Optimized Signal Analysis to Quantify the Non-Linear Behaviour 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, it was observed that the morphology of the VOR and eVOR may differ substantially. In this study, it was investigated if the analysis techniques for eVOR need to be adapted to optimize 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-vestibulopathy 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 95% CI, \( p = 0.018 \)). Half-cycle fitting lowered VOR gain in the dVOR condition (mean differ-
Bilateral vestibulopathy (BV) can lead to a bilaterally reduced or absent function of the vestibular organs, and it is associated with severely impaired balance and movement-induced blurred vision (oscillopsia) [Strupp et al., 2017]. This latter often results in a loss of visual acuity during head motions. Current treatment options for this disabling disease [Lucieer et al., 2020] are scarce, and results are limited [Porciuncula et al., 2012]. A non-invasive treatment using a balance belt was recently introduced, which is able to significantly improve balance but does not seem to improve the reduced dynamic visual acuity [Kingma et al., 2019]. However, another promising but invasive treatment, the vestibular implant (VI), has been proposed over the last years and feasibility was demonstrated [van de Berg et al., 2011, 2015; Guinand et al., 2016; Boutros et al., 2019; Fornos et al., 2019; Chow et al., 2021]. 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 [Guinand et al., 2015]. In order to objectively validate the contribution of the VI, the vestibulo-ocular reflex (VOR) is detected by video-oculography and quantified [Fetter, 2007; Perez Fornos et al., 2014; van de Berg et al., 2017]. In healthy (HL) subjects, this reflex moves the eyes in the direction opposite to the head movement, thereby keeping gaze stable. In patients with BV, the VOR is severely reduced or absent, which is generally believed to result in blurred vision during head movements [Tilikete, and Vighetto, 2011]. It has been demonstrated that the VI is an effective way to electrically evoke the VOR (electrically evoked VOR [eVOR]), replacing the physiological signal of the non-functional vestibular system [Perez Fornos et al., 2014; van de Berg et al., 2017]. However, at head impulses with high head peak velocities (>100°/s), a single HL 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) [Kingma and van de Berg, 2016]. Therefore, contribution from both symmetrically orientated vestibular organs is required at higher peak head velocities to produce symmetric responses in all head movement directions. Current VI trials involve unilateral implantation/stimulation, thus (partially) mimicking the "asymmetrical" unilateral vestibular function [Yoo, 2020]. Consequently, one can expect the eVOR to also show this asymmetry with higher gains for the excitatory stimulation.

Main outcome measures to assess the eVOR are [Perez Fornos et al., 2014; van de Berg et al., 2017] 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 [van de Berg et al., 2017]. 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 [Perez Fornos et al., 2014; van de Berg et al., 2017]. 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 [Perez Fornos et al., 2014], 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 [Perez Fornos et al., 2014; van de Berg et al., 2017], 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 eVOR responses obtained in BV patients fitted with a VI and traces of “natural” VOR responses obtained in HL subjects were analysed in this study. These eye movement traces have been already presented in previous studies [Perez Fornos et al., 2014; van de Berg et al., 2017]. 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 1 Hz and with a peak angular velocity of 30 deg/s. All trials were conducted in complete darkness and lasted 60 s 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 220 Hz. Experiments were conducted on HL 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 HL 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 standard deviation years. Data from eight VI patients were available for the analysis in the eVOR condition. Data from five VI patients were available for the analysis of eye movements in the dVOR condition. All patients were implanted in one ear with a VI prototype (MED-EL, Innsbruck, Austria) [Perez Fornos et al., 2014; van de Berg et al., 2017; Guyot and Perez Fornos, 2019]. Each VI patient fulfilled the following inclusion criteria [Perez Fornos et al., 2014]: (1) Reduced caloric response (sum of bithermal maximum slow phase eye velocity on each side ≤6°/s) [van de Berg et al., 2020], (2) a VOR gain <0.6 in the head-impulse test for horizontal and vertical semicircular canals, and (3) a VOR gain of <0.25 on rotatory chair tests. All patients were also profoundly deaf in the implanted ear [Perez Fornos et al., 2014]. Detailed characteristics of the HL 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 online supplementary Figure 1 (see www.karger.com/doi/10.1159/000525577 for all online suppl. material).

Table 1. Characteristics of the HL subjects and the VI patients including electrical stimulation parameters and the test condition

| 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          | Ménière’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   | SAN                 | Left                | 120±60                              | eVOR, dVOR     |
| BV8            | M   | 53          | Trauma     | Intra-labyrinthine   | SAN                 | Right               | 350±125                             | eVOR, dVOR     |

BV, bilateral vestibulopathy; AM, amplitude modulation; LAN, lateral ampullary nerve; SAN, superior ampullary nerve; PAN, posterior ampullary nerve.

Electrical Stimulation
The detailed explanation of the implantation procedure and the determination of the stimulation parameters can be found in the previous publications [van de Berg et al., 2012; Guinand et al., 2015]. 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 [Guinand et al., 2015]. 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 min 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 [Perez Fornos et al., 2014]. 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 30°/s [van de Berg et al., 2017]. 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).

**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 (MathWorks, Natick, MA, USA). Horizontal and vertical eye positions were first smoothed using a 11th order Savitzky-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) [van de Berg et al., 2017] 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 Fig. 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 online 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 Fig. 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 cycles 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.

**Fig. 1.** Examples of the stimulus traces (rotatory chair horizontal velocity) and raw eye velocity traces of one HL subject undergoing whole-body rotations (nVOR), and two BV patients fitted with a VI in the eVOR (subject sitting static on an immobile chair) and dVOR (subject sitting in the rotatory chair) conditions. LAN, lateral ampullary nerve electrode; SAN, superior ampullary nerve electrode.

**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 Fig. 1a).

**Fitting the Sine 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 φ₀ in Fig. 2a). The linear frequency of the fitted sine (see f in Fig. 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 HL subjects, all half cycles were classified as rightwards or leftwards 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 when the rotation was 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 used as the maximum values. Each peak was classified as either excitatory or inhibitory (see Fig. 2c).

Calculation of Outcome Measures

For the HL 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°/s, also separately for each trace.

Orientation of the 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 Fig. 2a). The angle was presented in the range of (0:360) degrees (see angles α and β in Fig. 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 HL subjects or phases of stimulation for the patients were calculated, in order to facilitate visual comparison between patients and HL subjects (see the angle γ in Fig. 2d: VOR axis). Asymmetry was calculated as (rightward gain – leftward gain)/(rightward gain + leftward gain) for the HL subjects and as (excitatory gain – inhibitory gain)/(excitatory gain + inhibitory gain) [van de Berg et al., 2017] for the eVOR and dVOR condition in VI patients.

The phase shift between the horizontal eye and head velocities was calculated only for the HL subjects and the dVOR condition in VI patients using the Spearman’s correlation [van de Berg et al., 2017]. 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 determined 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 eVOR has values close to 180 (or −180) degrees [van de Berg et al., 2017], 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° for positive values (phase lead) and to −180° for negative values (phase lag) (see φ in Fig. 2d: phase shift).
In order to estimate how well the fitted signals repeated 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 [Fisher, 1995]. 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. The eye movement analysis algorithm was set as the within-subject factor and asymmetry or phase shift was set as the dependent variable.

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**Fig. 3.** A one-cycle example of the raw, full-cycle fitted, and half-cycle fitted VOR response in a HL subject undergoing whole-body rotations (nVOR) and in two VI patients in two different conditions (eVOR; dVOR). 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; eVOR, electrical stimulation in VI patients without whole-body rotations; dVOR, electrical stimulation in VI patients with whole-body rotations.
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, the 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.

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 RANOVARs were calculated. The 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 [Haynes, 2013]. All statistical analyses were done in R (v.3.5.2).

**Results**

**Data Cleaning and Results per Test Subject**

In the HL 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. For each test subject, stimulation phase, and type of trace, the median values of the VOR gain, error of fitting, and VOR axis angle are shown in online supplementary Table 1, and the corresponding median values of asymmetry and the phase shift are shown in online supplementary Table 2.

**VOR Gain**

The mean VOR gain values for each condition, stimulation phase, and eye movement analysis algorithm are
presented in Figure 4 and online supplementary Table 3. In the HL 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 95% CI, \(p = 0.008\)) and half-cycle fitting (mean difference: 0.03 ± 0.01 95% CI, \(p < 0.001\)) 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 of eye movement analysis algorithm (raw traces or half-cycle fitting) (mean difference: 0.06 ± 0.02 95% CI, \(p < 0.001\)).

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 95% CI, \(p = 0.018\)). For half-cycle fitting, this difference was not statistically significant after Bonferroni correction (mean difference: 0.08 ± 0.05 95% CI, 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 95% CI, \(p = 0.046\)). 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 95% CI, \(p = 0.027\)) and half-cycle fitting (mean difference: 0.08 ± 0.05 95% CI, \(p = 0.019\)).

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 95% CI, \(p = 0.009\)). 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 95% CI, 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 95% CI, 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 95% CI, \(p = 0.003\)).

### Asymmetry

Mean asymmetry between directions of stimulation (right and left) for HL subjects or phases of stimulation (excitatory and inhibitory) for patients are presented in Figure 4 and online supplementary Table 4. In the HL 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 95% CI, \(p = 0.011\)), as well as between the half-cycle and full-cycle fitted traces (mean difference: 0.19 ± 0.12 95% CI, \(p = 0.024\)). In the dVOR condition, the mean asymmetry of the half-cycle fitted traces was higher than that of the full-cycle fitted traces (mean difference: 0.11 ± 0.06 95% CI, \(p = 0.016\)).

### VOR Axis

The absolute VOR axis angle between stimulation phases (see the angle \(\gamma\) in Fig. 2d: VOR axis) is shown in Figure 4 and online supplementary Table 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 HL subjects nor in the VI patients.

| Condition | Stimulation phase | Mean error of fitting ± SD |
|-----------|-------------------|---------------------------|
|           |                   | full-cycle fitting        | half-cycle fitting       |
| nVOR      | Rightwards        | 0.72±0.39                 | 0.31±0.12                |
|           | Leftwards         | 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                |

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; SD, standard deviation.
**Phase Shift**

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

**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: 0.47 ± 0.23 95% CI, \( p = 0.002 \)). 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 95% CI, \( p = 0.003 \)).

**Discussion**

This study aimed at comparing the VOR outcomes between three different eye movement analysis algorithms which are used to investigate the natural and eVOR. It was demonstrated that the type of eye movement analysis algorithm significantly influenced VOR outcomes, especially regarding VOR gain and asymmetry of the eVOR in NV patients fitted with a VI. VOR outcomes of the natural VOR obtained in HL subjects were less affected by the type of eye movement analysis algorithm due to lower variability and symmetry of the HL VOR response. VOR outcomes of the eVOR were more affected by the eye movement analysis algorithm than those of the natural VOR. This mainly resulted from the fact that the eVOR is asymmetric, which was demonstrated by the significantly higher than zero asymmetry values, in both conditions (see Fig. 3). This asymmetry was also previously described in other VI studies [Perez Fornos et al., 2014; van de Berg et al., 2017]. The asymmetric VOR response to high-velocity head movements is a characteristic of HL unilateral vestibular function [Kingma and van de Berg, 2016]. Therefore, symmetrical VOR responses can only be achieved with two HL 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 in this study (30°/s) which would most likely not explain the asymmetry, the asymmetry might be related to, e.g., the applied transfer function of the VI (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 eVOR 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 higher VOR gain values. However, this was not statistically proven in the present study due to small mean differences (see Fig. 4; online suppl. 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 excitatory phase was narrower than one to the inhibitory phase of stimulation (e.g., see Fig. 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 Fig. 1: eVOR superior ampullary nerve), 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 online suppl. Fig. 1 and also the results obtained in the HL subjects), it might be expected that the VOR gain differences between analysis algorithms will decrease with an increase of the VOR re-
response. For this, more data might be needed than currently available in VI 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 eVOR response should be taking into account in the analysis, it would be advised to investigate each phase of the VOR response separately in VI research. This should at least be done when the asymmetry is prominent, e.g., before long-term adaptation. Therefore, in addition to the analysis of raw traces, half-cycle fitting is also a useful eye movement analysis algorithm for VI 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. On 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, mostly due to compensatory strategies (e.g., refixation saccades) to overcome the deficiency in VOR [Guinand et al., 2012; Fetter, 2016]. Therefore, the role of the VOR gain values might be lower than in case of objective evaluation of the VOR. Based on this, 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 compared 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 a 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 eVOR, the excitatory and inhibitory phases of sinusoidal stimulation should be analysed separately due to the inherent asymmetry of the eVOR. 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.

Statement of Ethics

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.

Conflict of Interest Statement

MEDEL provided the VCI devices and funding for travel for Angélica Pérez Fornos, Nils Guinand, and Raymond van de Berg. MEDEL, ZonMw, Heinsius Houbolt Foundation, and the Weijerhorst foundation provided grants for vestibular implant research for Raymond van de Berg. Tomsk State University Development Programme ("Priority-2030") provided a grant for vestibular implant research for Dmitrii Starkov and Maksim Pleshkov.

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Author Contributions

Angélica Pérez Fornos, Nils Guinand, Maurizio Ranieri, Samuel Cavuscens, Raymond van de Berg, and Herman Kingma planned and conducted the experiment. Dmitrii Starkov and Maksim Pleshkov made the data processing and statistical analysis. Dmitrii Starkov and Raymond van de Berg wrote the manuscript. All the authors contributed to its editing.

Data Availability Statement

Data are available on the reasonable request to the corresponding author.
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