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TITLE:

Using Unidirectional Rotations to Improve Vestibular System Asymmetry in Patients with Vestibular Dysfunction

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Keywords:
compensation, vestibulo-ocular reflex, directional preponderance, rehabilitation, vertigo

SUMMARY:
A new rehabilitation method is presented for rebalancing the vestibular system in patients with asymmetric responses, which consists of unidirectional rotations toward the weaker side. By directly modifying the vestibular pathway rather than enhancing the multisensory aspects of compensation, asymmetry can be normalized within 1–2 sessions and show lasting effects.

ABSTRACT:
The vestibular system provides information about head movement and mediates reflexes that contribute to balance control and gaze stabilization during daily activities. Vestibular sensors are located in the inner ear on both sides of the head and project to the vestibular nuclei in the brainstem. Vestibular dysfunction is often due to an asymmetry between input from the two sides. This results in asymmetrical neural inputs from the two ears, which can produce an illusion of rotation, manifested as vertigo. The vestibular system has an impressive capacity for compensation, which serves to rebalance how asymmetrical information from the sensory end

organs on both sides is processed at the central level. To promote compensation, various rehabilitation programs are used in the clinic; however, they primarily use exercises that improve multisensory integration. Recently, visual-vestibular training has also been used to improve the vestibulo-ocular reflex (VOR) in animals with compensated unilateral lesions. Here, a new method is introduced for rebalancing the vestibular activity on both sides in human subjects. This method consists of five unidirectional rotations in the dark (peak velocity of 320°/s) toward the weaker side. The efficacy of this method was shown in a sequential, double-blinded clinical trial in 16 patients with VOR asymmetry (measured by the directional preponderance in response to sinusoidal rotations). In most cases, VOR asymmetry decreased after a single session, reached normal values within two sessions, with the effects lasting up to 6 weeks. The rebalancing effect is due to both an increase in VOR response from the weaker side and a decrease in response from the stronger side. The findings suggest that unidirectional rotation can be used as a supervised rehabilitation method to reduce VOR asymmetry in patients with longstanding vestibular dysfunction.

INTRODUCTION:

Vestibular dysfunction is a common disorder with a prevalence of ~35% in adults above 40 years old[1]. Most vestibular disorders result in an asymmetry between input from both sides, resulting in an illusion of rotation called vertigo. In the absence of normal vestibular function, even simple daily activities can be challenging. Vestibular dysfunction is often quantified by the vestibulo-ocular reflex (VOR). During natural activities, such as walking or running, the VOR moves the eyes in opposite directions and with the same velocity as head movement. This reflex has a short latency of ~5 ms, and it is mediated in the horizontal plane through a simple, three-neuron arc[2]. The information travels from vestibular receptors to the vestibular nuclei, then to the abducens motor neurons. These eye movements result in stabilization of horizontal gaze during daily activities. The symmetry of the VOR in response to clockwise and counterclockwise rotations is an important test of vestibular function.

Unilateral vestibular dysfunction produces central compensatory changes and centrally driven peripheral changes to overcome defective asymmetric VOR and resulting vestibular imbalance. Even after permanent vestibular lesions, such as a unilateral vestibular neurectomy, the vertigo and accompanying symptoms improve over a short period (days to weeks) of time. Due to this ability, the vestibular system has been a model for studying adaptation and compensation in neural pathways. It has been previously shown[3] that changes in central vestibular pathways can be implemented by a unidirectional rotation based on a hypothesis proposed about 20 years ago. Other studies have also shown compensatory changes in different parts of the sensory pathway, including the vestibular nuclei (VN)[4-8], commissural pathways between the VN on both sides[9], cerebellar input[10], and the vestibular periphery[11]. These compensatory changes result in a new balance in the activity of VN neurons on both sides.

Despite the impressive ability of the vestibular system to compensate for asymmetric inputs from the two ears, research has shown that responses to fast movements are never fully compensated[12,13]. It is now known that natural vestibular compensation does not use the full capacity of the system, and the compensated VOR response can be improved in animals that have participated in visual-vestibular training[14,15]. It has long been known that vestibular-rehabilitation exercises improve the compensation in patients with chronic imbalance problems by enhancing the (non-vestibular) multisensory nature of balance control[16-21]. The goal of these vestibular-rehabilitation exercises is to use physiological or behavioral approaches to improve symptoms as well as a patient's quality of life and independence[22,23].

Described herein is a rehabilitation method that uses unidirectional rotations toward the "weaker" side (**Figure 1A**). The basic idea for this method comes from Hebbian plasticity, in which neural connections become stronger when they are stimulated. This method specifically modifies vestibular input rather than enhancing multisensory integration, which is the basis for other vestibular-rehabilitation exercises. Previous research has shown that unidirectional rotations decreases VOR asymmetry in 1–2 sessions in patients with unilateral vestibular dysfunction[3]. This effect was mainly due to an increase in the activity of the side with a lower response (LR), as well as a slight decrease in the activity of the side with a higher response (HR). This change is most likely mediated by modifications in the central pathways (e.g., strengthening of afferent pathways, such as VN connections or changes in commissural inputs). In effect, this technique may be used as a supervised method for vestibular rehabilitation in those with longstanding vestibular asymmetry.

PROTOCOL:

The data presented here and previously published[3] were obtained by studies carried out in accordance with the recommendations of the Ethics Committee of Shahid Beheshti University of Medical Sciences, Tehran, Iran and a protocol that was approved by the Institutional Review Board of the University.

1. Participant screening and preparation

1.1. Recruit participants who have had a history of balance problems for more than one year.

NOTE: Vestibular compensation happens most effectively over the first month after a lesion. The one year timepoint was chosen to provide enough time for natural compensation to reach its plateau and also ensure that the patient does not have a fluctuating vestibular disorder.

1.2. Use the following exclusion criteria for patients:

1.2.1. History of central nervous system problems (e.g., head trauma, stroke, brain tumor, etc.) that may affect the central vestibular pathways, which are required for proper compensation.

1.2.2. Diagnosed with a fluctuating vestibular disorder (e.g., benign paroxysmal positional vertigo [BPPV] or Meniere's disease).

1.2.3. Patients using other forms of vestibular rehabilitation program or types of physical activity (e.g., athletes) that may improve vestibular compensation independent of the unidirectional rotation rehabilitation should be excluded.

NOTE: This criterion is suggested only for research purposes and to control for extraneous variables.

1.3. Do not limit participants based on age or gender.

NOTE: Similar to other compensation, this rehabilitation method is expected to have less pronounced effects in older subjects.

1.4. Instruct participants to refrain from using any medications that suppress the central nervous system, including antihistamines or any anti-vertigo drugs for at least 1 day prior to each experimental session.

1.5. Instruct participants not to use any nervous system stimulants, including amphetamines and caffeine for at least 1 day prior to each experimental session.

1.6. Instruct participants to refrain from drinking alcoholic beverages in quantities that impair normal functioning, as this can interfere with functioning of the vestibular system and affect the results.

2. Measurement of the vestibulo-ocular reflex (VOR)

2.1. Use either videonystagmography (VNG) or electronystagmography (ENG) to measure the VOR response during whole-body rotation.

NOTE: The data presented in the results section was recorded by ENG. The current equipment shown in the movie uses VNG.

2.2. Perform all recordings in the dark, with the head positioned 30° nose-down.

NOTE: For visualization purposes, the associated video is not performed in the dark.

2.3. Ask participants to sit in the rotary chair, secure them in the chair with the harness, put the infrared goggles on, and fix the head in the headrest at a ~30° nose-down position.

2.4. After participants acclimate to the dark, calibrate the eye signal by asking them to look at laser targets that are projected on the wall at ±10° angles (e.g., to the right, left, above, and below midline).

2.5. Begin running the protocol once the eye tracker is calibrated accurately, when the subjects are ready.

2.6. Keep subjects alert and distracted during all vestibular testing by asking them questions or having them do mental arithmetic (e.g., count backwards from 100).

3. Unidirectional rotation stimulus

3.1. With the subject seated in the rotary chair, use a unidirectional rotation that consists of an asymmetric triangular velocity profile with an acceleration of 80°/s^2 over 4 s to reach a maximum velocity of 320°/s^2, then slowly decelerate at 10°/s^2 to stop in about 30 s.

NOTE: The slow deceleration is particularly important in order to have a smooth stop in order to avoid stimulating the opposite side.

3.2. Perform five such rotations with 1 min intervals. The five rotations together are considered a rehabilitation session (**Figure 1B**).

3.3. Keep the subject in the chair after the last unidirectional rotation to test the symmetry with a bidirectional sinusoidal harmonic acceleration (SHA) rotation test at 40 min and 70 min post-unidirectional rotation.

NOTE: Keeping the patient in the chair will decrease the variability.

3.4. Perform the SHA test using a wide range of sinusoidal rotations at frequencies of 0.05 Hz, 0.2 Hz, and 0.8 Hz, with a peak velocity of 60°/s.

NOTE: For data presented in the results, a sinusoidal rotation at 0.2 Hz (40°/s) was used for all evaluations.

4. Experiment design

4.1. Evaluate subjects with a full battery of vestibular tests during the initial session (see below) in order to test VOR asymmetry and rule out any central problems.

4.2. One week later, expose the subjects to the unidirectional rotation and an SHA test (steps 3.1–3.4).

4.3. Repeat this process for a total of six sessions for 2x per week during the first 2 weeks, then 1x per week for the next 2 weeks (total of six sessions).

4.4. Administer an SHA test at the beginning (step 3.4) and end (steps 3.3 and 3.4) of each session and calculate the directional preponderance (DP) as a measure of asymmetry:

$$DP = \frac{V_{HR} - V_{LR}}{V_{HR} + V_{LR}} \times 100$$

Where: V_{HR} and V_{LR} represent peak eye velocities during rotations toward the side with higher responses (HR) and lower responses (LR), respectively.

NOTE: The directional preponderance provides a normalized measure of the difference in peak eye velocity for rotations in the two directions. While it is mainly used for measuring asymmetry in caloric responses, it can be (and is) used for quantifying VOR asymmetry in SHA[24-28].

4.5. Perform another SHA test (step 3.4) 1 week after the last rehabilitation session.

5. Sessions details

5.1. Initial session

5.1.1. During the first visit, take a brief history of the patient's imbalance problems to verify the duration of vestibular asymmetry and ensure no indication of a fluctuating disorder.

5.1.2. Perform a complete set of vestibular tests, including saccades, smooth pursuit, optokinetic, gaze holding, positional and positioning, caloric, and rotational tests.

5.1.3. Only recruit patients with VOR asymmetry during rotation who have clear abnormal directional preponderance (DP), typically with asymmetry values of more than 10%. This will be considered the initial (baseline) DP for each subject.

NOTE: Different equipment might provide different normal ranges and it is best to use the range specified for your device or to base the normal range on lab-specific normative data.

5.1.4. Clearly explain to the subjects the procedure of unidirectional rotation (5x in one session) and the total number of sessions (six times total).

5.1.5. Ask each subject to sign a consent form that has been approved by the local Institutional Review Board (or equivalent, for experiments performed outside of the United States), while clearly informing them that they can drop out of the study at any point and for any reason.

5.2. Unidirectional rotation sessions (six sessions)

5.2.1. Expose subjects to the unidirectional rotation (steps 3.1–3.4) during six sessions (steps 4.3 and 4.4).

5.2.2. At the beginning of each rehabilitation session, perform an SHA test (step 3.4) and calculate the DP value.

NOTE: This will provide the pre-rehabilitation DP for that session and long-term post-rehabilitation DP for the previous session.

5.2.3. Do not perform the unidirectional rotational rehabilitation if the pre-rehabilitation DP value falls in the normal range (<10%) in any of the sessions and instruct the subject to return for the next session.

5.2.4. If the pre-rehabilitation DP is in the abnormal range, wait 5 min after the SHA test and perform the unidirectional rotational rehabilitation.

5.2.5. Perform a second SHA test 40 min and 70 min after the end of unidirectional rotation rehabilitation (step 3.4) and calculate the post-rehabilitation DP for this session.

5.2.6. Instruct the subjects to return for the next session.

5.3. Final session

5.3.1. Perform an SHA test only (step 3.4) and calculate the DP value.

NOTE: This will serve as the final asymmetry measurement.

5.3.2. Do not use unidirectional rotation in the last session.

REPRESENTATIVE RESULTS:

Short-term effects of the unidirectional rotation were evaluated by measuring the VOR with a 0.2 Hz (40°/s) sinusoidal rotation test at 70 min after rehabilitation[3]. **Figure 2** shows the peak eye velocities during the VOR responses to rotations in the two directions (**Figure 2A**) and the change in the DP (**Figure 2B**). Following unidirectional rotation, the response to rotations in the direction of the side with the lower response (LR) was increased, and the response to rotations in the opposite direction (the direction with the stronger response [HR]) decreased, resulting in decreases in VOR asymmetry and DP value. It should be noted that the phase of the response is not calculated in the current study, since subjects had asymmetric VOR responses, while the VOR phase is a sensitive measure in compensated patients with normal symmetric gains and remains abnormal for low frequencies of rotation[26,29-31].

Exposing subjects to the unidirectional rotation during multiple sessions further decreased the DP value. The effect of this rehabilitation was retained between sessions (**Figure 2C**), and the cumulative effect resulted in most subjects having a normal DP after only two sessions. Similar to the short-term effect, the improvement in DP was the result of an increase in VOR responses for rotations toward the LR side and decrease in VOR responses during rotations toward the HR side[3].

FIGURE LEGENDS:

Figure 1: Unidirectional rotation decreases asymmetry between the two sides. (A) Schematic showing the hypothesis behind the unidirectional rotation. Stimulation of the side with lower

response (LR) and inhibition of the side with the higher response (HR, red arrows) will result in a change in commissural inputs as well as direct afferent inputs. This results in an increase in the response of LR neurons and decrease in the asymmetry between the two sides (black arrows). **(B)** Experimental design and rotational paradigms.

Figure 2: Short-term and long-term effect of the unidirectional rotation. (A) In the first session and 70 min after unidirectional rotation, peak eye velocity (°/s) showed a 14% increase in response to rotations toward the side with lower response (LR) and 16% decrease for rotations toward the side with higher response (HR, n = 16). Although these changes were not statistically significant (for LR: 25.0 ± 2.2 *vs*. 26.75 ± 5.3 °/s, paired Student's t-test, $p = 0.23$; for HR: 35.0 ± 3.6 vs. 26.0 ± 4.4 °/s, paired Student's t-test, $p = 0.15$), they resulted in a decrease in overall asymmetry. Error bars represent SEM. **(B)** Corresponding DP values decreased significantly (paired Student's t-test, $p = 0.0006$) and reached normal values. Error bars represent SEM. **(C)** The effect of the unidirectional rotation stayed for a longer time period and was cumulative. Pre-session values were measured before rehabilitation in a session and post-session values were measured 70 min after rehabilitation in that session. Negative DP values indicate reversal of the direction of asymmetry compared to the beginning of the study. Sessions are comparable to the **Figure 1B** schematic. Error bars represent SEM. This figure has been modified from Sadeghi et al.[3].

DISCUSSION:

The rehabilitation method presented here consisted of repeated unidirectional rotations in the dark toward the less responsive (LR) side in patients with vestibular imbalance and VOR asymmetry. Most rehabilitation techniques enhance multisensory integration in order to improve balance[16-20]. The method presented here targets the vestibular pathway, and its effects may be explained by a response increase in the VN on the LR side and a decrease in VN response on the HR side. These effects may be mediated at the afferent VN synapse due to the unidirectional stimulation of the sensors and nerves on the LR side and simultaneous decrease on the HR side. It may also affect VN activity through changes in the commissural inputs, which are known to play an important role in vestibular compensation[9]. Regardless of the mechanism, this method provides an effective way for decreasing asymmetry in responses of the two sides.

Previous studies have shown that repeated rotations could result in habituation of responses in normal animals and humans[32-37]. While this appears to be in contrast with these results, the conditions are different when the system is compensating for an asymmetry. Furthermore, a critical step in the design of the unidirectional rotation is to have a very slow deceleration in order to avoid stimulation of the other side. None of the previous studies have used such asymmetric stimulation.

It was found here that most subjects showed normal DP after two sessions[3]. This suggests that patients should be evaluated after two sessions to determine their progress and plan for future sessions. Furthermore, it is not known whether changes in DP are correlated with changes in subjective perceptions of retinal slippage. Future studies are required to evaluate this relationship using standardized vestibular/balance questionnaires before and after unidirectional-rotation sessions. Finally, a change in VOR asymmetry was only evaluated at lower frequencies of rotation (0.2 Hz). 1) The effects of this treatment on VOR phase or 2) whether or not this improvement transfers to higher frequencies of rotation or to the vestibulo-spinal pathways requires further investigation.

It is well-known that customized and supervised exercises provide better results in patients compared to unsupervised exercises that can be performed at home[38-43]. Here, to perform the unidirectional rotations, an expensive rotary chair is used that limits the use of this method. However, two important parameters for successful unidirectional rotation are a relatively high peak velocity during acceleration and a slow deceleration, which can be achieved by any rotating chair to which the patient can be securely attached using a trained partner to perform the asymmetrical rotation, or through the use of tele-health approaches. If confirmed by future studies, alternative low-tech approaches may provide a far less expensive alternative for performing this vestibular rehabilitation service.

Overall, in this preliminary study, unidirectional rotation provides an effective way for reducing VOR asymmetry in patients, even in the compensated stage. The results show that this method may be used as an effective supervised method for vestibular rehabilitation even in patients with longstanding vestibular dysfunction.

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DISCLOSURES:
The authors have nothing to disclose.

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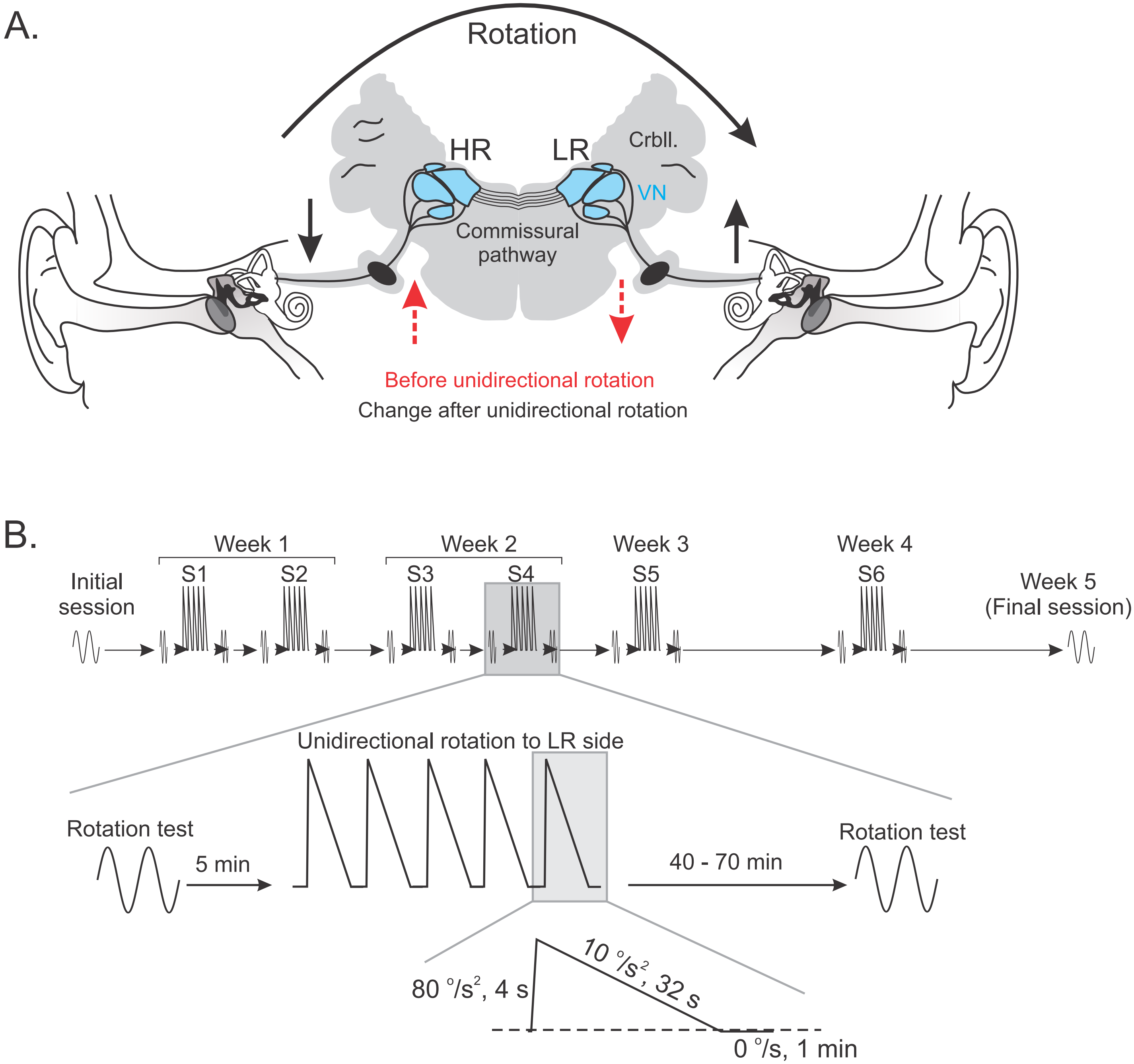
A.
Rotation
HR
LR
Crbll.
VN
Commissural pathway
Before unidirectional rotation
Change after unidirectional rotation
B.
Week 1
Week 2
Week 3
Week 4
Initial session
S1
S2
S3
S4
S5
S6
Week 5 (Final session)
Unidirectional rotation to LR side
Rotation test
5 min
40 - 70 min
Rotation test
80 °/s², 4 s
10 °/s², 32 s
0 °/s, 1 min

Figure 1

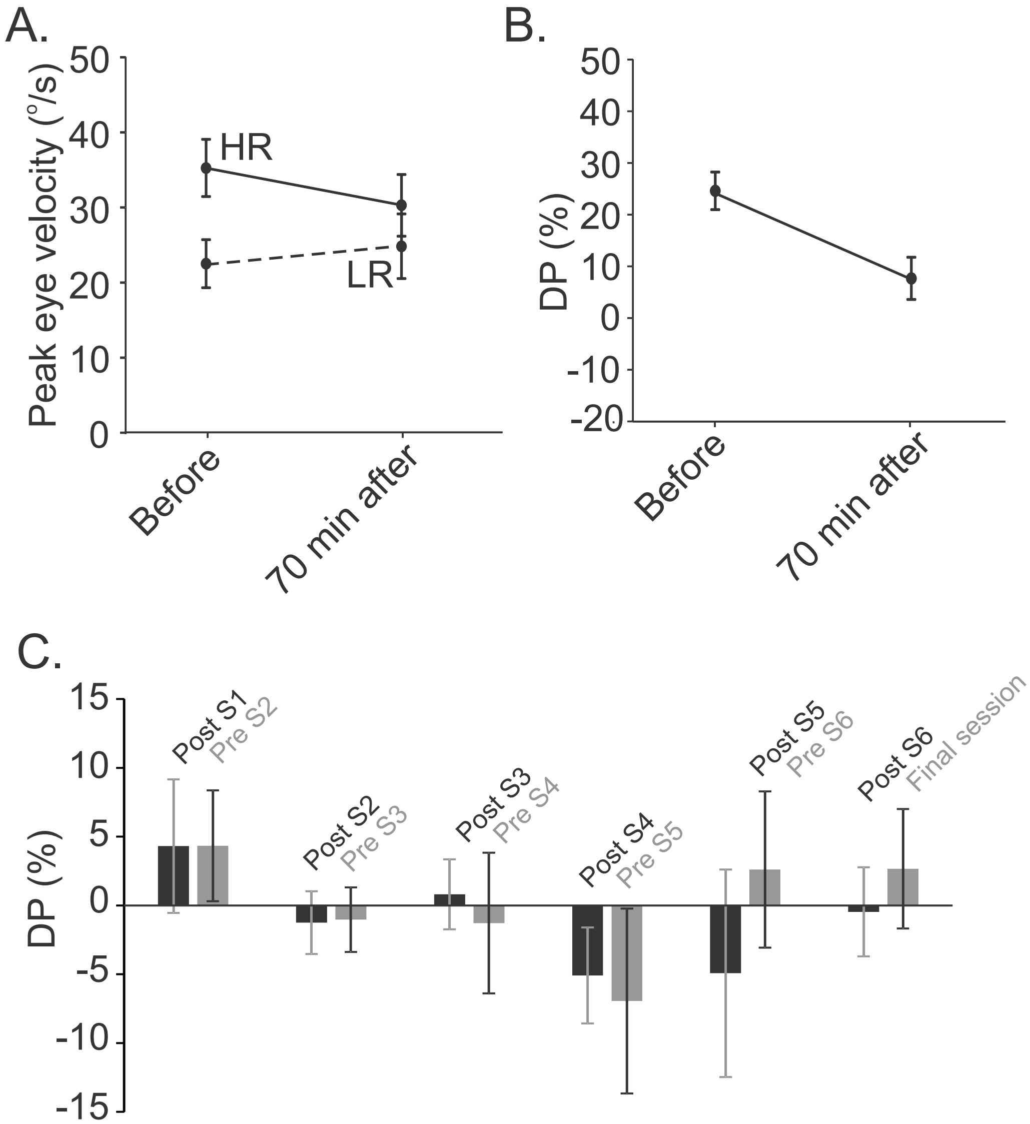
A.
Peak eye velocity (°/s)
50
40
30
20
10
0
HR
LR
Before
70 min after
B.
DP (%)
50
40
30
20
10
0
-10
-20
Before
70 min after
C.
DP (%)
15
10
5
0
-5
-10
-15
Post S1
Pre S2
Post S2
Pre S3
Post S3
Pre S4
Post S4
Pre S5
Post S5
Pre S6
Post S6
Final session

Figure 2

Figure 1

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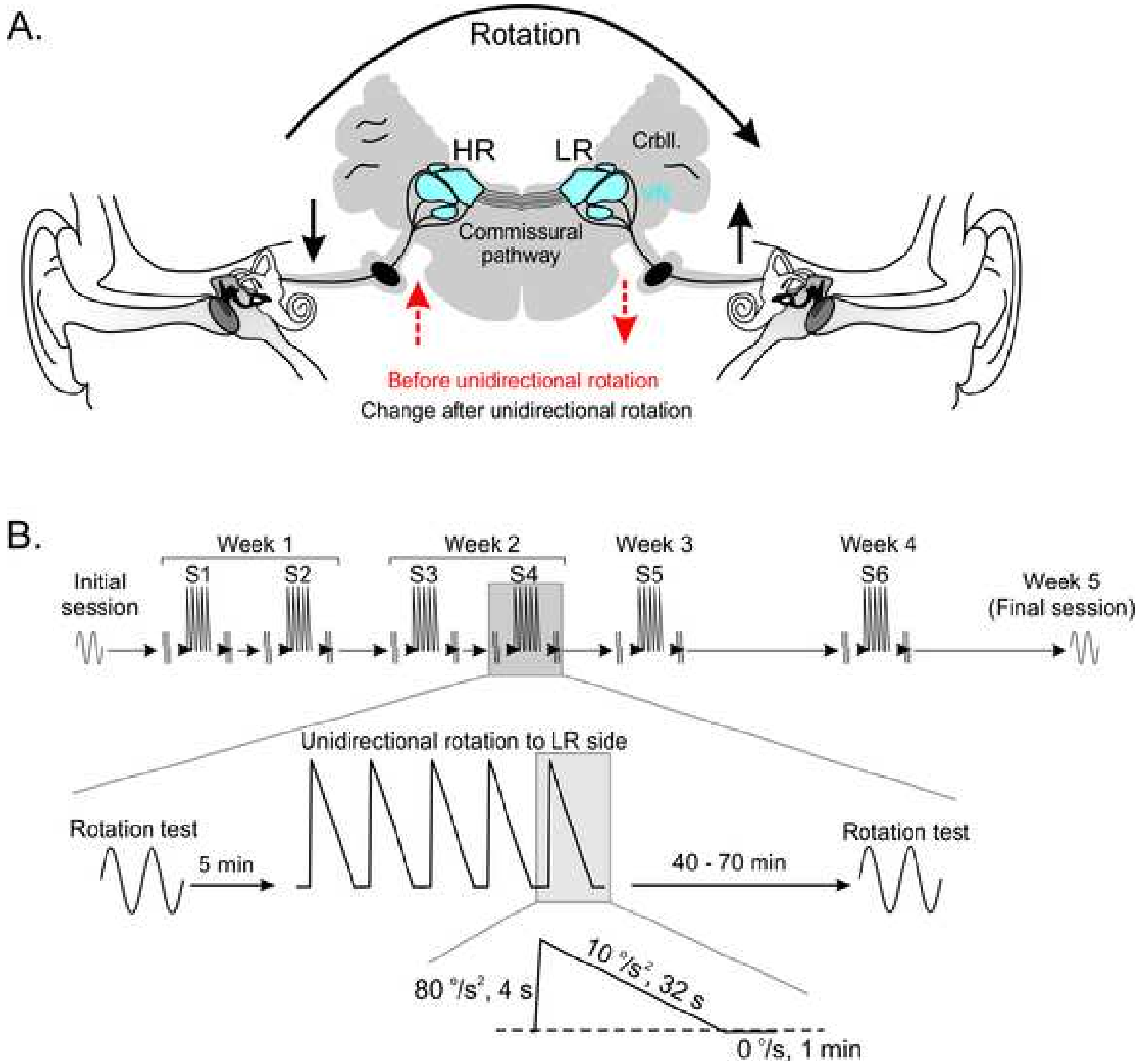
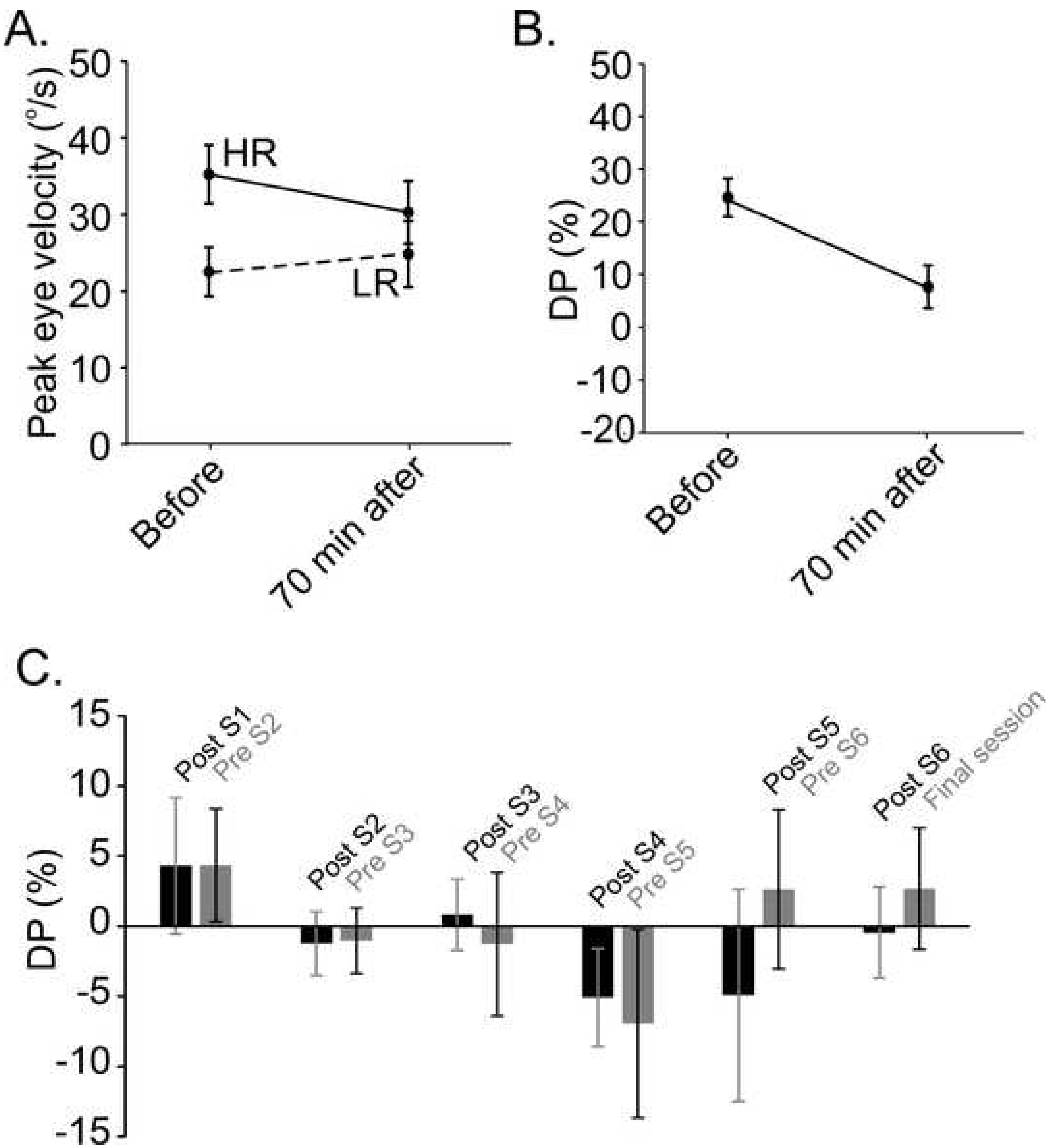


Figure 2


A.
Peak eye velocity (°/s)
50
40
30
20
10
0
HR
LR
Before
70 min after
B.
DP (%)
50
40
30
20
10
0
-10
-20
Before
70 min after
C.
DP (%)
15
10
5
0
-5
-10
-15
Post S1
Pre S2
Post S2
Pre S3
Post S3
Pre S4
Post S4
Pre S5
Post S5
Pre S6
Post S6
Final session

Name of Material/Equipment	Company	Catalog Number	Comments/Description
VEST operating and analysis software	NeuroKinetics		
Electronystagmograph	Nicolet	Spirit Model 1992	Equipment used for collecting the data presented in the Results section
I-Portal NOTC (Neurotologic Test Center)	NeuroKinetics		Equipment shown for current studies and shown in the movie

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Author(s):	Nayer Rassaian, Navid Sadeghi, Bardia Sabetazad, Kathleen McNerney, Robert Burkard, Soroush Sadeghi

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Signature: S Sadeghi Date: 3/28/2019

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Editorial Comments:

• Please take this opportunity to thoroughly proofread the manuscript to ensure that there are no spelling or grammatical errors.
We have proofread the article.

• Protocol Language: Please ensure that ALL text in the protocol section is written in the imperative voice/tense as if you are telling someone how to do the technique (i.e. “Do this”, “Measure that” etc.) Any text that cannot be written in the imperative tense may be added as a “Note”, however, notes should be used sparingly and actions should be described in the imperative tense wherever possible.
1) Examples NOT in imperative voice: 1.2–1.8, 3.1
All protocol steps were checked and changed to have the imperative voice/tense.

• Protocol Detail: Please note that your protocol will be used to generate the script for the video, and must contain everything that you would like shown in the video. Please add more specific details (e.g. button clicks for software actions, numerical values for settings, etc) to your protocol steps. There should be enough detail in each step to supplement the actions seen in the video so that viewers can easily replicate the protocol.
1) Please include an ethics statement before your numbered protocol steps indicating that the protocol follows the guidelines of your institutions human research ethics committee.
The ethics statement is added. Note that the data shown in the manuscript is from the published article in the Frontiers in Neurology and hence we mention the ethics committee of that institution.

2) 2.4: Unclear how the targets are presented in the dark. Are they projected using light/lasers on a wall?
That is correct and this is now mentioned in the text.

3) 2.5: how is the calibration performed?
We have added the calibration method to the text in Section 2.4.

4) 3.2: How are the rotations performed? Is the chair motorized?
We have added more details to the text.

5) 3.3, 5.2.2 ,5.2.5: Unclear what is done during SHA. Is an instrument used?
We have added step 3.4 to describe SHA and refer to it when SHA is mentioned later.

6) 4.2: is the unidirectional rotation performed exactly as in section 3?
That is correct and this is now referenced in the text.

7) 5.2.1: Please reference steps where you described the rotation.
We now reference the appropriate steps for this section.

• Protocol Highlight: Please highlight ~2.5 pages or less of text (which includes headings and spaces) in yellow, to identify which steps should be visualized to tell the most cohesive story of your protocol steps..
1) The highlighting must include all relevant details that are required to perform the step. For example, if step 2.5 is highlighted for filming and the details of how to perform the step are given in steps 2.5.1 and 2.5.2, then the sub-steps where the details are provided must be included in the highlighting.
2) The highlighted steps should form a cohesive narrative, that is, there must be a logical flow from one highlighted step to the next.
3) Please highlight complete sentences (not parts of sentences). Include sub-headings and spaces when calculating the final highlighted length.
4) Notes cannot be filmed and should be excluded from highlighting.
5) Please bear in mind that calculations cannot be filmed.

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Thank you for the reminder. We have addressed all of these points in the Discussion.

• Figure/Table Legends:
1) Figure 2: please define the scale bars.
We now mention in the caption that error bars represent the standard error of the mean. Otherwise, the figure does not have any scale bars.

• References: Please spell out journal names.
The references were made by using JoVE as the output style in EndNote, as instructed in author guidelines.

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Please note that the reviewers raised some significant concerns regarding your method and your manuscript. Please revise the manuscript to thoroughly address these concerns. Additionally, please describe the changes that have been made or provide explanations if the comment is not addressed in a rebuttal letter. We may send the revised manuscript and the rebuttal letter back to peer review.

Reviewer #1:
Manuscript Summary:
Nice work....
Thank you!

Minor Concerns:
Please emphasize that the patients have a directional preponderance, not necessarily a unilateral weakness. Each can be considered a vestibular "asymmetry" but they represent different processes as the authors know. Did any have a UW? How many, and how much?
We believe that the reviewer is referring to the first sentence of the Summary statement, which is the only place that unilateral weakness is mentioned. We have not in this document considered patients' diagnoses, except for excluding those with fluctuating disorders (e.g., Meniere's disease). Our concern was to find patients with asymmetric VOR responses, suggesting an input imbalance in the vestibular system between the two sides and then investigate whether this kind of stimulation could bring the two sides closer to each other. We have changed the sentence in the Summary section to 'patients with asymmetric responses'.

Reviewer #2:

Manuscript Summary:
The protocol described in this manuscript is quite simple and well-articulated, however, the design of this rehab procedure is flawed.
Below, we have tried to address the main two concerns of the reviewer, namely use of 'imbalance in patients' in the title (which we now understand was misleading, when what we meant to state was imbalance between the two sides) and use of phase for evaluating the VOR.

Major Concerns:

1. If the authors want to prove the procedure is effective to improve imbalance, then the outcome measures should be a test of balance function such as SOT, not VOR asymmetry.
The reviewer is absolutely correct if referring to balance ability, but as mentioned in the previous comment and stated in the text, we are referring to imbalance of the peripheral vestibular system on the two sides. The title of the paper may have been misleading and therefore we have changed 'imbalance' to 'asymmetry' in the title as well as in most other places in the manuscript.

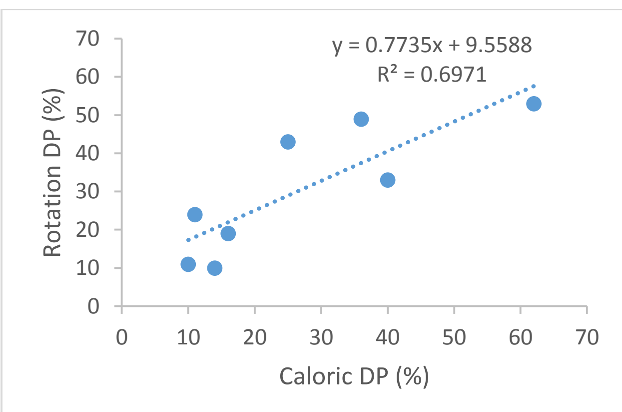
2. The VOR asymmetry is not the most effective measure of VOR, or peripheral vestibular loss. The most sensitive value of VOR is the VOR phase, then the gain.

The reviewer is correct that the VOR phase is an important measure. However, this measure may be most useful when assessing VOR responses in compensated patients with normal / symmetric VOR gains and mainly in the lower frequency range of rotations as a measure of the velocity storage function. In this study, our subjects had asymmetric gains as a recruitment criterion. In this case the change in gain and asymmetry are indeed a measure of improvement of the horizontal VOR responses after our rehabilitation. We have added a sentence to the text to address this point.

3. The data shown in Figure 2 did not indicate statistical significance.
The lack of significance is now mentioned in the figure caption. Note that changes in DP are significant (Fig. 2B).

Minor Concerns:

The definition of VOR asymmetry is the difference between the peak eye velocity during CW (right-beating) and CCW (left-beating) rotations, not directional preponderance (DP).
Using the difference in peak velocities, would also show the significant change (13.1 ± 1.9 vs. 4.6 ± 2.3, paired t-test, p = 0.01). The directional preponderance provides a normalized measure of the difference in peak eye velocity for CW and CCW rotations and has been traditionally used for measuring the VOR symmetry and is reported as % symmetry in most clinical studies (e.g., Funabiki and Naito, 2002, Zalewksi 2018). Furthermore, we found that rotation DP was well correlated with that of the caloric test as shown below (unpublished data from patients in Sadeghi et al., Frontiers in Neurol. 2019). We have added text to the manuscript to reflect these points (see below).



The term of DP is usually used in the caloric test, describing the difference between left-beating and right beating nystagmus. So, to use DP in VOR testing is misleading.
We have edited this section to make it clear that directional preponderance (DP) is referring to an asymmetry in VOR response from rotary chair measures.

For both these points, we have added the following text to step 4.4:
'Administer an SHA test (step 3.4) at the beginning and end of each session and calculate the asymmetry by calculating the directional preponderance (DP) as a measure of asymmetry […] Note: The directional preponderance provides a normalized measure of the difference in peak eye velocity for rotations in the

two directions and while it is mainly used for measuring asymmetry in caloric responses, it can be (and is) used for quantifying rotational asymmetry.'

We thank the reviewers for their constructive comments in this manuscript.

Nayer Rassaian
Navid G. Sadeghi
Bardia Sabetazad
Kathleen M. McNerney
Robert F. Burkard
Soroush G. Sadeghi

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