TITLE: Improved Oculomotor Physiology and Behavior After Unilateral Incremental Adaptation Training in a Person With Chronic Vestibular Hypofunction: A Case Report

RUNNING HEAD: VOR Training With Consolidation

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AUTHOR BYLINE: Carlo N. Rinaudo, Michael C. Schubert, Phillip D. Cremer, William V.C. Figtree, Christopher J. Todd, Americo A. Migliaccio

AUTHOR INFORMATION:

C.N. Rinaudo, BMedSc, MChiro, Balance and Vision Laboratory, Neuroscience Research Australia, Sydney, NSW, Australia, and University of New South Wales, Sydney, Australia.

M.C. Schubert, PT, PhD, Department of Otolaryngology – Head and Neck Surgery, Laboratory of Vestibular Neruro-Adaptation, Johns Hopkins University School of Medicine, Baltimore, Maryland, and Department of Otolaryngology – Head and Neck Surgery, Johns Hopkins University School of Medicine.

P.D. Cremer, BSc, MBBS, PhD, Balance and Vision Laboratory, Neuroscience Research Australia.

W.V.C. Figtree, BE, Balance and Vision Laboratory, Neuroscience Research Australia, and University of New South Wales.

C.J. Todd, BE, Balance and Vision Laboratory, Neuroscience Research Australia, and University of New South Wales.

A.A. Migliaccio, BSc, BE, MBiomedE, PhD, Balance and Vision Laboratory, Neuroscience Research Australia, Cnr Barker Street & Easy Street, Randwick NSW 2031, Sydney, Australia; University of New South Wales, Sydney, Australia; and Department of Otolaryngology – Head and Neck Surgery, Johns Hopkins University School of Medicine. Address all correspondence to Prof Migliaccio at: a.migliaccio@neura.edu.au.

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Background and Purpose. Traditional vestibular rehabilitation therapies (VRT) are effective in reducing vestibular hypofunction symptoms, but changes to the vestibulo-ocular reflex (VOR) are minimal. This controlled case report describes an increase in VOR after six months of incremental VOR adaptation (IVA) training in a person with chronic unilateral vestibular hypofunction.

Case Description. The patient was a 58-year-old female with a confirmed (Neurologist PDC) left vestibular lesion stable for 2 years prior to entering a clinical trial examining the effects of daily IVA training. She was evaluated monthly for self-reported symptoms (dizziness handicap inventory [DHI]), VOR function (video head impulse test [vHIT]) and VOR behavior (Dynamic Visual Acuity test [DVA]). Intervention consisted of 6 months of 15 minutes per day unassisted training using the IVA training regime with a device developed in our laboratory. The take-home device enables the VOR response to gradually normalize on the ipsilesional side via visual-vestibular mismatch training. The intervention was followed by a 6 month wash-out and 3 month control period. The control condition used the same training device set to function like standard VOR training indistinguishable to the subject.

Outcomes. After the intervention, ipsilesional VOR function improved substantially. The VOR adapted both via a 52% increase in slow-phase response, and via 43% earlier onset compensatory saccades for passive head movements. In addition, the patient reported fewer symptoms and increased participation in sports and daily activities.

Discussion. Here, a patient with chronic vestibular hypofunction showing improved oculomotor performance atypical for traditional VRT, subsequent to using the newly developed IVA technique, is presented. It is the first time an improvement of this magnitude has been demonstrated, as well as sustained over an extended period of time.

Dizziness and vertigo symptoms rank among the most common reasons for consultation with a primary care practitioner, with one in ten older people visiting their doctor at least once a year for dizziness.[1] The impact of dizziness, vertigo and imbalance has a significant effect on a person's quality of life, ie, 21% give up work and 57% have poorer social life.[2] Peripheral vestibular organ dysfunction is typically due to a partial or complete vestibular endorgan and/or vestibular nerve injury. It is often isolated to one side, eg, vestibular neuritis or labyrinthitis, and typically starts with a violent rotatory vertigo accompanied by nausea and vomiting. Acutely, these symptoms can persist for several days. Central compensation often becomes evident after 5 to 7 days and improvement continues so that after 6 weeks most patients are nearly symptom free, yet a large minority (~ 40%) remain in a chronic state of imbalance.[3]

One of the most debilitating aspects of vestibular hypofunction is its effect on the vestibular ocular reflex (VOR), which is the main vision stabilising mechanism during rapid head movements. Without the VOR the world appears to move every time the head moves quickly, eg, when walking or driving a car on a bumpy road. The VOR receives head movement signals from the vestibular organs and sends a signal to rotate the eyes at the same speed and in the opposite direction, to keep the visual world stable on the fovea of the retina. If the system fails, then there is relative motion of the visual world on the retina, so-called "retinal slip", which can be distressing for the patient.

For patients with chronic vestibular symptoms, vestibular rehabilitation therapy (VRT) can help, often enabling the patient to return to normal duties. One of the main aims of VRT is to improve gaze stability.[4] VOR gaze-stabilizing adaptation exercises are focussed on reducing the retinal image error during active head rotation under the presumption that repeated exposure to a retinal error signal increases the VOR to change and minimise the error. Some of the adaptation exercises involve turning the head while staring at a stationary

(VOR x 1) or moving target (VOR x 2). Commonly performed 'gaze-stability' exercises have yet to demonstrate large (> 5%) improvements in VOR function when objectively measured.[5,6] The frequency at which the head is moved during these exercises is typically 0.5Hz (one complete head rotation cycle every 2 seconds),[7] which is very low, and predominantly invokes the smooth pursuit vision stabilising mechanism, and is much lower than the 2Hz required to predominantly elicit the VOR.

Incremental VOR adaptation (IVA) training is a technique that controls visual target motion with respect to the head, so that the retinal image error changes in small increments, thereby demanding a gradual increase in the VOR gain (eye / head velocity).[8–10] Early studies in humans demonstrated significant increases of ~15% in VOR gain (eye / head velocity) with just 15 minutes of training. They also demonstrated that the VOR gain can be increased to one side only, while minimally changing the other side, i.e. unilateral adaptation.[9,10] Furthermore, although the incremental vestibular adaptation training is typically done with active head rotation, VOR gain during passive head rotation also improves.[8-10]

We hypothesised that improvements in gain would occur during the intervention period, decline during the washout period and stabilise during the control period.

[H1]Patient Information

The patient experienced two separate insults to her left vestibular system, in 2012 and in 2015. On each occasion she experienced 12 to 24 hours of acute rotational vertigo and vomiting, which was followed by vestibular insufficiency and imbalance. After the first attack in 2012, she was shown to have a 59% deficit of low-frequency left vestibular function on the standard bi-thermal caloric test. Following the second attack in 2012, she had 100% deficit of left vestibular function based on repeated caloric testing. This deficit remained stable from 2015, until she was entered into the current rehabilitation study in November

2017. It was thought the cause of her vestibular insufficiency was autoimmune, from Sjogren's disease based on serological testing, although her cochlear function was unaffected. Based on the tempo of her illness and the lack of auditory symptoms Meniere's disease was ruled out. The patient is otherwise fit and active, partaking in physical exercise regularly. She is married, has 2 children, and works as a physician 10 hours per week. The patient's clinical findings and timeline of events is depicted in Figure 1. The neurologist reviewed her case periodically (as indicated by the blue boxes in Fig. 1) and noted on each occurrence an unchanged VOR gain deficit as recorded by video-oculography.

[H1]Diagnostic Assessment

The patient was assessed by commonly utilized and supported tests that provide an indication of peripheral vestibular function, as well as its impact on gait and daily living activities. Quality of life was assessed by the self-reported Dizziness Handicap Inventory (DHI), with a minimally clinically important difference (MCID) of 18 points required.[11] Gait was assessed using the Dynamic Gait Index (DGI), primarily developed to assess a subject's ability to modify gait in response to changing task demands.[12] A MCID of 3.2 points is required,[13] specificity 74% and specificity 48%.[14] Head impulses are rapid, unilateral, transient head rotations with peak-amplitude ~ 10^{o}, peak-velocity ~ 150^{o}/s, and peak-acceleration ~ $2000^{o}/s^{2}$.[15] These are natural, physiologically relevant head movements. The head thrust Dynamic Visual Acuity Test (htDVA) was used to assess visual acuity during horizontal head impulses relative to baseline static visual acuity, with a score > 0.158 LogMAR considered abnormal.[16] DVA was assessed both *actively* during self-generated head impulses and *passively* via unpredictable in timing and direction, examiner-mediated head impulses to isolate peripheral vestibular contributions to the VOR.[16,17] The active and passive VOR gain was measured using the video head impulse test (vHIT) incorporated in the EyeSeeCam

(Interacoustics, Denmark) video goggle system that measures angular eye and head velocity.[18] The sensitivity and specificity of the vHIT is 100%.[19] There is no MCID known, although the DVA provides a clinically relevant behavioural measurement of VOR.

[H1]Therapeutic Intervention

We used the unilateral IVA technique for the intervention training[9,10] implemented using 'StableEyes' (Fig. 2).[10,20] In brief, for each daily intervention training session the initial VOR gain 'demand' for active head impulses towards the ipsilesional side was set at the patient's 'actual' VOR gain measured from the most recent vHIT assessment (measured monthly). For example, if the ipsilesional VOR gain demand was set to 0.3, the visual target moved relative to the head so that an actual VOR gain of 0.3 would perfectly stabilise the image of the laser target on the fovea during throughout the head movement, i.e. zero retinal slip error. The ipsilesional VOR gain demand setting was then incremented automatically by 0.1 every 90 seconds of training, so that by 15 minutes the gain setting was 1.2. The contralesional gain setting was set at 1.0 for the 15 minutes duration of the training.

Control training was identical to intervention training except that the ipsilesional and contralesional gain settings were set at 1.0 for the 15 minutes duration of the training, which is consistent with traditional VRT exercises, often referred to as VOR x 1 gaze stabilising exercises using a room-fixed target; however, these typically use slower sinusoidal head rotations (not head impulses). The patient was unaware of any differences between control and intervention training.

[H1]Testing Protocol

The patient was part of a randomised, double-blinded cross-over study and was the first to complete the trial. On initial assessment the patient underwent DHI, DGI, active and passive

htDVA, and active and passive vHIT measures in that order. The patient was instructed how to use 'StableEyes' at home. A laboratory review was scheduled every four weeks to repeat the above measures. The device log was checked at each review for training compliance.

At the end of the six months intervention training, 'StableEyes' was returned to the laboratory. For the subsequent six months no additional training was performed (*wash-out/ retention phase*). Full reviews were performed at three and six months during this wash-out/retention phase. Following the wash-out/retention phase, the patient was given 'StableEyes' set to control (fixed-target) training with a three month review. The subject was unable to distinguish between the control or intervention training, ie, the laser target did not seem stationary during control training because the subject's VOR was under-compensatory. The patient was instructed throughout the study to continue with normal daily activities that felt comfortable and safe to perform, including work, social and sports activities. The patient reported that she maintained all activities throughout the trial.

[H1]Follow-up and Outcomes

At each review the patient had an opportunity to report any challenges, including technical issues with the device, general health, or difficulties in performing the training. No adverse reactions were experienced during the entire study. Patient training compliance was close to 100%. During the intervention and control phases she trained on average 28.5/30 (95%) days per month, with 274 impulses per training session, with 97% having the correct velocity profile.

[H2]Role of Funding Source

The funders played no role in the writing of this case report.

[H1]Results

[H2]VOR Gain

Passive VOR gain, a direct measure of visual stability during head movement, increased significantly towards the ipsilesional side (linear regression: gain = 0.154 + 0.031*month, $P < .03$) from 0.23 to 0.35 (+ 52%) during the six-month intervention phase. During the wash-out/retention phase the ipsilesional VOR gain did not linearly increase (linear regression: $P = .33$) (Fig. 3). During the control phase, the passive gain significantly reduced from 0.43 to 0.35 (*t test*: $P < .001$).

[H2]Compensatory Saccades

Compensatory saccades help reacquire the visual target during a head rotation, to make up for the under-compensatory VOR. The earlier the compensatory saccades occur after onset of head movement, the less gaze instability is experienced by the patient.[21] The mean first saccade latency (or onset) reduced by ~18ms per month of training over six months (linear regression: $P < .001$), equating to a total reduction of 43% from 309 to 175 ms (Fig. 3). The short saccade latencies were maintained: there was no significant change in first saccade latency during the six-month wash-out/retention and three-month control phases.

[H2]DHI and DGI

The total DHI score reduced (improved) in magnitude from 52 to 40 over the six-month intervention, however, this change was not statistically significant ($P = .137$). Dynamic gait index scores (0-24) improved from 21 to 24 within three months of commencement, but remained at 24 for the rest of the study.

[H2]DVA

During the intervention phase, ipsilesional passive DVA scores significantly improved (R^2 = 0.69, slope co-eff = -0.08, $P < .05$) from 0.699 to 0.159 (77% improvement; Fig. 4), compared to 0.337 to 0.247 (27% improvement) on the contralesional side. This improvement was maintained with ipsilesional active DVA scores, as well as in active or passive DVA scores during the retention and control phases.

[H1]Discussion

Here we show the first documented case of a patient with unilateral vestibular hypofunction with a functionally relevant VOR gain increase as a result of daily, 15 minutes unilateral IVA training exercises for six months.

As the intervention progressed, she felt her abilities improve and gained confidence to increase activity level over time. We think this improvement in ability was directly related to the increase in passive VOR gain. In addition, the increase in activity likely contributed the patient to more visual-vestibular feedback that enabled further adaptation. Also, the decrease in difference between actual and ideal (gain = 1) VOR gains due to the intervention training, meant a smaller retinal image slip error signal was generated during the washout period, which we have shown facilitates adaptation.[8]

Strengths of the case report include a blinded subject and examiner, six months of intervention showing progressive changes, a 6-month washout period, and inclusion of her own control data. A weakness is that the patient's improvement in physical activity as a result of the intervention may have masked functional losses that would have otherwise occurred during wash-out/retention and control phases.

In contrast to current best practice exercises, the unilateral IVA (using active, patient-generated head impulses) technique resulted in long-term VOR gain changes for passive (investigator-driven) head impulses, which mimic the unpredictable non-volitional head movements that occur during typical activity. Recent studies suggest compensatory saccades

also contribute to visual stability during ipsilesional head rotations.[22] We showed the onset of these saccades significantly improved as a result of the intervention training. Passive DVA testing, which provides a behavioral measure of the VOR, also improved suggesting that the combination of increased VOR gain and reduced onset compensatory saccades resulted in improved practical vision during head rotations. Limited benefits were seen in subjective quality of life (DHI) and gait performance (DGI), likely due to a lack of sensitivity, eg, DHI is not geared to detect short-term changes, or ceiling-effect often seen in relatively more able adults.[23]

After 15 minutes of daily incremental IVA training, this patient with vestibular hypofunction showed improved visual stability. Research is needed to prove effectiveness of this intervention in this patient population.

[H1]Patient Perspective

"I started the clinical trial after 12 months of suffering from left vestibular dysfunction. At the time I had dizziness with all head movements and continual tiredness and mental fogginess. As a result of these symptoms it was necessary for me to reduce or suspend my participation in all my usual daily activities, work as a doctor, sport and social life.

After 2 to 3 months I started to notice less dizziness with daily activities, sport and driving. Gradually my energy levels improved. Over the course of the trial I have had an improvement in my quality of life enabling my resumption of activities such as cycling, less anxiety in crowds and more confidence when attending social activities."

Author Contributions

Concept/idea/research design: M.C. Schubert, A.A. Migliaccio

Writing: C.N. Rinaudo, M.C. Schubert, P.D. Cremer, C.J. Todd, A.A. Migliaccio

Data collection: C.N. Rinaudo, P.D. Cremer, C.J. Todd, A.A. Migliaccio

Data analysis: C.N. Rinaudo, P.D. Cremer, C.J. Todd, A.A. Migliaccio

Project management: A.A. Migliaccio

Fund procurement: A.A. Migliaccio

Providing participants: P.D. Cremer

Providing facilities/equipment: W.V.C. Figtree, A.A. Migliaccio

Providing institutional liaisons: P.D. Cremer, A.A. Migliaccio

Consultation (including review of manuscript before submitting): P.D. Cremer, C.J. Todd, A.A. Migliaccio

Ethics Approval

Participation in this study was voluntary, and informed consent was obtained as approved by the University of New South Wales Human Ethics Committee.

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Disclosures

The authors completed the ICJME Form for Disclosure of Potential Conflicts of Interest and reported no conflicts of interest.

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Figure Legends

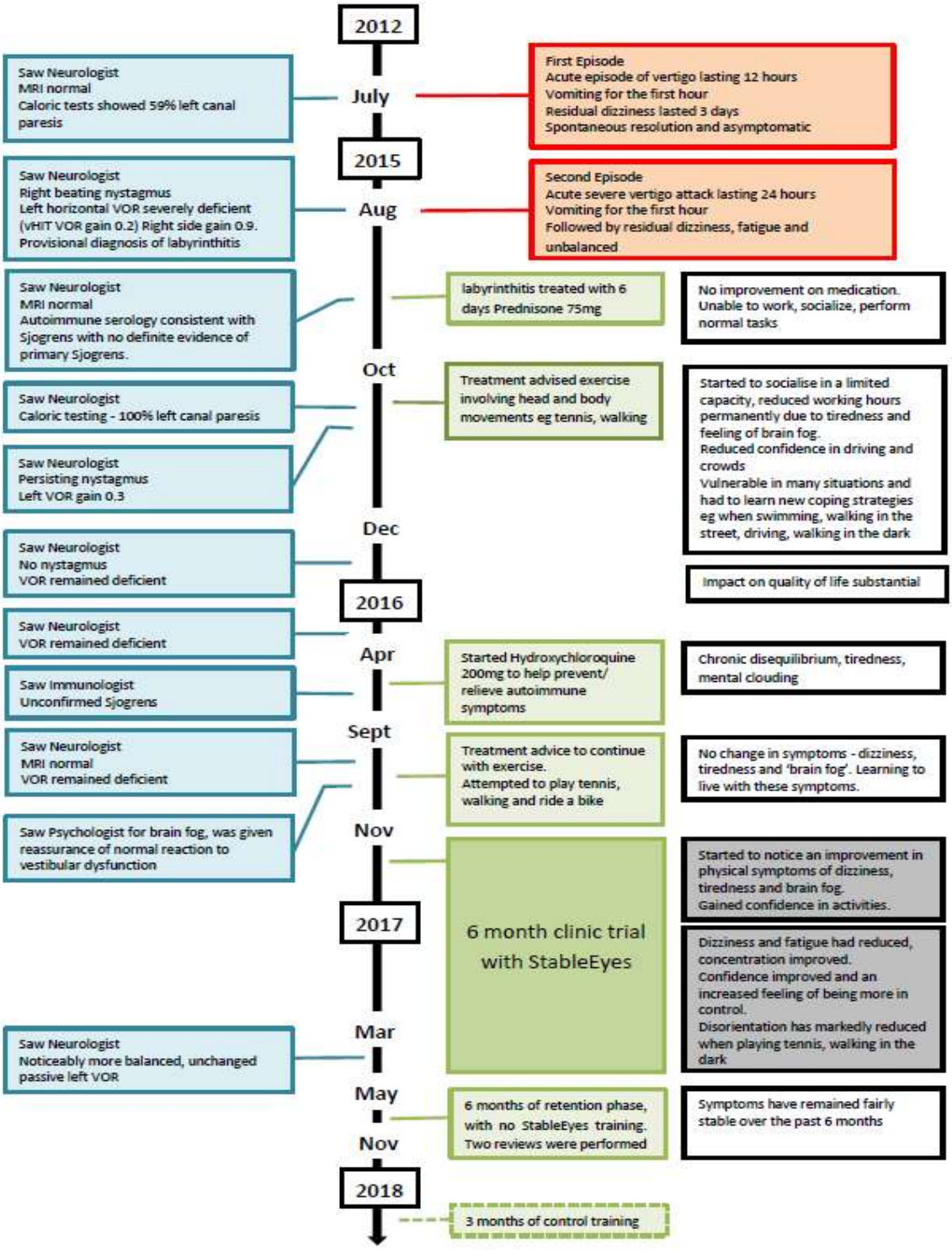

Figure 1. Patient timeline and therapy with incidents (red), medical opinions (blue), treatments (green), and subjective patient comments (black). vHIT = video head impulse test; VOR = vestibulo-ocular reflex.

Figure 2. The take-home rehabilitation training device 'StableEyes' used for both incremental VOR adaptation training and control training. The device comprises a control unit and head-mounted sensor unit that emits a moving laser target.

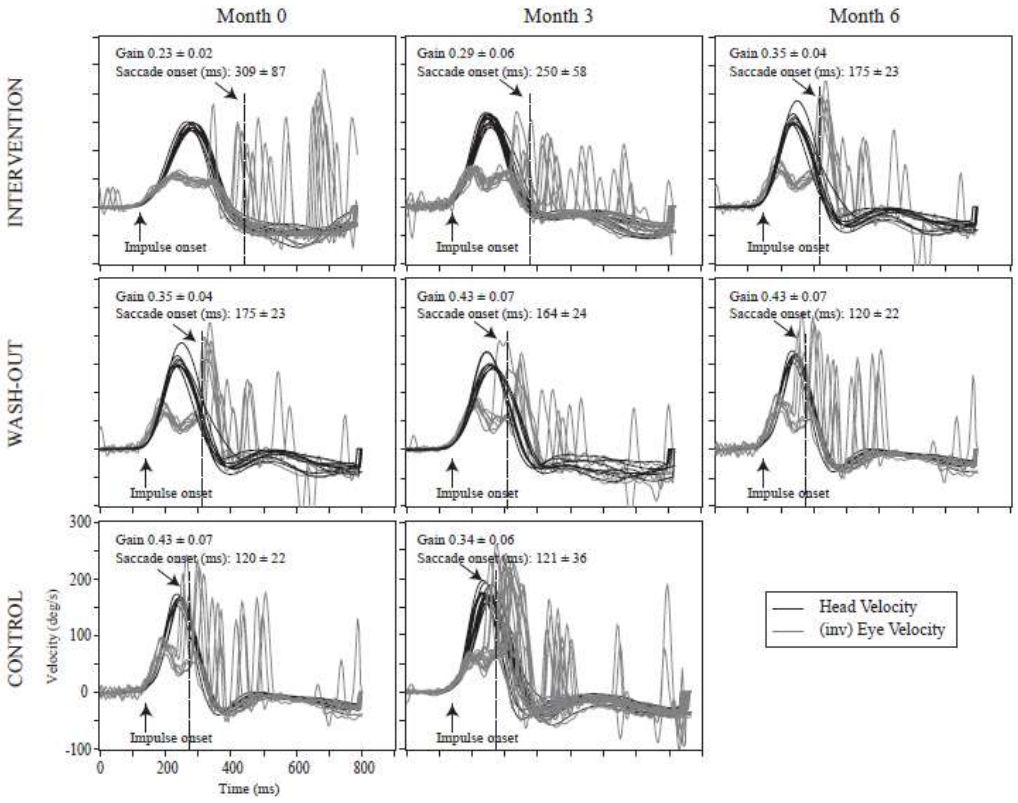

Figure 3. The top row shows the vestibulo-ocular reflex (VOR) response to passive head rotations towards the ipsilesional side for three out of the six once monthly reviews during the six month intervention phase of the study. The mean (standard deviation) for both the VOR gain and onset of the first corrective saccade are shown in each panel. The second and third rows show the VOR response during the six-month wash-out phase and three month control phase of the study, respectively. For facility of comparison, the month six data of the intervention was repeated as month zero for the wash-out phase. Similarly, month six of the wash-out was repeated as month zero for the control phase. During the intervention period the VOR response gradually improved with time, ie, the gain became higher and the saccade onset became smaller. The overt saccade onset (after head rotation stops, dashed line) continued to improve during the wash-out period only.

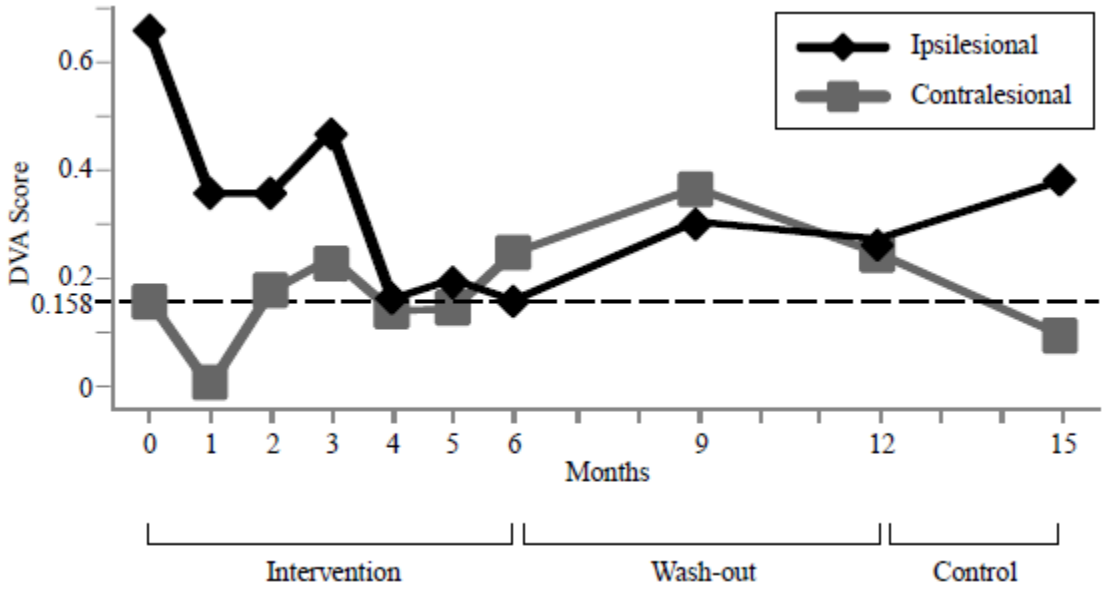

Figure 4. The DVA score to passive head rotations towards both the ipsilesional (black) and contralesional (grey) sides are shown at each monthly review. The dashed line denotes the normal DVA score threshold, ie, 0 to 0.158 is within normal. During the intervention period the ipsilesional DVA scores improved and were close to within normal at months four, five, and six. The DVA scores worsened during both the wash-out and control phases of the study. DVA = Dynamic Visual Acuity test.