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**Pilot study of a new rehabilitation tool: Improved unilateral
adaptation of the human angular vestibulo-ocular reflex**

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Running title: Unilateral vestibular adaptation improved

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Abstract

HYPOTHESIS: Unilateral vestibulo-ocular reflex (VOR) adaptation training causes some increase towards the non-adapting side (~30% of increase on adapting side). We conducted a pilot study to determine if the increase could be reduced by providing a visual stimulus during rotations to the non-adapting side.

BACKGROUND: Unilateral vestibular adaptation is a technique that could increase the ipsilesional VOR response of vestibular patients with unilateral hypofunction. However, this technique results in the VOR response increasing for rotations towards the non-adapting (normal) side, which is undesirable because the VOR will be over-compensatory (causing non-stable vision) during head rotations towards the normal side.

METHODS: We built a portable helmet device that sensed horizontal angular head velocity to generate a visual target that required a preset VOR gain (eye velocity / head velocity) for optimal image stabilisation that could be set differently for leftward and rightward head rotations. We tested 10 subjects (6 controls and 4 patients with vestibular hypofunction). We measured the active and passive VOR gain before and after unilateral VOR adaptation training.

RESULTS: In control subjects, for rotations towards the adapting side (target gain = 1.5) the VOR gain increased due to training by $26.1 \pm 23.4\%$ during active head impulses and by $14.6 \pm 13.0\%$ during passive head impulses. In contrast, for rotations towards the non-adapting side there were no statistically significant increases.

CONCLUSION: A visual stimulus driving the VOR gain to unity towards the non-adapting side aids unilateral adaptation more so than no visual stimulus.

KEYWORDS vestibulo-ocular reflex (VOR), unilateral vestibular adaptation, retinal image velocity slip, vestibular rehabilitation.

Introduction

The angular vestibulo-ocular reflex (VOR) maintains images stable on the retina during rapid head rotations by counter-rotating the eyes in the opposite direction to the head. Typically the gain of the VOR is unity, i.e., eye velocity magnitude is equal to head velocity magnitude, so that eye velocity divided by head velocity equals 1 (e.g., 1). However, after an injury to the peripheral vestibular organ the VOR becomes under-compensatory and the gain is < 1 (2, 3). Under this circumstance retinal image slip occurs resulting in visual instability during rapid head movements. Rehabilitation exercises attempt to improve visual stability during active head movements by increasing or ‘adapting up’ the VOR gain and enlisting other oculomotor systems (4, 5).

A number of human VOR studies have demonstrated a robust capacity for gain adaptation of the normal VOR by coupling head motion with target motion to elicit retinal slip as a velocity error signal, which is mediated via central vestibular mechanisms (6, 7, 8). While these experiments were critical to establish the plasticity of the VOR, they were not useful in a rehabilitation context, in part, because the adaptation was most evident when testing the VOR in darkness. In light, the adapted response significantly decreased (~70%). Recently, Schubert *et al.* (9) showed that the VOR could be robustly adapted in dim light using an incrementally increasing retinal image velocity slip stimulus during self-generated head rotations. In that study, the VOR gain increase after 15 minutes of adaptation training was 17.3% and 18.2% in control subjects and unilateral vestibular hypofunction (UVH) patients, respectively.

The Schubert *et al.* (9) study used a bilateral retinal image velocity slip stimulus. This is not ideal for patients with a unilateral lesion whose VOR is under-compensatory only for head rotation towards the lesioned side. Only the lesioned side needs to be increased. Increasing the

normal side is undesirable because it results in over-compensatory eye movements. The authors have recently showed that under laboratory conditions unilateral VOR adaptation is possible in humans (10). In that study, nine normal subjects underwent the same experimental protocol as Schubert *et al.* (9) for rotations to one side (adapting side), but for rotations towards the other (non-adapting) side the visual stimulus was removed. The VOR gain towards the adapting side increased after training from 0.92 ± 0.18 to 1.11 ± 0.22 ($+22.7 \pm 20.2\%$) during active (self-generated, predictable) head impulses, and 0.91 ± 0.15 to 1.01 ± 0.17 ($+11.3 \pm 7.5\%$) during passive (imposed, non-predictable) head impulses. In contrast, the VOR gain increase towards the non-adapting side was only 8% during active impulses and 2% during passive impulses. The 8% gain increase towards the non-adapting side was statistically significant and not ideal for unilateral adaptation.

The first aim of this study was to reduce the active VOR gain increase towards the non-adapting side by providing a visual stimulus that required a VOR gain = 1 for rotations towards that side. The second aim was to investigate whether an asymmetrical visual slip stimulus could unilaterally modify the VOR gain without incremental adaptation. The third aim was to determine if unilateral VOR adaptation could occur in patients with vestibular hypofunction. We built a portable device that replicated the large laboratory equipment from the Schubert *et al.* (9) and Migliaccio and Schubert (10) adaptation studies. The portable helmet device sensed horizontal angular head velocity and generated a visual target that required a preset VOR gain for optimal image stabilisation. The target gain could be adjusted asymmetrically, e.g., VOR gain = 1.5 for image stabilisation during rightward head rotations, and gain = 1.0 during leftward head rotations.

Materials and Methods

Subjects

We studied 6 normal subjects (mean age 45 years, range 24 - 68 years). None of these subjects had a history or clinical signs of vestibular disease. We studied 4 subjects with vestibular hypofunction, three with unilateral (UVH; 1 left superior vestibular neuritis, 1 right superior vestibular neuritis, 1 right labyrinthitis) and one with bilateral vestibular hypofunction (BVH; bilateral familial) (mean age 49 years, range 32 - 67 years). Vestibular hypofunction was confirmed by a positive clinical yaw head impulse test. Participation in this study was voluntary and informed consent was obtained as approved by the University of New South Wales Human Ethics Committee.

Recording System

The movements of the right eye were recorded in two-dimensions using video-oculography (VOG). This VOG system has been previously described by MacDougall *et al.* (11). In brief, right eye position was recorded at 250 Hz with a small, lightweight, high-speed digital video camera mounted onto a lightweight glasses frame with elastic strap that locked comfortably onto the bridge of the nose and around the eye sockets to minimize slippage of the camera relative to the head. The image of the eye, illuminated by 2 infrared light-emitting diodes (LEDs), was reflected from a hot mirror to the camera. Head velocity was measured by a miniature 6-degrees-of-freedom (yaw, pitch and roll rotation; up-down, left-right and forward-back translation) inertial measurement unit (IMU). The camera, hot mirror, and IMU were rigidly mounted onto the spectacle frame - total weight ~60 g. Horizontal and vertical eye position was calibrated *in vivo* by asking the subject to sequentially fixate on the centre and then 4 tips of a cross (subtending known angles) projected from a glasses-mounted cross-hair

projector. Video images were analyzed offline to calculate eye position using the center-of-gravity (function in LabVIEW, National Instruments, USA) pupil detection method. Horizontal and vertical eye velocity was calculated using a 3-point differentiator and 50-tap zero-phase low pass FIR filter with a bandwidth of 50 Hz.

Helmet laser target system

We used a laser and real-time single-axis / single-mirror galvanometer system (Model 6210H with 67721H single-axis servo driver amplifier, Cambridge Technology, USA) for display of a visual target (a 2mm diameter red-laser dot) onto a matte-black painted wall 111 cm directly in front of the subject along the naso-occipital axis. The laser projection unit was mounted on a safety helmet with twist-cap tightening strap that the subject wore (see figure 1A and 1B). The laser unit was positioned so that when the subject wore the safety helmet it laid approximately along the axis about which the head turned during yaw rotations. A single-axis gyro (GyroPak Analog MEMS Rate Sensor, O-Navi, USA) was oriented on the helmet to maximally detect yaw (horizontal) angular head (helmet) velocity $\pm 400^\circ/\text{s}$ (see figure 1C). Figure 1D shows the general signal processing of the laser target helmet system (Patent Pending C10585-P10585-02). The horizontal head velocity voltage signal from the gyro passed through either the positive or negative rectifying circuit depending on whether the head was rotating leftwards (positive voltage) or rightwards (negative voltage). The gain of the leftward or rightward signal could be independently adjusted via a (leftward and rightward gain) knob on the front of the control unit (figure 1A and 1E). The (velocity) signal was then inverted and integrated to generate the horizontal galvanometer / laser position signal. A reset switch allowed the user to set the laser position back to straight-ahead with respect to the subject (helmet). If the reset switch was not pressed, then the galvanometer (and laser if it was on) returned back to

straight-ahead within 2 seconds. A threshold velocity detection circuit turned the laser off for 2 seconds when absolute head velocity exceeded $120^\circ/\text{s}$.

Figure 1

Passive and active head impulse testing

A head impulse consists of a unilateral, transient, head rotation with peak-amplitude $\sim 15^\circ$, peak-velocity $\sim 150^\circ/\text{s}$ and peak-acceleration $\sim 3,000^\circ/\text{s}^2$ (12). Passive head impulses are unpredictable and delivered manually, whereas active head impulses are generated by the subject (13). Before the start of each head impulse, the subject's head was centred straight-ahead. The subject's task was to fixate a stationary LED placed at eye level on the wall 111 cm directly in front of them. Passive head impulses were delivered manually in the horizontal canal plane, i.e., leftward and rightward. Subjects were trained to perform active head impulses similar in profile to the passive head impulses. We measured the effect of unilateral VOR adaptation training by comparing the active and passive VOR gains before and after training. For pre- and post-training testing only, each subject completed 15 leftward and 15 rightward passive and active head impulses. The training consisted of active head impulses only.

Unilateral VOR adaptation training

Apart from the laser target (or LED during testing above) subjects were tested in dim light. Subjects were asked to make active (self-generated) head impulses from a neutral, neck-centred starting position alternating to the left and right. The subject commenced each head impulse when the head was in neutral position and the laser target appeared. When absolute head velocity exceeded $120^\circ/\text{s}$ the laser would turn off for 2 seconds. The laser turning off was an indication that the head impulse had the correct velocity profile. The $120^\circ/\text{s}$ velocity threshold was chosen to ensure that the head impulse was predominantly a vestibular stimulus, thus

limiting any effects of non-vestibular systems such as smooth pursuit, optokinetic and predictive oculomotor systems, which contribute to gaze stability at lower head velocities than the VOR (14, 15, 16). During these 2 seconds the subject completed the rest of the impulse (the entire impulse duration was ~150 ms), paused and slowly returned their head back to the neutral position. Reappearance of the laser target was the cue to perform an impulse to the opposite side. During the head impulse, the subject's task was to either fixate the visible laser target or fixate the last remembered location of the laser target before it turned off. Vertical laser position moved in the same direction and magnitude as the head for pitch head movements. Horizontal laser position was controlled by horizontal head velocity and head direction adaptation gain. All subjects performed about 300 active head impulses, i.e., 150 to each side. The non-adapting side gain was set so that the VOR gain (eye velocity / head velocity) required for target image stabilisation was 1.0, whereas the adapting side gain was set so that the VOR gain required for target image stabilisation was 1.5. We selected the training VOR gain of 1.5 based on pilot trials where two subjects with UVH underwent adaptation training with the adapting side target gain set at 1.25, 1.5, 1.75 and 2, over separate training sessions. The largest unilateral VOR gain increases were observed when the target gain was set at 1.5 (+43.2% and +39.2%, n=2). For UVH subjects the ipsilesional side was chosen as the adapting side, whereas for the BVH subject the side with the lowest pre-adaptation gain was chosen. For normal subjects we randomised the adapting side (leftwards for 2 subjects and rightwards for 4 subjects). The adaptation training typically took 15 minutes.

Data Analysis

The onset of each head impulse was calculated by fitting a polynomial curve to horizontal angular head velocity versus time. The point where the magnitude of the fitted curve was greater

than 2% of the curve's peak magnitude (typically this threshold was 4°/s) was defined as the time of onset (17). The horizontal VOR gain was calculated by dividing inverted horizontal eye velocity by horizontal head velocity during the 30 ms period prior to peak head velocity (18).

Statistical analysis

We used a multi-way analysis of variance (ANOVA) with three-factor interactions to analyse the data (19). Independent variables included: *subject* ('normal', 'patient'), *impulse* ('active', 'passive'), *time* ('pre', 'post') and head rotation *direction* ('adapting side', 'non-adapting side'). The only dependent variable was *gain*. All variables were included in the ANOVA initially and those found insignificant were subsequently removed. *Paired t-tests* were performed on the pre- and post-training passive and active VOR gains. Pooled data and pooled means are described as mean $\pm$ 1 SE.

The mean pre-adaptation active and passive gains for control subjects are ~1.0. At 80% power (mean1=0.5, mean2=0.7, standard deviation = 0.1, α =0.05, power = 0.8, 2-sided test), n=6 subjects are needed to detect an increase in VOR gain up to 17%. The mean ipsilesional (adapting side) pre-adaptation active and passive gains for subjects with vestibular hypofunction are ~0.5. At 80% power (mean1=0.5, mean2=0.7, standard deviation = 0.1, α =0.05, power = 0.8, 2-sided test), n=4 subjects are needed to detect an increase in VOR gain up to 40%.

Results

Active and passive pre- and post-adaptation VOR gains in control subjects

Our data show a significant difference in VOR gain adaptation depending on the type of head impulse (active or passive) (ANOVA: *impulse* variable, $F_{(1,36)}=4.26$, $P<0.05$).

For active head impulses towards the adapting side, the average pre-adaptation gain in controls ($n=6$) was 0.85 ± 0.22 and the average post-adaptation gain was 1.05 ± 0.20 (an increase of $26.1 \pm 23.4\%$). This 0.2 ± 0.13 increase was statistically significant (*paired t-test*: $P < 0.05$). In contrast, for active head impulses towards the non-adapting side, the average pre-adaptation gain was 0.96 ± 0.21 and the average post-adaptation gain was 0.97 ± 0.22 ($1.5 \pm 9.3\%$). This 0.01 ± 0.09 increase was not significant (*paired t-test*: $P = 0.79$).

For passive head impulses towards the adapting side, the average pre-adaptation gain was 1.05 ± 0.13 and the average post-adaptation gain was 1.19 ± 0.08 ($14.6 \pm 13.0\%$). This 0.14 ± 0.13 increase was significant (*paired t-test*: $P < 0.05$). In contrast, for passive head impulses towards the non-adapting side, the average pre-adaptation gain was 1.01 ± 0.19 and the average post-adaptation gain was 1.02 ± 0.18 ($1.5 \pm 8.2\%$). This 0.01 ± 0.10 increase was not significant (*paired t-test*: $P=0.81$).

The increase in VOR gain during passive head impulses towards the adapting side, i.e., due to training, was 56% of the increase during active head impulses (14.6: 26.1). Figure 2 shows the individual data under all conditions for all subjects ($n=6$ controls and $n=4$ UVH and BVH patients).

Figure 2

Active and passive pre- and post-adaptation VOR gains in UVH and BVH patients

Although we show a large change in VOR gain adaptation in patients with vestibular loss during active head impulses towards the (ipsilesional) adapting side (pre-adaptation VOR gain 0.59 ± 0.22 ; post-adaptation VOR gain 0.75 ± 0.30 ; an increase of $29.2 \pm 21.0\%$), this 0.17 ± 0.14 increase was not significant (*paired t-test*: $P = 0.17$).

For active head impulses towards the (contralesional) non-adapting side, the average pre-adaptation gain was 0.86 ± 0.21 and the average post-adaptation gain was 0.79 ± 0.22 ($-9.2 \pm 4.6\%$). This 0.07 ± 0.02 decrease was significant (*paired t-test*: $P < 0.05$). Figure 3 shows the active head impulse data in one UVH patient for ipsilesional head impulses pre and post adaptation. In this patient there was a 40% increase in VOR gain during impulses towards the (ipsilesional) adapted side, whereas there was a 5% (non-significant [*paired t-test*: $P=0.24$]) decrease in gain towards the (contralesional) non-adapted side.

Figure 3

For passive head impulses towards the adapting side, the average pre-adaptation gain was 0.43 ± 0.38 and the average post-adaptation gain was 0.37 ± 0.16 ($73.0 \pm 201.9\%$). This -0.06 ± 0.28 decrease was not significant (*paired t-test*: $P = 0.72$). Similarly, for passive head impulses towards the non-adapting side, the average pre-adaptation gain was 0.74 ± 0.23 and the average post-adaptation gain was 0.72 ± 0.2 ($-1.8 \pm 4.1\%$). This 0.02 ± 0.03 decrease was not significant (*paired t-test*: $P = 0.34$).

Discussion

Unilateral VOR adaptation in control subjects.

Our study shows that unilateral adaptation can be induced in normal subjects with 15 minutes of training using the helmet target device we developed. The VOR gain towards the adapting side was increased by ~26% during active and ~15% during passive head impulses. In contrast, for rotations towards the non-adapting side there was no significant increase for active or passive head impulses. In our previous unilateral adaptation study there was an 8% adaptation increase for rotations towards the non-adapting side during active head impulses, which we attributed to changes in the signals carried by the inhibitory commissural vestibular pathways from the adapting side, which contribute to the non-adapting side response (20, 21). In this current study, however, we did not observe a contextual adaptation transfer to the non-adapting side. This preliminary result supports our hypothesis that using a visual stimulus that requires VOR gain = 1 for rotation towards the non-adapting side is effective at maintaining the healthy VOR gain (contralesional VOR gain 1.0) compared to an absent visual stimulus. A possible explanation is that the presence of visual feedback during contralesional head rotations helps to prevent any ‘cross-over’ adaptation from the commissural (ipsilesional) vestibular pathways during exposure to ipsilesional head motion and retinal slip error signal.

We did not use the incremental (initial gain = 1.1 demand driven to a final target gain = 2) adaptation training technique, which for *bilateral* adaptation has been shown to more effectively increase the VOR gain compared to x2 ‘all-at-once’ adaptation training (9). Instead, in this study we used a continual x1.5 (‘all-at-once’) training, which for *unilateral* adaptation seems to be just as effective as the incremental adaptation training (10). This preliminary result

suggests that the 0.1 increment in target gain between training epochs during incremental adaptation training (9, 10) may be conservative.

Unilateral VOR adaptation in UVH and BVH subjects.

There was evidence of unilateral adaptation, albeit less consistent, in the UVH and BVH patients. Compliance may have been an issue. We originally recruited 6 patients. Two of these six patients, U1 and U2, quickly learnt the adaptation training exercise, i.e., within 5 minutes, and performed the training without complication. During active head impulses both these subjects had significant adaptation towards the ipsilesional adapting side (+43.2% and +39.2%) and minimal adaptation towards the non-adapting side (-14.3% and -5.6%). These increases were greater than those seen in previous studies on bilateral and unilateral incremental adaptation training in UVH subjects (9) and normal subjects (10), respectively. Out of the remaining four, two learnt the adaptation training exercise reasonably well, but were inconsistent in terms of rotating their head with the correct velocity profile and keeping their eyes on the laser target. Notwithstanding, there was evidence of unilateral adaptation in these subjects also, particularly in patient B1, whose VOR gain increased from 0.08 to 0.38 during passive head impulses towards the adapting side. The remaining two patients found the training task too difficult and could not proceed with the experiment.

If unilateral adaptation is possible, then why is recovery of the ipsilesional VOR in patients minimal?

There is some evidence that patients that suffer from vestibular dysfunction may change their movement strategies such that they move less toward the side of the lesion, which prevents an increase in gain due to the scarcity of retinal slip error in that direction. (22, 23, 24). Clendaniel *et al.* (25) showed that adaptation of gain during rapid head rotations could only

occur if the retinal slip error signal was paired with head rotations that were of similar frequency and velocity to the test stimuli. It may be that these patients are not moving their heads rapidly enough during everyday activity to induce the necessary gain increases in the ipsilesional direction. Another possible reason is that patients are using non-vestibular compensatory mechanisms to supplement the VOR, such as compensatory saccades (5, 26).

Another possible explanation is that VOR gain changing circuitry is located both upstream and downstream of neurons that compute the difference between inputs from the two labyrinths. During everyday activity the patient moves their head in both directions and never repeatedly in one direction, so there may be a conflict in the error signal induced by motion in the contralesional and ipsilesional directions. In this circumstance, both upstream and downstream gain circuitry might be adjusted, resulting in a bilateral gain change. By providing a retinal image slip signal when rotating in one direction the result might be adjustment of unilateral upstream circuitry only, resulting in a unilateral gain change.

Will vestibular patients retain an adapted gain?

The rehabilitative potential of our technique depends on retention being possible. Several lines of evidence support this possibility. For example, the classic Gonthor and Melville-Jones (8) study that produced VOR direction reversal after 27 days of adaptation training using reversing spectacles in normal subjects, showed that adaptation was retained overnight and added to with subsequent sessions. They also showed that de-adaptation (lack of retention) occurred over a long period, i.e., 14 - 21 days. De-adaptation is likely to be less of an issue in vestibular patients because their normal visual environment will, if anything, further drive up their adapted (but still <1) VOR gain to bring it closer to ideal (unity gain), whereas a normal subject's adapted gain (>1) will be driven down to unity.

Technical challenges

There are differences in the experimental techniques used in this study compared to our previous adaptation studies (9, 10), which may have contributed to the variability in results. We used a head coupled helmet based system to provide the visual target. We used a strap with tightening mechanism to firmly couple the helmet to the head. However, we did not quantify the amount of slip between head and helmet during active (training) head impulses. If slip did occur due to helmet inertia, then it would likely be symmetrical and would act to increase the required VOR gain for vision stabilization towards both sides, i.e., it would not affect the desired asymmetric adaptation. In this study, we also used the portable video-oculography (VOG) technique to measure horizontal head and eye velocity to calculate VOR gain instead of the ‘gold standard’ scleral search coil technique, which is affected by electromagnetic devices such as a galvanometer.

Conclusion

The results from this pilot study show that a visual stimulus driving the VOR gain to unity towards the non-adapting side is effective at preventing VOR gain increase in the unwanted (contralesional) direction. We also show that an asymmetrical retinal image velocity slip signal induces robust unilateral VOR adaptation in normal subjects and that it can also induce such changes in patients with vestibular hypofunction. Further development and testing will be needed to determine the full rehabilitative potential of the portable helmet device used to drive the adaptation.

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Figure Legends

Figure 1. (A) The helmet laser target system consists of a safety helmet with head strap, gyro (which is oriented to maximally measure horizontal angular head velocity), galvanometer and mirror, laser and control box. The control box has adjustable gain knobs for leftward and rightward head rotations and a push button switch that resets the galvanometer / mirror position back to neutral (Patent Pending C10585-P10585-02). (B) The subject is wearing the helmet target device and video-oculography (VOG) system which measures horizontal eye position. The VOG goggles have a built in gyro, thus allowing synchronous measurement of head velocity and eye position. (C) Close up of the three-piece unit comprising: gyro sensor (left and above of image centre), galvanometer / mirror (right of image centre) and laser (centre of image). The pitch of the three-piece unit was adjusted to ensure its base was in the Earth-horizontal plane after the helmet had been placed on the subject's head. (D) Signal flow of the helmet laser target system. The laser target (galvanometer) velocity was proportional to head (helmet) velocity; this proportionality was adjusted independently for leftward and rightward head rotations. Once the signals were scaled they were summated, inverted and integrated to drive the horizontal galvanometer / mirror position. A threshold circuit detected when absolute head velocity exceeded the preset (but adjustable) value of $120^{\circ}/s$. Upon detection the laser target turned off for 2 seconds. (E) The leftward and rightward gains on the control box were calibrated so that a gain of 1 required a perfectly compensatory VOR gain ($\text{gain} = [\text{eye velocity} / \text{head velocity}] = 1$) for target image stabilization when the head rotated towards that side (centre image). A gain of 0, requires no VOR, i.e., the eyes are fixed with respect to the head (left image), whereas a gain of 2, requires the VOR response to be doubled (see right image, when the head is turning to the right).

Figure 2. Pre- and post-adaptation, active and passive VOR gains for all subjects (n=6 controls C1-6; n=3 UVH patients U1-3; n=1 BVH patient B1). (A) Comparison of the pre- and post-adaptation active VOR gain for all subjects except C6 and B1 (coil broke during experiment). Although there is variation between subjects, there is a consistent unilateral increase in the active VOR gain due to adaptation training. (B) Comparison of the pre- and post-adaptation passive VOR gain for all subjects. Albeit different to the active head impulse training context, there is a consistent unilateral increase in the passive VOR gain due to training in control subjects. This increase is ~60% of that observed in the active VOR gain.

Figure 3. Comparison of ipsilesional (adapting side) active VOR gain pre and post-adaptation training. In this UVH patient the gain increased from 0.79 ± 0.07 to 1.10 ± 0.08 , a gain increase of ~40%. In this same patient, the contralesional non-adapting gain went from 0.90 ± 0.5 pre-adaptation to 0.85 ± 0.8 post-adaptation, a ~5% decrease that was not significant.

Figure 1

Figure 2

Figure 3