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

Dmitrii Starkov^{a, b} Nils Guinand^c Florence Lucieer^a Maurizio Ranieri^c Samuel Cavuscens^c
Maksim Pleshkov^{a, b} Jean-Philippe Guyot^c Herman Kingma^{a, b} Stefano Ramat^d
Angelica Perez-Fornos^c Raymond van de Berg^{a, b}

^aDivision of Balance Disorders, Department of Otorhinolaryngology and Head and Neck Surgery, Maastricht University Medical Center, School for Mental Health and Neuroscience, Maastricht, The Netherlands; ^bFaculty of Physics, Tomsk State Research University, Tomsk, Russia; ^cService of Otorhinolaryngology Head and Neck Surgery, Department of Clinical Neurosciences, Geneva University Hospitals, Geneva, Switzerland; ^dDepartment of Electrical, Computer and Biomedical Engineering, University of Pavia, Pavia, Italy

Keywords

Vestibular prosthesis · Vestibular implant · Neural prosthesis · Bilateral vestibulopathy · Functional head impulse test · Dynamic visual acuity

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-year-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 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; and (6) System OFF, 25 min 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 to 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.

© 2019 The Author(s)

Published by S. Karger AG, Basel

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 [Curthoys and Manzari, 2017; Halmagyi et al., 2017]. 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 [Guinand et al., 2012]. This method mainly involves head movements in the vertical plane at relatively low velocities (maximum peak 30°/s) and at a relatively low frequency (approximately 2 Hz). A new complementary test involving fast and high-frequency head movements was recently proposed: the functional Head Impulse Test (fHIT) [Ramat et al., 2012; Versino et al., 2014]. 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 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 3 months [Corallo et al., 2018]. 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 [van de Berg et al., 2012; Perez Fornos et al., 2014; Guinand et al., 2015; van de Berg et al., 2015]. A functional benefit of the

VI was already demonstrated by restoring the DVA during walking [Guinand et al., 2016]. The goal of this case study was to investigate the feasibility of restoring high-frequency DVA with a prototype VI, using the fHIT.

Materials and Methods

Patient and VI

A 72-year-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 [Perez Fornos et al., 2014; Guinand et al., 2015; van de Berg et al., 2015]. 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 the 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; STMicroelectronics; 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 [van de Berg et al., 2012]), 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 μ s. The lowest current level was determined by slowly increasing the current by 10–25 μ A, 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 μ A). Baseline of stimulation was set at 250 μ A, 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 [Guinand et al., 2015]. 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 $I = g_z \omega_z + \text{baseline}$, where I = current (μ A), g_z = gain (μ A/°/s), ω = head angular velocity (°/s), and z referred to the projection on the longitudinal axis. Gain g_z was set at 3 μ A/°/s. 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

Fig. 1. The functional Head Impulse Test. **a** The patient is positioned at 1.5 m 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 $10^\circ/\text{s}$, a Landolt ring appears for 80 ms (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.

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 [van de Berg et al., 2017]. 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 (F.L.) 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]. 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 Fig. 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 ms after head velocity exceeded $10^\circ/\text{s}$, a Landolt ring appeared at the same location for 80 ms. 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 $3,000\text{--}6,000^\circ/\text{s}^2$ 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.

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-opto-

types varied from 0.7 to 1, while duration of appearance ranged from 60 to 160 ms. After this training, the experimental procedure started. It consisted of six consecutive trials, with different electrical stimulation conditions of the VI 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 poststimulation 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 min 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 ($\chi^2 = 0.000$, $df = 8$, p value = 1), the likelihood ratio test ($\chi^2 = 38.208$, 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 poststimulation 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

Table 1. Percentage and absolute number of correctly determined Landolt C optotypes in left- and rightward directed impulses during different test conditions

Side	Left (implanted)	Right
	% correct answers, (absolute number)	% correct answers, (absolute number)
Condition		
System _{off}	19 (3/16)	19 (3/16)
System _{on} ^{baseline*}	50 (8/16)	56 (9/16)
System _{on} ^{reversed}	38 (6/16)	25 (4/16)
System _{on} ^{motion*}	94 (15/16)	75 (12/16)
System _{off} ^{0min}	44 (7/16)	38 (6/16)
System _{off} ^{25min}	38 (6/16)	19 (3/16)

* Significant improvement compared to condition System_{off}.

the referent condition System_{off}^{0min} fitted the data well (Hosmer-Lemeshow test: $\chi^2 = 0.000$, $df = 8$, p value = 1; likelihood ratio test: $\chi^2 = 14.486$, p 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 value = 1; the likelihood ratio test $\chi^2 = 22.043$, p 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 to 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 min, 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 [Guinand et al., 2016]. These findings are complementary, since fHIT scores probably reflect much more the capability of the VI 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 [Aboshanif et al., 1929; Lempert et al., 1997; Goldberg and Cullen, 2011; van Dooren et al., 2019].

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 [Wuehr et al., 2016]. 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 poststimulation 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 ad-

aptation 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 that the improvement was most likely not a placebo effect. With a dynamic range of 150–350 μ A, baseline stimulation at 250 μ A, and a modulation gain of 3 μ A/°/s, stimulation already saturated with head velocities above approximately 33 °/s. Since the lowest accepted head impulse was 102 °/s, 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 VI seems capable of improving the high-frequency DVA. This functional benefit of the VI illustrates again the feasibility of this device for clinical use in the near future.

Acknowledgments

H.K., R.B., and D.S. were supported by a grant from the Russian Science Foundation (project No. 17–15–01249).

References

- Aboshanif M, Itasaka Y, Omi E KK and IK: Otolith Dysfunction can Affect Head Stability during Gait. *J Comp Neurol*. 1929;47:155–69.
- Colagiorgio P, Colnaghi S, Versino M, Ramat S. A New Tool for Investigating the Functional Testing of the VOR. *Front Neurol*. 2013 Oct;4:165.
- Corallo G, Versino M, Mandalà M, Colnaghi S, Ramat S. The functional head impulse test: preliminary data. *J Neurol*. 2018 Oct;265(S1 Suppl 1):35–9.
- Curthoys IS, Manzari L. Clinical application of the head impulse test of semicircular canal function. *Hear Balance Commun*. 2017;15(3):113–26.
- Goldberg JM, Cullen KE. Vestibular control of the head: possible functions of the vestibulocollic reflex. *Exp Brain Res*. 2011 May;210(3-4):331–45.
- Guinand N, Van de Berg R, Cavuscens S, Stokroos R, Ranieri M, Pelizzzone M, et al. Restoring Visual Acuity in Dynamic Conditions with a Vestibular Implant. *Front Neurosci*. 2016 Dec;10:577.
- Guinand N, Pijnenburg M, Janssen M, Kingma H. Visual acuity while walking and oscillopsia severity in healthy subjects and patients with unilateral and bilateral vestibular function loss. *Arch Otolaryngol Head Neck Surg*. 2012 Mar;138(3):301–6.
- Guinand N, van de Berg R, Cavuscens S, Stokroos RJ, Ranieri M, Pelizzzone M, et al. Vestibular Implants: 8 Years of Experience with Electrical Stimulation of the Vestibular Nerve in 11 Patients with Bilateral Vestibular Loss. *ORL J Otorhinolaryngol Relat Spec*. 2015;77(4):227–40.
- Halmagyi GM, Chen L, MacDougall HG, Weber KP, McGarvie LA, Curthoys IS. The Video Head Impulse Test. *Front Neurol*. 2017 Jun;8:258.
- Lempert T, Gianna CC, Gresty MA, Bronstein AM: Effect of otolith dysfunction. Impairment of visual acuity during linear head motion in labyrinthine defective subjects. *Brain*. 1997 Jun;120(Pt 6):1005–13.
- Perez Fornos A, Guinand N, van de Berg R, Stokroos R, Micera S, Kingma H, et al. Artificial balance: restoration of the vestibulo-ocular reflex in humans with a prototype vestibular neuroprosthesis. *Front Neurol*. 2014 Apr;5:66.
- Ramat S, Colnaghi S, Boehler A, Astore S, Falco P, Mandalà M, et al. A Device for the Functional Evaluation of the VOR in Clinical Settings. *Front Neurol*. 2012 Mar;3:39.
- van de Berg R, Guinand N, Guyot JP, Kingma H, Stokroos RJ. The modified ampullar approach for vestibular implant surgery: feasibility and its first application in a human with a long-term vestibular loss. *Front Neurol*. 2012 Feb;3:18.
- van de Berg R, Guinand N, Nguyen TA, Ranieri M, Cavuscens S, Guyot JP, et al. The vestibular implant: frequency-dependency of the electrically evoked vestibulo-ocular reflex in humans. *Front Syst Neurosci*. 2015 Jan;8:255.
- van de Berg R, Guinand N, Ranieri M, Cavuscens S, Khoa Nguyen TA, Guyot JP, et al. The Vestibular Implant Input Interacts with Residual Natural Function. *Front Neurol*. 2017 Dec;8:644.
- van Dooren TS, Lucieer FM, Duijn S, Janssen AM, Guinand N, Pérez Fornos A, et al. The Functional Head Impulse Test to Assess Oscillopsia in Bilateral Vestibulopathy. *Front Neurol*. 2019 Apr;10:365.
- Versino M, Colagiorgio P, Sacco S, Colnaghi S, Quaglieri S, Manfrin M, et al. Reading while moving: the functional assessment of VOR. *J Vestib Res*. 2014;24(5-6):459–64.
- Wuehr M, Nusser E, Decker J, Krafczyk S, Straube A, Brandt T, et al. Noisy vestibular stimulation improves dynamic walking stability in bilateral vestibulopathy. *Neurology*. 2016 Jun;86(23):2196–202.

Statement of Ethics

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.

Disclosure Statement

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

S.R. is the author of a Patent Deposit Application regarding the technique used in the fHIT and is a shareholder of a company producing the fHIT system used in this study (Beon Solutions srl, Zero Branco, Italy).

Author Contributions

All authors participated in the design of the experimental protocol and analysis. F.L., M.R., and S.C. carried out the experiments. M.P. performed the statistical analysis. D.S., R.B., and A.P.-F. wrote the manuscript, and all authors contributed to its editing. S.R. critically revised the manuscript. R.B., A.P.-F., N.G., J.-P.G., and H.K. supervised all aspects of the work.