Journal of Neuroscience Methods 283 (2017) 7–14

Contents lists available at ScienceDirect

Journal of Neuroscience Methods

journal homepage: www.elsevier.com/locate/jneumeth

Research paper

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

Kara H. Beaton[a], Mark J. Shelhamer[a], Dale C. Roberts[b], Michael C. Schubert[a,c,*]

[a] Department of Otolaryngology – Head and Neck Surgery, USA
[b] Department of Neurology, USA
[c] Department of Physical Medicine and Rehabilitation, The Johns Hopkins University School of Medicine, Baltimore MD, USA

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.

ARTICLE INFO

Article history:
Received 2 February 2017
Received in revised form 7 March 2017
Accepted 9 March 2017
Available online 12 March 2017

Keywords:
Ocular misalignment test
Otolith asymmetry
Heterophoria test
Dissociative test
Retinal disparity

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.

* Corresponding author at: 601 N. Caroline Street, 6th Floor Baltimore, MD 21287-0910, USA.
E-mail address: mschube1@jhmi.edu (M.C. Schubert).

http://dx.doi.org/10.1016/j.jneumeth.2017.03.009
0165-0270/

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

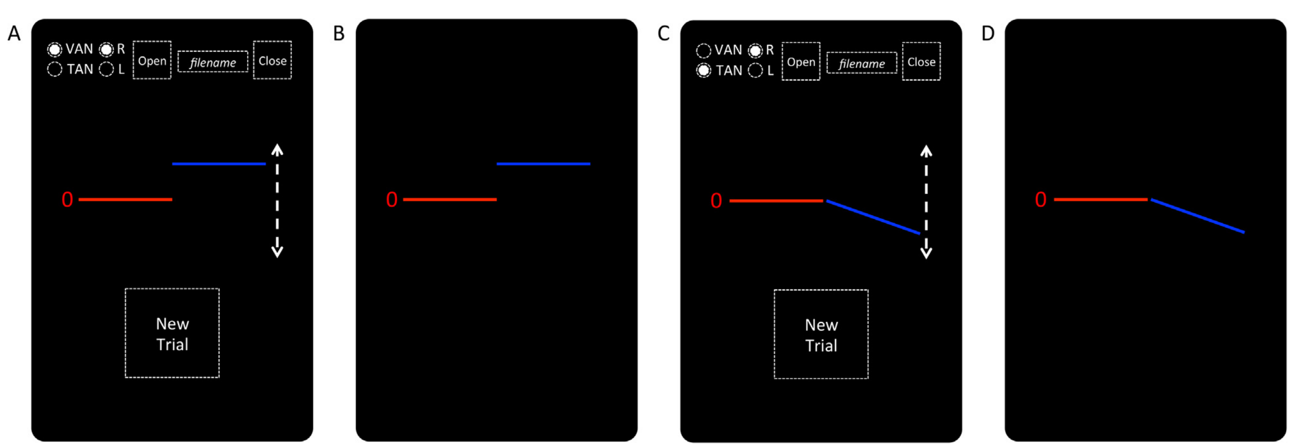

Fig. 1. VAN and TAN screen layouts. The subject wears plastic 3D glasses with a red filtered lens on the left and a blue filtered lens on the right. The task for the subject is to align the blue line with the red line until it appears perfectly in-line with the stationary red line. The white arrow illustrates 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.

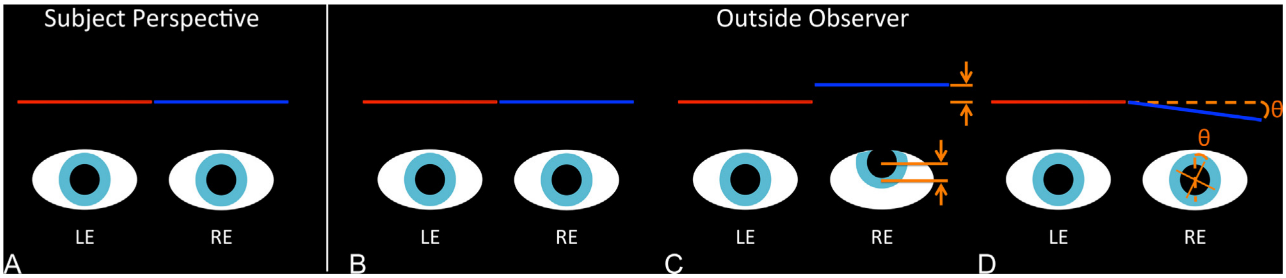

Fig. 2. Examples of ocular misalignments inferred by VAN and TAN results. (A) The subject repositions the moving line until it appears in line with the stationary line, thereby positioning each line on the center of each retina. Binocular misalignment is inferred from the relative positioning of the 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.

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.

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		

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

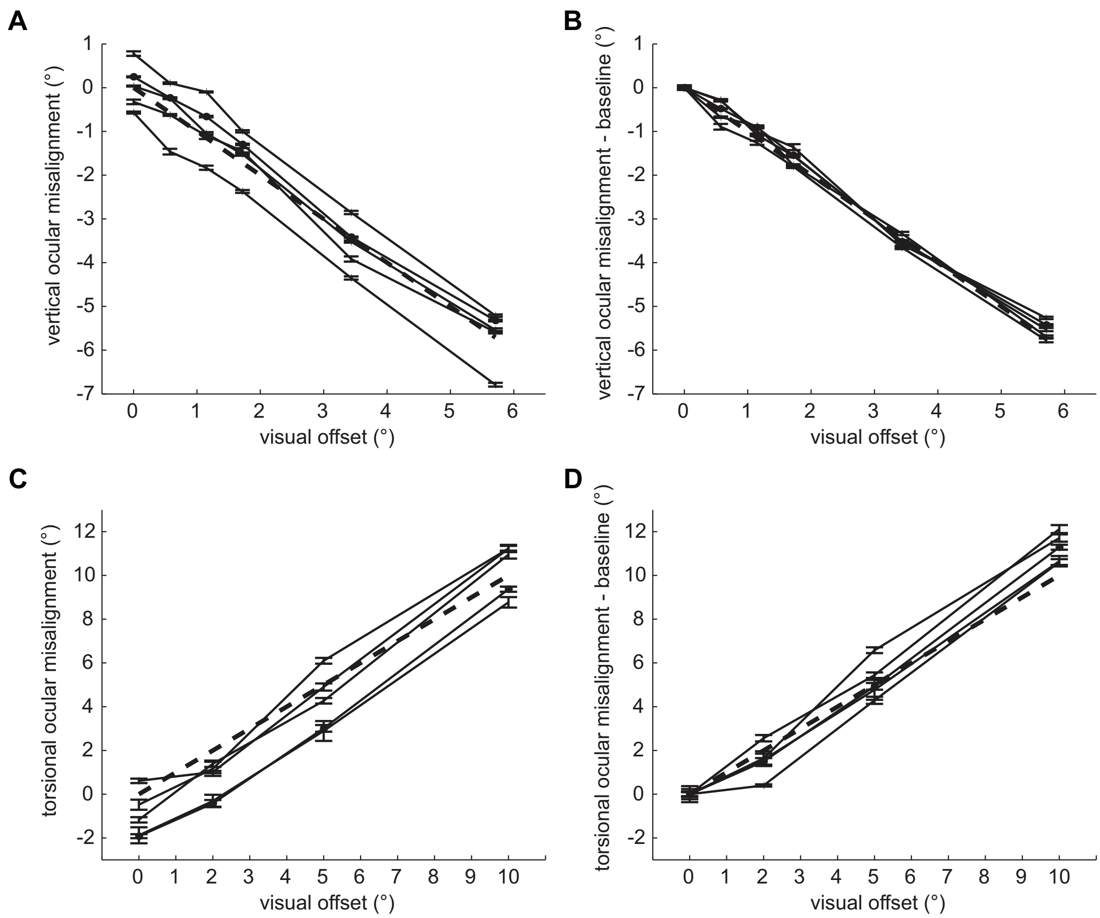

Fig. 3. VAN (A and B) and TAN (C and D) conventional test results from five subjects viewing through vertical displacing prisms and rotational displacing prism (Dove), respectively, in front of the right eye. Zero (0) visual offset represents the baseline control tests without prisms. Dashed lines represents 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

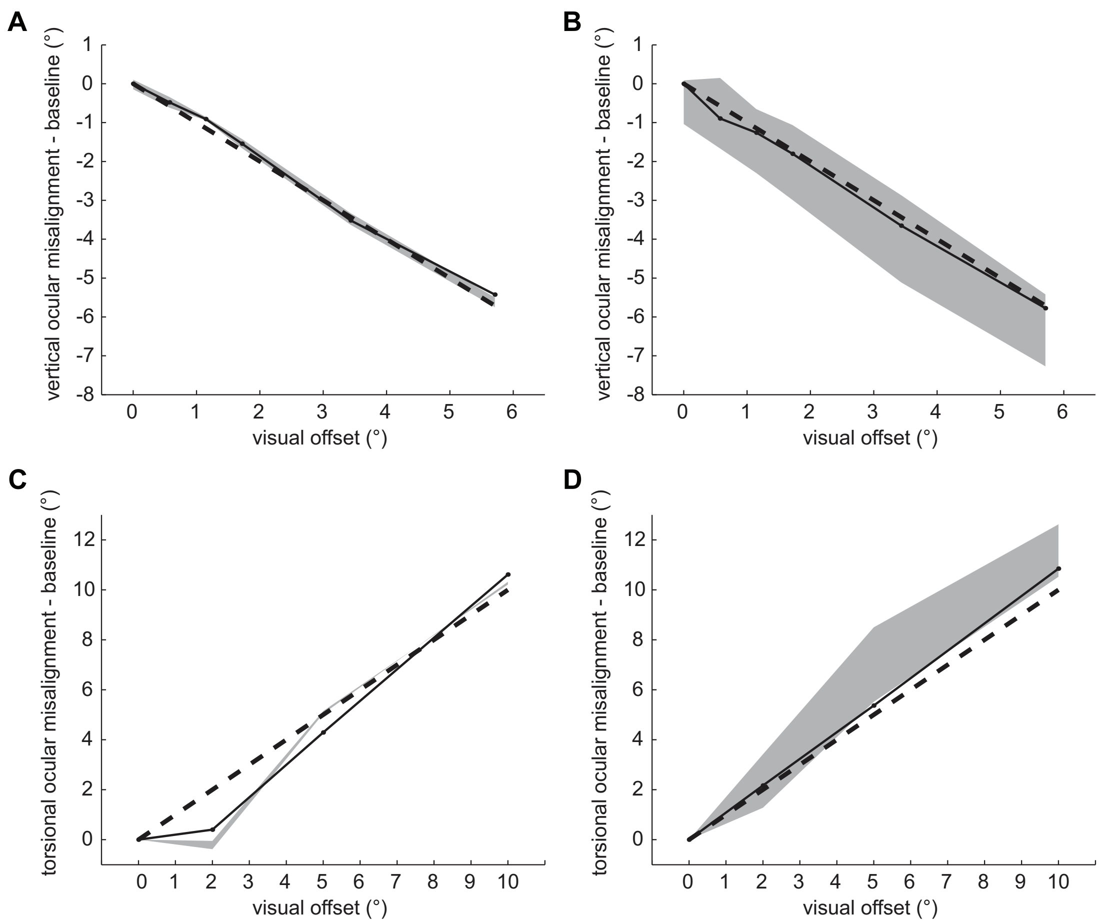

Fig. 4. VAN and TAN always above and always below results for two different subjects who exhibited smaller (A and C) and larger (B and D) difference in perception of binocular alignment. The top of the shaded boundary is the mean of the subject's always above results, the bottom of the shaded boundary 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 ± 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 ± 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 ± 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 strabismus, 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

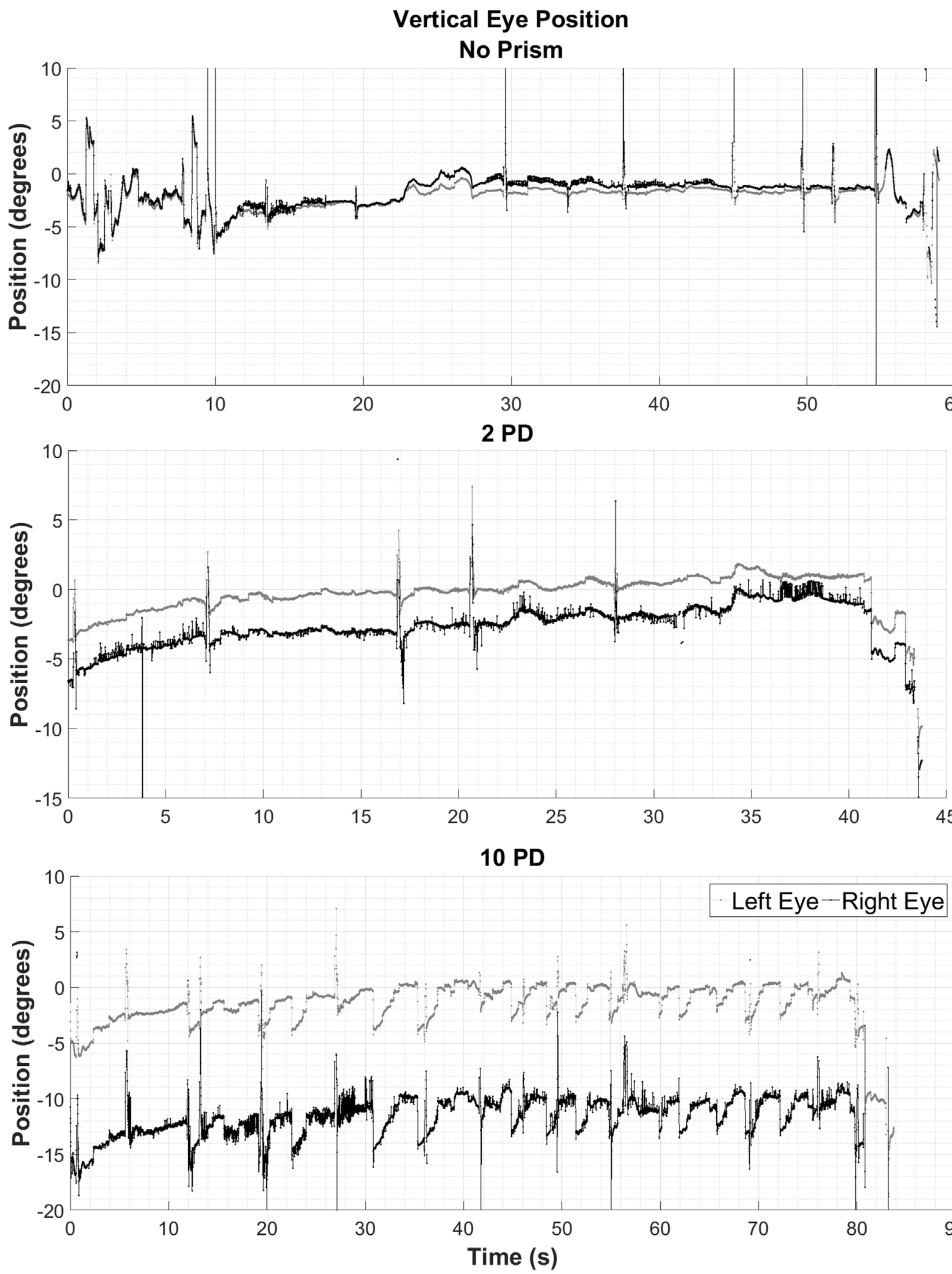

Fig. 5. One subject performing VAN wearing binocular VOG recording goggles during normal viewing (top panel), while wearing a 2PD (middle panel) and 10PD (bottom panel) 3M Press-On Optics positioned base-up over the right eye. The PD strength is correlated with a larger misalignment between the right 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.

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.

Acknowledgements

This work was funded by NASA through the Human Research Program grant NNX10AO19G and Department of Defense grant W81XWH-15-1-0442. The authors gratefully acknowledge Dr Daniel Gold for review and Dr. Elizabeth Colantuoni and Dr Chuck Rohde for their assistance with statistical analyses. Finally, we thank Mehdi Rahman, Nicolas Valentin Contreras and Natan Davidovich for development and use of the binocular video-oculography equipment.

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

References

Awadein, A., 2013. A computerized version of the Lancaster red-green test. J. AAPOS 17 (April (2)), 197–202, PMID: 23622452.
Bagolini, B., 1976. Sensorio-motorial anomalies in strabismus: (anomalous movements). Doc. Ophthalmol. 41, 23–41.
Beaton, K.H., Huffman, W.C., Schubert, M.C., 2015. Binocular misalignments elicited by altered gravity provide evidence for nonlinear central compensation. Front. Syst. Neurosci. 9 (June (2)), 81.
Brandt, T., Dieterich, M., 1994. Vestibular syndromes in the roll plane: topographic diagnosis from brain stem to cortex. Ann. Neurol. 36, 337–347.
Brodsky, M.C., Donahue, S.P., Vaphiades, M., Brandt, T., 2006. Skew deviation revisited. Surv. Ophthalmol. 51, 105–128.
Burian, H.M., 1939. Fusional movements: role of peripheral retinal stimuli. Arch. Opthalmol. 21, 486–491.
Christoff, A., Guyton, D.L., 2006. The lancaster red-green test. Am. Orthopt. J. 56, 157–165 (PMID: 21149144).
Cooper, E.A., Jiang, H., Vildavski, V., Farrell, J.E., Norcia, A.M., 2013. Assessment of OLED displays for vision research. J. Vis. 13 (12), 16 (PMCID: PMC3807585).
Crone, R.A., Everhard-Hard, Y., 1975. Optically induced eye torsion. I. Fusion cyclovergence. Graefes Arch. Clin. Exp. Ophthalmol. 195, 231–239.
Donnelly, U.M., Stewart, N.M., Hollinger, M., 2005. Prevalence and outcomes of childhood visual disorders. Ophthalmic Epidemiol. 12, 243–250.
Guyton, D.L., 1988. Ocular torsion: sensorimotor principles. Graefes Arch. Clin. Exp. Ophthalmol. 226, 241–245.
Guyton DL. Personal communication. November 2, 2016.
Halmagyi, G.M., Gresty, M.A., Gibson, W.P.R., 1979. Ocular tilt reaction with peripheral vestibular lesion. Ann. Neurol. 6, 80–83.
Harris, L., Beykirch, K., Fetter, M., 2001. The visual consequences of deviations in the orientation of the axis of rotation of the human vestibulo-ocular reflex. Vision Res. 41, 3271–3281.
Houtman, W.A., Roze, J.H., Scheper, W., 1977. Vertical motor fusion. Doc. Ophthalmol. 44, 179–185.
Irsch, K., 2015. Optical issues in measuring strabismus. Middle East Afr. J. Ophthalmol. 22 (July–September (3)), 265–270 (PMCID: PMC4502167).
Kattah, J.C., Talkad, A.V., Wang, D.Z., Hsieh, Y.H., Newman-Toker, D.E., 2009. HINTS to diagnose stroke in the acute vestibular syndrome: three-step bedside oculomotor examination more sensitive than early MRI diffusion-weighted imaging. Stroke 40 (November (11)), 3504–3510 (PMID:19762709).
Maxwell, J.S., Schor, C.M., 2006. The coordination of binocular eye movements: vertical and torsional alignment. Vision Res. 46, 3537–3548.
Ogle, K.N., Prangen, A.D., 1953. Observations on vertical divergences and hyperphorias. AMA Arch. Ophthalmol. 49, 313–334.
Roberts, J., Rowland, M., Refractive status and motility defects of persons 4–74 years, United States 1971–1972. Vital and health statistics: series 11, DHEW publication no. (PHS) 78–1654. Hyattsville MD. National Center for Health Statistics 1978.
Schor, C.M., Maxwell, J.S., Stevenson, S.B., 1994. Isovergence surfaces: the conjugacy of vertical eye movements in tertiary positions of gaze. Ophthalmic Physiol. Opt. 14, 279–286.