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TITLE: Sensorimotor Assessment and Rehabilitative Apparatus

PRINCIPAL INVESTIGATOR: Michael Schubert

CONTRACTING ORGANIZATION: Johns Hopkins University
Baltimore, MD 21218

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13. SUPPLEMENTARY NOTES

14. ABSTRACT

In veterans and civilians exposed to blast or blunt head trauma or those suffering from inner ear disorders, a clinical pattern of damage to the auditory, visual, and vestibular (inner ear balance mechanism) sensorimotor systems has emerged; collectively known as multi-sensory impairment (MSI). MSI related symptoms affect ~ 300-500/100000 population. The purpose of this study is to examine subjects for sensorimotor impairments within the visual and vestibular systems using a portable technology that rapidly and unobtrusively measures how these interdependent systems are functionally integrated. We call this device SARA, Sensorimotor Assessment and Rehabilitation Apparatus. The scope of the project involves recruiting Veterans from the War Related Illness and Injury Study Center (WRIISC) in East Orange NJ and civilian subjects with vestibular hypofunction from the Johns Hopkins University School of Medicine Clinics. We will also collect age-matched healthy control data. The study's duration is three years. An early, yet major finding suggests that veterans with MSI have a significant ocular misalignment in their eye position relative to healthy controls. This finding suggests that SARA may serve as an excellent proxy of more elaborate laboratory equipment that requires expertise in use, is cumbersome and impractical for many unique environments.

15. SUBJECT TERMS

Multisensory Impairment, Vestibular, Visual, Dynamic Visual Acuity, Imbalance, Mild Traumatic Brain Injury, Sensorimotor, Assessment, Portable, Sensors, Otolith, Semicircular Canal, Gait

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1. INTRODUCTION

Exposure to brain injury via blast or blunt mechanisms disrupts multiple sensorimotor systems simultaneously in nearly 20% of veterans of the Gulf War and OIF/OEF campaigns, causing physical, sensory, cognitive, and behavioral/emotional changes. Therefore, a significant population of our wounded veterans suffer long term functional consequences including visual deficits, postural and locomotor instabilities, disorientation, dizziness, sensitivity to visual and body motion, and an impaired ability to read. A clinical pattern of damage to the auditory, visual, and vestibular (inner ear balance mechanism) sensorimotor systems has emerged, which has collectively been given the name multi-sensory impairment (MSI). In the US civilian population, MSI related symptoms are also a common sequelae of damage to the inner ear and mTBI, collectively affecting ~ 300-500/100000 population. Therefore, irrespective of the environment (military or civilian) or cause (mTBI or peripheral vestibular injury), the inner ear is commonly involved when symptoms of MSI are experienced. The purpose of this study is to examine subjects for sensorimotor impairments within the visual and vestibular systems using a portable technology that rapidly and unobtrusively measures how these interdependent systems are functionally integrated. We call this device SARA, Sensorimotor Assessment and Rehabilitation Apparatus. The scope of the project involves recruiting n=42 Veterans from the War Related Illness and Injury Study Center (WRIISC) in East Orange NJ and n=42 civilian subjects with vestibular hypofunction from the Johns Hopkins University School of Medicine Clinics (otolaryngology, rehabilitation, and neurology). We will collect age-matched healthy control subjects at the Johns Hopkins site. The duration of the study is three years.

2. KEYWORDS

Multisensory Impairment, Vestibular, Visual, Dynamic Visual Acuity, Imbalance, Mild Traumatic Brain Injury, Sensorimotor, Assessment, Portable, Sensors, Otolith, Semicircular Canal, Gait

3. ACCOMPLISHMENTS

a. Major Goals

The major goals of this project as established by the approved SOW include

I. Establish project management system to ensure success of project

This goal is 100% complete, though did take 11 months to complete. The 11-month duration delayed data collection.

We continue to have biweekly meetings at JHU and monthly meetings with the WRIISC (phone) in addition to 'as-needed' conversation with both JHU and WRIISC grants management offices to ensure adequate oversight from expenditure of funds, to human subjects protection, to salary support, data collection and progress towards the major goals. In addition,

1. A member of the research team from JHU travels to WRIISC to assist with data collection and to ensure an 'in person' visit to troubleshoot any difficulties that have arisen.
2. The PI has a monthly meeting with the JHU grant management office to go over expenditures of this award and the PI received monthly summary statements of the budget.

Per this 1st major goal, the following milestones have been achieved:

a. Both sites have trained individual's independently collecting data. Both sites are actively collecting data.
b. Both sites have the necessary software and hardware to data collect.
c. Only the JHU site has a trained Physical Therapist to carry out the rehabilitation AIM 3. Please see Section 5. (Changes/Problems) regarding the Physical Therapist hire at the WRIISC.

II. Obtain Institutional Review Board approval at VA NJ and JHU

This goal is 100% complete.

Per this 2nd major goal, the following milestones has been achieved

a. HRPO/ACURO Approval
b. Local IRB Approval

III. Develop recruitment plan to identify and enroll Veterans with MSI.

This goal 100% complete.

Per this 3rd major goal, the following milestone has been achieved

a. Local IRB approval at both sites of the recruitment flyers and telephone scripts needed to assist with subject recruitment.

IV. Determine the effectiveness of SARA to identify vestibular function

We project to be completed with data collection at the final year of the award. At JHU, we have collected data on 20 patients. This is 48% completed. We have also collected data on 13 healthy controls. This is 31% completed. The original sample size for healthy controls that we projected to collect was to be 42, however, we also originally planned to use age-matching against the patient subjects. The mean age of patients is 54 ± 11 years compared with healthy controls being 51 ± 14 years. We, therefore, will continue to collect healthy controls, but have realized we have

enough control data.

With approval (April of 2017) from Dr Wang, science officer, we revised our recruitment projections as contingency in case our recruitment did not increase pace. Based on these revised projections (**green shading, Table 1**), we have met target recruitment at JHU. At the VA site (WRIISC), we have collected data in n = 13 Veterans. This is 31% completed. In another 2 weeks we will have exceeded the revised projections (**blue shading, Table 1**) when we study two currently scheduled veterans.

Table 1. Revised recruitment

	Year 1				Year 2				Year 3		
Target Enrollment (per quarter)	**Total Count Year 1**				**Q1**	**Q2**	**Q3**	**Q4**	**Q1**	**Q2**	**Q3**
JHU VH				6	2	4	4	4	5	5	
JHU HC				5	0	4	4	4	5	5	
Total Screened					4	10	10	10	12	12	
WRIISC					2	4	4	4	5	5	
Total Screened					4	6	6	6	7	7	
Target Enrollment (cumulative, recruited only)					**27**	**39**	**51**	**63**	**78**	**93**	
Target Enrollment (cumulative, recruited and screened)					**79**	**107**	**135**	**163**	**197**	**231**	

Based on this revised projection, our total subject count would be n=30 at JHU site and n=27 at VA site. We believe however, that we may still be able to meet our original subject recruitment target (n=42 at both JHU and VA sites) given our recruitment pace has increased. This may however entail enacting a No-Cost Extension (NCE). The PI has had a brief discussion (email) with Dr Wang - who suggested considering a NCE. We agree this may be valuable, though hope unnecessary, presuming our recruitment exceed the current revised projections. We suggest considering the NCE based on recruitment totals at the end of the 1st quarter of Year 3 (March 2018).

What has been accomplished under these goals?

We have three Aims for this study:

AIM I. Correlate our behavioral measure of binocular alignment symmetry (via SARA) against gold standard measures of otolith function and visual function in an mTBI, vestibular deficit, and age-matched control population.

AIM II. Investigate difference in dynamic visual acuity for near versus far viewing as a means to distinguish vestibular oculomotor from visual oculomotor control dysfunction in an mTBI, vestibular deficit, and an age-matched control population.

AIM III. Investigate how well our MSI test (SARA) can predict those veterans and civilians with vestibular hypofunction that respond well to vestibular rehabilitation intervention.

The major activities involved in the reporting period representing this 2nd year have been extensive. We have had a second manuscript accepted for publication (*Schubert MC, Stitz J, Cohen HS, Sangi-Haghpeykar H, Mulavara, AP, Peters BT, Bloomberg JJ. Prototype tests of vertical and torsional alignment nulling for screening vestibular function. J Vestibular Research. In Press.*), in addition to three, SARA related research presentations:

1. Military Health Science Research Symposium (August 2017)
2. APTA combined sections meeting (February 2017)
3. Association for Research in Otolaryngology (February 2017)

Aim I

We have developed the Vertical Alignment Nulling and Torsional Alignment Nulling tasks (VAN, TAN) to examine for any misalignment in oculomotor position. The task asks subjects to adjust a movable blue line so that it lines up horizontally with a stationary red line and both thus appear as a single line. If the right eye is elevated above the left eye (**Figure 1C**) or if the right eye is rotated (i.e. clockwise) away from the left eye (**Figure 1D**), the subject will mis-align the two lines. We test in both upright and supine position to examine differences in oculomotor position due to musculoskeletal or vestibular (otolith) injury. For example, when subjects lie supine, the vestibular contribution to an abnormal skew (vertical eye displacement as in **Figure 1C**) is abolished and the skew resolves (as in **Figure 1B**), yet a musculoskeletal or cranial nerve injury to that same eye muscle would not change and the skew would still be present.

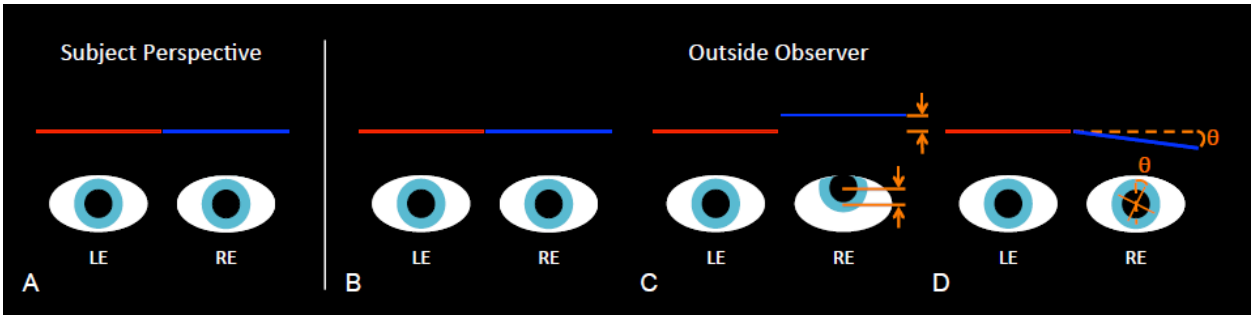

Figure 1. Examples of ocular misalignments inferred by VAN and TAN results. (A) The subject repositions the moving line (blue in this example) until it appears in line with the stationary line (red), thereby positioning each line on the center of each retina. Binocular misalignment is inferred from the relative positioning of the lines at the end of each trial. (B) If the subject has perfect binocular alignment, then the lines will be perfectly aligned at the end of the trial. (C) If the subject sets the right line above the left line during VAN, we infer that the right eye is elevated above the left eye. (D) If the subject orients the right line clockwise relative to the left line in TAN, we infer that the right eye is extorted relative to the left eye.

Our portable measure of ocular alignment is revealing differences between patients (MSI and UVD) and healthy controls. However, the direction of misalignment is not uniform – some patient and healthy controls adjust the line above or below true horizontal, (**Figure 2**). As can be seen in Figure 2, with few exceptions both MSI and UVD subjects adjust the line at magnitudes different than the healthy controls.

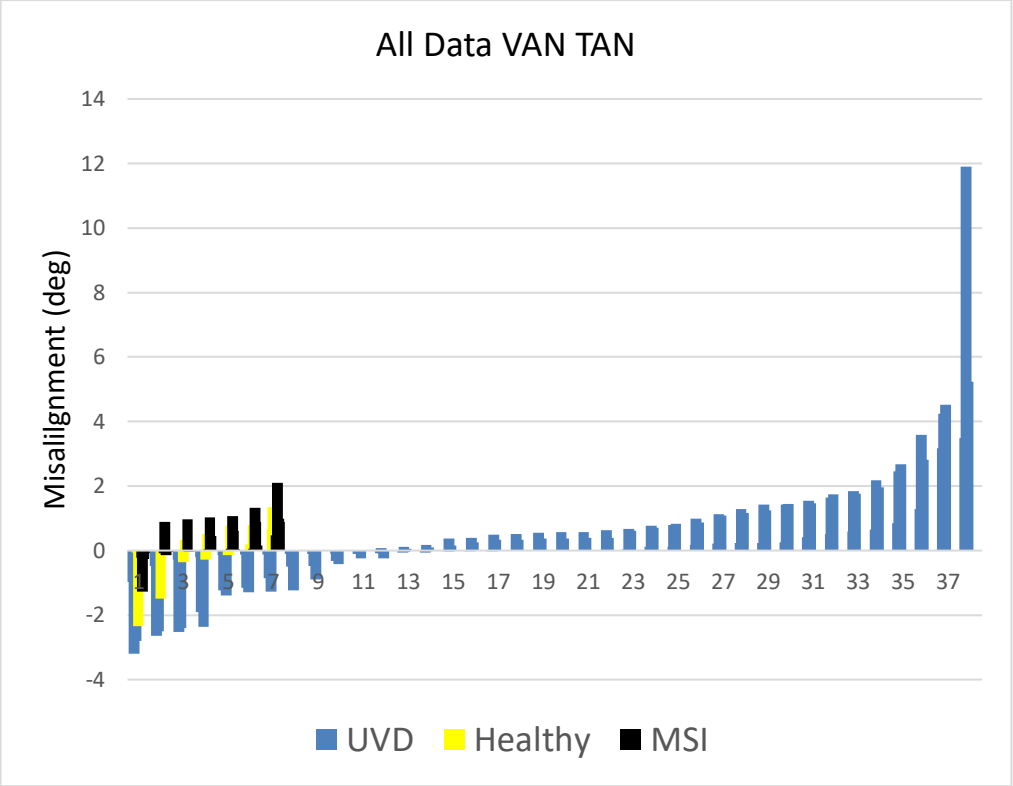

Figure 2. VAN and TAN scores for upright and supine across UVD, Healthy and MSI cohorts. The zero baseline reflects perfect alignment. It appears that patient cohorts more often positively align the measure.

Due to this tendency, we have examined VAN and TAN scores based on positive or negative alignment. To date, the still preliminary TAN data is appearing to sort out differences between MSI/UVD and healthy cohorts, **Figure 3**.

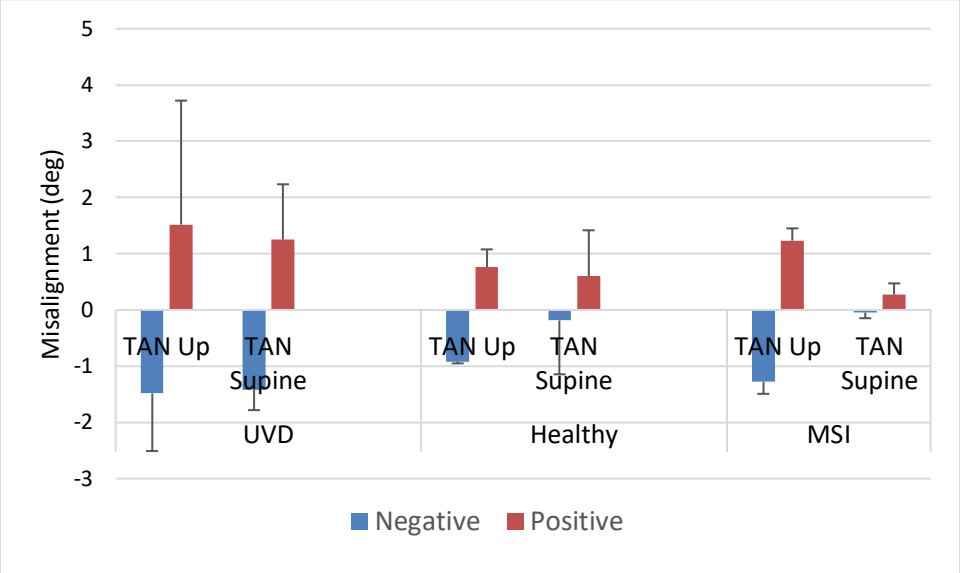

Figure 3. TAN scores appear to be distinguishing MSI and UVD from Healthy controls. The variability is greater in the subjects with UVD, which may have relevant information.

We are validating VAN and TAN using vestibular evoked myogenic potentials (ocular and cervical VEMP), which measure function from the otolith end organs. In our patient subjects, both the oVEMP and cVEMP have abnormally short amplitudes, **Table 2**.

Table 2. VEMP response in Patient Subjects

	oVEMP Left Amplitude	oVEMP Right Amplitude	cVEMP Left Amplitude	cVEMP Right Amplitude
Patients	2.6 ± 3.6	2.0 ± 1.4	49.5 ± 23.8	81.6 ± 44
Healthy	27 ± 13.7		325 ± 198	

Aim II

We developed a second measure of oculomotor function on the handheld tablet using Dynamic Visual Acuity (DVA). DVA tasks subjects to identify a letter that flashes on a monitor only when the head is moving above 120 deg/sec. We are examining DVA while looking at near (.5m) and far (2m) distances while the subject makes active up, down, left and right head rotation. We hypothesized that near target viewing distances would be more difficult than far target given the combined linear and angular vestibulo-ocular reflex effort to stabilize the eyes. Current results suggests this is not the pattern, but instead that far viewing is more difficult (**Figure 4**).

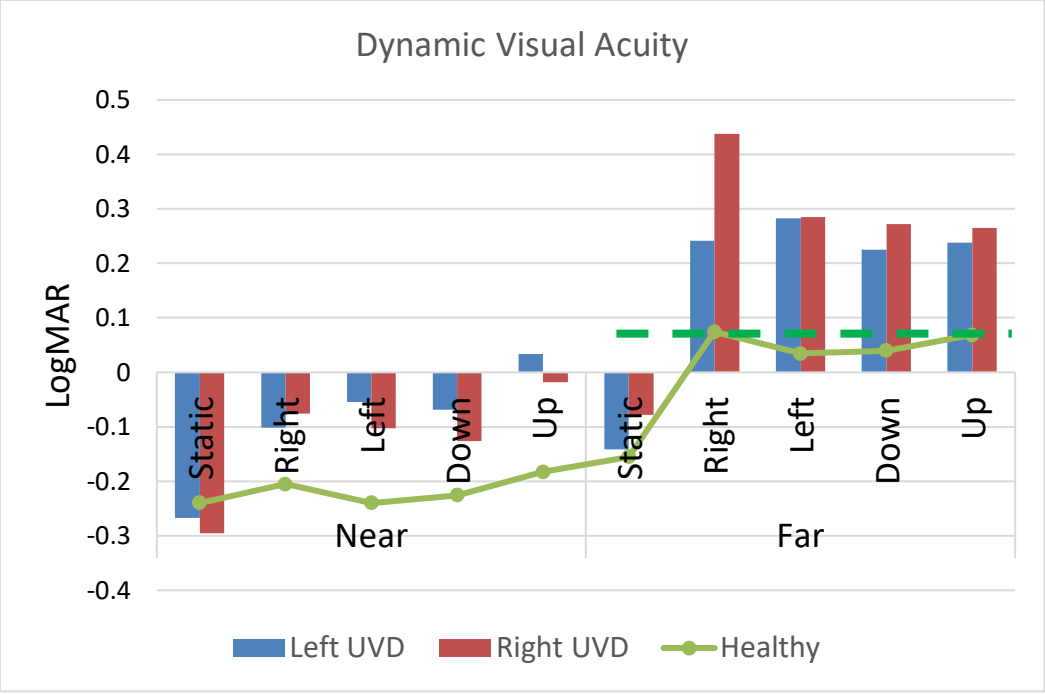

Figure 4. DVA in Patients subjects compared with Healthy subjects. The stippled green line reflects published DVA scores in age-matched healthy subjects (5th decade) for 'Far' target (Herdman 1998), which matches our population age. The patient subjects have much worse DVA for 'Near' and 'Far' relative to controls. LogMAR – logarithm of the minimum angle resolvable. A score of 0 Logmar denotes 20/20 acuity.

The DVA scores in the patient subjects for 'Near distance' are 2-2.5 times worse than for 'Far distance' and nearly 9 times worse than healthy controls. Near DVA is better than Far DVA for both patient and healthy subjects. As we collect more data, we will analyze for statistical significance. We expect to find meaningfully significant differences in DVA between the cohorts.

We are validating the DVA near and far test using the video head impulse test. We have identified VOR function in each of the semicircular canals (six) in the subjects with VOR deficit, **Figure 5**.

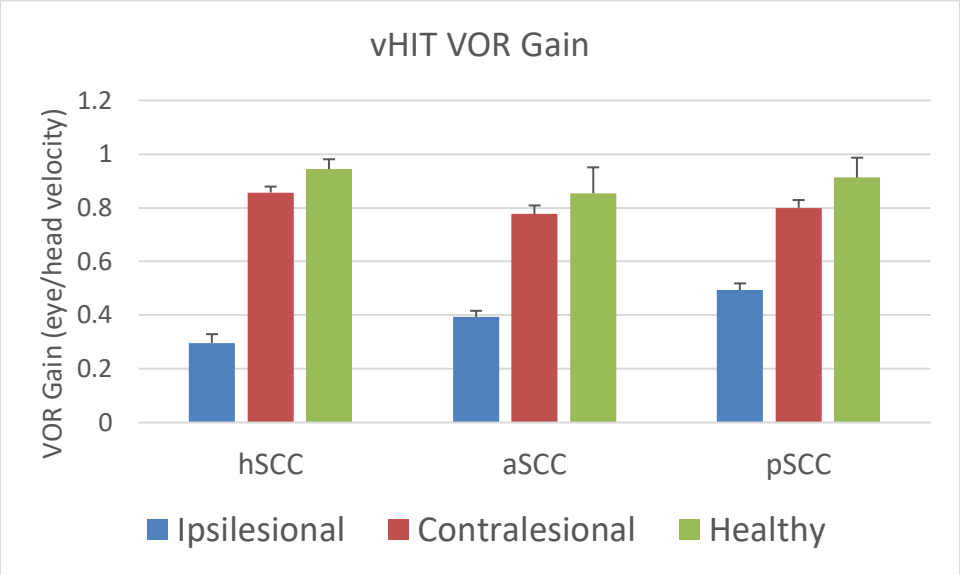

Figure 5. VOR gain during passive head impulse testing of each semicircular canal (horizontal hSCC, anterior aSCC, posterior pSCC). VOR gain within the plane of the affected canal (ipsilesional) is worse.

b. Gait (component of Aim III)

While not a direct aim or goal of our project, we will be quantifying gait using 5 wireless sensors (Aim III measures fall risk and collects outcomes related to gait) attached to each leg, the trunk, the pelvis, and the head. To process data using these sensors, we have developed new measures of balance and posture performance. As an example, **Figure 6** illustrates the mediolateral sway of a subject performing the tandem walk.

Figure 6. Mediolateral sway as measured by portable, wireless sensors during tandem walking eyes closed. The data reveal head and trunk move in unison, while the pelvis is relatively more stable.

c. Rehabilitation (component of Aim III)

We are collecting functional outcome variables that include the Dynamic Gait Index, the Timed Up and Go test, gait speed (m/s), and the 2-minute walk test, (**Table 3**). In our patient subjects,

the DGI (scores > 20 out of 24 possible) and the TUG scores (<13sec) are normal – suggesting they are not sensitive indicators to identify fall risk at the time of measurement (Bischoff et al 2003). The mean gait speed of our patient subjects is borderline slow (1.31 – 1.43 depending on gender. The two-minute walk test appears to be normal in our patient subjects, based on healthy age-matched subjects 177-191 meters depending on gender (Bohannon et al 2015).

Table 3. Functional Gait Measures

	DGI	TUG	GAIT_VELOCITY	TWOMWT_METERS
Mean	22	8.168	1.291142857	175.7882353
SD	3.5	1.781	0.294905483	69.60022538

Oddly, however is the significant perception of disability that our subjects are reporting. Our patient subjects have Activity-specific Balance Confidence score (ABC) scores (77) that are lower than those community dwelling elderly (mean age 71 ± 6.9 years) **Table 4**. Although ABC scores < 67% indicates a risk for falling in those subjects with positive fall history, these data do suggest our patient subjects are at risk for fall. This suggests perception of disability does not match the performance variables we have measured.

The Dizziness Handicap Inventory is measure of perceived disability spread across three sub-components (physical, functional, emotional). Values between 16-34 points suggests patients perceive a mild disability (**Table 4**).

Table 4. Perception of Disability as Measured by ABC and DHI

ABC_PERCENT	DHI_PHYSICAL	DHI_FUNCTIONAL	DHI_EMOTIONAL	DHI_TOTAL
76.86111	12.27778	9.055556	12.5	33.55556

Opportunities for training and professional development?
There was never an intention/purpose to train or provide professional development. However, last year, discussion with clinicians from the WRIISC suggested interest in the PI delivering a continuing education. This has not developed any further. The PI remains interested to do so, if feasible and the VA warrants it valuable.

Dissemination of Results to communities of interest
In the last year, we present three abstracts to relevant communities of interest –

d. Association for Research in Otolaryngology and Combined Sections Meeting of the American Physical Therapy Association. These two communities include clinicians and researchers in the field of otolaryngology and rehabilitation that diagnose and treat dizziness and balance disorders due to mTBI or vestibular hypofunction present preliminary results in a poster format and a platform presentation.
e. Military Health Science Research Symposium (MHSRS).

Plans for next reporting period
We will continue to collect data and begin to apply statistical analysis to examine for clinical and statistical relevance. We will plan to publish the results. This will be the focus of our efforts during the 3rd year of the award.

4. IMPACT

The principal disciplines of this research project are to develop robust measures of sensorimotor

function that can be delivered in environments that do not allow the space for cumbersome laboratory equipment, that do not require specialized training for use, and do not involve any invasive procedure to gather relevant function of multiple medical systems.

During this 2nd year, most of our efforts have revolved around patient recruitment and ensuring the quality of the data.

What was the impact on other disciplines?
Nothing to report.
What was the impact on technology transfer?
Nothing to report.
What was the impact on society beyond science and technology?
Nothing to report.

5. CHANGES/PROBLEMS

Unanticipated Problem
We continue to have difficulty identifying a physical therapist at the WRIISC site to carry out the rehabilitative component of the study (see below). The problem seems primarily related to the VA not allowing salary support from grant funding to offset clinical responsibilities in order to protect time for research. This prevents an ability to pay existing physical therapy staff for their time at the WRIISC to participate in research. Although they are commissioned to engage in research, the clinic schedule is too encompassing of their time.

Additionally, many of the veterans have difficulty traveling to the WRIISC, often taking multiple bus routes all of which, in their experience, causes us to believe that we should reduce the number of visits to the WRIISC for rehabilitation. We have reduced the number of visits. Additionally, we have developed a library of videos illustrating the exercises, which we will post on a website. Our plan is to have them follow the website for exercise prescription.

As noted earlier, we were delayed in data collection partly based on the time to secure HRPO approval. As a result, our recruitment is lower than anticipated. We do hope to recover those numbers over the final year, though we may apply for a NCE.

Changes to expenditure
We have not had any significant change in expenditure.

Changes to human subjects
There has been no change to care of human subjects.

6. PRODUCTS

The VAN and TAN technology has been awarded a patent (mentioned in Year 1).

The following papers have been published:
1. Beaton KH, Schubert M, Shelhamer M. Assessment of vestibulo-ocular function without measuring eye movements. J Neurosci Methods. 2017 PMID: 28336357

2. Beaton KH, Shelhamer MJ, Roberts DC, Schubert MC. A rapid quantification of binocular misalignment without recording eye movements: Vertical and torsional alignment nulling. J Neurosci Methods. 2017 May 1;283:7-14. doi: 10.1016 PMID: 28300605

This paper is in Press:
Schubert MC, Stitz J, Cohen HS, Sangi-Haghpeykar H, Mulavara, AP, Peters BT, Bloomberg JJ. Prototype tests of vertical and torsional alignment nulling for screening vestibular function. J Vestibular Research. In Press.).

Three abstract have been presented in poster or oral presentation:

1. Military Health Science Research Symposium (August 2017)
2. APTA combined sections meeting (February 2017)
3. Association for Research in Otolaryngology (February 2017)

One additional abstract has been accepted for poster presentation:
1. APTA combined sections meeting (February 2018)

We have no books, websites, else submitted. We are building a website as described above.

7. PARTICIPANTS AND OTHER COLLABORATING ORGANIZATIONS

Ten individuals across two institutions (Johns Hopkins and the East Orange VA (WRIISC)) have worked on the project. There has not been any change in either the PI or any of the senior personnel in this reporting period. The following personnel are listed by sub-site:

Johns Hopkins

a. Michael Schubert — PI
Identifier (era commons) — mschube1
Person Month — 5
Contribution — Oversight and science lead for both sites, patient recruitment
Funding Support: — VBMRI (DMRDP/CDMRP)

b. Mark Shelhamer — Co-I
Identifier (era commons) — mshelha1
Person Month — 1
Contribution — model development for Aim III (predictors of beneficial responders) Engineer, software development
Funding Support: — None

c. Chuck Rohde — Co-I
Identifier (era commons) — crohde1
Person Month — 1
Contribution — Biostatistician
Funding Support: — NIH

d. Dan Gold — Co-I
Identifier (era commons): dgold7
Person Month: 1
Contribution: Clinician performing oculomotor exam
Funding Support: None

e. Dale Roberts — Engineer
Identifier (era commons): drobert7
Person Month: 2
Contribution: hardware and software development, data analysis, data processing
Funding Support: See Other Support Document

f. Yoav Gimmon — Post-doctoral Fellow
Identifier (era commons): ygimmon1
Person Month: 8.5
Contribution: data collection, data analysis, data processing
Funding Support: None

g. Jennifer Millar — Physical Therapist
Person Month: 4
Contribution: clinical delivery of rehab; data collection, data analysis, data processing
Funding Support: Supported by JHH as a hospital employee

WRIISC

a. Jorge Serrador — Co-I
Identifier (era commons): JORGESERRADOR
Person Month: 1
Contribution: Oversight and science lead at VA site (WRIISC), data interpretation

b. Kelly Brewer — Research Assistant
Person Month: 11
Contribution: study coordinator at WRIISC, data collection, data analysis, oversight operations

c. Bemin Ghobreal — Engineer
Person Month: 1
Contribution: hardware and software development, data collection, data processing

Physical Therapist TBD

Change in Active Other Support
Nothing to Report.

What other organizations were involved as partners?
Organization Name: Veterans BioMedical Research Institute
Location of Organization: 385 Tremont Ave., Bldg 11, Room 117 B, East Orange, NJ
Partner's Contribution to the project: Grant provides financial support to the subsite; Facilities, Collaboration

References

Bischoff, Heike A.; Stähelin, Hannes B.; Monsch, Andreas U.; Iversen, Maura D.; Weyh, Antje; von Dechend, Margot; Akos, Regula; Conzelmann, Martin; et al. (2003). "Identifying a cut-off point for normal mobility: A comparison of the timed 'up and go' test in community-dwelling and institutionalized elderly women". Age and Ageing. 32 (3): 315–20. PMID 12720619. doi:10.1093/ageing/32.3.315.

Bohannon RW, Wang YC, Gershon RC. Two-minute walk test performance by adults 18 to 85 years: normative values, reliability, and responsiveness. Arch Phys Med Rehabil. 2015 Mar;96(3):472-7. doi: 10.1016/j.apmr.2014.10.006. Epub 2014 Oct 25.

Herdman SJ, Tusa RJ, Blatt P, Suzuki A, Venuto PJ, Roberts D. Computerized dynamic visual acuity test in the assessment of vestibular deficits. Am J Otol. 1998 Nov;19(6):790-6.PMID: 9831156

Huang, T. T. and Wang, W. S. (2009). "Comparison of three established measures of fear of falling in community-dwelling older adults: psychometric testing." International Journal of Nursing Studies 46(10): 1313-1319

Kim HJ, Lee JH, Kim JS.Ocular vestibular evoked myogenic potentials to head tap and cervical vestibular evoked myogenic potentials to air-conducted sounds in isolated internuclear ophthalmoplegia. Clin Neurophysiol. 2014 May;125(5):1042-7.

Lajoie, Y. and Gallagher, S. P. (2004). "Predicting falls within the elderly community: comparison of postural sway, reaction time, the Berg balance scale and the Activities-specific Balance Confidence (ABC) scale for comparing fallers and non-fallers." Archives of Gerontology and Geriatrics 38(1): 11-26.

8. SPECIAL REPORTING REQUIRMENTS

SARA - *Sensorimotor Assessment and Rehabilitation Apparatus*

MR141166 Clinical and Rehabilitative Medicine Research Program 2014

PI: Michael Schubert **Org:** Johns Hopkins University and WRIISC East Orange NJ VA **Award Amount:1.5M**

Study/Product Aim(s)

AIM I. Correlate our behavioral measure of ocular misalignment from otolith damage (via SARA) against gold standard measures of otolith function in an mTBI, vestibular deficit, and age-matched control population.

AIM II. Investigate difference in dynamic visual acuity for near versus far viewing as a means to distinguish vestibular oculomotor from visual oculomotor control dysfunction in similar population.

AIM III. Investigate how well our multisensory impairment (MSI) test (SARA) and current standard of care variables can predict those veterans and civilians with vestibular hypofunction that respond well to vestibular rehabilitation intervention.

Approach

This is an applied research application to examine subjects for MSI using a portable technology that rapidly and unobtrusively measures how these interdependent sensorimotor subsystems are functionally integrated. We will investigate the validity of our portable measure of MSI to identify pathology and predict return to duty/function in both veteran and civilian populations. Our device (SARA) has been validated in the challenging environment of reduced gravity and shown to accurately identify misalignment in eye position due to changing gravitational force.

Left 2 panels shows the hardware (top) and body-worn shirts/straps (bottom) of the portable MSI test known as SARA. Right panel shows SARA in use during parabolic flight measuring ocular misalignment related to altered gravity.

Timeline and Cost

Activities CY	15	16	17	18
Establish the protocol, IRB, central database, hire students				
Begin data collection, prepare MS				
Publish MS, predictor benefit model building				
Estimated Budget ($K)	**$200K**	**$500K**	**$500K**	**$300K**

Updated: December 29, 2016_Quarter 4 report

MS – manuscript; **blue square** represents % activity completed relative to size of the cell; **olive drab** cell represents remaining time to complete activity.

Goals/Milestones

CY15/CY16 Goal – Obtain IRB approval, establish protocol, set up data sharing agreement. IRB approval obtained

- [X] Functional tests of integrated firmware and software
- [X] Subject recruitment
- [X] Begin data collection

X denotes item initiated/completed

CY16/17 Goal – Continue data collection

- [X] Manuscript accepted
- [ ] 75% completed Aims I and II

CY17/18 Goal – Presentation of research; complete all 3 Aims

- [ ] Statistical model building
- [X] Manuscript preparation
- [X] Research presentation at DOD meeting
- [ ] Submit follow-on grant

Comments/Challenges/Issues/Concerns

If timelines change, we will re-analyze priorities. Proj Expend: 1.5M

9. Appendix

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Research paper

A rapid quantification of binocular misalignment without recording eye movements: Vertical and torsional alignment nulling

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HIGHLIGHTS

- We developed vertical and torsional alignment nulling (VAN, TAN) to quantify ocular misalignments.
- VAN and TAN employ portable, non-invasive hardware that can be self-administered.
- VAN and TAN can measure misalignment within 0.04 deg vertical and 0.1 deg torsional resolution, which correspond to the resolution of the screen for the chosen testing distance.
- VAN and TAN are valid and reliable perceptual measures of ocular alignment.

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ABSTRACT

Background: Small, innate asymmetries between the left and right otolith organs can cause ocular misalignment with symptoms that include double vision and motion sickness. Additionally, ocular misalignment affects nearly 5% of the US population. We have developed a portable, non-invasive technology that uses subjective perception of binocular visual signals to estimate relative binocular alignment.
New method and results: The Vertical Alignment Nulling (VAN) and Torsional Alignment Nulling (TAN) tests ask subjects to view one red and one blue line on a tablet computer while looking through color-matched red and blue filters so that each eye sees only one of the lines. Subjects align the red and blue lines, which are initially vertically offset from one another during VAN or rotated relative to one another during TAN, until they perceive a single continuous line. Ocular misalignments are inferred from actual offsets in the final line positions. During testing, all binocular visual cues are eliminated by employing active-matrix organic light-emitting diode (AMOLED) technology and testing in darkness. VAN and TAN can accurately account for visual offsets induced by prisms, and test-retest reliability is excellent, with resolution better than many current standard clinical tests.
Comparison with existing method(s): VAN and TAN tests are similar to the clinical Lancaster red-green test. However, VAN and TAN employ inexpensive, hand-held hardware that can be self-administered with results that are quickly quantifiable.
Conclusions: VAN and TAN provide simple, sensitive, and quantitative measures of binocular positioning alignment that may be useful for detecting subtle abnormalities in ocular positioning.

1. Introduction

In healthy vestibular function, when the head is tilted about the naso-occipital axis (head to shoulder), the utricular otolith organs generate conjugate, torsional eye rotations opposite to head tilt. This is termed ocular counter-roll and is the torsional vestibulo-ocular reflex. In addition to the eyes rolling about a naso-occipital axis during head tilt, the ipsilateral (with respect to the head tilt) eye will elevate while the contralateral eye will depress in order to counter the change in head position and maintain binocular alignment. This is known as skew deviation and is normal during a head tilt. Combined with the head tilt, the physiological "ocular tilt reaction" (OTR) is therefore a reflexive triad of signs (head tilt, eye torsion, skew) that align the vertical axes of the head and eye

Abbreviation: Δ, prism diopter.

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with earth vertical (Brodsky et al., 2006). The physiologic OTR is normal and common when, for example, we walk on uneven terrain and our body unpredictably rolls, as might occur were one foot to step into a hole. If for example the left foot only was to step into a hole, the head would tilt to the left and stimulate the utricles which would excite the left superior oblique and superior rectus muscles thereby rolling the left eye inward (intorsion) and slightly upward. Concurrently, the right inferior oblique and inferior rectus muscles would be excited and cause the right eye to roll outward (extorsion) and slightly downward (Harris et al., 2001).

A pathophysiologic OTR, on the other hand, indicates damage to the utriculo-ocular pathway and will cause the same triad of signs to favor one side; therefore an acutely damaged left utricle can cause a leftward head tilt, the left eye to be lower than right eye, and the superior poles of each eye to be rotated in torsion to the left. Lesions in the lower brainstem (medulla and the peripheral vestibular afferent pathways) can cause an ipsiversive OTR (ocular counter-roll and head tilt occur in the direction of the lesion) while lesions rostral to the decussation of these fibers in the mid-upper brainstem (medial longitudinal fasciculus and midbrain) may cause a contraversive OTR (Halmagyi et al., 1979; Brandt and Dieterich, 1994; Brodsky et al., 2006).

Investigating for the presence of any skew deviation is critical to differentiate dangerous lesions to the vestibulo-ocular pathways from less serious acute peripheral vestibular lesions (Kattah et al., 2009). The measurement of skew deviation (and ocular alignment) is commonly done in ambient room lighting with cover-uncover, alternate cover (both objective tests) or Maddox rod testing (subjective test), and can be quantified in prism diopters. Measurements in prism diopters (PD) does not provide information about torsional misalignment (Awadein 2013) and is prone to error based on common pitfalls associated with using prisms such as positioning, stacking, or measuring through corrective spectacle lenses (Irsch, 2015). The Lancaster Red-Green test, where subjects view a calibrated chart of dots positioned 1 or 2 m away (Christoff and Guyton, 2006), is another method used to measure ocular misalignment. Subjects wear red-green goggles (the red filter over the right eye and the green filter over the left) to block fusion while viewing a green (and separately) a red streak. The subject then uses a similar streak of light to superimpose on the calibrated chart, how they view the examiner provided streak. The primary limitation of this test is the requirement of dedicated wall space. A computerized version of the Lancaster Red-Green test requires non-portable equipment and dedicated wall space (Awadein 2013).

We sought to develop a portable, handheld, binocular, dissociated and objective means to assess ocular misalignment using perceptual tasks and integrated software that provides monocular visual cues (fusion blocked). We call the procedure to make this measure the vertical alignment nulling and torsional alignment nulling (VAN, TAN).

2. Materials and methods

2.1. VAN and TAN design

The VAN and TAN hardware consists of a small (8.1 × 5.3 × 0.3in, 12.3oz) active-matrix organic light-emitting diode (AMOLED) tablet computer (e.g. Toshiba AT270, Android OS) and a customized, light-occluding, portable shroud to ensure complete darkness (Beaton et al., 2015). When a dark room is available, use of the shroud is unnecessary. An Android application runs the VAN and TAN tests and exports the misalignment results to a text file for offline analysis.

During VAN and TAN testing, the subject views one red and one blue line on the tablet screen through the color-matched red and blue filters (Fig. 1).

This arrangement provides separate visual information to each eye. One line, designated as the *stationary line*, remains fixed on the screen, while the other line, the *moving line*, is repositioned by the subject: vertically (up and down) during VAN and torsionally (clockwise and counter-clockwise) during TAN. The subject's objective during both VAN and TAN is to adjust the moving line until it appears perfectly in-line with the stationary line (i.e., to null any apparent vertical or rotational offset between the two lines). If there exists a small range for which the moving line appears aligned with the stationary line, meaning that the subject can perceptually fuse a slight physical offset in the two lines, the subject is instructed to find the middle of that range. The final amount by which the lines are separated from one another vertically or rotated relative to one another provides a measure of perceived vertical and torsional ocular misalignment, respectively. For example, if a subject sets the right line above the left line during VAN, then we infer that this individual has a vertical misalignment such that the right eye is elevated relative to the left eye (i.e., the right fovea is elevated above the left fovea) (Fig. 2C). If a subject orients the right line clockwise relative to the left line during TAN, then we infer that this subject has a torsional misalignment such that the right eye is extorted relative to the left eye (Fig. 2D). If a subject perfectly aligns the two

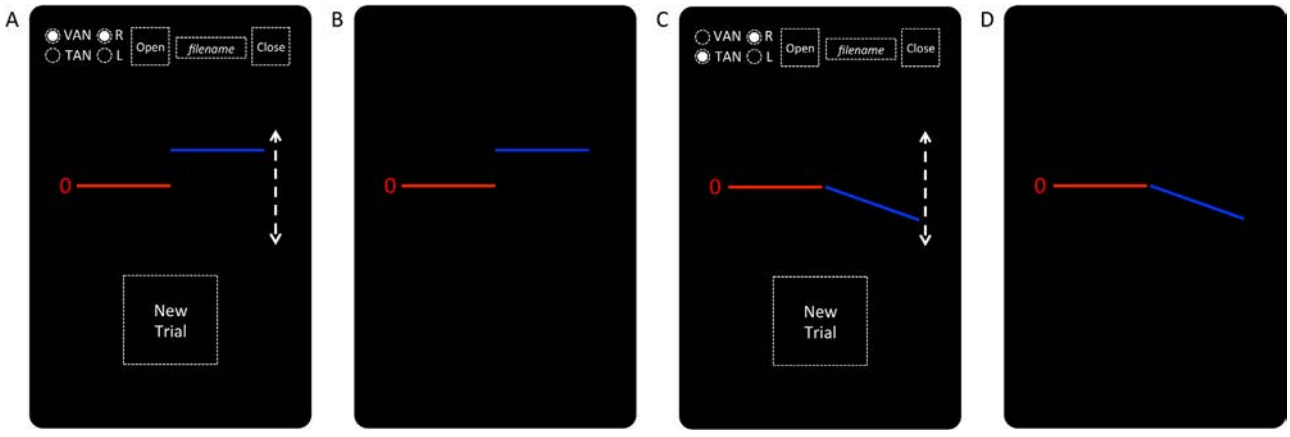

Fig. 1. VAN and TAN screen layouts. The subject wears plastic 3D glasses with a red filtered lens on the left and a blue filtered lens on the right. The task for the subject is to align the blue line with the red line until it appears perfectly in-line with the stationary red line. The white arrow illustrates finger slide on the tablet screen to vertically (A) or torsionally (C) adjust the blue line. Radio buttons in the upper left enable the examiner to select VAN or TAN and choose which line is adjustable (R – right; L – left). All white text is extinguished during testing (B, D). A) VAN initial screen and setup. B) VAN testing. C) TAN initial screen and setup. D) TAN testing.

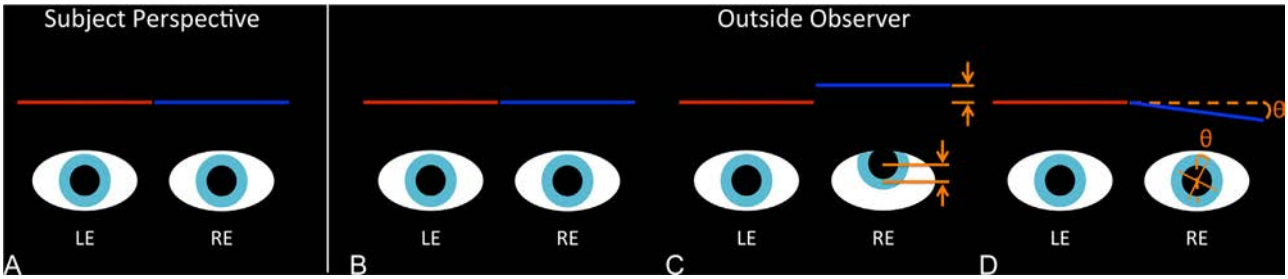

Fig. 2. Examples of ocular misalignments inferred by VAN and TAN results. (A) The subject repositions the moving line until it appears in line with the stationary line, thereby positioning each line on the center of each retina. Binocular misalignment is inferred from the relative positioning of the lines at the end of each trial. (B) If the subject has perfect binocular alignment, then the lines will be perfectly aligned at the end of the trial. (C) If the subject sets the right line above the left line during VAN, we infer that the right eye is elevated above the left eye. (D) If the subject orients the right line CW relative to the left line in TAN, we infer that the right eye extorted relative to the left eye.

lines during both VAN and TAN, then we infer that this individual has normal vertical and torsional binocular alignment (Fig. 2B).

At the beginning of each test session, the subject selects the test to be completed (VAN or TAN) and which line to set as the moving line (right or left), and then opens a data file that automatically records the alignment responses. At the beginning of each trial, the moving line is vertically offset from the stationary line during VAN or rotated relative to the stationary line during TAN. The amount of this initial offset is randomized between 2° and 4° for VAN and 3° and 6° for TAN; these bounds require repositioning of the moving line in healthy individuals, but not by so much that unnecessary time is wasted nulling large offsets. The subject then uses the tablet's touch-screen interface to drag the moving line up or down until no perceptual offset between the two lines remains. For the Toshiba AT270 tablet used in the validation experiments described below, responses can be fine-tuned with a precision of 0.04° for vertical and 0.1° for torsional offsets, which correspond to the resolution of the screen for the chosen testing distance. Once a trial is completed, the subject presses the *New Trial* button to save the final line positions and generate a new offset for the next trial. A color-matched trial counter tallies the number of completed trials. If during testing the *New Trial* button is inadvertently pressed, the application enables the subject to press the volume button (located on the side of the tablet) to flag the previous trial for elimination during post-test analysis. Once the desired number of trials has been completed, the subject presses the upper right-hand corner of the screen (the location of the *Close* button) to close the data file. The data file contains the trial numbers, moving line positions and corresponding tablet timestamps, and any inadvertent *New Trial* flags.

Ocular misalignments are calculated from the stored data as follows:

$$\textit{vertical ocular misalignment} = \frac{180^\circ}{\pi}\tan^{-1}\frac{(pm - ps)/(pp)}{d},$$

where p_M is the subject-selected position of the moving line in pixels, p_S is the position of the stationary line in pixels, d is the distance between the subject's eyes and the tablet screen in inches, and pp is the tablet's resolution in pixels per inch; and

$$\textit{torsional ocular misalignment} = a_M,$$

where a_M is the subject-selected angle of the moving line in degrees. By convention, a positive vertical ocular misalignment means that the eye associated with the moving line is lower than the eye associated with the stationary line, and a positive torsional ocular misalignment means that the eye associated with the moving line is rotated clockwise relative to the eye associated with the stationary line. Once the *New Trial* button is pressed at the beginning of a test, only the red and blue lines and color-matched trial counter are visible; all other visual cues on the tablet screen are removed (Fig. 2B and D). The functions of the *New Trial* and *Close File* buttons remain active through vibrotactile feedback. Pressing the *Close* button re-illuminates the test screen, so that conditions can be configured for the next test.

Table 1
Prismatic powers used in VAN and TAN validation experiments. When Dove prisms are rotated about their longitudinal axis, the transmitted images are rotated twice as much.

VAN		TAN	
Prism Diopters (Δ)	Visual Offset (°)	Prism Angle (°)	Visual Offset (°)
0	0.0	0.0	0.0
1	0.57	1.0	2.0
2	1.15	2.5	5.0
3	1.72	5.0	10.0
6	3.43		
10	5.71		

Importantly, all testing is performed in complete darkness, which is critical for ensuring that extraneous visual cues do not mask the binocular misalignments by providing alternative peripheral alignment information (Burian 1939; Ogle and Prangen 1953; Crone and Everhard-Hard 1975; Guyton, 1988). AMOLED technology allows only the designated pixels on the tablet to be illuminated, so that any visual artifacts, including the backlighting visible on traditional LCD screens, are not present. Additionally, AMOLED technology has a 'first detectable luminance' value that has been matched to the photodiode's sensitivity (0.01 cd/m^2) (Cooper et al., 2013). In contrast, LCD and CRT displays vary from 0.5–500 cd/m^2 to 1–100 cd/m^2 respectively. True black should have a luminance of 0 cd/m^2.

2.2. Prism validation experiments

Prism validation experiments were performed in five healthy test subjects to demonstrate that VAN and TAN can accurately account for visual disparities induced by prisms during straight-ahead gaze as approved by the Johns Hopkins Institutional Review Board. Four of the five subjects were naïve to the objectives of these experiments and the details regarding how the prisms altered the visual images. Throughout the experiments, the prisms were placed in front of the right eye, thereby inducing systematic visual shifts in the right line (Bagolini 1976). We hypothesized that in order for the subjects to perceive the right and left lines to be aligned, they would need to adjust the right line by an amount equal in magnitude but opposite in direction to the visual disparity induced by the prisms.

VAN tests employed triangular ophthalmic prisms (3M Press-On Optics, The Fresnel Prism and Lens Co.) placed in front of the right eye and oriented base-up to generate downward visual shifts of the right line (Table 1). The initial program settings in this set

of experiments were such that the right line was initially offset either above or below the current prism's deflection angle plus a random amount between 2° and 4°. For example, the initial conditions for the 10 PD test, in which the prism deflects the image by 5.71°, were set so that the initial position of the right line was between 5.71° + 2° = 7.71° and 5.71° + 4° = 9.71° above the left line, or between 7.71° and 9.71° below the left line. This was done so that subjects were required to reposition the moving line by an amount proportional to the deviation angle of the prism. Additionally, VAN was validated while wearing binocular video-oculography goggles with the triangular ophthalmic prisms oriented base-up over the right eye only, thereby shifting the image of the right line downward.

TAN tests employed a Dove prism (Edmund Optics, Inc.) rotated about its longitudinal axis to generate counterclockwise rotations of the right line (Table 1). To control for any angular offset between this Dove prism and the tablet, which would result in inaccurate TAN results, a second un-rotated Dove prism was place in front of the left eye and stabilized against the right Dove prism. Again, the initial offsets were re-programmed so that the right line was initially rotated either clockwise or counterclockwise by the current visual rotation angle induced by the prism plus a random amount between 3° and 6°. So, for example, the initial conditions for the 10° stimulus condition were set so that the initial orientation of the right line was between 10° + 3° = 13° and 10° + 6° = 16° clockwise, or between 13° and 16° counterclockwise. During these tests, the prisms were placed on a machinist's micro-adjustable angle block (Anytime Tools Precision Measuring, Inc.) to ensure the small rotation angles were accurate and stable.

For each VAN and TAN prism, three tests were performed: (1) *conventional*, (2) *always above*, and (3) *always below*. In the *conventional* tests, the initial offset of the moving line was randomly selected from positions on either side of the stationary line: either above or below the stationary line during VAN testing and either rotated clockwise or counterclockwise to the stationary line during TAN. During these *conventional* tests, if subjects experienced a range of values for which the moving line was in-line with the stationary line, they were instructed to find the middle of this range.

In the *always above* tests, the initial offset of the moving line was randomly set to a position that was always above the stationary line during VAN and always rotated counterclockwise to the stationary line during TAN. During these *always above* tests, subjects were only allowed to re-position/re-orient the moving line in one direction: down during VAN and clockwise during TAN. Subjects were instructed to adjust the moving line incrementally and stop as soon as they perceived it to be aligned with the stationary line. In the *always below* tests, the initial offset of the moving line was randomly set to a position that was always below the stationary line during VAN and always rotated clockwise to the stationary line during TAN. During these *always below* tests, subjects were only allowed to re-position/re-orient the moving line up during VAN and counterclockwise during TAN. Again, they were instructed to adjust the moving line incrementally and stop as soon as they perceived it to be aligned with the stationary line. All experiments were performed in a completely dark room with color-matched red and blue eyeglasses.

To maintain a consistent subject-to-screen distance (crucial for VAN) and to ensure that the head wasn't rotated relative to the tablet screen (which may have made the TAN test more difficult if the fixed line appeared tilted with respect to the horizon), subjects were seated upright in a chair with the head secured via a custom-molded dental biteboard and the tablet mounted 17in directly in front of them. Testing of VAN and TAN were performed on separate days to prevent fatigue.

Subjects were trained on VAN and TAN procedures in the light for approximately 10 min prior to testing. Training was done in the light for the additional benefit that the vergence angle can be held stable when misalignment is initially tested in light (Guyton personal communication, 11/2/16). Prismatic power and *conventional*/*always above*/*always below* tests were counterbalanced across subjects. There was a total of 18 VAN blocks ([0,1, 2, 3, 6, 10PD] × [*conventional*, *always above*, *always below*]) and 12 TAN blocks ([0,2, 5, 10°] × [*conventional*, *always above*, *always below*]). Fifteen trials were completed for each block. Breaks with full-field vision were taken between blocks to minimize adaptive effects of the prisms (Maxwell and Schor 2006).

2.3. Repeatability experiments

Five separate test sessions each consisting of 10 trials of VAN and TAN were repeated on the same day in 10 additional subjects to assess repeatability. For repeatability testing, only the conventional method was examined.

2.4. Statistics

Statistical analysis was completed using SPSS (version 22, Chicago, Il, USA). Pearson correlation analysis was performed to examine the relationship between PD offset and the subjective measurement obtained from VAN and TAN. Stability of VAN TAN was assessed using multivariate ANOVA to compare VAN vs TAN considering the day of test and the individual subjects.

3. Results

3.1. VAN and TAN quantify the visual disparities induced by prisms

Raw data results from the VAN and TAN *conventional* tests are displayed in Fig. 3A and C. The dashed line indicates the stimulus condition, an intentional misalignment induced in the subjects based solely on prismatic power. All subjects expressed small, non-zero vertical and torsional misalignments during the baseline control (0° visual offset) tests; when these values were subtracted from the prism results, each subject's response curve aligned closely with the dashed stimulus line (Fig. 3B and D).

The correlations between degrees of stimulus offset and mean degrees of misalignment measured by VAN and TAN were exceptional ($r = 0.97$, $p < 0.00001$). Note that the vertical misalignment data is negative and recall that by convention, negative vertical misalignments mean that the right line is positioned above the left line at the end of the trial. This is exactly what we expect from healthy individuals in response to a right line visually displaced below the left line: to null such a visual disparity, the right line must be moved up for the subject to perceive a single continuous straight line. Thus, to an outside observer, the right line will be positioned above the left line at the end of the trial. Similarly, note that the torsional misalignment data is positive and recall that by convention, positive torsional misalignments mean that the right line is rotated clockwise with respect to the left line at the end of the trial. Again, this is what we would expect from healthy individuals in response to a right line visually rotated counterclockwise to the left line.

VAN and TAN *conventional* results were highly consistent within the individual subjects (note the small error bars within each test block), with subjects having scores different from each other ($p < 0.0001$). The VAN and TAN results were also highly correlated with the PD strength across each of the five subjects (small scatter among the subject means for each test block; Pearson correlation 0.967, $p < 0.0001$).

Results from the VAN and TAN *always above* and *always below* tests are displayed in Fig. 4 for two representative individuals who expressed differences in their perception of binocular alignment

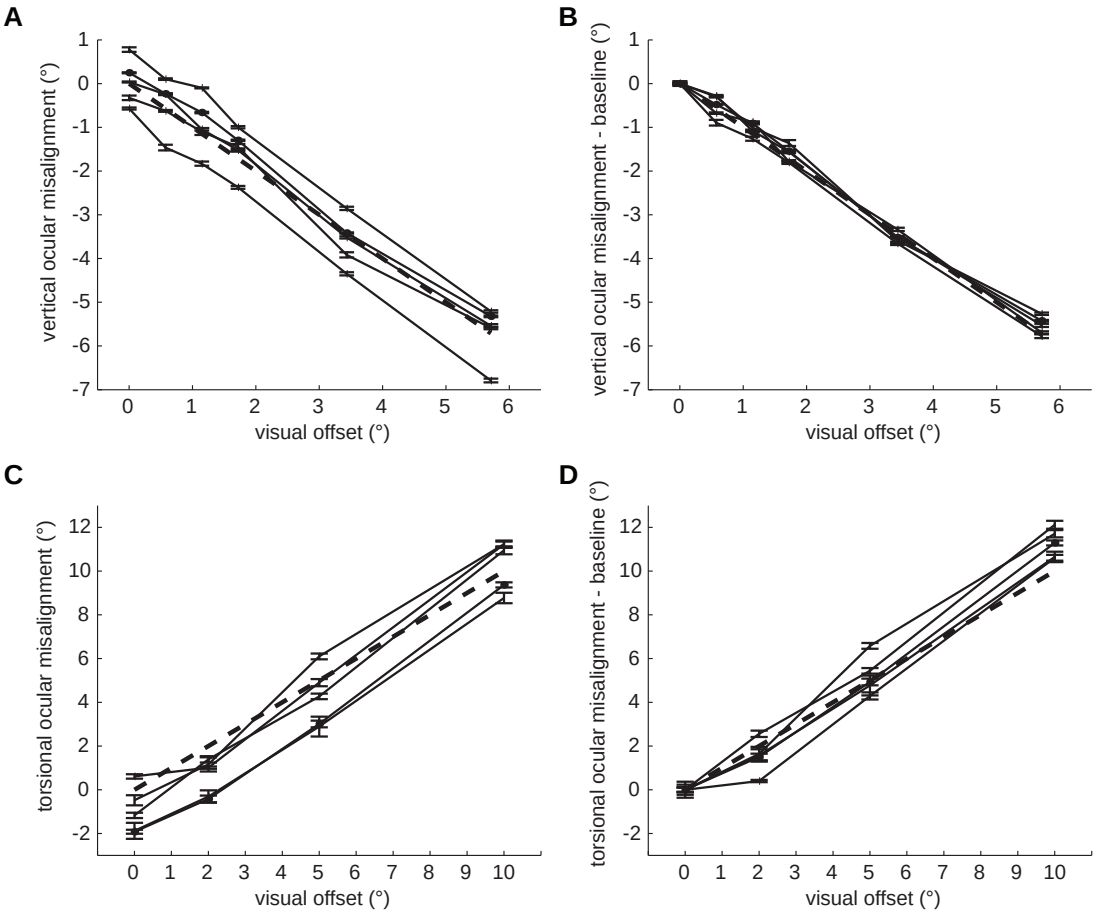

Fig. 3. VAN (A and B) and TAN (C and D) conventional test results from five subjects viewing through vertical displacing prisms and rotational displacing prism (Dove), respectively, in front of the right eye. Zero (0) visual offset represents the baseline control tests without prisms. Dashed lines represents the visual offset stimulus induced by the prisms. Error bars are 1SE. By convention, negative vertical misalignments indicate that the right line was positioned above the left line during VAN. All subjects showed a small vertical misalignment during the upright control test, which is subtracted out in (B). By convention, positive torsional misalignments indicate the right line was rotated CW relative to left line. All subjects showed a small torsional misalignment during the upright control test, which is subtracted out in (D).

(small (A) and large (C)) as compared with the *conventional* method. VAN and TAN *always above and always below* results were both highly consistent within the individual subjects and subjects had scores different from each other ($p < 0.0001$).

3.2. VAN is correlated with eye position

VAN was performed during normal viewing, wearing 2PD and again wearing 10PD (3M Press-On Optics) oriented base-up over the right eye while recording each eye using binocular video oculography (http://patents.justia.com/patent/20150223683). The VAN scores were correlated ($r = 0.99$) with the progressive PD strength (0PD 0.12 ± 0.07; 2PD 0.72 ± 0.17; 10PD 4.1 ± 0.11), Fig. 5.

3.3. VAN and TAN are quick to perform

During all testing, subjects were asked to be as accurate as possible, regardless of how long it took to perform each trial. Nonetheless, subjects performed VAN and TAN relatively quickly, on the order of several seconds per trial. Tables 2 and 3 outline the average time in seconds to complete one trial for the *conventional* prism tests. Of note, the individual who took the longest time to complete the VAN trials (subject C) was the individual who exhibited the largest error as observed through his *always above* and *always below* tests and compared to the *conventional* test.

Table 2
Average time of completion (in seconds) per VAN trial during *conventional* tests.

Subject	0	1	2	3	6	10
A	6.72	8.33	7.15	9.95	10.57	10.23
B	4.98	3.21	4.61	5.31	8.50	4.90
C	9.81	10.18	11.78	7.12	15.90	9.96
D	8.48	4.03	4.98	5.52	5.53	8.52
E	8.12	4.81	8.89	5.17	11.30	9.07

Table 3
Average time of completion (in seconds) per TAN trial during *conventional* tests.

Subject	0	2	5	10
A	6.57	9.64	8.34	12.05
B	3.59	2.62	3.91	4.90
C	6.93	5.15	4.16	6.80
D	4.27	3.95	4.72	6.70
E	5.40	5.10	6.97	7.39

3.4. VAN and TAN are reliable

Repeatability testing revealed the VAN test has less variability than the TAN test; mean VAN scores were always within a quarter of a degree (0.12 deg) of each other, as outlined in Table 4. TAN scores were more variable, though mean scores were still small and within a half degree (0.32 deg) of each other. When uniquely considering those subjects that scored either consistently negative

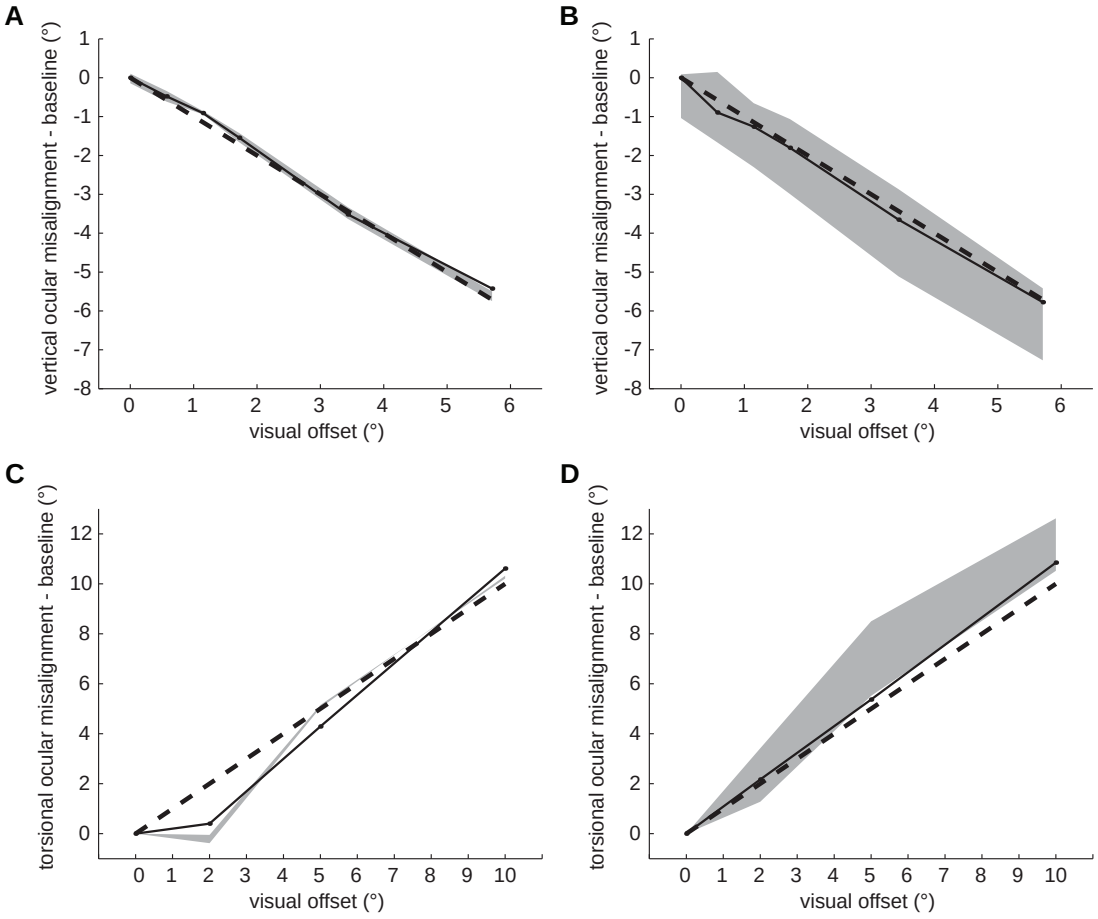

Fig. 4. VAN and TAN always above and always below results for two different subjects who exhibited smaller (A and C) and larger (B and D) difference in perception of binocular alignment. The top of the shaded boundary is the mean of the subject's always above results, the bottom of the shaded boundary is the mean of the always below results. The dashed line marks the stimulus conditions and the solid line denotes the results from the conventional tests.

Table 4
Mean and one standard deviation of VAN and TAN results across multiple test sessions within the same day during conventional tests.

	VAN 1	VAN 2	VAN3	VAN4	VAN5	TAN1	TAN2	TAN 3	TAN 4	TAN 5
Mean ±SD (°)	0.24 ± 0.4	0.25 ± 0.4	0.27 ± 0.3	0.37 ± 0.3	0.28 ± 0.26	0.25 ± 1.1	0.035 ± 0.9	0.34 ± 0.7	0.27 ± 0.8	0.36 ± 0.3
Grand Mean ± 1 SD (°)	0.28 ± 0.4					0.25 ± 0.9				
Median (°)	0.3	0.18	0.25	0.38	0.25	0.3	0.17	0.3	0.36	0.31
	VAN 1	VAN 2	VAN3	VAN4	VAN5	TAN1	TAN2	TAN 3	TAN 4	TAN 5
Mean ± 1 SD (°)	0.24 ± 0.4	0.25 ± 0.4	0.27 ± 0.3	0.37 ± 0.3	0.28 ± 0.26	0.25 ± 1.1	0.035 ± 0.9	0.34 ± 0.7	0.27 ± 0.8	0.36 ± 0.3
Grand Mean ± 1 SD (°)	0.28 ± 0.4					0.25 ± 0.9				
Median (°)	0.3	0.18	0.25	0.38	0.25	0.3	0.17	0.3	0.36	0.31

or consistently positive values on VAN or TAN testing, the mean scores for negatively biased tests were −0.28 ± 0.2 for VAN, and −0.78 ± 0.7 for TAN. For those subjects that scored positive tests, the mean VAN scores were 0.38 ± 0.3, while TAN scores were mean 0.69 ± 0.6.

4. Discussion

Ocular misalignment is also known clinically as strabismus, which can result from oculomotor or neurovestibular causes. The estimated prevalence of strabismus in the general population is from 2 to 5% (Roberts and Rowland, 1978; Donnelly et al., 2005). For individuals aged 55–75 years, the prevalence of strabismus increases to 6.1 percent (Roberts and Rowland, 1978). Strabismus is measured in PD and 1 PD implies a light deflection of 1 cm at a distance of 1 m. The relationship between PD and degrees is trigonometric, not linear. For angles smaller than 45°, the number of PD per degree is less than 2 (Irsch, 2015). Converted to degrees, 1 PD is equal to roughly 0.57 deg. VAN and TAN may be a useful hand-held apparatus for screening strabismus with a sensitivity to measure relative ocular misalignment within 1 PD. The rapid assessment and self-administration capabilities, along with the minimal hardware, make VAN and TAN ideal for evaluating ocular misalignment in operational settings with minimal resources (e.g., time, equipment, or personnel), such as bedside clinical assessment or remote field testing. In particular, we suggest that VAN and TAN are a more applicable test of adult patients with acquired vestibular causes of vertical and torsional misalignment, rather than strabis-

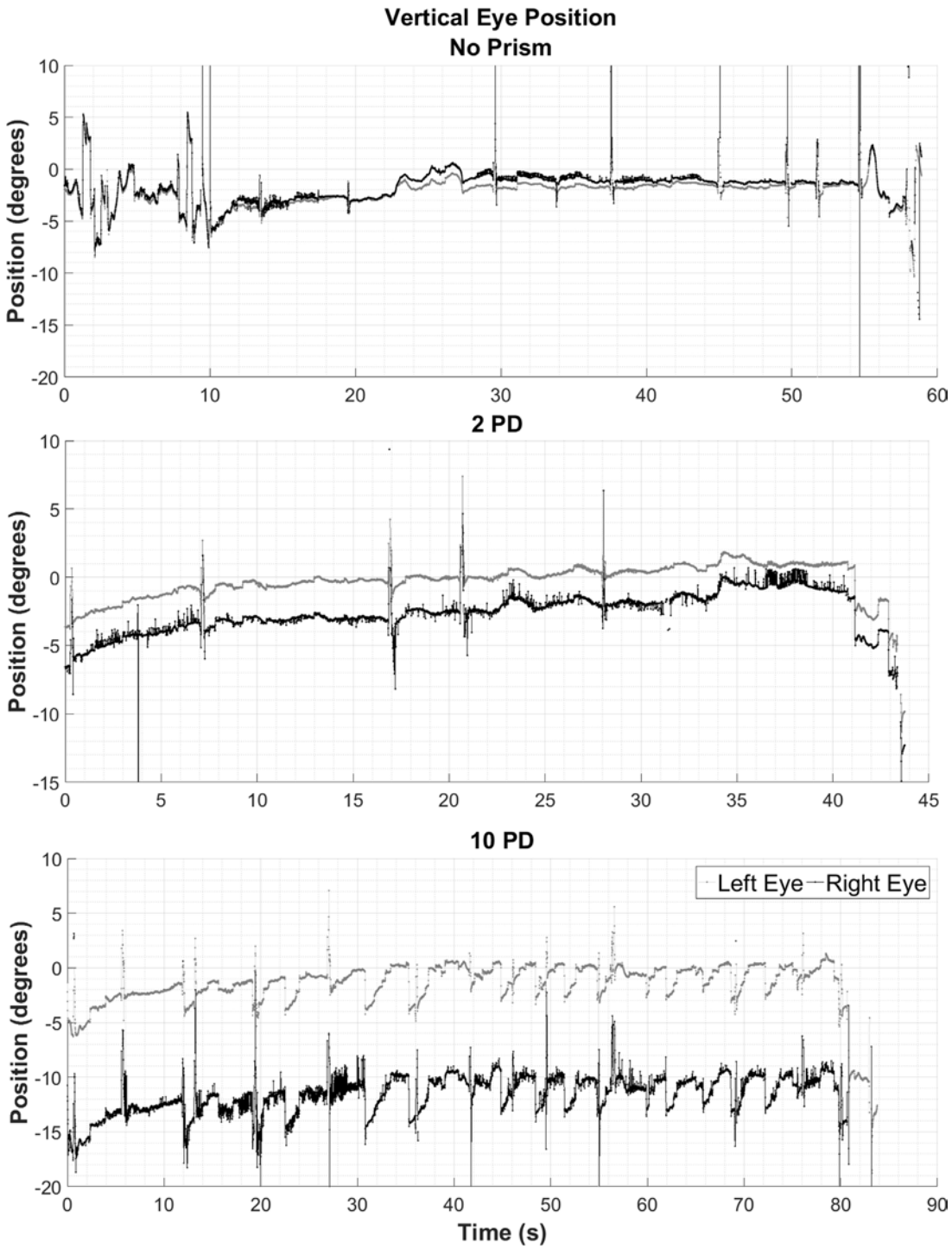

Fig. 5. One subject performing VAN wearing binocular VOG recording goggles during normal viewing (top panel), while wearing a 2PD (middle panel) and 10PD (bottom panel) 3M Press-On Optics positioned base-up over the right eye. The PD strength is correlated with a larger misalignment between the right and left eye, as only the right eye is shifted down. The spikes in the trial indicate blinking. The eye position varies initially and in part reflects the subject moving the hand-held tablet.

mus, in part because VAN and TAN only consider the subjective angles of vertical and torsional deviation, which may suffer from a false negative reading due to the adaptation capacity in strabismus patients. Our VAN and TAN software and hardware are stable and perform reliably in challenging settings (Beaton et al., 2015).

In contrast to traditional ocular position testing, VAN and TAN measure ocular misalignment by controlling for sensory fusion by ensuring only monocular sensory input. Our paradigm also tests subjects in complete darkness. Both criteria are imperative to achieve accurate and consistent results. Ocular positioning misalignments can be suppressed by binocular vision given the visual system's remarkable capacity to fuse disparate visual scenes (up to 2° vertically and 15° torsionally) (Ogle and Prangen 1953; Crone and Everhard-Hard 1975; Houtman et al., 1977; Guyton, 1988). Most of our subjects did not set the VAN or TAN scores at zero, instead subjects offset the lines within 0.3° of each other. We believe that these 'natural offsets' represent a static misalignment that are present in most humans, though are not perceived given

the robust ability of the brain to fuse retinal disparity. Others have reported natural vertical eye alignment within 0.25° (Schor et al., 1994).

VAN and TAN are stable when measured over time, with little variability in test scores (within 1 °). Instructions in the use of VAN and TAN are critical to ensure validity. In particular, subjects should be advised to set the moving line *relative* to the stationary line. For example, if during TAN the stationary line appears tilted with respect to the subject's perception of the Earth's horizon, the subject must rotate the moving line until it is in-line with the fixed line, not in-line with the perceived horizontal. Furthermore, if during TAN the lines appear vertically offset from one another, for example due to an inherent vertical misalignment of the eyes, the subject must make the lines parallel to one another. Subjects should be warned that depending on their horizontal vergence angle, the red and blue lines may appear either overlaid or horizontally separated.

4.1. Practical suggestions

We used AMOLED screens to ensure complete darkness, though not all AMOLED screens are programmed to zero backlight – some have residual backlight. While this could be fixed by adding diffusion filters to the red-blue eyeglasses that will eliminate the faint "glow" of screen, it would be preferable to use AMOLED screens that can be programmed to zero backlight. It is imperative to ensure the red/blue filter glasses/goggles are positioned close to the eyes such that each eye cannot see through the alternate lens. The user must only see one color with each eye (i.e. red left eye, blue right eye). Additionally, the operator can use data from the tablet's three-axis linear accelerometer to detect if the tablet screen (and hence the red and blue lines) was tilted relative to the local g-vector during the test, or if the orientation of the tablet changes during the test (e.g., due to arm fatigue if the subject is holding the tablet). Finally, wireless motion sensors might be incorporated (synchronized into the VAN and TAN program via Bluetooth) to record various types of kinematic movement; for example, a head-mounted sensor could track relative head-to-tablet movement during testing.

4.2. Limitations

We reported the TAN misalignment data was 1° larger than the stimulus prediction for the 10° test block. This may have been due to a slightly imprecise orientation of the Dove prism; although care was taken in precisely rotating the prism by the desired amount. The 11° center (instead of 10°) can be explained simply if the prism was unintentionally rotated by an additional 0.5°. Recall that Dove prisms rotate the visual scene by twice the angle with which they themselves are rotated. The fact that the spread among the mean TAN scores for the five subjects during this block is consistent with the other test blocks lends this to be the most probable cause of the small discrepancy.

Our device does not measure horizontal deviation, neither does it attempt to stabilize it, which limits its utility. We have not tested our device in gaze positions other than straight ahead. Therefore, the validity of our device to measure misalignment in horizontal, vertical, or oblique gaze positions has not been established, which limits the devices ability to be used in the precise manner an ophthalmic surgeon would prefer (i.e. strabismus surgical correction). Our ultimate goal was to develop a clinical tool that could be performed quickly as a screening of oculomotor misalignment. In doing so, we recognize the limitation of not having subjects wait in the dark to allow their eyes to settle to a more stable location. This method of 'darkness adaptation' might improve precision of the VAN TAN method.

5. Conclusions

The hand-held, portable nature and rapid self-assessment capabilities make VAN and TAN ideal for scientists and clinicians to quickly quantify vestibulo-oculomotor performance and ocular alignment.

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The VAN and TAN technology described herein is protected by US Patent 9,072,481.

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Research paper

Assessment of vestibulo-ocular function without measuring eye movements

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HIGHLIGHTS

- A method to assess the vestibulo-ocular reflex without measuring eye movements is described.
- This new method involves the nulling of perceived visual motion as the head moves.
- This provides a functional measure that accounts for a range of sensorimotor mechanisms.
- This technology enables simple and rapid assessments with minimal apparatus and time.

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ABSTRACT

Background: The vestibulo-ocular reflex (VOR) maintains stable gaze during head motion. Deficiencies lead to apparent world motion due to incomplete stabilization of eyes in space. VOR measurement requires specialized apparatus, trained operators, and significant setup time.
New method: We present a system (VON: *vestibulo-ocular nulling*) for rapid vestibulo-ocular assessment without measuring eye movements *per se*. VON uses a head-mounted motion sensor, laptop computer with user input control, and laser target whose position is controlled by the computer. As the head moves, the target is made to move in the same manner with a gain set by the subject. When the subject sets the gain so the target appears stationary in space, it is stationary on the retinas. One can determine from this gain the extent to which the eyes move in space when the head moves, which is the amount by which the VOR is deficient. From this the gain of the compensatory eye movements is derived.
Results: VON was compared with conventional video-based VOR measures. Both methods track expected changes in gain over 20 min of adaptation to minifying spectacles. VON measures are more consistent across subjects, and pre-adaptation values are closer to compensatory.
Comparison with existing method: VON is a rapid means to assess vestibulo-ocular performance. As a functional perceptual measure, it accounts for gaze-stabilizing contributions that are not apparent in the standard VOR, such as pursuit and perceptual tolerance.
Conclusions: VON assesses *functional* VOR performance. Future implementations will make VOR assessment widely available to investigators and clinicians.

1. Introduction

The vestibulo-ocular reflex (VOR) facilitates gaze stability during head motion. As the head rotates and translates in space, the VOR generates compensatory eye movements so that the visual scene remains stable on the retinas. The ability to read signs while walking down the street or to study flight-control instruments when flying through turbulent weather is mediated by an accurate VOR.

The primary approach to quantifying the VOR is to simultaneously record eye and head movements and compare their amplitudes and timings. A head-mounted video-oculography (VOG) device offers the best portability for eye-movement recordings, but this delicate and expensive equipment requires headgear that must be connected to a high-powered laptop computer with extensive processing algorithms. Frequent occlusion of the pupil by

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the eyelids limits the range of vertical eye movements that can be accurately tracked by most VOG software.

Recording eye movements provides a direct, objective measure of the oculomotor response to a given head movement. However, this motor output does not incorporate cognitive or perceptual factors (i.e., a sensory component) that may also aid in gaze stability. The dynamic visual acuity (DVA) test was developed to evaluate the ability to read during head motion without recording eye movements (Herdman et al., 1998; Longridge and Mallinson, 1984, 1987). It is a functional correlate of the VOR (Benson and Barnes, 1978; Longridge and Mallinson, 1984). In the DVA test, head movements faster than a specified velocity trigger the presentation of an optotype, such as the letter E or C. Subjects are asked to report its orientation (up, down, left, right). Correct responses lead to the generation of progressively smaller optotypes, until the individual can no longer accurately distinguish the letter's orientation. At the end of the test, a dynamic visual acuity score is given, which relates the ability to see clearly with the head moving relative to the ability to see clearly with the head still. DVA can reliably distinguish among healthy individuals and patients with vestibular deficits (Herdman et al., 2007, 2003, 1998). However, it can be time consuming (more than ten minutes), and is less than ideal for use in experiments that adaptively alter VOR gain since it can serve as a de-adapting stimulus.

2. Methods

We present an innovative assessment technique to evaluate the VOR without measuring eye movements. This technique bridges some of the gap between traditional measures of motor responses such as VOR gain and phase, and subjective measures of functional performance, by employing a perceptual nulling task that quantifies how stable a target must be in order for it to be perceived as stationary in space. Laboratory experiments described here compare results from this nulling task to standard measures of VOR gain. The technology described here is protected by US Patent 9,072,481 to M Shelhamer.

2.1. Conceptual design

If the vestibulo-ocular reflex (VOR) is miscalibrated, so that eye movements do not appropriately compensate for head movements, a stationary target will appear to move when the head moves. This is termed *oscillopsia*. If head movement is measured in real time, and used to control target motion through a variable gain (Fig. 1), the subject can adjust that gain so that the target appears stationary during head motion: this is the key aspect of our method of Vestibulo-Ocular Nulling (VON). The motion-gain setting determines to what extent the target must be moved – either more or less than the head movement – so that it matches the eye movements in space and appears to be stationary in space. If the VOR gain is too low, the eyes move less than the head, in the opposite direction, and the motion-gain setting will be less than 1.0 in order to null the perceived target movement. Likewise a VOR gain that is too high will lead to a motion-gain setting greater than 1.0. Thus the motion-gain value, set by the subject to null perceived target movement, provides a surrogate measure of VOR gain, without actually measuring eye movements.

By definition, a VON motion-gain value of 1.0 means that the target is physically fixed in space. In other words, when VON motion-gain is set to 1.0, the target does not move regardless of how the head moves. This is appropriate for an individual with a perfectly compensatory VOR: when viewing a stationary target while moving the head, the target does not appear to move – it remains fixed both physically and perceptually. In contrast, a VON motion-gain value of 0.0 means that the target moves in perfect synchrony with the head. This is equivalent to a VOR cancellation task, in which the target moves in the same direction and at the same speed as the head, and would permit following of the target if the VOR gain were 0: no compensatory eye movement is made. If the VON motion-gain is set to a value less than 1.0, then, to a healthy individual with a perfectly compensatory VOR, the VON target will appear to move *in the same direction* as the head but by a lesser amount than the head moves. Thus, when such a person performs the VON task, the VON motion-gain will have to be increased (to 1.0) in order for the target to appear stationary during head motion. Alternatively, if the VON motion-gain is initially set to a value greater than 1.0, then, to this healthy individual, the VON target will appear to move *in the opposite direction* of the head, and VON motion-gain will have to be decreased (to 1.0) in order for the target to appear stationary during head motion.

2.2. Hardware implementation – current

Our development work, and the experiments described here, use a version of VON that requires a dedicated dark testing room. A planned portable implementation is described subsequently. The apparatus consists of a laptop computer, mirror galvanometer, back-projected laser target, data acquisition board, rate sensor, and motion-gain potentiometer.

The rate sensor, a cube of approximately 3 cm, is attached to a dental biteboard custom-fit to each individual subject. This sensor transduces head movements about all three axes; only yaw-axis motions are invoked and sensed in the work described here. The head-movement signal is provided to a software program running on a dedicated laptop computer, via analog-to-digital conversion on a data-acquisition board. The program is written in the C programming language and runs on the MS-DOS operating system for better real-time performance than is readily achievable with other operating systems with graphical user interfaces. The computer program scales the head-motion signal by a multiplicative factor that is set by the test subject using a hand-held potentiometer. The scaled signal is sent to a galvanometer that controls the angle of a small mirror, off of which is reflected a red laser dot. This dot then appears on a back-projection screen, 1.5 m from the subject. The subject can continuously alter the motion-gain setting (scaling factor) in the computer program while making head movements.

2.3. Hardware implementation – planned

A later hardware implementation, currently under development, uses a handheld tablet computer to replace the laptop computer, laser, galvanometers, and projection screen. A wireless motion sensor is still used to transduce head motions. The tablet enables testing to be performed in complete darkness, either in a dark room or within a black shroud. This is critical for ensuring that background visual cues do not influence VON motion-gain values. The goal of VON is to adjust the motion-gain until the target appears to be fixed-in-space during head motion, not fixed relative to a known stationary object, for example. As such, if the subject can see the border of the display, it is easily recognized that a "perfect" VON motion-gain is achieved by simply centering the target in the center of the display. Therefore, testing without extraneous visual cues is important.

2.4. General procedures

In a subject with a proper compensatory VOR, the subject should select VON motion-gain values equal to 1.0. Values above or below 1.0 describe the amount of deficiency in the vestibulo-ocular system. Suppose an individual has a deficient VOR with a gain of 0.5,

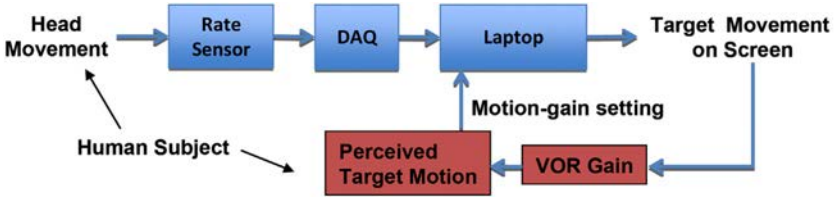

Fig. 1. Basis of VON technique is the control of visual target motion based on head motion, with a variable gain set by the subject. When the motion-gain is set so that the target appears stationary during head movements, its value indicates the extent to which the vestibulo-ocular reflex (VOR) is miscalibrated.

so that eye movements compensate for only half of the amount of head motion. When this person makes a head rotation to the right by 10°, the eyes will move left in the head but only by 5°, leading the eyes to be off the target by 5°. Suppose that this person performs the VON test and the initial motion-gain is set to 1.0. At the start of the test when fixating the stationary VON target before moving the head, the target is in the center of the fovea. When the head is rotated to the right, the target will appear to move to the left because the eyes do not rotate far enough to compensate for the head movement. In order to perceive the target as fixed in space during the head movement, the VON motion-gain must be set so that the target moves in the same direction as the head but only 50% as much as the head moves. This is accomplished by selecting a VON motion-gain less than 1.0.

Subjects trained on VON are taught these strategies. Although the VON task itself is highly intuitive for most people, engraining these concepts early enables subjects to perform the individual trials rapidly, as it automates the task so that subjects do not need to think about which direction the motion-gain should be adjusted based on how they perceive the target to be moving relative to their head motion.

2.5. Experiment: demonstration of comparable adaptation in VOR and VON

We were interested in how our perceptual measure of vestibulo-ocular function (VON motion-gain) compares to a traditional measure of the vestibulo-ocular system (VOR gain), and so VON motion-gain and VOR gain were measured during adaptation to a pair of telescopic lenses.

To induce adaptation, twelve healthy subjects wore ×0.5 minifying lenses for 20 min, during which they made active head movements. All subjects provided written, informed consent to a protocol approved by the Johns Hopkins Medicine Institutional Review Board. None of the subjects suffered from visual or vestibular pathology, as self-reported. They ranged in age from 20 to 52; four were female. The adaptation protocol consisted of 20 min of active, yaw-plane, sinusoidal head rotations while wearing the lenses. Movements were paced with a metronome at 90 bpm (one half-cycle per beat, 0.75 Hz sinusoidal motion) and rotated the head through approximately 40° on each cycle. The adaptation procedure was divided into four 5-min blocks. During these blocks, subjects focused on a stationary target 1.5 m away in a lighted room. VON motion-gain and VOR gain were probed between each adaptation block in the dark without lenses. During the VON tests, the laser VON target was the only visible cue, and was projected 1.5 m in front of the subject. Traditional VOR-gain testing was performed in complete darkness with subjects imagining a stationary target. At the beginning of each VOR-gain test, subjects fixated on this stationary target (the same laser target as used for VON testing) for several seconds, which was extinguished just prior to the start of the head movements. At the end of the adaptation period, a 5-min washout session was implemented, in which subjects performed the same active, sinusoidal head movements in the light without the lenses. Following this washout, VON motion-gain and VOR gain were measured one final time in the dark. During each test probe, five VON trials were performed and twenty cycles of VOR gain data were collected. Acquisition of VON data took less than two minutes in each case, while VOR measurements were much longer due to the need to put on, adjust, and calibrate the VOG system.

Nine of the twelve test subjects (all subjects except A, H, and J) were naïve to the objectives of the experiment and how minifying lenses alter motion of the visual scene. These nine subjects had also never performed the VON task before. All subjects were trained on the VON task and completed twenty practice trials prior to the start of the experiment to reduce training effects. Furthermore, because it was anticipated that some subjects might have difficulty remembering the location of an imaginary target during VOR gain testing, subjects practiced making the twenty cycles of head movements while fixating an imaginary target three times.

When a healthy individual first dons ×0.5 minifying lenses, head movements elicit compensatory eye movements equal in amplitude and opposite in direction: the VOR gain is 1.0. Complete adaptation to such lenses means that stationary objects remain on a fixed location on the retina during head motion. To achieve this, eye movements must be adaptively adjusted so that they only move half as much, still in the opposite direction, for a given head movement (VOR gain of 0.5). Therefore, as adaptation progresses, VOR gain should decrease from 1.0 toward 0.5.

3. Results

Both VOR gain and VON motion-gain in Fig. 2 follow the expected adaptation trend. With each measurement method, gains are initially high and decrease monotonically over the course of adaptation. However, two further results are readily observed. First, the baseline VOR gains for most subjects are significantly different from 1.0, even though none of these subjects experience oscillopsia in everyday life. Values vary across individuals, with all but one subject's baseline gain less than 1.0. There is no relationship between subject age and initial VOR gain (Spearman rank-order correlation coefficient $r_s = 0.15$ $p = 0.32$ for a one-sided test). Baseline VON motion-gain values, on the other hand, are generally much closer to 1.0. Second, the VOR gain adaptation curves for some subjects do not follow smooth, monotonic decrements from one gain probe to the next. In some instances relatively little adaptation is achieved, as seen by a small difference in consecutive VOR gain values, while in other cases substantial adaptation occurs. The VON motion-gain adaptation curves are much more systematic, with regular decrements in motion-gain values as adaptation progresses.

As expected, measurements made at different times in the adaptation process yielded different values. It is also true that the values were significantly different between the VOR and VON methods. This is shown by a two-way ANOVA, with subjects as replications, and with factors of time into adaptation (0, 5, 10, 15, 20 min, washout) and VOR versus VON. Both measurement method and adaptation time were significant ($p = 5 \times 10^{-5}$, 1.7×10^{-19}). However, for each subject, we also compared the mean measures from VON with those from VOR, across adaptation. Correlation coefficients ranged from 0.83 to 0.98 with a mean of 0.91. Thus, both

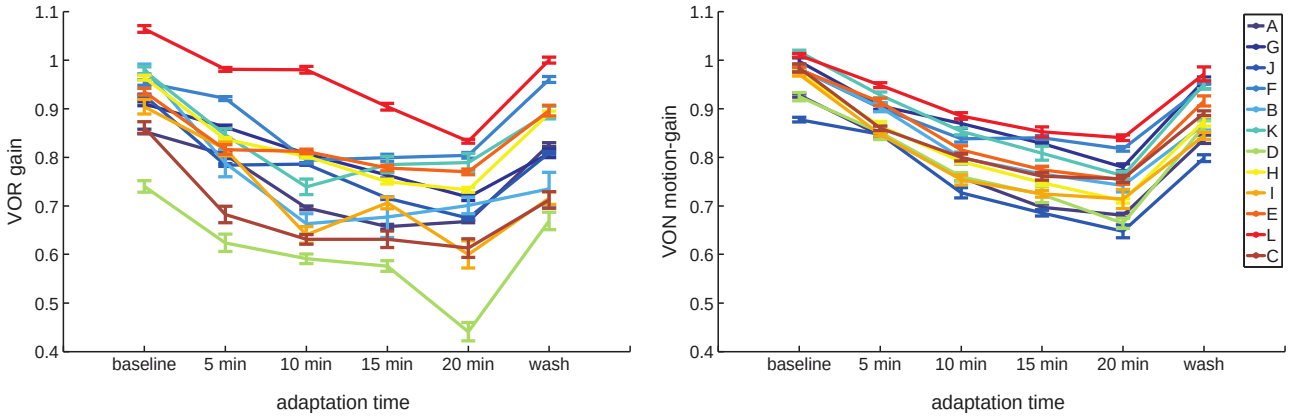

Fig. 2. VOR gain and VON motion-gain results during adaptation. Baseline data were collected prior to donning of the lenses, probe tests were performed after 5, 10, 15, and 20 min of adaptation, and washout data were collected after the 5 min washout. Error bars represent 1 SE.

measurement methods track adaptive changes, with values that are different but show very similar trends.

This type of adaptation stimulus can sometimes produce nausea and motion sickness in subjects. While we did not systematically assess motion sickness during adaptation, subjects did not complain of nausea or motion sickness. Any symptoms were mild and not disruptive to the experiments. The short-term, active, yaw-axis movements that our subjects made are generally well tolerated.

4. Discussion

4.1. *VON is a* functional *measure of vestibulo-ocular performance*

Here we demonstrate a new vestibulo-ocular nulling technique to assess vestibulo-ocular function quickly with minimal apparatus. The VOR compensates for head motion, but it is typically augmented with other sensory and motor responses such as catch-up saccades, visual following, motor preprogramming, prediction, and mental set (Baloh et al., 1984; Barr et al., 1976; Demer, 1995; Fetter et al., 1995; Matta and Enticott, 2004; Moller et al., 1990a; Moller et al., 1990b; Paige et al., 1998; Weissman et al., 1989). It is this entire functional repertoire that is assessed by our vestibulo-ocular nulling task. By quantifying the perceptual consequences of a deficiency in this compensatory system, we can define a *functional* performance metric that may have more utility than VOR gain alone.

Because eye movements were not measured during VON testing, the possibility of catch-up saccades could not be directly verified, but others have demonstrated that they are readily employed during adaptation to left-right reversing prisms (Melvill Jones et al., 1988) or graded velocity error signals (Schubert et al., 2008) and in compensating for vestibular hypofunction (Halmagyi et al., 1990; Tian et al., 2000; Weber et al., 2008; Schubert et al., 2010; Ramaioli et al., 2014).

4.2. *VON quantifies visual-vestibular adaptation*

VON was demonstrated by evaluating adaptive changes during a standard paradigm that alters the gain of the VOR using minifying lenses. The primary result is that VON provides a consistent and meaningful assessment of the adaptive changes. It also revealed some characteristics that show its value as a functional measure in comparison with the VOR: more consistent and systematic gain changes during adaptation, and initial gain values closer 1.0. Both of these are expected from a system that properly marshals available sensorimotor resources to maintain gaze.

VOR gains in our adaptation experiment (Fig. 2) are variable and initially low. This is likely because VOR gain was measured in complete darkness with subjects imagining a stationary target (Collewijn et al., 1983; Das et al., 2000; Fetter et al., 1995); as noted above, other mechanisms interact synergistically to optimize compensatory eye movements in everyday experience in the light. Furthermore, if subjects are distracted, fatigued, daydreaming, or their eyes begin to close, VOR gains are variable and low (Matta and Enticott, 2004; Weissman et al., 1989). Low VOR gains for subjects A and J are further due to the fact that these individuals routinely wear eyeglasses that correct for myopia. Such spectacles induce a prismatic magnification (Cannon et al., 1985), which can be approximated by $M = 40/(40 - D)$, where D is lens power in diopters and M is magnification power (Rubin, 1974). Subjects A and J wear −4D and −7D prescriptions, which correspond almost exactly with their baseline VOR gain values of 0.92 and 0.85, respectively.

4.3. *Stability of spatial memory*

Another finding is that subjects varied in the amount of adaptation from one adaptation block to the next, as seen in consecutive VOR gain probes. These gains did not follow smooth, monotonic decrements, especially as compared to the more consistent VON data. This may be due to difficulty to consistently recall the location of an imagined target during VOR gain testing. Many subjects commented that knowing "where to look" during the VOR gain tests was difficult. Three subjects (A, H, J) who had previously performed VOR adaptation experiments appeared to have less difficulty.

In five subjects, the error bars for the individual VON motion-gain probes were smaller than those for the corresponding VOR gain probes. This was unexpected, as one might anticipate that perceptual responses would be more variable than ocular reflex responses. However, in light of the discussion above, this was likely due to the fact that during VON, subjects had a visible target. This is consistent with other studies which have demonstrated that VOR gain variability is significantly smaller when an actual fixation target, rather than an imagined one, is present (Baloh et al., 1984; Demer, 1992).

A related report was that VON became more difficult as adaptation progressed, although this was not manifest as a systematic increase in the amount of time or number of head movements required to complete the VON trails. This might be because subjects recognized quickly that this residual motion did not disappear with additional head movements or fine-tuning of the motion-gain, and so performed the test as best as possible and moved on to the next trial. This effect may be seen in the VON error bars, as a systematic increase in the mean standard error: baseline $\mu_{SE} = 0.0051 \pm 0.0019$, after 5 min of

adaptation $\mu_{SE} = 0.0071 \pm 0.0030$, and after 20 min of adaptation, $\mu_{SE} = 0.0091 \pm 0.0046$. This is mirrored in the VOR gain data, as some subjects demonstrated less consistent gain changes during the later test probes. We believe that VON became more difficult during the later test probes because, as noted above, subjects may experience a loss in spatial referencing during adaptation. In VON, subjects are asked to null apparent visual motion. However, as adaptation progresses, what they perceive as stationary is actually moving. Furthermore, none of the subjects achieved complete adaptation during the four adaptation blocks, and so gaze stability was disrupted throughout the duration of the experiment. Hence, it is likely that during the adaptation process, the ability to accurately localize a target's position or velocity, especially in the absence of other sensory cues, is impaired.

A related observation was made when we attempted to test VON while subjects wore various telescopic spectacles ($\times 0.5$, $\times 2$) for brief periods of time. When VON was attempted while wearing lenses of any magnification power, the nulling task was simply not feasible. While it was possible to reduce the apparent motion of the VON target by adjusting the motion-gain, the motion could never be eliminated.

4.4. Sensory-Motor fusion

The brain can augment motor responses with sensory adjustments to produce stable percepts. This sensory-motor fusion is common in oculomotor systems. For example, while binocular alignment is primarily driven by vergence movements, a sensory component completes the perceptual alignment (Panum, 1858; Perlmutter and Kertesz, 1978; von Tschermak-Seysenegg, 1942). Vestibulo-ocular function incorporates both sensory and motor components as well. The motor component can be quantified by measuring VOR gain with simultaneous recordings of eye and head movements. The sensory component can be quantified by performing VON and comparing the results to VOR gain.

It is likely that there is a range of sensory inputs that facilitate adequate gaze stability during head motion. We observed this during the adaptation experiment when subjects reported during some of their VON probes that there existed a small *range* of motion-gain values over which they could perceive the target to be stationary during head motion. In addition, baseline VON gains were closer to compensatory (1.0) than were the VOR gains (Fig. 2). This indicates that subjects likely employed sensory strategies to determine when the VON target was stable. Similarly, Demer and Amjadi (1993) showed that the visual system can tolerate up to 2°/s of retinal slip before functional decrements in dynamic acuity occur. Grunfeld et al. (2000) examined adaptation to oscillopsia in vestibular patients and found that compensation was related partly to increased tolerance to movement of images on the retina during self-motion (Grunfeld et al., 2000).

An early study very similar in approach to ours was conducted by Wallach and Kravitz (1965a,b). They used a mechanical transmission to modify the amount by which a visual target moved in response to head movement. The experimenter rather than the test subject adjusted the ratio of target to head motion (our gain-factor) in discrete increments. This ratio was adjusted so that the subject indicated that the target was stationary during head motion, yielding a functional gain assessment analogous to ours from VON. They used this apparatus to assess "constancy of visual direction" – stability of the visual world – before and after adaptation with minifying lenses. Like us they found a range of ratios over which the target was perceived as stationary. However, the authors seemed not to be aware of the VOR as no mention is made to eye movements, nor to the vestibular system.

4.5. Advantages of the VON method

On average, subjects required 5–10 sinusoidal head cycles (8–15 s) to complete each VON trial. Although some subjects stated that the nulling task was more difficult later in adaptation, there was no significant difference in the length of time to complete a trial early versus late (5 versus 20 min) in adaptation (paired *t*-test, $p > 0.05$). Thus, completing five VON trials during a given gain probe took less than two minutes, including short breaks between trials. A VOR gain measurement is much longer: approximately four minutes to start the software, don the goggles and adjust for comfort, center the camera on the eye, and perform a calibration. With 20 cycles of head movements and several seconds of stationary data, one round of VOR gain testing took approximately five minutes.

Although the VON target is visible during testing, VON is not a de-adapting stimulus during an adaptation experiment. This is because the subject controls how the target moves relative to head motion. For example, suppose a subject is presented with a VON target whose motion-gain is 1.0, but this individual has an adapted VOR gain of 0.8. As soon as this subject initiates a head movement, he or she will see the target appear to move, and begin to adjust the VON motion-gain (to approximately 0.8). Thus, as long as subjects perform VON correctly – they do not execute repeated head movements with a motion-gain setting where the target clearly moves during head motion – VON does not wash out adaptation. This is an important advantage over other assessment techniques, such as VOR gain measures made while viewing a stationary target, or DVA testing.

4.6. Alternative testing procedures and suggested improvements

Given that setting of motion gain in the current implementation requires several cycles of head motion, and a trained subject, it is useful to consider alternatives that might make the process more rapid and intuitive. One possibility is to have the subject make a single head movement, observe the apparent motion of the target, and then adjust a control setting to indicate an estimate of that motion. In fact this control setting would modify the motion-gain as currently implemented. However, the subject's instruction would no longer be to null apparent motion but rather to indicate the extent of such motion on each trial.

In general, VON testing can be performed with rotational or translational head movements to evaluate the angular and linear VORs, which can be generated actively or passively. Testing with translational head movements would require knowledge of the subject-to-target distance to compute the appropriate compensatory gain values. Furthermore, larger visual scenes could be employed, especially in a laboratory environment, to evaluate the vestibulo-ocular system in the presence of more realistic visual stimuli, and also to make the test amenable for evaluation of the roll VOR.

Perhaps the most useful improvement would be to arrange a display system that would not require the testing to be performed in darkness. Stationary objects provide a frame of reference by which subjects can accurately judge motion of the displayed target. This renders it difficult, if not impossible, to adjust feedback gain so that the target appears stationary in space. One approach would be to have a large display screen situated close enough to the subject's head that only the screen is visible (not the edges). A more practical solution might be realized with wearable optics that greatly expand the limited field of view provided by a small display screen, with appropriate modifications at the edges to compensate for optical distortion typical of such fish-eye lenses. Since it is the *motion* of the target that us the key aspect of our methods, some optical distortion could be readily accommodated.

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