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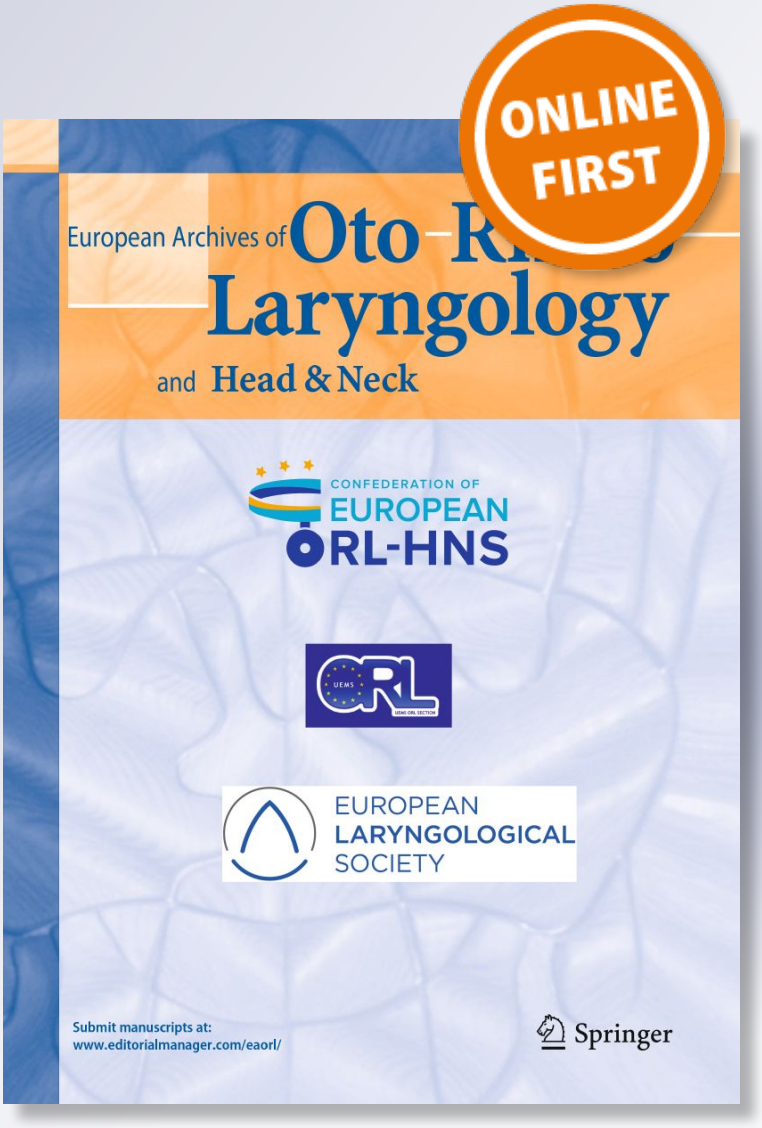

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OTOLOGY

Rehabilitation of dynamic visual acuity in patients with unilateral vestibular hypofunction: earlier is better

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Abstract

Purpose Patients with acute peripheral unilateral hypofunction (UVH) complain of vertigo and dizziness and show posture imbalance and gaze instability. Vestibular rehabilitation therapy (VR) enhances the functional recovery and it has been shown that gaze stabilization exercises improved the dynamic visual acuity (DVA). Whether the effects of VR depend or not on the moment when it is applied remains however unknown, and investigation on how the recovery mechanisms could depend or not on the timing of VR has not yet been tested.

Methods Our study investigated the recovery of DVA in 28 UVH patients whose unilateral deficit was attested by clinical history and video head impulse test (vHIT). Patients were tested under passive conditions before (pre-tests) and after (post-tests) being subjected to an active DVA rehabilitation protocol. The DVA protocol consisted in active gaze stabilization exercises with two training sessions per week, each lasting 30 min, during four weeks. Patients were sub-divided into three groups depending on the time delay between onset of acute UVH and beginning of VR. The early DVA group ($N=10$) was composed of patients receiving the DVA protocol during the first 2 weeks after onset (mean = 8.9 days), the late group 1 ($N=9$) between the 3rd and the 4th week (mean = 27.5 days after) and the late group 2 ($N=9$) after the 1st month (mean: 82.5 days). We evaluated the DVA score, the angular aVOR gain, the directional preponderance and the percentage of compensatory saccades during the HIT, and the subjective perception of dizziness with the Dizziness Handicap Inventory (DHI). The pre- and post-VR tests were performed with passive head rotations done by the physiotherapist in the plane of the horizontal and vertical canals.

Results The results showed that patients submitted to an early DVA rehab improved significantly their DVA score by increasing their passive aVOR gain and decreasing the percentage of compensatory saccades, while the late 1 and late 2 DVA groups 1 and 2 showed less DVA improvement and an inverse pattern, with no change in the aVOR gain and an increase in the percentage of compensatory saccades. All groups of patients exhibited significant reductions of the DHI score, with higher improvement in subjective perception of dizziness handicap in the patients receiving the DVA rehab protocol in the first month.

Conclusion Our data provide the first demonstration in UVH patients that earlier is better to improve DVA and passive aVOR gain. Gaze stabilization exercises would benefit from the plastic events occurring in brain structures during a sensitive period or opportunity time window to elaborate optimal functional reorganizations. This result is potentially very important for the VR programs to restore the aVOR gain instead of recruiting compensatory saccades assisting gaze stability.

Keywords Acute unilateral peripheral vestibulopathy · Early rehab · Late rehab · Dynamic visual acuity · aVOR gain · Directional preponderance · Compensatory saccades · DHI

Introduction

Patients with acute peripheral unilateral vestibular hypofunction (UVH) suffer severe vestibular symptoms including spinning vertigo, spontaneous nystagmus, posture and gait imbalance, oscillopsia, and associated neuro-vegetative symptoms (nausea and vomiting). Particularly important in

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daily life is the angular VOR (aVOR) that generates eye movements in opposite direction and equal magnitude with respect to head displacement in healthy subjects, ensuring therefore clear vision during fast head rotations. When eye velocity does not fit exactly head velocity, that is, when the aVOR gain (eye velocity/head velocity) is reduced as a result of vestibular hypofunction on one side, the patients complain of oscillopsia and blurred vision, a very disabling handicap for the patients.

The measure of visual acuity during head movement has been used in the last decades to assess the functional impact of vestibular hypofunction [1]. Decrements in dynamic visual acuity (DVA) lead potentially to serious problems that impact the patient's quality of life: avoidance of driving, difficulty in reading or watching TV, reduced activity level, and social isolation as well. Using computerized DVA, Herdman et al. [1] showed that the test was reliable in terms of sensitivity and specificity, and was able to distinguish normal subjects and vestibular loss patients. Investigation of how UVH patients stabilize gaze during head movement has pointed to different compensatory mechanisms. First described in the unilateral labyrinthectomized frog [2], the saccadic substitution process has been hypothesized later on for the compensation of the ocular motor disorders in UVH patients [3].The main idea was that internally generated signals related to gaze can replace a deficient and uncompensated aVOR. The gaze substitution hypothesis was investigated more recently in UVH patients during the HIT head thrust test [4].The vestibular catch-up saccades in the direction of the deficient aVOR reduce the amplitude of the eye position error and contribute to stabilize gaze and improve DVA. Other mechanisms such as enhancement of the cervico-ocular reflex gain was not observed in UVH patients [5, 6], and potentially enlarged range of the smooth pursuit system cannot contribute to gaze stability for head movements performed at high velocity (>150°/s) [7]. Another potential mechanism is based on the high degree of plasticity of the aVOR as evidenced with the sensory conflict protocol. Gauthier and Robinson [8] were the first to report an enhancement of the aVOR in healthy subjects wearing magnifying lenses. More recently, the group of Michael Schubert demonstrated it was possible to drive a gradual increase in the aVOR by coupling the movement of a visual laser target with head motion in healthy controls [9–11]. This incremental adaptation technique [12] increased significantly the normal aVOR gain on the side being trained. However, the literature showed limited evidence of aVOR recovery in UVH subjects during passive, unpredictable fast head rotations. As reported by Schubert et al. [4], the passive aVOR recorded during the HIT head trust test does not commonly recover in chronic vestibular loss patients. However, using passive unidirectional rotations in the dark toward the weaker side in patients with chronic vestibular dysfunctions, Sadeghi et al. [13] found a rebalance of the vestibular system characterized by a significant reduction of the directional preponderance (DP) resulting from a slight increased aVOR gain on the disease side and a slight decreased aVOR gain on the healthy side. The data are in agreement with previous data in unilateral labyrinthectomized macaques showing that unidirectional head rotations at high velocity to the lesion side reduce the aVOR gain asymmetry by enhancing the ipsilesional aVOR response [14].

Vestibular rehabilitation therapy (VR) is effective for improving balance, dizziness and quality of life in vestibular loss patients [15, 16]. Gaze stability is also improved in vestibular loss patients subjected to gaze stabilization exercises. The DVA [17] and the Dizziness Handicap Inventory (DHI: [18]) scores showed significant improvements following such exercises [12]. In prospective randomized double-blind studies in both unilateral [17] and bilateral [19] vestibular loss patients, the authors showed that patients receiving vestibular exercises designed to enhance the aVOR improved significantly the DVA score compared to patients receiving placebo exercises. As suggested by Schubert et al. [4], gaze stability exercises improve DVA via enhancement of the active aVOR and an increased number of compensatory saccades. One remaining open question is to know when gaze stabilization exercises must be done. Our basic researches in animal models of vestibular lesion clearly pointed to an opportunity window in the early stage of the recovery process during which active training interacts dynamically with the vestibular lesion-induced neural plasticity mechanisms to promote optimal functional reorganizations [20–23]. To our knowledge, there is no clinical data supporting the concept that earlier is better to rehabilitate UVH patients. This crucial aspect regarding both the patients' quality of life and the health-care costs was highlighted recently by the American Physical Therapy Association [24]. Among the APTA clinical research recommendations, the first is "to examine the concept of critical period for optimal vestibular compensation through studies that examine early versus delayed interventions". Another open question is to know whether VR drives similar recovery mechanisms when applied early and at later stages after acute UVH.

The present study was conducted in UVH patients submitted to the same DVA rehab protocol at different time periods after onset of vestibular pathology. It was aimed at determining whether (1) DVA improvement is better when gaze stabilization exercises are performed very early after acute UVH, (2) recovery mechanisms are similar with early versus delayed DVA rehabilitation, and (3) recovery of DVA and gaze stabilization are correlated to the self-perceived handicap (DHI score).

Materials and methods

Participants

This prospective study included 28 patients with UVH that was diagnosed as acute unilateral vestibulopathy (vestibular neuritis) on the basis of patients' history and clinical examination. The inclusion criteria were in accordance with the so-called big five defined by Strupp and Magnusson [25]: acute onset of spinning vertigo, postural imbalance, nausea, spontaneous horizontal rotatory nystagmus beating toward the non-affected side, positive head impulse test (HIT) toward the affected side. The HIT was defined as pathological when the aVOR gain was below 0.65 and when overt and/or covert saccades were recorded. Abnormal DVA score (> 0.20 Log MAR) was also required for inclusion. Central vestibular or ocular motor dysfunctions as well as positional vertigo constituted exclusion criteria. 22 out of the 28 patients had pathological HIT responses on the hypofunction side to horizontal canal test, vertical anterior canal test and posterior canal tests (impairment of the inferior and superior divisions of the vestibular nerve), while the remaining 6 patients showed abnormal responses to the horizontal canal test and vertical anterior canal tests (impairment of the superior branch). All patients underwent passive head thrust test HIT and aVOR gain measurement using the VHIT Ulmer recording device (Synapsis, Marseille, France) to measure the deficit of the three pairs of semicircular canals and to document possible aVOR recovery after VR. The caloric test was not systematically performed because of its unpleasant side for patients, and when it was done the response was lacking on the lesion side. The VEMPs were not done due to lack of necessary equipment. Only two patients with suspicion of vestibular schwannoma had an MRI of the head, which turned out to be negative.

The whole population of UVH patients was subdivided into three groups, depending on the time period between the onset of the acute vertigo crisis and beginning of VR. A first group ($N=10$) was made of ten patients submitted to an early VR. This group comprised five males and five females (mean age 66.1 ± 8.7 years; range 39–86 years) who started VR in the first 2 weeks after onset (mean 8.5 days cf Fig. 1a). A second group included nine patients (4 males and 5 females; mean age 63.1 ± 9.3 years; range 37–83 years) receiving VR between the 3rd and the 4th week after onset (mean 24.5 days). The third group was composed of nine patients (4 males and 5 females; mean age 60.2 ± 9.1 years; range 47–79 years) who were tested in the time period 1–4 months (mean 87.5 days) after onset of acute vertigo attack (cf Table 1). Eight among these nine patients had their first inclusion visit more than 60 days (88%) after onset, that is, at time periods when patients of the two previous groups had already finished their VR (Fig. 1b). These

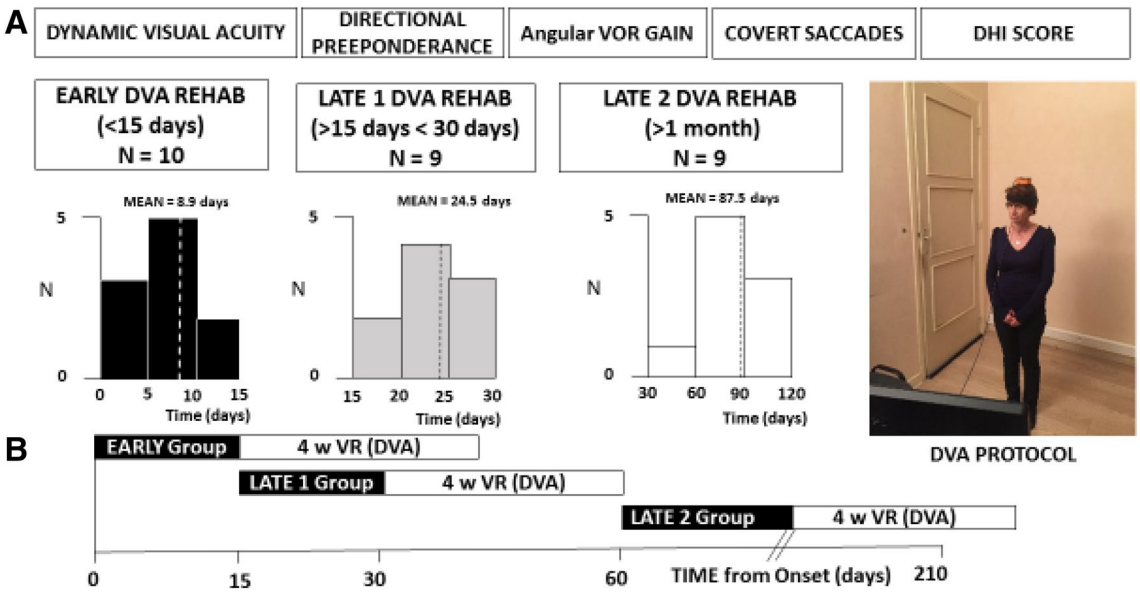

Fig. 1 **a**, **b** Experimental protocol. **a** Parameters recorded in the three groups of patients with acute unilateral vestibular vestibulopathy: dynamic visual acuity (DVA) score, angular VOR gain, directional preponderance, percentage of covert saccades, and Dizziness Handicap Inventory (DHI) score. The histograms show the time delays in days between onset of the acute crisis of vertigo and the first visit and rehabilitation session by the physiotherapist. The group submitted to an early DVA rehabilitation ($N=10$) was rehabilitated 8.9 days after vertigo onset on average, while the late group 1 ($N=9$) and the late group 2 ($N=9$) groups were rehabilitated 24.5 days and 87.5 days after vertigo onset on average. The DVA protocol for rehabilitation is illustrated on the right panel (see text). **b** Each group of patients was submitted to the same DVA rehabilitation program including two sessions (mean duration: 30 min) per week, during 4 weeks, at the physiotherapist office

Table 1 Subject characteristics

N	Early DVA rehab *n* = 10	Late 1 DVA rehab *n* = 9	Late 2 DVA rehab *n* = 9
Gender	5 Males 5 Females	4 Males 5 Females	4 Males 5 Females
Mean age (range)	63.1 (37–83)	66.1 (39–86)	60.2 (47–79)
Side	4 right 6 left	4 right 5 left	4 right 5 left
Time from onset (days) (range)	8.9 (0–15)	24.5 (16–30)	87.5 (60–240)

The number of vestibular patients in each of the three groups with acute unilateral peripheral vestibulopathy. Mean time (and range, in days) from vertigo onset and beginning of vestibular rehabilitation with the dynamic visual acuity protocol are indicated for the early group, the late groups 1 and 2. Gender, mean age (and range) as well as side of the hypofunction side are indicated

patients reported several visits to general practitioners without any clear diagnosis, and finally a correct diagnosis by an ENT very late after their vertigo attack. They constituted a control group without VR during this long time period for comparison with the two previous groups of patients, since their own day life activity was the only rehabilitation they did.

All the patients in the present study were not under drug treatment when included and not allowed to use anti-vertigo drug treatments after inclusion. They gave written informed consent to participate. The study was conducted according to the Helsinki Declaration and the experimental protocol was approved by the local ethics committee (CCPPRB Nice).

Head thrust impulse test (HIT)

Horizontal and vertical head thrust tests (HITs) were performed passively by the physiotherapist to produce unpredictable manual head rotations regarding timing and direction of head movements. Eye and head movements were recorded by means of the VHIT Ulmer system (Synapsis, Marseille, France). This is a non-invasive test with no mask on the patient's head (goggleless camera), allowing to test all six semicircular canals independently in a fast and simple way. Head rotation had peak amplitude of about 10°, peak velocity of about 200°/s and acceleration about 2000°/s. The head impulse test (HIT) was performed in seated patients whose head was kept in the horizontal plane, slightly tilted down by 30° to record the horizontal aVOR response. The patient's head was turned 45° to the right (LARP) and then 45° to the left (RALP) by the physiotherapist to record the aVOR of the vertical semicircular canals. The passive aVOR responses recorded pre-vestibular rehab served as baseline for the evaluation of the changes recorded in the post-rehab aVOR responses.

DVA test protocol

Patients were standing 1.2 m in front of a high-resolution screen on which optotypes (different letters) were randomly projected. Static visual acuity was measured first with the patients' head still. Patients were asked to recognize five different optotypes of the same size presented during 50 ms. Optotype size was then decreased by steps corresponding to changes of 1/10 on the Snellen visual acuity chart. The static visual acuity score was obtained when the patients failed to correctly identify five optotypes, and the score value was transformed in log MAR (= $\log_{10}$ [10/x], where x is the patient score). Log MAR scores of 0, 0.3, 0.7 and 1.0 correspond to Snellen equivalencies of 10/10, 5/10, 2/10 and 1/10 static acuity, respectively.

Dynamic visual acuity (DVA) was investigated with the AVD-Framiral equipment (Framiral, Grasse, France). Patients had a light helmet (200 g) secured on the head by an adjustable belt. A 3D gyroscope located at the top of the helmet provided the head velocity in real time. The DVA score was evaluated by the physiotherapist by passively rotating the patient's head with low amplitude (about 10°) and high velocity (150°–300°/s). DVA was recorded in the same experimental conditions than for the static session (5 optotypes to be recognized by level of Snellen acuity, same transformation in log MAR to evaluate DVA). DVA was evaluated first in the horizontal plane, and thereafter in the vertical planes by turning the head in the LARP (head turned 45° to the right) and RALP (head turned 45° to the left) planes. At the end of the session, a DVA score was calculated for each patient and for each canal on both sides by subtracting the static visual acuity LogMAR score from the dynamic visual acuity LogMAR score. DVA scores were calculated at the first visit and at the end of the VR training by the physiotherapist with passive DVA tests.

Data analysis of the aVOR gain and covert saccades

Gain values of the ipsilateral and contralateral (relative to the side of the deficit) horizontal and vertical semicircular canals were evaluated from the Synapsis software by the ratio peak eye velocity/peak head velocity. Five trials were

done for each canal and an average value was calculated. The directional preponderance (DP) was measured for each pair of canals by the following formula:

$$DP = (\text{contralateral canal} - \text{ipsilateral canal})/(\text{contralateral canal} + \text{ipsilateral canal}) \times 100.$$

The DP parameter evaluates the asymmetry for each pair of canals and constitutes a good index, in association with the absolute value of the aVOR gain, to measure the deficit and/or recovery of gaze stability. The software evaluated also the total number of catch-up saccades that occurred during and after the end of the head movement. The latency of the saccades relative to onset of head rotation was measured, and the percentage of those occurring during head rotations in the direction of the vestibular slow phase component (covert saccades) was evaluated. As a rule, the covert saccades were present in the first 100–180 ms after onset of head rotation.

DVA rehabilitation

The VR exercises aimed at improving DVA were similar for the three groups of patients submitted to the DVA rehab protocol. The patients were first trained to do actively fast head rotations toward the hypofunction side with the same kinematic parameters than for the passive DVA test (10° amplitude, 150–300°/s). They were helped to perform correct head rotations by a small counter on the screen which displayed a moving needle indicating the correct range of velocity to perform (in green) and the too low or to fast velocity ranges (in red, below 150°/s and above 300°/s). When patients correctly performed the head movements, a sound was triggered to signal that both amplitude and velocity of head rotations were accurate, and an optotype was projected during 50 ms on the screen. Patients were trained to do active head rotations in the planes of the three semicircular canals. When the training session was achieved, the patients were asked to perform the tests while standing in front of a screen located 1.2 m at eye level (Fig. 1). Exercises were performed twice per week during 4 weeks. At the end of the DVA rehab, that is, after eight to ten rehab sessions with the DVA protocol, the patients were tested again by the physiotherapist in passive conditions (passive vHIT tests and passive DVA tests).

Statistical analysis

Analysis of variance (ANOVA) was performed to evaluate the differences in age across the three groups of patients. The mean value and the variance of each parameter tested (DHI score, DVA score, directional preponderance, aVOR gain, and percentage of covert saccades) were calculated in the three groups of vestibular patients. Since the size of our groups was small, and the distribution of the values for each parameter in each group did not follow a normal Gaussian law, non-parametric tests were used to analyze the differences between the groups and between the pre- and post-rehab measurements in each group. Comparison between the groups was done with the Mann–Whitney *U* test, while the Wilcoxon signed rank test served for the comparison between pre- and post-values in each group. Results were considered significant for $p < 0.05$.

Results

DHI score

The ANOVA did not find any significant difference in age between the three groups of unilateral vestibular hypofunction patients ($p = 0.88$). The total DHI score incorporating the physical, functional and emotional items did not differ significantly between the three groups of patients at the first visit, before DVA rehabilitation. It was observed however that the early group and the late group 1 were in the same range of moderate handicaps (DHI = 54.4 ± 23.7 and 56.2 ± 24.06, respectively), while the late group 2 exhibited a stronger, however, non-significant handicap (DHI = 72.1 ± 15.8) (Fig. 2). After VR with the DVA

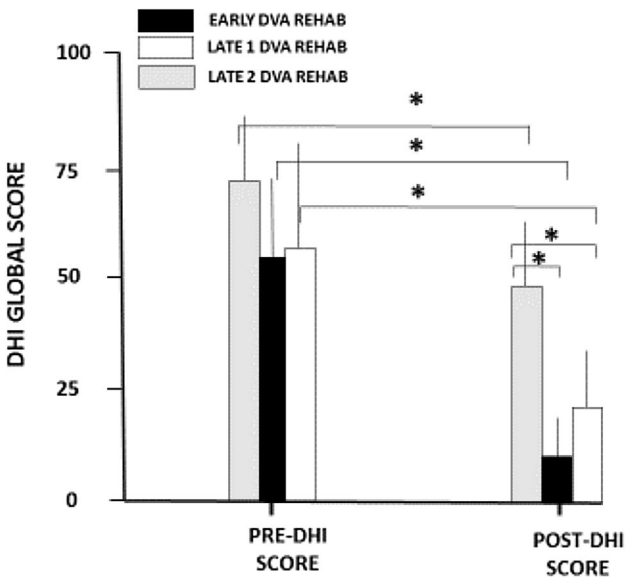

Fig. 2 Dizziness Handicap Inventory scores before and after vestibular rehabilitation with the Dynamic Visual Acuity Protocol. The global DHI scores incorporating the physical, functional and emotional items are shown on the ordinates for the three groups of patients receiving the DVA rehabilitation early after onset of vertigo attack (filled histograms), or at later stages (late group 1: open histograms; late group 2: grey histograms). DHI scores are shown for the pre- and post-DVA rehabilitation. *Significant differences between the pre- and post-values

protocol, the DHI scores were significantly reduced in all groups of patients who shifted from moderate to slight handicaps for the early group and late group 1 (9.8 ± 10.1 and 17.6 ± 13.8; $p < 0.00003$ and $p < 0.0001$, respectively), and from strong to moderate handicaps for the late group 2 (72.1 ± 15.8 to 47.8 ± 16.4; $p < 0.003$). The DHI scores corresponded to mean improvements of 44.6 ± 18 points, 38.6 ± 20 points and 24.3 points for the early group, late group 1 and late group 2, respectively. While the early and late group 1did not differ significantly from each other ($p = 0.18$) at the end of VR, the late group 2 exhibited significantly higher DHI scores compared to the two other groups ($p < 0.001$).

DVA score

The pre-DVA scores recorded in the three groups on the healthy contralesional side were slightly reduced compared to their static visual acuity scorse (0.11 ± 0.07, 0.15 ± 0.09, and 0.16 ± 0.10 for the anterior, posterior and lateral canal tests, respectively). No significant changes were observed in the post-DVA scores. By contrast, the pre-DVA scores were significantly increased on the ipsilesional hypofunction side in the three groups of patients. The values recorded for each ipsilesional canal in each groups being similar ($p = 0.13$, $p = 0.25$ and $p = 0.59$ for the lateral, anterior and posterior canal tests, respectively), an averaged value used as pre-rehab baseline was elaborated (0.28 ± 0.13 for the posterior canal test, 0.30 ± 0.18 for the anterior canal test, and 0.36 ± 0.21 for the lateral canal test, respectively: initial DVA scores, grey squares: Fig. 3). Pre- to post-rehab DVA scores on the hypofunction side are illustrated in Fig. 3 for the three groups of patients. The strongest DVA score improvement was found in the early DVA rehab group (Fig. 3, filled squares), with values decreasing to 0.13 ± 0.06 for the posterior canal test ($p < 0.006$), 0.08 ± 0.11 for the anterior canal test ($p < 0.001$) and 0.11 ± 0.11 for the lateral canal test ($p < 0.007$). The corresponding percentages of DVA score decrease were 54 ± 21% (range 10–80%), 73% ± 30% (range 40–99%), and 70 ± 21% (range 33–98%) for the three canal tests, respectively. In the patients of the late group 1 (Fig. 3, open squares) and late group 2 (Fig. 3, open circles), DVA was also reduced significantly, except for the posterior canal test. These two late DVA rehab groups differed significantly from the early DVA group with significantly lower DVA improvements ($p < 0.01$ and $p < 0.02$ for the anterior and lateral canal tests, respectively).

aVOR gain, directional preponderance and covert saccades

The pre-rehab aVOR gains recorded on the contralateral healthy side during passive head rotations were 0.82 ± 0.19

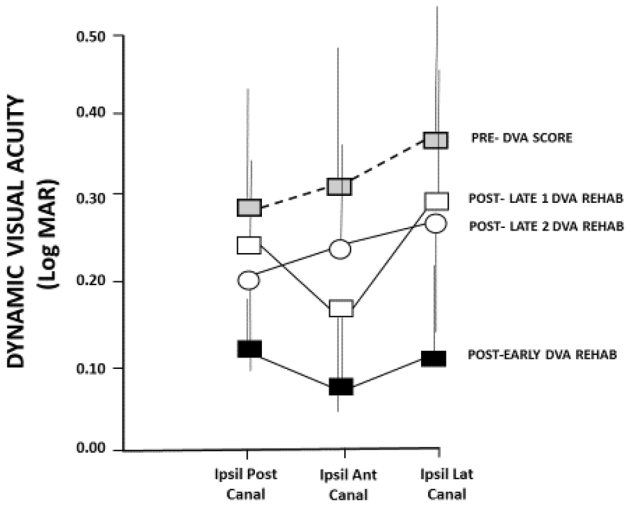

Fig. 3 Recovery of the dynamic visual acuity after rehabilitation in the three groups of patients. The dynamic visual acuity score (expressed in LogMAR) recorded in the three groups of patients is plotted on the ordinates for passive head movements performed in the planes of the posterior, anterior and lateral canals on the hypofunction side. The mean DVA scores (± SD) obtained before DVA rehabilitation (base line: pre-DVA score) are shown as gray squares. The mean post-DVA scores (± SD) recorded after the end of active DVA rehabilitation are shown as filled squares (early DVA rehab group), open squares (late group 1) and open circles (late group 2). The best DVA recovery was observed in the group of patients submitted to an early DVA rehabilitation

for the anterior canal, 0.82 ± 0.15 for the lateral canal and 0.60 ± 0.22 for the posterior canal. These values were in the normal range of the aVOR gains of healthy people aged 60–90 years [cf 26], except the posterior canal for which the values were slightly lower. These aVOR gains did not change significantly post-rehab (0.88 ± 0.15, 0.86 ± 0.14, and 0.70 ± 0.24 for the three canals, respectively). As expected by the patients' pathology, the ipsilesional hypofunction side showed significant aVOR gain reductions: 0.39 ± 0.22 (range 0.10–0.59), 0.29 ± 0.29 (range 0.01–0.64), and 0.45 ± 0.26 (range 0.10–0.63) for the anterior, lateral and posterior canals, respectively, without any significant differences between the three groups ($p = 0.88$). The post-rehab gain values were significantly modified on the ipsilesional hypofunction side in the early DVA rehab group only. This is first illustrated by the reduced directional preponderance (DP) observed in each of the ten patients constituting this group, with a value for the horizontal canal significantly decreasing from 53.5 ± 32.2 to 27.9 ± 32.6 ($p < 0.001$; Fig. 4a). By contrast, the DP remained unchanged between the pre- and post-values in the late group 1 ($p = 0.59$) and the late group 2 ($p = 0.62$) groups (Fig. 4b and Table 2). This result strongly suggests a recovery of the passive aVOR gain in the early DVA group only.

Figure 5a illustrates the post-rehab changes of the ipsilateral horizontal aVOR gain during passive head rotations.

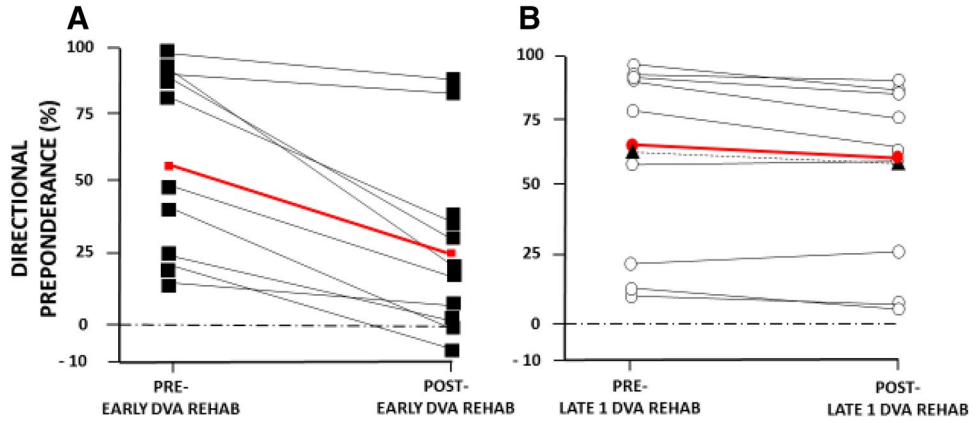

Fig. 4 **a**, **b** Changes of the directional preponderance for the horizontal angular vestibulo-ocular reflexes recorded in the three groups of patients. The directional preponderance was evaluated during passive horizontal head thrust tests to the intact and the lesion sides and expressed in percent (ordinates) before (pre-) and after (post-) active DVA rehabilitation in the groups of patients submitted to an early (**a**) or later (**b**) rehabilitation. Early DVA rehab shows a reduction of the directional preponderance for each of the patients in this group (average: red line), while directional preponderance is not significantly modified for each of the patients in the late group 1 (open circles; average: red line). The mean values for the late group 2 are shown as filled triangles and dashed line

Table 2 Effects of dynamic visual acuity rehabilitation on the directional preponderance of the three pairs of semicircular canals

	Lateral canal		Anterior canal		Posterior canal	
	Pre-rehab	Post-rehab	Pre-rehab	Post-rehab	Pre-rehab	Post-rehab
Early DVA	53.5 (32.1)*	27.9 (36.6)	41.3 (28.5)*	16.9 (22.2)	20.5 (28.9)*	3.8 (15.3)
Late 1 DVA	62.1 (38.5)	57.5 (37.6)	44.6 (29.5)	29.4 (31.1)	13.4 (15.7)	25.1 (19.9)
Late 2 DVA	60.6 (24.3)	56.9 (24.5)	41.5 (30.5)	41.6 (35.8)	16.7 (26.4)	23.0 (37.4)

Directional preponderance (DP) was evaluated for each pair of semicircular canals pre- and post- DVA rehabilitation in the three groups of patients by the following formula: DP = (aVOR gain contralateral − aVOR gain ipsilateral)/(aVOR gain contralateral + aVOR gain ipsilateral) × 100. Head thrust impulse tests were performed passively in the horizontal (lateral canal test), LARP and RALP planes (anterior and posterior canal tests). Mean DP values (± SD) are shown

*Significant differences ($p < 0.01$)

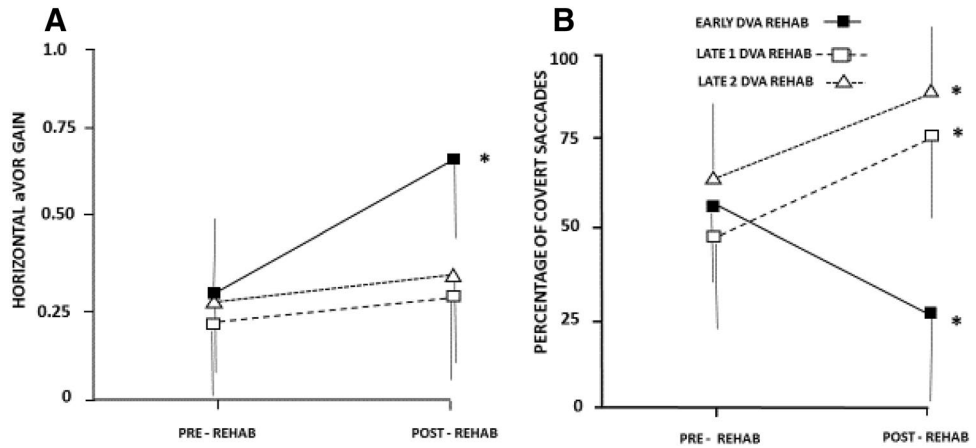

Fig. 5 A-B: Modifications of the horizontal angular vestibulo-ocular reflex gain and of the percentage of covert saccades in the three groups of patients. The modifications of the horizontal angular vestibulo-ocular reflex gain (**a**) and of the percentage of covert saccades (**b**) during passive HIT performed on the lesion side are illustrated for the three groups of patients before (pre-rehab) and after (post-rehab) active DVA rehabilitation. One can see a significant improvement of the passive aVOR gain associated with a significant reduction of the percentage of coverts saccades in the early DVA rehab group (filled squares), while the late group 1 (open squares) and the late group 2 (open triangles) DVA show no passive aVOR improvement and a significant increased percentage of covert saccades. Mean values are plotted with their standard deviation. *Significant differences ($p < 0.01$)

Indeed, the early DVA rehab group showed an increased gain jumping from 0.28 ± 0.23 pre-rehab to 0.69 ± 0.28 post-rehab ($p < 0.003$; Fig. 5a), that is, a mean gain increase of 246% ± 49%. By contrast, the late group 1 and the late group 2 did not show any significant changes in the horizontal aVOR gain (0.20 ± 0.21 to 0.27 ± 0.30; $p = 0.27$; Fig. 5a). An opposite pattern was observed when one considers the percentage of covert saccades occurring during the passive head rotation test. The percentage was roughly similar in the three groups pre-rehab ($p = 0.46$). When the percentage was significantly reduced post-rehab in the early DVA rehab group (from 57% ± 18% to 29% ± 27%; 50% decrease; $p < 0.003$), it was significantly increased in the late group 1 (from 47.5% ± 29% to 73% ± 25%; 155% increase; $p < 0.008$) and the late group 2 (from 65.1% ± to 86.5 ± 19%; 133% increase) groups.

Discussion

Taken together, our data in patients with acute unilateral vestibulopathy indicate that early training with the DVA rehab protocol brings the DVA scores back to roughly normal values after 4 weeks of active rehab in the planes of the different canals. These DVA improvements are associated with significant reductions of the directional preponderance for each pair of canals, a result due to an increase of the passive aVOR gain and a concomitant decrease of the percentage of covert saccades, at least for the horizontal aVOR on the hypofunction side. In contrast, later rehab with the DVA protocol induces less DVA score improvement, a result associated with neither directional preponderance modifications nor horizontal aVOR gain changes, but with an increased percentage of compensatory saccades for the canal tests done on the same hypofunction side. Moreover, the patient's perception of dizziness handicap was reduced in the three groups of patients, with significantly greater reductions when rehab was performed in the early postlesional stages.

Subjective perception of dizziness handicap

Our data confirm previous studies showing that VR improves the DHI score of patients with vestibular hypofunction. All the patients in the early and late DVA protocol rehab groups showed greater than 18-point difference between pre- and post-scores, a point difference considered as a measure of change with the DHI questionnaire [18]. The percentage reduction of the DHI score was higher in our study (82% and 69% for the early group and late group 1, respectively) compared to other reports indicating around 35% improvement only [4, 27, 28]. These studies investigated mainly chronic patients tested a longer time after the acute onset of vestibular pathology, at time delays corresponding to our late group 2 that showed around 25% improvement only. This suggests that VR must be done early after the acute attack to get the best and faster improvement in the patient's perception of dizziness handicap. The decrease in the DHI score seems however independent of the mechanisms underlying the changes in dynamic visual acuity (aVOR gain recovery or covert saccades), as suggested by a recent report in patients with vestibular neuritis [29], by the absence of correlation between the DHI and the vestibular function tests [30], and by our own results (see below).

Recovery of dynamic visual acuity

Our data confirm previous studies indicating that gaze stability exercises improve DVA in patients with unilateral vestibular hypofunction [17], via two primary mechanisms [4]: an enhanced active aVOR gain and an increased number of compensatory saccades. The novelties with our study are (1) these two mechanisms develop differently as a function of the time delay between the onset of pathology and the beginning of DVA rehab, and (2) the passive aVOR gain observed during the head thrust test HIT recovers only when rehab is performed early.

Improvement of the aVOR gain has not been reported in the previous literature for high-velocity (>120°/s) passive head rotations [19, 31] and, as stated by Schubert et al. [4], "gaze stabilization exercises do not cause much improvement in aVOR gain during passive head thrust rotations". The major difference in our study is that rehab with the early DVA protocol was performed in acute and not in chronic patients. Interestingly, it was recently reported that the passive aVOR gain could be improved if UVH patients were enrolled for rehabilitation within 1 month after their acute symptoms [32], a result in total agreement with our data. Animal models of vestibular pathology have demonstrated that the acute stage constitutes a sensitive period, or opportunity window during which most of the plastic events are expressed and used to get an optimal functional compensation [21]. It is well known now that the brain remodelings after stroke and many other pathologies are both time and neural activity dependent, a process inherently sensitive to behavioral experiences (see [33] for review). This supports targeting the early dynamic period of vestibular-induced neural plasticity with vestibular rehabilitation. Our data show that an early active training restores a quite normal DVA during fast passive head rotations, a result due to the reduction of the directional preponderance and the improvement of the passive aVOR gain, accompanied by the concomitant reduction in the number of compensatory saccades. We confirm in our study the inverse correlation between the aVOR gain and the recruitment of compensatory saccades reported in patients with acute peripheral vestibulopathy [34,

35]. Unidirectional passive whole body rotations toward the lesion side acutely after unilateral labyrinthectomy in the macaque was also found to reduce the horizontal aVOR gain asymmetry by increasing the ipsilesional aVOR gain [14]. In addition, the horizontal aVOR asymmetry was decreased after unidirectional passive head rotations to the hypofunction side in patients with vestibular dysfunction [13]. Two potential mechanisms could restore the aVOR gain on the hypofunction side. A first one is a collateral sprouting of new terminals from remaining intact afferent vestibular fibers making new synaptic contacts onto the deafferented vestibular nuclei cells. This structural process may play a role in acute UVH patients. Indeed, animal models of lesioned afferents to adult brain structures may exhibit growth cones on the remaining afferent fibers after 5 days, expanding up to 50 µm and inducing a total synaptic reoccupation within 1 month, that is, with a time constant compatible with our data (see [36], dentate gyrus, rat). A second mechanism known to be expressed early after a lesion (several hours or days) is the increased number of post-synaptic receptors, which could account for the reweighting of remaining vestibular afferents (see [37, 38], unilateral labyrinthectomy, frog). Both mechanisms have been found to be time and neural activity dependent, the reason why earlier should be better for DVA recovery. Another possibility would be a learning process including the cerebellar cortex to modify in an adaptive way the vestibulo-ocular reflex gain [39, monkey].

These hypotheses would explain why late rehab with the DVA protocol showed significantly less reduction of the DVA score compared to early rehab, as a consequence of no change in the passive ipsilesional aVOR gain and no reduction of the aVOR asymmetry. When DVA rehab is performed at the end of the sensitive time window, that is, in the late groups 1 and 2, the ability of the patients to use their neural plasticity would be reduced or lost. Patients of these groups showed however a significant increase in the percentage of compensatory saccades that assist gaze stability during DVA testing. According to many previous reports, these saccades are related to retinal position errors [4, 40–42] and triggered by visual inputs [43]. The recruitment of these saccades develops as a behavioral process substituting the aVOR and improves the patient's ability to see clearly during fast head rotation, reducing his/her perception of dizziness handicap (see above).

Conclusions

As far as we know, the present study is the first to confirm in unilateral vestibular loss patients the concept supported by our animal models of a critical period for optimal vestibular compensation. Earlier is better for dynamic visual acuity recovery, because gaze stabilization exercises during this opportunity time window interact dynamically with the vestibular lesion-induced neural plasticity to restore a near normal aVOR gain in both unpredictable (passive head rotations) and predictable (active head rotations) conditions. When gaze stabilization training is performed later, at the end (around 1 month: late group 1) or well after the end of the critical period (late group 2), the dynamic visual acuity recovery relies mainly on the recruitment of compensatory saccades which play a functional role in predictable conditions only. Our data suggest important implications for gaze stability rehabilitation programs that should be started very early and actively after onset of the vestibular pathology.

Limitations of the study

The first limitation is the small sample of patients in each group. Our data would have to be confirmed in larger clinical trials. A second limitation is the short period (4 weeks) and the limited number of vestibular rehab sessions (8–10) provided to each patient in our study. One may wonder if a longer and/or more intense training with a graded program of gaze stability exercises would benefit to the patients for restoring more the aVOR in passive unpredictable conditions.

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Author contributions LT diagnosed and selected the patients included in the study; AT did the vestibular rehabilitation of the patients; ML, AT and LT elaborated the experimental protocol; ML wrote the paper; and LT, AT and ML corrected together the manuscript.

Compliance with ethical standards

Conflict of interest The authors declare having no conflict of interest.

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