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ORIGINAL COMMUNICATION

The integration of multisensory motion stimuli is impaired in vestibular migraine patients

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Abstract

Background Vestibular migraine (VM) is a relatively recently acknowledged vestibular syndrome with a very relevant prevalence of about 10% among patients complaining of vertigo. The diagnostic criteria for VM have been recently published by the Bárány Society, and they are now included in the latest version of the International Classification of Headache Disorders, yet there is no instrumental test that supports the diagnosis of VM.

Objective In the hypothesis that the integration of different vestibular stimuli is functionally impaired in VM, we tested whether the combination of abrupt vestibular stimuli and full-field, moving visual stimuli would challenge vestibular migraine patients more than controls and other non-vestibular migraineurs.

Methods In three clinical centers, we compared the performance in the functional head impulse test (fHIT) without and with an optokinetic stimulus rotating in the frontal plane in a group of 44 controls (Ctrl), a group of 42 patients with migraine (not vestibular migraine, MnoV), a group of 39 patients with vestibular migraine (VM) and a group of 15 patients with vestibular neuritis (VN).

Results The optokinetic stimulation reduced the percentage of correct answers (%CA) in all groups, and in about 33% of the patients with migraine, in as many as 87% of VM patients and 60% of VN patients, this reduction was larger than expected from controls' data.

Conclusions The comparison of the fHIT results without and with optokinetic stimulation unveils a functional vestibular impairment in VM that is not as large as the one detectable in VN, and that, in contrast with all the other patient groups, mainly impairs the capability to integrate different vestibular stimuli.

Keywords Vestibular migraine · International classification of headache disorders · Functional head impulse test · Vestibular ocular reflex · Optokinetic stimulation

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Introduction

A significant number of studies over the past decades have dealt with the recognition of vestibular migraine as an autonomous clinical entity [1–12], an effort that has led to a recent consensus from the Bárány society that made possible the definition of diagnostic criteria [13] which have been included in the Appendix of the very recent ICHD-III [14]. Vestibular migraine (VM) is likely to be the most common cause of spontaneous episodic vertigo in adults and accounts for about 10% of all patients presenting at a dizziness unit [2], with a prevalence in the general population of about 1% [9]. VM is generally underdiagnosed, which occurs more frequently when the vertigo attacks are not temporally related to headache [1, 5, 8]. Vestibular abnormalities have been found in up to 70% of VM patients (see von Brevern and Lempert 2016 [15] for a review); they include ictal [16] and interictal signs [17] and these latter are not specific to VM but can be also observed in migraineurs without a history of vestibular symptoms [4, 18–22], so that the features of vestibular impairment in VM are still elusive.

We developed a test suggested by two observations characterizing VM patients: their susceptibility to head motion-induced vertigo or dizziness [3, 12] and to visually induced vertigo, triggered by a complex or large moving visual stimulus [3, 6].

Hence, we predicted that combining the functional head impulse test (fHIT, see the following "Materials and methods" section for a description of the test) [23–26] implying abrupt head motion, with a rotating background providing large-field torsional optokinetic stimulation (fHITOks), could represent a testing condition which would present difficulties to VM patients. We, therefore, compared the performance between the regular fHIT and the fHITOks in terms of the percentage of correctly read optotypes (percentage of correct answers, %CA), i.e., the measure used in the fHIT, to assess whether it could differentiate VM patients from healthy subjects and from patients with non-vestibular migraine, and to compare the behavior of VM patients with that of patients with a unilateral vestibular deficit.

Materials and methods

The fHIT is a relatively new functional test of gaze stabilization abilities that has proven useful in assessing vestibular patients [23, 26, 27] and their recovery [28].

The test is carried out in two phases:

1. A static visual acuity (SVA) assessment phase, during which the subject sits in front of a PC monitor with the head still and a Landolt ring optotype (Fig. 1a) briefly appears on the screen for about 80 ms in one out of the eight possible orientations. After each optotype appearance the subject is asked to identify the seen optotype using a customized numeric keypad, as shown in Fig. 1b, without timing constraints. The sequence of optotype sizes is determined by the Quest algorithm [29] based on the subject's correct and wrong answers to find the minimum readable size, reported in LogMAR.
2. A dynamic phase during which the sitting subject, wearing a head-mounted custom inertial motion unit (IMU) is exposed to unpredictable passive head impulses manually delivered by the experimenter at varying angular accelerations (3000–6000 deg/s^2). During the movement, a Landolt ring optotype, sized 6 LogMAR lines larger than determined during the SVA test, appears on the monitor, triggered by the IMU signal, in one of the eight possible orientations. The subject is again asked to recognize the orientation of the shown optotype using the same keypad [24, 25]. Subjects declaring that they

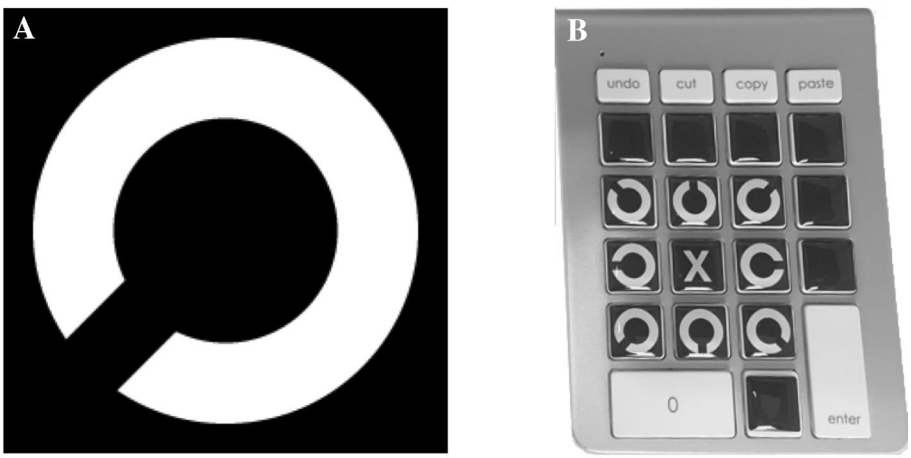

Fig. 1 fHIT testing. **a** Landolt C optotype in one of the eight possible orientations used in the fHIT test. **b** Detail of the custom numeric keyboard held by the tested subject for indicating the viewed optotype

were not paying attention during the head impulse may select the X key to cancel the impulse from the test statistics. Subjects that did not see or recognize the letter should select the black key in the bottom row of the keypad to mark the corresponding impulse as an error, instead of attempting a guess.

Three neuro-otology clinical centers (Pavia, Siena and Perugia) participated in the study. The study was approved by the local ethical committee (IRB) of each clinical center. Written informed consent was signed by all subjects participating in the study.

Each center recruited subjects in four groups: controls (Ctrl), migraine but not vestibular migraine (MnoV), vestibular migraine (VM), and vestibular neuritis (VN) as listed in Table 1. Altogether, we considered 44 subjects in the Ctrl group, 42 in the MnoV group, 39 in the VM group, and 15 in the VN group.

The Ctrl subjects were normal volunteers recruited among the staff, friends and family members, which had not to suffer of (1) previous or current vestibular disorder (with the exception of benign paroxysmal positional vertigo in at least the past 2 weeks before examination) and (2) migraine or other headache disorders with the exception of episodic tension-type headache, to be included in the study. The MnoV and the VM patients were enrolled among those attending the headache or the vertigo centers of our Institutions. Subjects enrolled in the MnoV group were diagnosed with migraine with or without aura using the ICHD-III diagnostic criteria; while, those in the VM group were diagnosed with vestibular migraine according to the consensus criteria of the International Headache Society (HIS) and Bárány society [13]. All patients suffered from episodic migraine, none of them was under prophylactic treatment, and they were tested at least 5 days after their last episode of migraine or vertigo. To be included in the MnoV group, the patient's clinical history had to be negative for any previous or current vestibular disorder. About 10% of the VM patients showed some slight and isolated vestibular signs, as can be seen in VM [4, 17], gaze-evoked nystagmus, positional gaze-evoked nystagmus, positional down beat nystagmus on lateral gaze.

Motion sickness was annotated for each subject, and all subjects autonomously underwent the Dizziness Handicap Inventory (DHI), the Situational Vertigo Questionnaire (SVQ) and the Activity Balance Confidence scale (ABC) [30]. All patients were tested in the interictal period after at least 72 h from the last episode. In all the involved clinical centers, the experimental tests were performed using the fHIT system (Beon Solutions s.r.l.), using a customized software version allowing the addition of a rotating background to the regular fHIT paradigm.

We considered also a group of 15 patients (8 men, 7 women) with a unilateral vestibular deficit due to vestibular neuritis (VN). VN was right sided in 13 subjects, and the patients were examined about 9.22 days after onset (range 6–13 days); to be included in the VN group, the patients had not to be migraineurs. The diagnostic criteria for VN were: (1) acute onset of spinning vertigo, postural imbalance and nausea lasting more than 24 h, (2) a horizontal rotatory nystagmus beating towards the non-affected side, lasting more than 24 h, (3) a pathological head impulse test, (4) abnormal caloric test on the affected side, (5) no evidence of central vestibular or ocular motor dysfunction and (6) no acute unilateral hearing loss. In the following analysis, all VN patients were considered to be affected on the right-side, therefore we switched side to the data on the two patients that were affected on the left side. The VN was included in the study as a group of subjects with a well-defined vestibular condition, to be specifically compared with the VM patients.

Each subject enrolled in the study was then tested as follows.

1. We tested the subject's SVA as described above for determining the size of the optotype to be used in the dynamic part of the testing.
2. We tested the subject's horizontal gaze stabilization abilities with the described regular fHIT paradigm:

Table 1 Demographics of enrolled subjects

Subjects' number and demographic characteristics											
	Pavia	Siena	Perugia	Total	M/F	Age (mean; range)	Motion sickness %	Aura (with/without)	DHI	SVQ	ABC
Ctrl	23	8	13	44	22/22	38.4; 20-71	9.1	– 0/0	33.4	24	53.3
MnoV	23	8	11	42	3/39	34.2; 16-60	42.8	10/32	44.9	41.5	42.1
VM	17	10	12	39	1/38	44.3; 25-67	48.6	7/32	68.4	55	23.9

Each row shows the subjects in one of the three study groups (Ctrl, MnoV, VM)

Columns show numerosities in the three clinical centers, total, gender, percentage affected by motion sickness, the subjects without and with aura, and the mean rank scores in the DHI, SVQ and ABC questionnaires

We imposed at least 20 head impulses in each direction during which the pre-sized (6 LogMAR lines larger than SVA threshold) Landolt C optotype appeared on screen for 80 ms with randomized orientation.

Peak head angular accelerations were varied between 3000 and 6000 deg/s^2 and the subjects' responses were recorded to compute the percentage of correct answers (%CA).

3. We then tested the subject's horizontal gaze stabilization abilities using the fHIT paradigm as in step 2), but with the addition of a background (fHIToks condition) consisting in a cloud of pseudo randomly distributed yellow dots that rotated about the center of the screen, where the optotype appeared, at a speed of 36 deg/s.

The order of fHIT and fHIToks testing conditions was alternated within each clinical center's population of subjects.

Head angular acceleration and the %CA for clockwise (CW) and counter-clockwise (CCW) head impulses were recorded during each trial.

During the execution of all testing paradigms, movements of the left eye of the subjects tested in Siena (8 Ctrl, 8 MnoV, and 10 VM) were recorded using the monocular EyeSeeCam system (EyeSeeTech, GmbH) running at 220 Hz.

Statistical analysis

We considered the %CA for fHIT, fHIToks and the fHIT–fHIToks difference; the CW and the CCW data were analyzed separately.

The mean values of the different groups of subjects were compared by the analysis of variance; in case of a significant difference, we used the Scheffé test to classify the groups with a similar behavior. The comparison of the number of subjects with an abnormal %CA value in each group was based on the Chi-square test; for these analyses, we considered not only the CW and CCW data separately but also the CW OR CCW condition, where a subject was considered as abnormal if he/she showed an abnormal value in either the CW or CCW rotation. Again, we included in the analysis the option for pairwise comparison to classify groups with similar behavior.

As an additional analysis, the mean VOR gain values from the subjects recorded in Siena were compared using a repeated measure analysis of variance considering both a within-subject factor (the task factor: fHIT without or with oks) and a between-subject factor (the group factor: Ctrl, MnoV and VM) and their interaction; the CW and the CCW data were analyzed separately.

The scores of the DHI, SVQ and ABC questionnaires were compared using the Kruskal–Wallis test.

The correlation analysis was made based on Pearson's correlation coefficient r.

The statistical analyses were performed using the SPSS v 21 software and the significance level was set at $p = 0.05$.

Results

For all tested groups, the distributions of %CA in response to fHIT and fHIToks are shown in Fig. 2, while those of fHIT–fHIToks differences are presented in Fig. 3.

Comparisons between Ctrl, MnoV and VM groups

- The following data are reported in Table 1. Motion sickness was more frequent in the MnoV and in the VM than in the Ctrl and VN groups. The mean age of the 3 groups was statistically different ($F(2,122) = 6.19$, $p = 0.001$), as the VM patients were slightly older than the MnoV and the Ctrl subjects. The scores of the three questionnaires (DHI, Chi square = 27.5, $p < 0.001$; SVG, 23.7, $p < 0.001$; ABC, 21.8, $p < 0.001$) were statistically different between the three groups and always worse in the VM group.
- %CA mean values comparisons (Table 2). Because VM were older than MnoV patients the analysis of variance to check the difference between groups, we used subjects' age as a covariate. Both for CW and CCW, the mean values of the three groups proved to be statistically different for fHIT, for fHIToks and for fHIT–fHIToks difference. The Scheffé test showed that the Ctrl and the MnoV groups showed the same behavior; whereas, the VM group was always different from the other two: more specifically the VM fHIT and fHIToks mean values were lower and the fHIT–fHIToks ones were larger than those of the other two groups. The MnoV values always fell between the Ctrl and the VM values but, as already said, they were not different from the Ctrl ones.
- %CA number of abnormalities (Table 3). These results were similar to those reported above about the mean value comparisons. The three groups proved to be different both for CCW and for CCW directions. The VM group invariably showed the largest occurrence of abnormalities, especially so for fHIToks and for the fHIT–fHIToks difference. In the pairwise comparisons, in the fHIT task, VM was significantly worse than Ctrl but not than MnoVM. In the fHIToks and in the fHIT–fHIToks tasks, the VM group was significantly worse than both Ctrl and MnoV groups, and the MnoV was significantly worse than the Ctrl group.

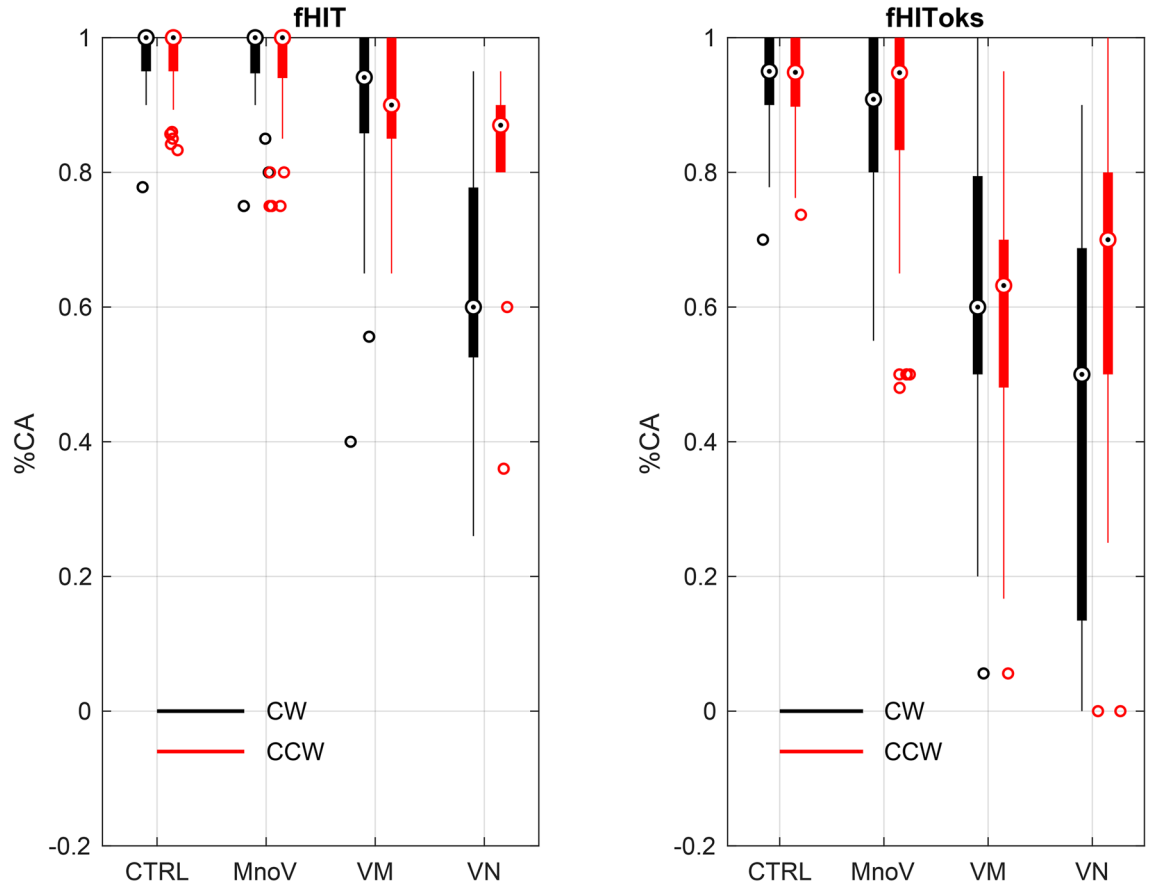

Fig. 2 Distribution of clockwise and counter-clockwise %CA data in the four tested groups. Left panel: %CA in standard fHIT test. Right panel: %CA with fHITtoks testing. Each set of data is represented by a box plot with the central mark representing the median, the top and bottom edges indicate the 75th and the 25th percentiles, respectively, the lines extend to the most extreme data not considered as outliers and the latter are plotted individually as empty circles

Comparisons between VM and VN groups

Here, we must remind that for the VN patients, the data were re-arranged so as CW and CCW rotations corresponded to rotation toward the affected and the healthy side, respectively (see "Materials and methods" section). The subjects in the VN group were slightly (mean 47.46 years; range 24–64 years) but not significantly older than those in the VM group.

- %CA mean values comparisons (Table 2). The VN group showed significantly lower mean values than the VM group in the fHIT task for both CW and CCW directions, especially for the CW rotation, namely for the rotations toward the affected side of the VN group. A lower mean value was also seen for the fHITtoks evaluation but for the CW direction only. As an additional information, the fHIT–fHITtoks difference in the VN patients was not correlated with the time from symptoms' onset (CW: $r=0.39$, $p=0.29$; CCW: $r=0.47$, $p=0.19$).
- %CA number of abnormalities (Table 3). For the fHIT task, the VN group showed a significantly larger occurrence of abnormalities than the VM groups for CW (i.e., toward the affected side) but nor for CCW direction. For the fHITtoks task, the two groups were not statistically different. Finally, when we considered the fHIT–fHITtoks difference, we found a borderline significant effect when we considered the CW OR CCW condition, with a higher occurrence of abnormalities in the VM group.

VOR gains

The group of subjects that were tested in Siena underwent simultaneous eye movement recording (see "Materials and methods" section) while performing the fHIT and fHITtoks tasks, allowing us to compute the gain values of the VOR during the tasks (Table 4).

- Both for the CW and the CCW directions, there was no statistically significant difference between the three

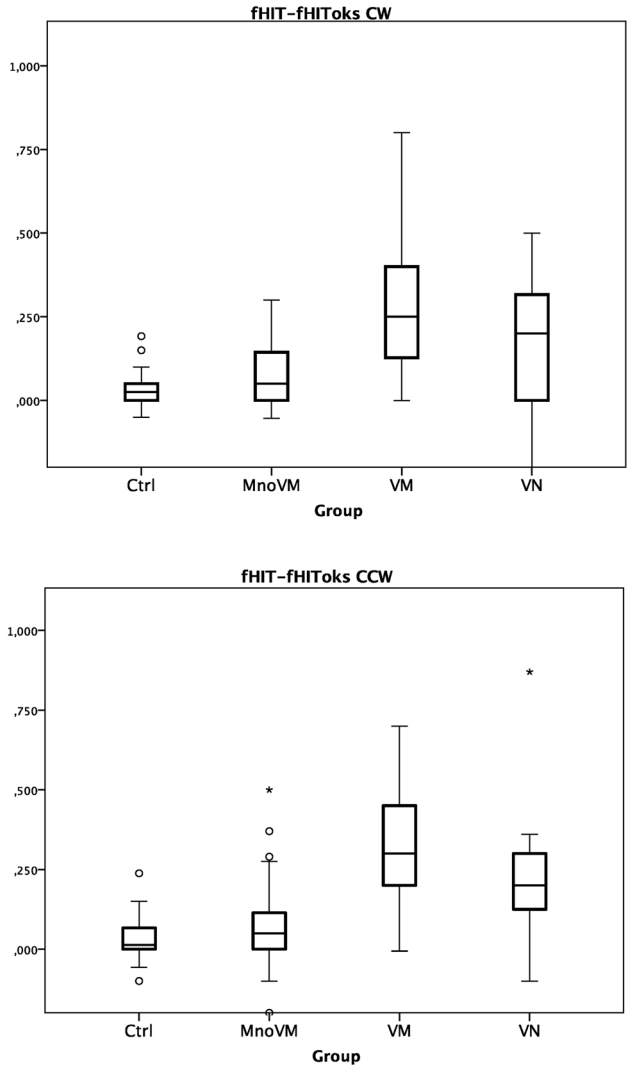

Fig. 3 Distribution of %CA differences in all tested groups. The distribution of the results in each group is represented as a boxplot with the middle bar indicating the median, the box extending between the 25th and the 75th percentiles, the whiskers including the 5th and 95th percentiles and the empty circles representing the outliers. Upper panel: CW direction. Lower panel; CCW direction

groups, whereas the VOR gain values proved to be significantly lower in the fHITOks than in the fHIT task. However, this reduction was the same in the three groups as suggested by the not significant stimulus × group interaction.

- In the subjects from Pavia, we tested the capability to read the optotype in the same condition of the fHITOks but keeping their head still, and they all achieved 100% of correct answers.
- The occurrence of motion sickness was not significantly correlated with the abnormality of %CA when we considered all the subjects, only the migraineurs (MnoV and VM) or only the VM group.

Discussion

Our data showed that the VM patients have some vestibular stigmata such as motion sickness and that, when evaluated by vestibular questionnaires, they score worse than controls and migraine patients who never experienced vertigo. It is useful to remind that SVQ focuses on vestibular disturbances induced by visual stimulations and visuo-vestibular mismatch.

Our data also showed that the capability of reading while performing the head impulse test is slightly impaired in VM subjects as compared to Ctrl and MnoVM. In VM, this impairment becomes larger, and the difference with the other two groups is more evident, when the reading capability is challenged by the combination of head motion and optokinetic stimulation, namely when motion signals of different origin must be integrated. Even if the following considerations derive from analyses performed on subgroups of subjects, this impairment is attributable to a reduced capability in the integration of visual and vestibular signals, and not to a reduced visual acuity or a VOR gain reduction induced by the presence of the optokinetic stimulation. Indeed, we did observe a gain reduction in the fHITOks task as compared to the fHIT task, but this gain reduction was the same in the VM group and in the other 2 groups.

A similar, but smaller, reduced capability of integrating different vestibular signals, was detectable in VN, a condition characterized by a vestibular deficit. Obviously, the VN group was already significantly worse not only than normal, but also than VM group, in the fHIT task, namely when multisensory motion integration was not needed. When we considered the integration of different sensory inputs (fHITOks and fHIT–fHITOks difference), the percentage of abnormal subjects was always larger in the VM than in the VN group, and reached a borderline significant level for the fHIT–fHITOks difference in the CW OR CCW condition.

Overall, VM subjects showed a vestibular abnormality that mainly consisted in the reduced capability to integrate different sensory signals reporting motion. To a much lesser extent, this reduction is detectable in MnoV and it can be regarded as a vestibular sign, since it is detectable also in VN. It is noteworthy that, compared to VN, VM patients showed a lesser impairment in the fHIT, but at least the same and frequently an even larger impairment when the integration of vestibular and visual information is required.

A similar impairment was described for the integration of rotational and gravitational cues [31] and visual motion stimulation is able to impair postural stability in VM patients [32].

Multisensory integration is a key feature of the vestibular system that takes place at different loci and processing

Table 2 Mean values of the percentage of correct answers (%CA) with the functional head impulse test for the three groups of subjects (Controls—Ctrl, Migraine without Vestibular Migraine—MnoV, Vestibular Migraine—VM, and Vestibular Neuritis—VN, for clockwise (CW) and counter-clockwise (CCW) head rotations in two different tasks (fHIT, fHITOks)

Percentage of correct answers						
Group	Task					
	fHIT		fHITOks		fHIT – fHITOks	
	CW	CCW	CW	CCW	CW	CCW
Ctrl ($n=44$)	97.4 (0.04) [86.7]	96.2 (0.05) [83.3]	93.9 (0.06) [75.5]	93.1 (0.07) [75.5]	3.5 (0.05) [17.1]	3.1 (0.06) [19.6]
MnoV ($n=42$)	94.1 (0.06)	93.5 (0.08)	87.3 (0.11)	85.1 (0.17)	7.1 (0.09)	8 (0.13)
VM ($n=39$)	89.2 (13.7)	90.2 (9.5)	62.7 (21.9)	59.4 (19)	26.5 (17.9)	30.8 (15.9)
VN ($n=15$)	62.2 (19.9)	82.1 (15.4)	46.6 (31.3)	60.3 (30.8)	15.6 (21.2)	21.8 (23.1)
Ctrl vs MnoV vs VM	$F=9.5$; $\boldsymbol{p<0.001}$	$F=4.5$; $\boldsymbol{p=0.002}$	$F=47.9$; $\boldsymbol{p<0.001}$	$F=51.1$; $\boldsymbol{p<0.001}$	$F=44.6$; $\boldsymbol{p<0.001}$	$F=58.4$; $\boldsymbol{p<0.001}$
VM vs VN	$F=32.3$; $\boldsymbol{p<0.001}$	$F=5.6$; $\boldsymbol{p=0.01}$	$F=4.6$; $\boldsymbol{p=0.03}$	$F=0.2$; $p=0.9$	$F=3.6$; $\boldsymbol{p=0.06}$	$F=2.7$; $\boldsymbol{p\ 0.11}$

The last two columns show the difference between the stable (fHIT) and the rotating background condition (fHITOks), i.e., fHIT–fHITOks. The numbers in parentheses show the standard deviation values and those in square brackets show the normal limits [defined as the mean ± 2.5 standard deviations (SD)] computed from the control group values

These were used to rate the subject as normal or abnormal in the following analyses. The last two rows show the results from the analyses comparing the Ctrl vs MnoV vs VM groups and the VM vs VN groups. Bold font is used for statistically significant values

Table 3 Percentage of abnormally classified subjects (%abnormalities) based on the normal limits (mean ± 2.5×STD) computed on the Ctrl group and reported in parentheses in Table 2

Percentage of abnormalities									
Group	Task								
	fHIT			fHITOks			fHIT–fHITOks		
	CW	CCW	CWor CCW	CW	CCW	CW or CCW	CW	CCW	CW or CCW
Ctrl ($n=44$)	2.3 [a]	0[a]	2.2[a]	2,3[a]	1.8[a]	2.3[a]	2.2[a]	2.2[a]	4.4[a]
MnoV ($n=42$)	7.1[a,b]	11.9,[a, b]	14.3[a,b]	14.3[a]	16.4[b]	21.4[b]	19[b]	19[b]	33.3[b]
VM ($n=39$)	25.6[b]	20.5[b]	33.3[b]	69.2[b]	87.2[c]	89.7[c]	64.1[c]	76.9[c]	87.1[c]
VN ($n=15$)	93.3	33.3	93.3	80.0	66.7	80	53.3	60	60
Ctrl vs MnoV vs VM									
Chi square; p	12.4; $p=\mathbf{0.002}$	9.5; $p=\mathbf{0.009}$	15; $p=\mathbf{0.001}$	52.1; $p<\mathbf{0.01}$	70.6; $p<\mathbf{0.001}$	74.5; $p<\mathbf{0.01}$	42; $p<\mathbf{0.01}$	58; $p<\mathbf{0.01}$	59.9; $p<\mathbf{0.01}$
VM vs VN									
Chi square	20.1; $p<\mathbf{0.001}$	0.97; $p=0.48$	15.6; $p<\mathbf{0.001}$	0.27; $p=0.51$	3.02; $p=0.12$	0.91; $p=0.38$	0.53; $p=0.54$	1.54; $p=0.31$	4.93; $p=\mathbf{0.05}$

For each considered condition (fHIT, fHITOks, fHIT–fHITOks), each column reports the % abnormalities considering the clockwise (CW), counter-clockwise (CWW), and the logical OR between CW and CCW results (CWorCCW)

The table also reports the Chi square and the significance values from the comparison of the different groups both for the Ctrl vs MnoV vs VM groups and for the VM vs VN groups. In the context of the Ctrl vs MnoV vs VM comparisons, the superscript letters refer to the pairwise comparison between groups: the groups that did not prove to be statistically significant are labeled with the same letter. Bold font is used for statistically significant values

stages (vestibular nuclei, cerebellum, thalamus, vestibular cortical areas) to control the vestibulo-ocular and vestibular spinal reflexes, the perception of self-motion and spatial orientation [33]. Very recently, the attention of the scientific community has been focused on the possible role of the thalamus both in vestibular multisensory integration [34] and in the pathophysiology of migraine [35] and vestibular migraine [36]. Moreover, functional

Table 4 Mean VOR gains (Standard Deviation) and number of subjects considered (*n*) in the 3 groups of subjects

fHIT and fHITOks VOR gains				
Group	Test			
	CW fHIT	CW fHITOks	CCW fHIT	CCW FHITOks
Ctrl ($n=8$)	0.95 (0.09)	0.90 (0.05)	0.88 (0.05)	0.86 (0.05)
MnoV ($n=8$)	0.94 (0.12)	0.90 (0.06)	0.88 (0.14)	0.84 (0.09)
VM ($n=(10)$)	0.93 (0.1)	0.90 (0.11)	0.87 (0.07)	0.85 (0.09)
Stimulus	$F=7.84$; $p=0.01$		$F=6.9$; $p=0.01$	
Group	$F=0.34$; $p=0.97$		$F=0.34$; $p=0.97$	
Stimulus × Groups	$F=0.02$; $p=0.98$		$F=0.75$; $p=0.93$	

Ctrl controls, *MnoV* non-vestibular migraine, *VM* vestibular migraine, *CW* tested in the Siena center for clockwise, *CCW* counterclockwise, head rotations with the fHIT and the fHITOks condition

and voxel-based MRI findings in VM patients showed a modified interaction between the visual and the vestibular system during VM episodes [37, 38], an abnormal gray matter volume in vestibular multisensory areas [39] and a reduced gray matter volume in visual and vestibular processing areas in VM patients [40]. Several papers [38, 41–45] have shown that the vestibular cortical areas are interconnected and that these connections may result in a reciprocal inhibition aimed at modulating the relative weight of the vestibular or the visual signals depending on their relevance in the specific context. In our fHITOks paradigm, there are both a vestibular signal in the yaw plane and a visual optokinetic signal in the frontal plane. The subject is asked to read a letter, a task in which compensation for the vestibular signal is more important than that for the visual optokinetic one, which can be seen as a noisy background. Therefore, we expect the visual cortex to be deactivated by the parieto-insular vestibular cortex, and hence, we predict a possible reduction of visual acuity. Indeed, even in Ctrl, the percentage of correct answers in fHITOks drops by about 3.5%. We already know that in acute VN there are metabolic changes at the cortical level with an increase in regional cerebral glucose in many multisensory vestibular areas and a reduction in the visual, somatosensory and auditory areas [44]. In our VN group and even more so in the VM one, patients seemed to have more difficulties to handle this multisensory conflict and the deactivation of the visual cortex appears to be larger than normal.

About 90% of VM subjects are already labeled as migraineurs before the diagnosis of VM and our VM group is older than the MnoV group; therefore, it is likely that at least part of our MnoV subjects will be diagnosed with VM in the future. As we already reported above, the impairment in the integration of vestibular cues was detectable also in the MnoV group but it was smaller than the one shown by VM. It would be interesting to understand the underlying and maybe progressive mechanisms that make this impairment larger and lead to the appearance of vertigo spells. VM seems to be an acquired condition that affects only some patients suffering from migraine, and it will be interesting to follow up the MnoV patients and see if the presence of an abnormal fHIT–fHITOks difference predicts the onset of VM.

Finally, we can consider the issue of a possible role of fHIT and fHITOks in the diagnosis of VM that at present is based on clinical grounds only. We suggest that this approach can be useful in patients suffering from migraine when they start presenting episodes of vertigo but cannot be diagnosed as having VM because they still have not reached the threshold of 5 episodes and/or the association with migraine's symptoms in at least 50% of their episodes: in this scenario, a negative or inconclusive clinical and instrumental examination associated with an abnormal fHIT–fHITOks result may support the diagnostic hypothesis of VM. Another possible application would be in patients with "atypical" VN: a fast recovery of fHIT evaluation, with little asymmetry, and the persistence of an abnormal fHITOks, may suggest to consider VM as an alternate diagnosis. A further step will be to check if this approach will be useful for the differential diagnosis of a condition such as Ménière disease that can mimic VM.

Compliance with ethical standards

Conflicts of interest Stefano Ramat is a shareholder of Beon Solutions srl (Zero Branco, TV, Italy), a company producing the fHIT system used in this study.

Ethical standards All the procedures performed were in accordance both with clinical and with the ethical and privacy standards of the institutional ethical committees and with the 1964 Helsinki declaration.

Informed consent The participants signed an informed consent form.

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