same location for 80 msec. The head impulses were randomly delivered to both directions, in order to avoid prediction by the patient. After each impulse, the patient had to indicate the correct orientation of the Landolt ring, by choosing one of the eight options on a keyboard. All head turns not within the acceleration range of 3000 – 6000 ◦/sec^2 were excluded from analysis. The percentage of correct answers for each trial was separately recorded for impulses to the left and to the right. This percentage was considered to reflect the high-frequency DVA.

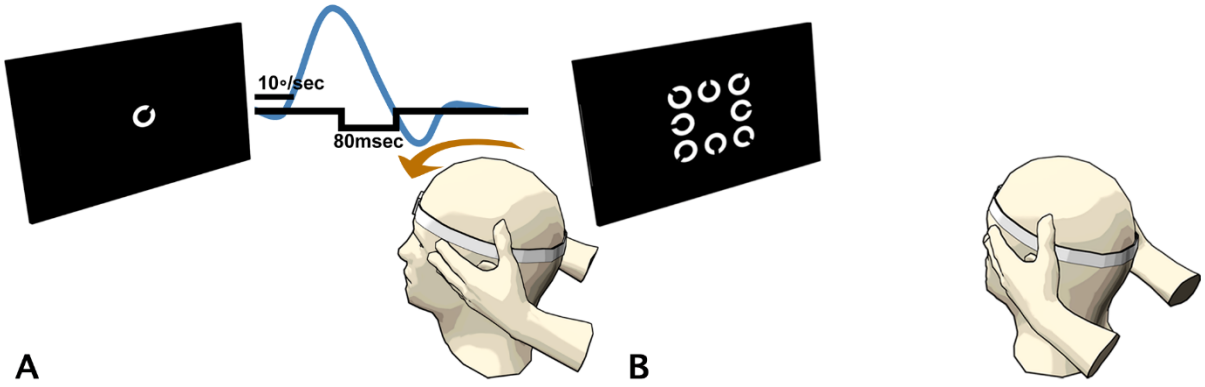

Figure 1. The functional Head Impulse Test: ***(A)*** *– the patient is positioned at 1.5m from the screen. A gyroscope is tightly strapped on the head by a head band. The patient is instructed to stare at the fixation target (not shown) presented on the screen. The laboratory technician delivers randomly directed head impulses in the lateral plane. Eighty milliseconds after head velocity (blue trace) exceeds 10 ◦/sec, a Landolt ring appears for 80 msec (black trace).* ***(B)*** *– after each impulse eight possible orientations of the Landolt ring are demonstrated on the screen, and the patient is asked to choose the correct one*

Experimental procedure

In order to get acquainted with the procedure, seven "training" fHIT trials were initially conducted without simultaneous stimulation of the VI. During these trials, the LogMAR size of the C-optotypes varied from 0.7 to 1, while duration of appearance ranged from 60 to 160 msec. After this training, the experimental procedure started. It consisted of six consecutive trials, with different electrical stimulation conditions of the vestibular implant in the following order: 1) System OFF ($System_{off}$); 2) System ON, baseline stimulation ($System_{on}^{baseline}$); 3) System ON, reversed stimulation ($System_{on}^{reversed}$); 4) System ON, positive stimulation ($System_{on}^{motion}$); Two conditions were added to assess any potential post-stimulation effects, where the VI stimulation was turned off and the fHIT was repeated: 5) immediately after turning the System OFF ($System_{off}^{0min}$) and 6) 25 minutes after turning the System OFF ($System_{off}^{25min}$). During the System ON conditions, only the patient was blinded for the type of VI stimulation.

Statistics

To investigate improvement of high-frequency DVA by the VI, fHIT scores of the first trial ($System_{off}$ condition) were compared to the fHIT scores of the other trials. Logistic regression was used to determine the influence of the stimulation condition and the head impulse direction. The binary output of each impulse (Correct/Incorrect) was used as a dependent variable. Variables "Condition" describing the type of stimulation and "Side" describing the head impulse direction, were used as independent variables. The

significance of model coefficients was estimated using the Wald test followed by Holm – Bonferroni correction (6 hypothesized predictors). The model showed no significant interactions of the variables, as well as no significant impact of the variable "Side". Therefore, this variable and the interactions were excluded from the analysis and the model was reconstructed. Three methods for assessing the logistic regression models, The Hosmer–Lemeshow test (χ^2 = 0.000, df = 8, p-value = 1), the Likelihood ratio test (χ^2 = 38.208, p-value < 0.001), and the Nagelkerke pseudo R^2 = 0.242, demonstrated that the model fitted the data well. Odds ratios were calculated by exponentiating the model coefficients. The same statistical method was applied to assess a potential post-stimulation effect after the VI was turned off. To that end, two logistic regression models, each incorporating the independent variable "Condition" consisting of conditions $System_{on}^{baseline}$, $System_{on}^{motion}$ and one referent condition ($System_{off}^{0min}$ and $System_{off}^{25min}$), were built and assessed using the previously mentioned procedures. The model with the referent condition $System_{off}^{0min}$ fitted the data well (Hosmer–Lemeshow test: $\chi^2 = 0.000$, $df = 8$, $p\text{-value} = 1$; Likelihood ratio test: $\chi^2 = 14.486$, $p\text{-value} < 0.001$; and the Nagelkerke pseudo $R^2 = 0.189$). The model with the referent condition $System_{off}^{25min}$ also fitted the data well (Hosmer–Lemeshow test $\chi^2 = 0.000$, $df = 8$, $p\text{-value} = 1$; the Likelihood ratio test $\chi^2 = 22.043$, $p\text{-value} < 0.001$; and the Nagelkerke pseudo $R^2 = 0.275$). All procedures were carried out in R (v.3.5.2).

Results

Table 1 presents the results obtained during the 6 consecutive fHIT-trials in the different experimental conditions of the VI. The percentage of correct answers improved from 19-44% (minimum-maximum) in all System OFF conditions to 75-94% with positive stimulation ($System_{on}^{motion}$). Positive stimulation showed the strongest significant improvement among all trials ($p < 0.001$, odds ratio = 23.4). Interestingly, baseline stimulation ($System_{on}^{baseline}$) also showed a significant, though smaller, improvement ($p = 0.02$, odds ratio = 4.9). fHIT results from the other trials were not significantly different from the first trial with no stimulation ($System_{off}$). After turning the VI off, the percentage of correct fHIT scores in the last two conditions significantly decreased with respect to positive stimulation ($System_{off}^{0min}$: $p = 0.002$, odds ratio = 7.9; $System_{off}^{25min}$: $p < 0.002$, odds ratio = 13.8). Regarding baseline stimulation, no significant difference was observed in fHIT scores directly after turning the VI off ($System_{off}^{0min}$). After 25 minutes, a significant decrease in fHIT scores was found with respect to baseline stimulation ($System_{off}^{25min}$: $p = 0.05$, odds ratio = 2.9). The side to which head impulses were directed, did not significantly contribute to the fHIT results.

Discussion

This case study investigated the possibility of restoring the high-frequency DVA in a patient implanted with a prototype VI, using the fHIT test. Positive and baseline electrical vestibular stimulation significantly improved the high-frequency DVA compared to no stimulation.

This is the second time a functional benefit of the VI is illustrated, after the ability of restoring DVA during walking on a treadmill (11). These findings are complementary, since fHIT scores probably reflect much more the capability of the vestibular implant to selectively restore the high-frequency DVA in the horizontal plane, while DVA tested on a treadmill probably reflects more the capability of restoring the whole vestibular system in a different plane and frequency range. After all during walking, other mechanisms like the vestibulo-collic reflex could also help stabilizing the gaze [van Dooren et al., 2019; Goldberg, and Cullen, 2011; Lempert et al., 1997; Aboshanif et al., 1929].

Positive stimulation (how the VI should work in daily life) was more effective than baseline stimulation. However, a significant effect was obtained with baseline stimulation. It could be hypothesized that stochastic resonance might play a role in improvement when applying baseline stimulation. Baseline stimulation could function as "white noise" to boost an initially weak signal of the natural vestibular system. This was previously demonstrated by using white noise galvanic vestibular stimulation to improve the walking stability in patients with bilateral vestibulopathy (18). After turning the VI off, the percentage of correct fHIT scores did not significantly differ from the scores obtained with baseline stimulation. This might imply that an "after effect" could have occurred, which was able to improve the fHIT scores to a certain extent. A learning effect seems to be less likely, since fHIT scores in the last two trials did not significantly differ with respect to the first trial. However, this condition had the lowest mean peak head velocity among all conditions, which might also mimic a post stimulation effect. More studies are necessary to verify these findings with a VI.

Limitations

Testing patients with the VI requires significant time and attention of the patients. Although randomization and multiple testing of each condition using a Latin square design would have been favorable, multiple testing was therefore not possible in this setting with this given patient. However, the patient was blinded for each condition. After optimizing biomechanical parameters (e.g. stimulation profile) and using chronic stimulation (no adaptation period necessary), this might be possible in the future. The fact that positive stimulation showed higher fHIT scores than the other conditions (with and without electrical stimulation), confirmed than the improvement was most likely not a placebo effect. With a dynamic range of 150-350 μA, baseline stimulation at 250 μA, and a modulation gain of 3 μA/◦/sec, stimulation already saturated with head velocities above approximately 33◦/sec. Since the lowest accepted head impulse was 102◦/sec, all impulses with both positive and reversed modulation received the same level of stimulation. This modulation gain was chosen to get strong eye movement responses for the purpose of showing feasibility. Therefore, the best stimulation paradigm should still be explored.

Conclusion

The vestibular implant seems capable of improving the high-frequency dynamic visual acuity. This functional benefit of the vestibular implant illustrates again the feasibility of this device for clinical use in the near future.

Ethics Statement

The subject gave written informed consent for participation and publication of the indirectly identifiable data in accordance with the Declaration of Helsinki. Approval of the ethical committees of the Geneva University Hospitals (NAC 11-080) and the Maastricht University Medical Center (NL36777.068.11/METC 11-2-031) was obtained.

Conflict of Interest

The authors have received travel and research grants from MED-EL (Innsbruck, Austria).

SR is the author of a Patent Deposit Application regarding the technique used in the functional head impulse test and is a shareholder of a company producing of the fHIT system used in this study (Beon Solutions srl, Zero Branco (TV), Italy)

Author contribution

All authors participated in the design of the experimental protocol and analysis. FL, MR and SC carried out the experiments. MP performed statistical analysis. DS, RvdB and AP wrote the manuscript, and all authors contributed to its editing. SR critically revised the manuscript. RvdB, AP, NG, JG and HK supervised all aspects of the work.

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Chapter VII

General discussion and valorization

The main aims and findings

Vestibular hypofunction is missed or misdiagnosed in many cases. One of the reasons is that the current vestibular testing battery is very extensive, but it still faces many diagnostic challenges (1–6), which can lead to inter- and intra-laboratory differences when diagnosing vestibular hypofunction. Therefore, the first aim of this thesis was to complement the existing knowledge on methodology underpinning the main tests for assessing the high-frequency VOR and DVA.

The second aim was related to the vestibular implant outcome measures. The VI is able to (partially) replace the vestibular organ by electrically stimulating the vestibular system (8). To evaluate the electrically evoked VOR in case of harmonic stimulation, the VOR response is often fitted with a harmonic signal, although the reponse is known to be non-linear (9). Furthermore, it was not yet investigated whether the electrically evoked VOR is able to restore DVA during fast, unpredictable head movements (measured with the functional head impulse test). Therefore, the second aim of this thesis was to evaluate eye movements analysis algorithms and the functional head impulse test, in relation to the electrically evoked VOR.

This thesis demonstrated that:

- When using SHIMP testing, predictability of head impulses lowered the VOR gain and latency of saccades in healthy volunteers;
- Different commercially available vHIT systems showed discrepancies in the diagnosis of bilateral vestibulopathy, resulting from the use of different VOR gain calculation algorithms and methods for eye and head movement recording;
- The ability to accomplish the DVA test on a treadmill was decreased in patients with bilateral vestibulopathy and decreased with age;
- Fitting VOR responses with a harmonic signal separately for each phase of the electrical stimulation was found to be an accurate method for studying the electrically induced VOR in case of unilateral vestibular implantation;
- The vestibular implant was able to restore DVA during fast unpredictable head impulses (measured by the functional head impulse test).

Evaluation of the high-frequency VOR

The VOR can be measured in different frequency domains, e.g. in the low frequency domain by the caloric test, in the middle frequency domain by rotatory chair testing, and in the high frequency domain by vHIT. VHIT is currently widely utilized in vestibular laboratories over the world. It can be performed in many ways, in which target position, head impulse type, and gain calculation methods vary. Although the influence of this variation on test outcomes has been extensively studied, one still needs to fill many “gaps” in the current knowledge to improve the clinical application of vHIT (10,11). However, standards regarding test methodology, data collection, and gain calculation methods are yet to be developed. The present work aimed to facilitate this process focusing only on VOR gain values and saccades latencies,

which are considered the most informative outcomes for evaluating high-frequency vestibular function with vHIT.

Target position

One of the factors that can be modified during VHIT testing is position of the target: a fixed target (HIMP), or a target moving along with the head (SHIMP). A different target position alters the saccadic response in both healthy subjects and patients with vestibular hypofunction (12). For example, compared to HIMP, SHIMP can significantly reduce saccades in vestibular patients which appear during head impulses (covert saccades). This absence of covert saccades can, depending on the gain calculation method used, improve reliable calculation of VOR gain (TS van Dooren and D. Starkov, in preparation). Furthermore, SHIMP can increase appearance and magnitude of saccades in healthy subjects, who never produce large saccades when tested with HIMP. This latter can be used in research settings to study saccadic responses to high frequency stimuli in a healthy population. It should be noted that the choice of the target position can slightly affect gain: gain is lower in SHIMP (13,14) (TS van Dooren and D. Starkov, in preparation). However, the clinical relevance of this difference (<0.1) seems to be low and might most likely be neglected.

Head movement paradigm

Another factor that can be modified during VHIT testing, is the head impulse itself: inward versus outward, and active versus passive head impulses. Inward or outward head impulses can be applied depending on the patient's physical state. For example, inward head impulses are more tolerated by patients with decreased neck mobility, which reduces the burden of testing. Active head impulses (performed by the test subject) are "close to reality", which allows to assess how the patients compensate to a reduced VOR in real life during active head movements. However, with active head impulses it might be more difficult to obtain impulses with the same velocities (Chapter 2). Obtaining similar head velocities is important since VOR gain is known to decrease with an increase of head impulse velocity (15). Therefore, preliminary trainings are required for patients before active head impulses are tested. However, this can prolong testing time and, consequently, increase burden of testing.

Different type of head impulses (inwards versus outward; active versus passive) can be classified by the level of predictability. For example, inward head impulses are more predictable than outward head impulses, since the direction of the head turn is already known. Apparently, active head impulses (performed by the test subject) are more predictable than passive head impulses (performed by the examiner). Taking all these aspects into account, passive outward head impulses can be considered the least predictable.

Contradictory findings exist regarding the influence of predictability on VOR gain: it is either decreased or unchanged in more predictable inward head impulses as well as in less predictable passive head impulses (16–21). In the present work, in healthy subjects tested with SHIMP, it was found that in passive head impulses the knowledge about the direction of the impulse (inward direction) only slightly lowered the VOR gain (Chapter 2). These small differences can be taken into account by obtaining normative values for each type of head impulse separately. Active head impulses demonstrated significantly higher VOR gain (about 0.2) than passive head impulses. Although this again can be taken into account by the use of separate normative values, much attention should be paid to the origin of these high gain values (see discussion below).

Knowledge about saccade latencies in the literature is scarce but consistent: latencies are shortened in case of more predictable inward head impulses (20,22,23). Finding of the present work were in line with this: saccades appeared much earlier in more predictable (active or inward) head impulses. In active head impulses, this difference was most prominent, where saccades appeared almost at the start of the impulse. From a gain calculation perspective, neglecting such differences in latencies can significantly influence VOR gain values.

Saccade latency can influence VOR gain

As discussed in Chapter 2, saccade latency differences change the intervals used for VOR gain calculation. This implies that depending on the position of the saccade, two impulses of the same patient can have significantly different VOR gain values. For the sake of accuracy, it is especially important to consider saccade latency when calculating VOR gain using the area under the curve method, although other methods might be affected as well. Therefore, standardized VOR gain calculation methods need to be proposed, validated, and implemented. One of the possible solutions is to consider only points present in all head impulses. However, since position of these points might vary among patients due-to different saccade latencies, corresponding normative values for intervals at least before, after, and including head peak velocity, might be required.

Clinical relevance of the absence of common standards of the vHIT systems

The lack of VHIT standards resulted in a variety of commercially available vHIT systems, which use different VOR gain calculation algorithms and eye tracking methods. This is already known to influence VOR gain in a healthy population and in patients with unilateral vestibulopathy (24,25). In this thesis, the influence of the type of vHIT system on VOR gain and saccadic eye responses was thoroughly evaluated in patients with bilateral vestibulopathy (Chapter 3). The VOR gain threshold was chosen in accordance with the Bárány Society diagnostic criteria Consensus document (10). Among three commercially available systems only 79% (22/28 patients) agreement was achieved on the diagnoses of bilateral vestibulopathy. Two main reasons were proposed: the type of the camera fixation (head or earth), which led to different eye and head recording and tracking methods, and the VOR gain calculation algorithms, which differed among all three systems. In regular clinical practice, diagnostic decision should not depend on the vHIT system used. Given the fact that the same patient can be diagnosed differently using different (but validated) vHIT systems, all systems should urgently be standardized regarding eye and head tracking methods, and regarding VOR gain calculation algorithms.

Evaluation of the DVA

DVA is a functional outcome of the interplay between the vestibular system, the oculomotor system and central processing in the brain. Just like the VOR, DVA can be tested in different ways. Evaluating DVA while walking is thought to be one of the most “close to reality” tests.

Age might influence DVA

Contradictory evidence exists regarding the influence of age on DVA: it is either present but weak, or absent (26–28). In this thesis, the age effect was undetectable with relatively large groups of tested healthy subjects and patients with bilateral vestibulopathy (Chapter 4). Summarizing all existing evidence, one can assume that age has no significant effect on DVA while walking. However, these findings do not

rule out the need of obtaining normative values for each age category. After all, the age effect might be hidden by compensatory strategies (e.g. preferred walking strategies or compensatory saccades) used by subjects to overcome the potential DVA decline. In addition, people with different height produce different number of steps at the same speed, which varies the head movement velocity, amplitude, and frequency. This variation leads to patients being tested in different conditions, which might have an impact on DVA on group level. One of the ways towards minimizing this variation on group level might be the use of the number of steps per second instead of treadmill speed. Simultaneous recording of the VOR and DVA, as well as the body movements, might also facilitate this assessment. Further investigation is required to uncover (if present) the age effect on DVA.

Imbalance and age can make the test unaccomplishable

In addition, the main drawback of DVA tested while walking on a treadmill is the choice of the same walking speeds for all test subjects, regardless of age and mobility problems. This is of high relevance, since imbalance is one of the most frequent symptoms in bilateral vestibulopathy (29). In addition, the effect of age on the ability to accomplish the test was not yet investigated. In this thesis, balance impairments and age substantially reduced the ability to accomplish the test with predetermined speeds, especially at high walking speeds (by about 40%, Chapter 4). Therefore, an individual range of speeds between 2 and 6 km/h for each test subject might be considered to increase the test feasibility on subject level. An alternative way could be to use only head movements, whilst the body is immobile. This idea was implemented in the fHIT (30). However, the correlation between DVA while walking and fHIT is poor (31). This is most likely due to several factors: 1. the use of different head movements (i.e., slow-moderate active/passive vertical movements while walking or fast active/passive movements in the fHIT), 2. the involvement of different sensory systems (i.e., all semicircular canals, otoliths, and proprioception while walking or only one semicircular canal in the fHIT), and 3. different gait and gaze stabilization strategies during walking (e.g., length of stride and minimization of head movements). Therefore, these tests should be considered as complementary rather than substitutable. Corresponding normative values should be obtained for each type of evaluation.

Evaluation of the VOR and DVA when stimulating with the vestibular implant

The vestibular implant is a novel treatment, which might help people with severely reduced vestibular function to significantly improve their quality of life (8). Since one of the aims of the vestibular implant is to improve dynamic visual acuity, it is of high importance to assess its ability to restore the VOR and DVA.

The asymmetry of the VOR response determines the preferred method of VOR analysis

Accurate and fast evaluation of the VOR response is necessary to clinically implement the vestibular implant in the future (e.g. when fitting the vestibular implant). Since harmonic electrical stimulation is often used when testing the vestibular implant, raw VOR traces can be replaced with harmonically fitted signals. This will facilitates calculation of the VOR main outcome measures, while minimizing effects of artefacts and noise. However, the current transfer function used in vestibular implant research, results in an asymmetric electrically evoked VOR response (9,32,33). In the “natural” vestibular system, an asymmetry is also present in the VOR response, but mainly for high head velocities (34). Therefore, asymmetry should be considered when developing a uniform paradigm for analyzing the electrically evoked VOR. In this thesis it was found that in case of harmonic electrical stimulation, fitting each

stimulation phase with a harmonic signal separately, did not cause significant discrepancies in the outcomes (Chapter 5) when compared to analysis of the raw traces. Therefore, half-cycle fitting can be considered an accurate method for evaluating the electrically evoked VOR in clinical trials. These results can be used to facilitate development of a robust VI fitting procedure, which (currently) predominantly utilizes harmonic electrical stimulation.

High-frequency DVA tested in a patient with a vestibular implant

It was previously demonstrated that the vestibular implant is able to restore DVA when walking on a treadmill. (35). In this thesis, the feasibility of improving the high-frequency DVA with a vestibular implant, was tested with the fHIT. In one patient with a vestibular implant prototype, a significant improvement of 75% was found in the condition when the implant was ON (Chapter 6). This implies that the fHIT might be considered as a complementary test (see above) or as an alternative for DVA on a treadmill, if the patient cannot walk at the speed of at least 2 km/h due-to age, imbalance, or other reasons. In addition, like the vHIT, the fHIT can test each pair of oppositely located semicircular canals (horizontal left and right, right anterior – left posterior, left anterior – right posterior). This thesis is therefore the next step in additionally quantifying the functional benefit of a vestibular implant in patients with vestibular hypofunction.

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Summary

Bilateral vestibulopathy is a heterogeneous disorder of the peripheral and/or (rarely) central vestibular system, leading typically to disabling symptoms like dizziness, imbalance, and/or oscillopsia (1–3). It affects up to 95 million adults in Europe and the USA (4). However, in many cases vestibular hypofunction is missed or misdiagnosed. One of the reasons is that the vestibular testing still faces many diagnostic challenges (5–10), which lead to inter- and intra-laboratory differences regarding diagnosing vestibular function loss (11). Therefore, it is imperative to standardize vestibular testing (**Chapter I**).

The current vestibular test battery mainly involves tests of the Vestibular-Ocular Reflex (VOR). One of the most frequently used tests of the high- frequency VOR, is the video Head Impulse Test (vHIT) (6). Different type of head movements (inwards versus outwards, active versus passive) can be performed during VHIT testing, which all differ regarding predictability. To evaluate the influence of the predictability of head movements on the VOR gain and saccadic response, sixty-two healthy subjects were tested using SHIMP (suppression head impulse paradigm) in four conditions: active and passive head movements, for both inward and outward head impulses. VOR gain, latency of the first saccade, and the level of saccade grouping (PR-score) were compared among conditions. Inward and active head movements were considered to be more predictable than outward and passive head movements. It was found that a higher predictability in head movements lowered gain only in passive impulses, and shortened latencies of compensatory saccades overall. For active impulses, gain calculation was affected by short-latency compensatory saccades, hindering reliable comparison with gains of passive impulses. Predictability did not substantially influence grouping of compensatory saccades (**Chapter II**).

A bilateral horizontal VOR gain of < 0.6, measured by vHIT, is one of the diagnostic criteria for bilateral vestibulopathy according to the Bárány Society (1). Sixty-four patients with bilateral vestibulopathy were tested using three commercially available vHIT systems, which utilized different techniques of tracking head and eye movements and methods of gain calculation. The systems showed clinically significant differences in the VOR gain, which might hinder proper diagnosis of patients with bilateral vestibulopathy. This result demonstrated an urgent need for standardization of vHIT testing (**Chapter III**).

Dynamic visual acuity (DVA) can be measured using different testing procedures. Testing DVA while walking on a treadmill, is considered to be a “close to reality” tests. Forty-four patients with bilateral vestibulopathy and 63 healthy subjects performed the DVA test on a treadmill at 0 (static condition), 2, 4 and 6 km/h (dynamic conditions). A significant loss of DVA was demonstrated in the group of bilateral vestibulopathy patients. However, since bilateral vestibulopathy and age significantly increased the drop-out rate at faster walking speeds, it was recommended to use age-matched controls and individual “preferred” walking speeds in older subjects, when testing DVA on a treadmill (**Chapter IV**).

There is no clinically available therapeutic option to restore the vestibular function. Fortunately, the vestibular implant (VI) could become a clinically useful device in the near future (12), which is able to (partially) restore vestibular function by electrical stimulation, similar to the cochlear implant restoring the function of the cochlea.

Different eye movement analysis algorithms are used in vestibular implant research to quantify the electrically evoked vestibulo-ocular reflex (eVOR). It was investigated whether these analysis techniques need to be adapted to optimise quantification of the electrically evoked VOR (eVOR). For this, “Natural” VOR responses were obtained in six age-matched healthy subjects and eVOR responses were obtained in

eight bilateral vestibulopathy patients fitted with a vestibular implant. VOR outcomes were calculated using three different eye movement analysis paradigms: raw eye trace analysis, half-cycle fitting of traces, full-cycle fitting of traces. It was demonstrated that the type of eye movement analysis algorithm significantly influenced VOR outcomes, especially regarding the VOR gain and asymmetry of the eVOR in bilateral vestibulopathy patients fitted with a vestibular implant. VOR axis and phase shift did not differ significantly between eye movement analysis algorithms. In healthy subjects no clinically significant effect of eye movement analysis algorithms on VOR outcomes was observed. For the analysis of the eVOR, the excitatory and inhibitory phases of stimulation should be analyzed separately due to the inherent asymmetry of the electrically evoked VOR. A half-cycle fitting method can be used a more accurate alternative to analyzing full-cycle traces (**Chapter V**).

Finally, the high-frequency DVA was tested using the functional head impulse test (fHIT), in a 72-years old patient with bilateral vestibulopathy and fitted with a vestibular implant (MED-EL, Innsbruck, Austria). aIt was found that the vestibular implant was able to significantly improve the high-frequency DVA. This functional benefit of the VI illustrated again the feasibility of the VI for clinical use in the near future (**Chapter VI**).

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Curriculum vitae

Dmitrii Starkov was born in Prokopievsk, a Russian town located in Siberia. From 2009 until 2015 he studied at the faculty of physics at Tomsk State University (Tomsk, Russia). From 2015 until 2017 he studied at a double master program “TOMA” created by professor Vladimir Petrovitsj Demkin at Tomsk State University and by professor Herman Kingma at Maastricht University. Right after graduation he applied for a PhD position at Maastricht University arranged by prof. Herman Kingma and Dr. Raymond van de Berg, which was devoted to evaluation of the vestibular function. Simultaneously with the PhD, Dmitrii Starkov worked as a junior researcher at Tomsk State University, where he contributed to development of a new optimized electrical stimulation paradigm for the vestibular implants. During his study Dmitrii Starkov put vast effort into the development of skills in analysis of numerical data and programming.