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REVIEW

Aspects of cerebral plasticity related to clinical features in acute vestibular neuritis: a "starting point" review from neuroimaging studies

La plasticità cerebrale correlata alle caratteristiche cliniche nella neuronite vestibolare acuta: una revisione della letteratura di neuroimaging

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SUMMARY

Vestibular neuritis (VN) is one of the most common causes of vertigo and is characterised by a sudden unilateral vestibular failure (UVF). Many neuroimaging studies in the last 10 years have focused on brain changes related to sudden vestibular deafferentation as in VN. However, most of these studies, also due to different possibilities across diverse centres, were based on different times of first acquisition from the onset of VN symptoms, neuroimaging techniques, statistical analysis and correlation with otoneurological and psychological findings. In the present review, the authors aim to merge together the similarities and discrepancies across various investigations that have employed neuroimaging techniques and group analysis with the purpose of better understanding about how the brain changes and what characteristic clinical features may relate to each other in the acute phase of VN. Six studies that strictly met inclusion criteria were analysed to assess cortical-subcortical correlates of acute clinical features related to VN. The present review clearly reveals that sudden UVF may induce a wide variety of cortical and subcortical responses – with changes in different sensory modules – as a result of acute plasticity in the central nervous system.

KEY WORDS: Vestibular neuritis • Neuroimaging • Cerebral • Group analysis • Vertigo

RIASSUNTO

La neuronite vestibolare (NV) rappresenta una delle cause più frequenti di vertigine ed è definita come caratterizzata da una perdita vestibolare monolaterale (UVF) improvvisa. Negli ultimi dieci anni molti studi sono stati condotti al fine di valutare il coinvolgimento cerebrale in corso di deafferentazioni vestibolari improvvise, come quelle in corso di NV. Tuttavia, la maggior parte di essi, anche per le non omogenee possibilità nei vari centri di studio, sono stati eseguiti con diverse tempistiche di acquisizione dall'insorgenza dei sintomi, molteplici tecniche di neuroimmagini, disparate analisi statistiche e correlazioni con i reperti otoneurologici e neuropsicologici. Pertanto nella presente revisione gli autori hanno avuto l'obiettivo di far emergere somiglianze e discrepanze nei lavori che hanno impiegato tecniche di neuroimmagini ed analisi statistica di gruppaggio, con l'intento di approfondire le modalità con cui i cambiamenti cerebrali correlassero con i reperti clinici durante la fase acuta di NV. A tal scopo, sei lavori – selezionati secondo i criteri di inclusione – sono stati analizzati al fine di rivelare quegli aspetti corticali e sottocorticali correlati ai corrispettivi clinici delle fasi acute nella NV. In conclusione la presente revisione mostra chiaramente come una UVF improvvisa sia in grado di generare un'ampia varietà di risposte corticali e sottocorticali – con cambiamenti in differenti moduli sensoriali – come risultato di una plasticità critica del sistema nervoso centrale.

PAROLE CHIAVE: *Neuronite vestibolare • Neuroimmagini • Cerebrale • Analisi di gruppo • Vertigine*

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Introduction

Vestibular neuritis (VN) is one of the most common causes of vertigo [1], and is defined as sudden unilateral labyrinthine failure, which is probably due to reactivation of latent herpes simplex virus 1 in the geniculate ganglion [2] or to other infectious diseases of the inner ear. As is known, the characteristic signs and symptoms of VN include sudden onset of severe rotational vertigo associated with horizontal rotatory peripheral vestibular spontaneous nystagmus toward the unaffected ear, postural imbalance, nausea, vomiting, emotional disturbances and no other neurologic or cochlear symptoms and findings [3]. This symptomatology can be very severe in the first few days (acute VN) due to a sudden loss of environmental landmarks determining cerebral changes [4].

Functional neuronatomy of vestibular networks

The vestibular system is based on the principle of fusion of bilateral sensors, the input of which is distributed in a bilaterally organised neuronal network [5]. The core circuitry of this network includes ocular motor function that mediates the vestibular-ocular reflex (VOR) and is imbedded in a complex multisensory system containing numerous ascending and descending pathways subserving perceptual, postural and vegetative functions as well as navigation and spatial memory [5]. Thus, vestibular input, which is fed into the VOR structures, is also fed into adjacent but separate fibres for perception and balance control [5]. As ocular motor function consists of a rapid three-neuron arc (for a more comprehensive review: see reference [5]) ascending from both labyrinths – via the vestibular nuclei – to their corresponding pair of extraocular eye muscles (for review see reference [6]), perceptual functions operate via pathways that run through the lateral and ventroposterior lateral thalamus to the multisensory cortical neural network. The latter includes, in the brain of monkey, a number of temporo-parietal cortex areas such as the strongly interconnected area 2v, area 3aV and the parieto-insular vestibular cortex (PIVC), as well as retroinsular areas, superior temporal gyrus, inferior parietal lobule [5 7-11] (Fig. 1). At this level, metabolic studies during irrigation in right- and left-handed human volunteers have shown that the handedness of subjects and the side of the stimulation affect bilateral cortical activation pattern of vestibular areas. In fact, vestibular dominance in the non-dominant hemisphere and stronger activation occurring in the hemisphere ipsilateral to the stimulated ear were found [12].

Interestingly, navigation function seems to be mediated by 'head direction cells' in the thalamus (for review see reference [13]) and 'place cells' in the hippocampus [14]. Various anatomical connections have been proposed to join the vestibular nuclei to the hippocampus [15 16]. Using functional MRI, Vitte and co-workers [17] demonstrated that vestibular caloric stimulation even activates the hippocampal formation in humans.

The postural control of head and body is mediated via the descending tracts such as the medial vestibulo-spinal tract for head position and the lateral vestibulo-spinal tract for head and body position in space [18]. Finally, vegetative functions are conveyed by pathways from the vestibular nuclei to the locus coeruleus, nucleus of the solitary tract, area postrema and the central nucleus of the amygdale [19] as well as the parabrachial nucleus, infralimbic cortex and hypothalamus [20 21].

Since neuroimaging protocols are available, many studies in the last 10 years have focused on the cortical and subcortical changes related to sudden vestibular deafferentation as in VN. However, most of these, also due to different possibilities across diverse centers, were based on different times of first acquisition from the onset of VN symptoms, neuroimaging techniques, statistical analysis and correlation with otoneurological and psychological findings.

The aim of the present review is to merge the similarities and discrepancies across studies that employed neuroimaging techniques with the purpose of better understanding brain changes and characteristic clinical features during the acute phase of VN.

Materials and methods

Study selection and inclusion/exclusion criteria

A thorough analysis on PubMed was searched using the following key words: vestibular neuritis, unilateral vestibular failure (UVF), neuroimaging, magnetic resonance imaging (MRI), positron emission tomography (PET), near infra-red spectroscopy (NIRS), single positron emission computer tomography (SPECT), voxel-based morphometry (VBM), cerebral, cortical, sub-cortical and cerebellum. Only studies written in English were selected. Studies focusing on simultaneous cochleo-vestibular, vestibular surgical de-afferentation and/or bilateral vestibular impairment were excluded as well as those not enrolling acute VN patients and not employing voxel-based analysis.

Herein, T1 will be used only to indicate acute phase of VN and T2 only for the delayed phase, even if VN subjects were only studied during the latter.

Results

A preliminary examination of the existing literature highlighted that four major neuroimaging techniques have been employed in the study of acute phase of VN: [18F] fluorodeoxyglucose (FDG) - PET/computer tomography (CT) [4 22 23], SPECT [24], VBM [25-27] and functional MRI (fMRI) [28 29].

According to the above-mentioned criteria, the studies by Alessandrini et al. [24], Helmchen et al. [26] and Zu Eulenburg et al. [25] were excluded, and the present review included 6 studies.

Moreover, all included studies [4 22 23 27-29] investigated cerebral correlates of acute and delayed phase of VN and in three [4 28 29] acute phase images were compared to both delayed and control groups (CG).

Differences in subjects, time of acquisitions from the VN symptoms onset, neuroimaging technique, statistical analysis and contingent correlations with neuropsychological and otoneurological tests are shown in Table I.

Discussion

Cortical correlates of acute and delayed VN phase

FDG-PET/CT imaging studies

Under physiological conditions, as well as in several diseases affecting the brain, glucose metabolism is tightly connected to neuronal activity. Therefore, changes in neu-

Table I. Systematic analysis of nine studies.

Study	Subjects/ Sample	Side of VN	Neuroimaging technique	T1	T2	Presence of control group	Main Oto-neurological test	Neuropsychological and clinical test	Statistical analysis/images handling	Inclusion
Bense et al. 2004	5 right-handed patients (4 male, 1 female; mean age: 64 years ± 10)	5 right VN	FDG-PET/CT	6.6 days after symptom onset	3 months after symptoms onset	None	DC-EOG, SVV, caloric testing	None	SPM99	Yes
Alessandrini et al. 2009	9 right-handed patients (4 male, 5 female; mean age: 51.6 years ±13.8)	7 left VN; 2 right VN	SPECT	72 hours after symptom onset	1 month after symptoms onset	None	ENG	None	visual evaluation by a well experienced nuclear physician	No
Helmchen et al. 2009	15 right-handed patients (8 males, 7 females; mean age: 49 ± 13.9)	4 left VN; 11 right VN	VBM	None	3 months after symptom onset	15 (8 males, 7 females; mean age: 49 ± 13.7 years)	CVS, SVDS, SVV, Caloric testing, DC-EOG	SVDS	VBM toolbox for SPM2	No
Zu Eulenburg et al. 2010	22 right-handed patients (9 females, 13 males; mean age: 56.7±10.4)	10 right VN, 12 left VN	VBM	None	2.5±1.6 years after symptomonset	Not specified in the text	Caloric testing, DC-EOG, HIT, Underberger test, VEMPs, rotatory chai test, SVV	VSS, VHQ	VBM toolbox for SPM5	No
Alessandrini et al. 2013	8 right handed patients (five females, 3 males; mean age: 48±7 years)	8 right VN	FDG-PET/CT	48±6 hours symptom onset	1 month after symptom onset	30 (16 female, 14 males; mean age 49.5±12 years)	DC-EOG	Zung Instrument, depersonalization/derealization inventory, Gomez test	SPM2	Yes
Alessandrini et al. 2014	8 right handed patients (5 females, 3 males; mean age 48±7 years)	8 right VN	FDG-PET/CT	48±6 hours symptom onset	1 month after symptom onset	None	DC-EOG, Bucket test	Zung Instrument, depersonalization/derealization inventory, Gomez test	AAL	Yes
Hong et al. 2014	9 right-handed patients (6 males, 3 females; mean age: 49.2 ± 18.1 years)	5 right VN; 4 left VN	VBM	72 hours after symptom onset	3 months after symptom onset	None	VNG, Caloric testing, rotatory chai test	K-DHI	VBM toolbox for SPM8	Yes
Helmchen et al. 2013	20 right-handed patients (11 males, 9 females; mean age: 55.1 ± 13.9)	10 right VN; 10 left VN	fMRI	72 hours after symptom onset	96.6 ± 24 days after symptom onset	20 (11 males, 9 females; mean age: 50.2 ± 11.7 years)	DC-EOG, Caloric testing, SVV, HIT, static posturography	CVS, SVDS, VADL	SPM8, ICA	Yes
Klingner et al. 2014	14 right-handed patients (6 females, 8 males; mean age: 51.1 ± 10.4 years)	7 right VN, 7 left VN	fMRI	4.9 ± 1.9 days after symptom onset	12 ± 4.6 months after symptom onset	28 age and gender matched controls (12 females, 16 males)	VNG, Caloric testing, Saccadic eye movements, smooth pursuit, optokinetic nystagmus, gaze test	None	SPM8, ICA	Yes

VN, vestibular neuritis; T1, acute phase of VN; T2, delayed phase of VN; FDG-PET/CT, [18F] fluorodeoxyglucose – positron emission tomography/computer tomography; SPECT, single positron emission computer tomography; VBM, voxel-based morphometry; fMRI, functional magnetic resonance imaging; DC-EOG, binocular electrooculography; SVV, subjective visual vertical; ENG, electronystagmography; CVS, clinical vestibular score; SVDS, subjective vestibular disability score; HIT, head impulse test; VEMPs, vestibular evoked myogenic potentials; VSS, vertigo severity score; VHQ, vertigo handicap questionnaire; K-DHI, Korean version of the dizziness handicap inventory; VNG, videonystagmography; SVDS, self-assessment of vestibular disability; VADL, self-assessment of vestibular disability in daily life; SPM, statistical parametric mapping, AAL, automated anatomical labelling, ICA, independent component analysis.

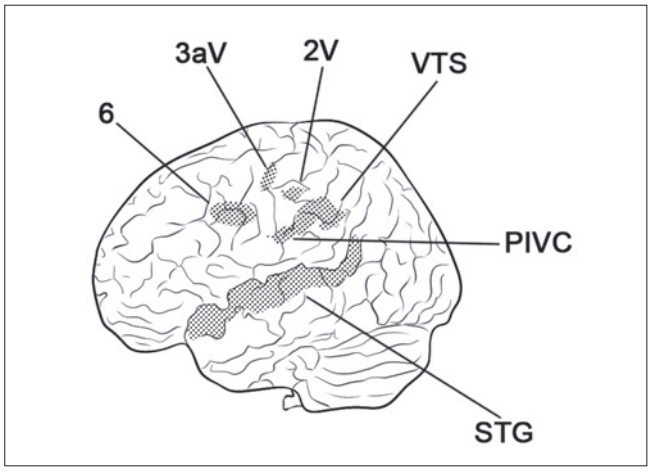

Fig. 1. Schematic drawing of a monkey brain with the neurophysiologically determined multisensory vestibular areas. PIVC, parieto-insular vestibular cortex; STG, superior temporal gyrus; VTS, visual temporal sylvian area.

ronal activity induced by disease are reflected in alteration of glucose metabolism. FDG is suitable for imaging regional cerebral glucose consumption with PET since it accumulates in brain tissue depending on facilitated transport of glucose and hexokinase-mediated phosphorylation [30].

In agreement with this assumption, the study of Bense and colleagues [22] on the acute and delayed phases of VN showed that 6 days after onset of VN symptoms unilateral regional cerebral glucose metabolism (rCGM) increases in the left PIVC, contralateral to right-sided vestibular failure. This asymmetry could be explained by assuming that the more dominant ipsilateral right-sided ascending projections to the right insular cortex are depressed by right-sided vestibular neuritis, since there is no tonic endorgan input (decreased resting discharge) [22]. Alternatively, the vestibular tonic imbalance at the vestibular nuclei level (with a higher resting discharge rate of the unaffected left vestibular nuclei complex induced by the acute right-sided vestibular failure) could mimic left-sided vestibular excitation [22]. This supposition is compatible with an activation of pontine and pontomesencephalic brainstem and left vestibular cortex areas, as well as the concurrent deactivation of the visual and somatosensory cortex areas [22]. Conversely, a bilateral rCGM decrease was found during the acute stage of VN in "secondary" multisensory vestibular cortex areas (i.e. superior temporal gyrus, inferior parietal lobule, and precuneus), appointing this metabolic pattern to cortical mechanisms that restore adequate spatial orientation by using the undisturbed visual and somatosensory input [22]. Furthermore, a bilateral rCGM decrease in visual cortex was seen, possibly indicating an effort to reduce sensory conflicts induced by nystagmic movement and a "false" primary vestibular signal [22] (Figs. 2 and 3).

Finally, some parts of "secondary" vestibular cortex areas appear to be involved in special aspects of vestibular function. In fact, the amount of spontaneous nystagmus during the acute stage of vestibular neuritis correlated positively with the increase of glucose metabolism in part of the vestibular area of the superior temporal gyrus bilaterally (Brodmann Area, BA, 22), as well as in part of an ocular motor area in the right inferior medial frontal gyrus (BA 9/44) that includes the frontal eye field [22]. The index of vestibular failure, measured as the caloric asymmetry between the affected and unaffected ears, was positively correlated with the rCGM in an area in the left inferior parietal lobule (BA 40) known to represent a multisensory vestibular cortex area involved in modulating the gain and time constant of the vestibular ocular reflex [31] (Figs. 2 and 3).

These findings were partially confirmed by another study by Alessandrini and colleagues [4] in which eight right-sided VN patients underwent FDG-PET/CT scan about 48 hours after onset of symptoms. However, rCGM increase in posterior insula was shown only when comparing acute VN subjects with the control group (Figs. 2 and 3).

In both studies, all patients suffered only from right-sided VN; images were realigned, stereotactically normalised into the standard anatomical space of Talairach and Tournoux [32] by linear and nonlinear transformation [33] and smoothed with a three-dimensional Gaussian filter using a 12 mm full-width at half-maximum kernel [4 22]. Thus, coordinates of some regions tend to mainly collimate with minimal differences in anatomical identification as for left posterior insula and right BA 11 (for in-depth analysis see the table in [4] and Tables I and II in [22]).

Moreover, the within-subject comparison between T1 and T2 in the study by Alessandrini et al. [4] highlighted for the first time a rCGM increase in the entorhinal cortex (EC; BAs 28/34; Fig. 4) and in the superior temporal gyrus (BA 38) (data also confirmed when contrasting VN subjects with CG) (Fig. 2).

In particular, the authors hypothesised that the EC activation could be ascribed to the physiological role of this region in attempting to reorganise one's orientation in space, as a response to the unexpected vestibular information alteration impairing one's orientation in space. This finding seems to be more relevant if coupled with parallel subjective balance impairments score behaviour (see Fig. 3 in reference [4]) at the early phase of vertigo.

In addition, the T1-related rCGM increase in BA38 found in VN patients (Fig. 2) was suggested as a characteristic feature of the early phase of VN that disappears as the acute symptoms fade away. Thus, it was hypothesised that this activation is the cortical representation of the common clinical emotional component related to symptoms of vertigo, supporting this with a parallel increase in the anxiety and depersonalisation/derealisation (DD) during vertigo onset. In agreement with this, the activation of BA38 was found only on the right side aligning with the

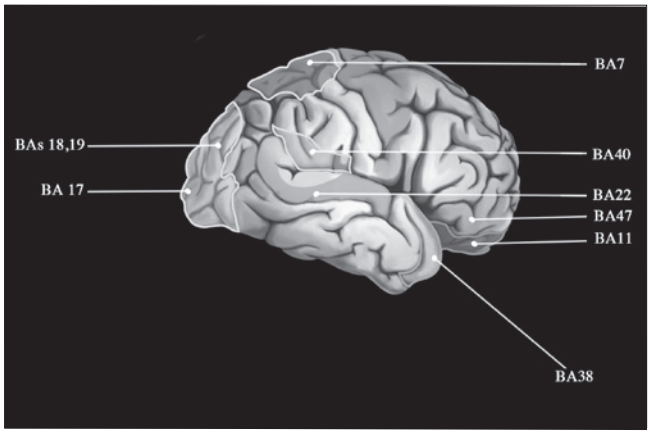

Fig. 2. 3D rendering of the brain (right hemisphere) showing, respectively, in red boundary line and orange areas the rCGM increase and decrease in T1 vs. T2 in Bense et al. [22]; in blue areas and yellow boundary lines the rCGM increase and decrease in T1 vs. T2 in Alessandrini et al. [4]; in green boundary line and violet area the rCGM increase and decrease in T1 vs. CG in Alessandrini et al. [4]. BA(s), Brodmann area(s).

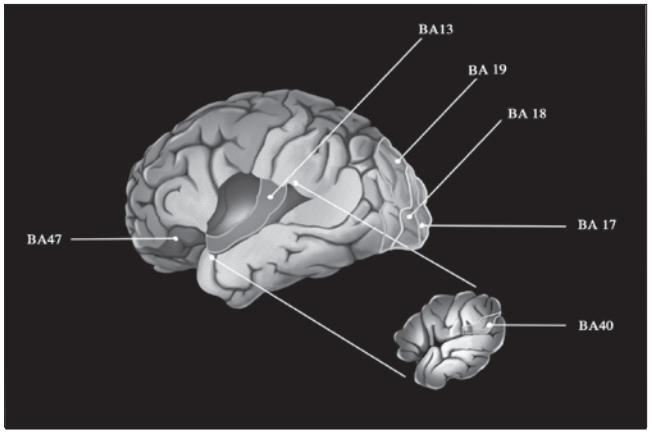

Fig. 3. 3D rendering of the brain (left hemisphere) showing, respectively, in red and orange areas the rCGM increase and decrease in T1 vs T2 in Bense et al. [22]; in yellow boundary lines the rCGM decrease in T1 vs. T2 in Alessandrini et al. [4]; in green and violet boundary lines the rCGM increase and decrease in T1 vs. CG in Alessandrini et al. [4]. BA(s), Brodmann area(s).

emotional asymmetry theory positing that the right hemisphere may be dominant over the left one in emotional processing [34 35].

Finally, the authors addressed the positive correlation (see Fig. 4A in the original text) between the hypermetabolism at T1 and the DD score in the cluster comprising the BAs 28/34, BA 38 and inferior-frontal cortices (BAs 11, 25 and 47) as an increase in the perception of depersonalisation symptoms during disease onset. Conversely, the negative correlation (see Fig. 4B in the text) found between DD, balance and anxiety and hypometabolism at T1 suggested that a freezing in the metabolism of visual (BAs 17, 18, 19) and somatosensory (BAs 5, 7) associative cortices could represent an early attempt to reduce the distressing ''false'' primary vestibular signal [22], which may be at the neural base of the increase in DD, balance and anxiety scores during disease onset.

Differences in cortical areas and laterality could be probably explained by discrepancies in the acute and delayed time of scanning phases. In fact, first and second acquisitions were set, respectively, at 6.6 days and 3 months in the study by Bense et al. [22] and 48 hours and one month in that by Alessandrini et al. [4]. Furthermore, the different choices in scanning phases gave researchers the chance to: i) better study those brain regions involved in recovery network due to the choice of deferring, in the first study, T2 phase 3 months after symptoms onset and ii) to understand, in the second protocol, those early metabolic changes involved in anxiety processing and body orientation rearrangement by anticipating T1 phase 48 hours after VN onset.

Voxel-based morphometry imaging studies

VBM is an automated technique that uses statistics to identify differences in brain anatomy between groups of subjects, which in turn can be used to infer the presence of atrophy or, less commonly, tissue expansion in subjects with disease [36]. The technique has been applied to a number of different disorders, including neurodegenerative diseases [37], movement disorders [38], epilepsy [39], multiple sclerosis [40] and schizophrenia [41], contributing to the understanding of how the brain changes in these disorders and how brain changes relate to characteristic clinical features [36].

When focusing on VN-related VBM in the study by Hong et al. [27], a preliminary review (see Table I) highlighted non-homogeneous laterality of included vestibular lesions. In fact, with respect to FDG-PET/CT studies, they did not recruit patients with the same side of VN. Thus, brain imaging data from patients with different lesion

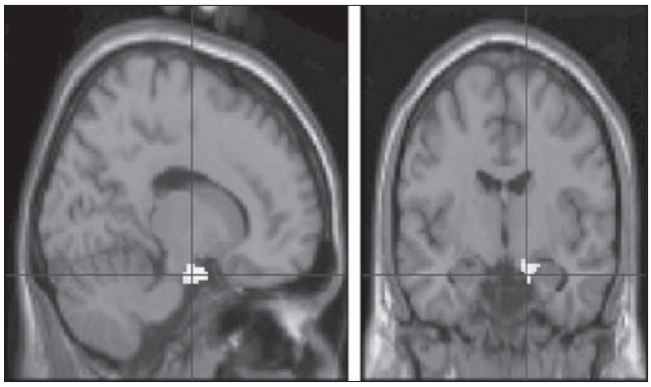

Fig. 4. T1 MRI superimposition showing the cluster of voxels in the right parahippocampal gyrus (BAs 34 and 28) in which FDG uptake was significantly higher at T1 compared to T2 (on the left sagittal and on the right coronal projections) (illustration taken from artwork in [4]).

sides were collapsed, in contrast with most previous VBM studies that artificially equalised the lesion side by flipping brain images of patients with lesions on the opposite side (e.g., flipping images of left VN patients to simulate right VN) [26 42 43]. Moreover, nine right-handed VN subjects were studied in T1 and T2 phase and the within-subject model found a significant decrease in grey matter volume (GMV) in the right superior medial gyrus, right middle orbital gyrus, cerebellar vermis and right cerebellar hemisphere in T1 compared to T2 (see Table II in the original text). However, authors focused their discussion on GMV increase related to processes involved in vestibular compensation (T2) rather than in cortical atrophy found in these regions during the acute stage. This aspect may be in line with the employed technique, which is more useful in visualising brain volume changes over the time rather than in the acute stage of disease when a paucity of cortical hypertrophy/atrophy is found.

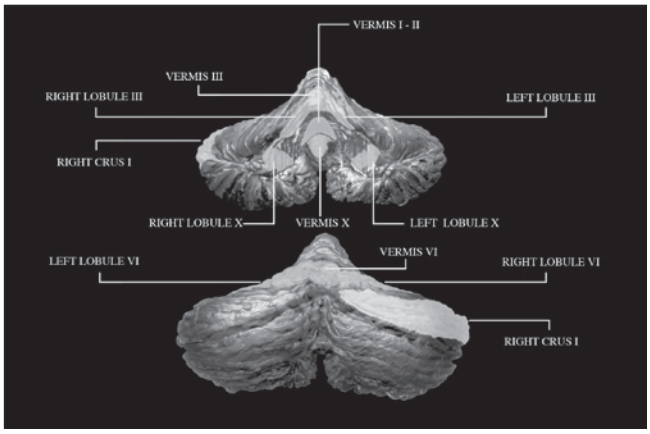

Fig. 5. 3D rendering of cerebellum showing in orange and green colours the VOIs in which FDG uptake was significantly lower and higher, respectively, at T1 compared to T2. On the top the ventral; on the bottom the dorsal cerebellar surface (illustration modified from artwork in [23]).

Sub-cortical structure involvement related to the early phase of VN

Alessandrini et al. [23] used the same VN patients of a previous study [4] to provide an exclusive cerebellar analysis of FDG uptake changes comparing T1 and T2, by using anatomical automatic labelling (AAL) structural volumes of interest (VOIs). The authors attempted to correlate these findings with those at the cortical level due to cerebellar involvement in different cerebro-cerebellar loops previously highlighted [44].

In particular, a relative hypometabolism in the early phase of VN in anterior cerebellar lobe was found, including vermis 1-2, 3 and 6, and bilateral lobule III and VI (Fig. 5). These findings were postulated to be consistent with a cortical rCGM decrease in bilateral sensory-motor and parietal cortices, suggesting the relative rCGM decrease in the anterior cerebellar lobe is associated with such hypometabolism [4]. In addition, the hypometabolism seen in the anterior cerebellar lobe was hypothesised to support a bottom-up regulation of sensory conflict during controversial inflow between optical and vestibular input, as it occurs during the early phases of VN [23]. Thus, such a behaviour was interpreted by the authors as a realignment of the relationship between sensory inputs [45] such as those coming from optical [46], proprioceptive [47 48] and vestibular [49] organs and cerebellum [50] via olivary climbing fibers [51] that could convey an erroneous signal arising from mismatch between mentioned sensory inflow.

Moreover, the study by Alessandrini et al. [23] highlighted a relative hypometabolism in the nodulus and flocculus at T1 compared to T2, suggesting a primary adaptive behaviour of these regions in response to abrupt conflicting inputs conveyed by retinal slip and vestibular loss in the early phase of VN. Curiously, the negative correlation found between metabolism in the right lobule 10 and slow phase velocity (SPV) scores highlighted a specific pivotal role of the flocculus in modulating and controlling nystagmus parameters and in adapting VOR by mediating the functional interaction between vestibular inputs and the eye movement network [52].

Finally, the study found a significant rCGM increase when comparing T1 to T2 in right crus I and a significant positive correlation between the metabolism found in this structure at VN onset and anxiety score (see Table I and Figs. 2 and 3 in the text of [23]). These data, along with anxiety/rCGM correlation findings in crus I, were interpreted to add information regarding the function of this region during the acute phase of VN and in subserving cortical emotional processing affecting the early stages of disease [23].

Hong et al. found a T1-related GMV increase (a relative T2-related GMV decrease) in cerebellar vermis and right Lobule VIIIa [27]. In line with the discussion topic of their longitudial work (see chapter 1.2 in the text above), the authors explained the former finding as the consequence of a dominance of afferent input in the cerebellar vermis (GM atrophy following loss of peripheral sensory input), which could be underpinned by those cortico-cerebellar loop previously mentioned. The latter finding was found to be related over time with a decrease in nystagmus after impulse acceleration and deceleration; GM atrophy in this area was also associated with better recovery of peripheral vestibular sense [27]. However, although speculative, authors highlighted this area functions to subserve the earliest stages of VN, and hypothesised that as peripheral vestibular function recovers, the functional contribution from this area may decrease and, subsequently, decrease GMV.

Finally, these data could be not completely conflicting as it was chosen to investigate patients in different T2 moments with a more strengthened rehabilitation protocol in

Hong et al. and by using different methods of scanning and data and imaging handling.

Functional connectivity in VN

It has been shown that brain networks known to support visual, motor, attentional, or cognitive functions show spontaneous [53] and anticorrelated fluctuations [54] even without a specific task. In fact, large-amplitude spontaneous low-frequency (0.1 Hz) fluctuations in blood-oxygen-level dependent (BOLD) signal, investigated by fMRI, are temporally correlated across functionally related areas [55]. By using these methods, many authors have attempted to identify changes in functional connectivity within neural networks [56 57] with the basic idea that spontaneous fluctuations in brain activity during rest reflect the interconnectivity of brain areas necessary to accommodate highly diverse processing demands. Indeed, using resting state analysis it has been shown that the brain is organised into ''dynamic, anticorrelated functional networks'' [54].

According to these aspects, Helmchen and colleagues [28] evaluated the BOLD signal changes in 20 right-handed VN patients with acute VN at T1 (within 3 days from symptom onset) and 3 months later (T2). In addition, they compared T1 brain images both with T2 phase and an age- and sex-matched CG. For patients with right peripheral vestibular failure, the smoothed images were mirrored along the y axis so that the left side was the lesion side for all patients. They performed two statistical analyses, an independent component analysis (ICA) and a region-of-interest analysis based on the local-to-global ratio. A similar fMRI approach was recently adopted by Klingner et al. [28] in order to discover the inter-network functional connectivity changes in 14 patients during the early (mean: 4.9 ± 1.9 days after onset of symptoms) and delayed (mean: 12 ± 4.6 months) phase of VN.

In the former study, one component (''component 50'') showed significant between-group changes in resting-state activity at T1. This component revealed a functional network of the parietal lobe, medial aspect of the superior parietal lobule, posterior cingulate cortex, middle frontal gyrus, middle temporal gyrus, parahippocampal gyrus, anterior cingulate cortex, insular cortex, caudate nucleus, thalamus and midbrain. VN patients at T1 showed decreased resting-state activity in the contralateral intraparietal sulcus (IPS) in close vicinity to the rostro-dorsal aspect of the IPL, i.e. the supramarginal gyrus (SMG), compared with CG. When the two measurements of the patients were compared, a change in resting-state activity in the same region became apparent indicating normalisation of resting-state activity in patients over time.

While the network revealed by component 50 in that study likely supports multiple functions, it is interesting to note that several of the implied areas have been shown to process vestibular signals (see review in [5]). Within this neural network, significant differences between patients and controls were found in IPS contralateral to the vestibular lesion.

The IPS [58] extends ventrally to the parietal operculum, including the parietal opercular area OP2, which has recently been identified as the core region for vestibular processing in humans [59], and therefore suggested to be the human equivalent to the PIVC previously described in monkey [60]. This findings – and subsequent seed-based functional connectivity analysis based on resting-state oscillations [59] – led some authors to suggest that the IPL is a cortical multisensory integration area [59].

Moreover, in VN patients of this study the IPS coordinates of reduced resting-state activity overlapped with the ventral intraparietal area (VIP) contained in its fundus, the neuronal responses of which are more strongly influenced by vestibular than visual inputs [61] and are strongly linked to heading, which make them well equipped to play a role in multisensory integration for heading perception [62].

In addition, effective connectivity analysis has shown a role of the IPS for memory retrieval [63]. The SMG along the IPS, which also showed changes of resting-state activity in patients in that study, is critical for mediating spatial working memory and shifts in spatial attention [64]. This is of interest as the IPS is linked to the hippocampal formation [65], and reduced resting-state activity in IPS might also influence hippocampal and parahippocampal function. Thus, it was speculated that reduced vestibular input [66] leads to changes of resting-state activity in IPS, which in turn may trigger adaptive hippocampal reorganisation and impairment in navigational and spatial orientation tasks.

However, VN patients might suffer from impaired spatial navigation which has been shown for bilateral [67], but not unilateral nor surgical vestibular nerve deafferentation [68]. Furthermore, lesion studies in humans have provided evidence for a cortical influence on vestibular function in the context of spatial representation [31]. In line with these studies and findings from PET and neuropsychological investigations [4 69], one might speculate that the reduction of resting-state activity in the IPS and adjacent SMG in the acute stage of VN patients could be related to impaired spatial orientation, i.e. by deficient spatial working memory or spatial attention [64].

In the latter study, Klingner et al. [29] found decreased inter-network connectivity in T1 compared to T2 (after complete clinical remission of symptoms) between the "default mode" network (DMN) and multiple other networks such as the somatosensory cortex, auditory/vestibular/insular cortex, motor cortex, occipital cortex and left and right fronto-parietal cortex (FPC). By comparing the first measurement in T1 with the group of healthy control subjects, the same areas (except the occipital cortex) showed decreased connectedness to the DMN (Fig. 1 in the original text). It is generally agreed that the brain is composed of two spatially distinct functional networks: the DMN and "task-positive" network

(TPN) [54 70 71]. During performance of attention-demanding tasks, prefrontal and parietal structures that comprise the task-positive network are characterised by increased activity; in contrast, the DMN, including the posterior cingulate and medial prefrontal cortices, is characterised by decreased activity. During wakeful rest, the opposite pattern emerges [54 70-72].

The reduced connectivity between these two networks was suggested to be related to the diverging information arising in the resting condition from vestibular, spontaneous eye movements and other sensory modalities [29]. The attempt to integrate this conflicting information requires significantly greater capacity for the processing information about spatial orientation and brings sensory information processing to our attention, which is normally an automated process that does not require attentional demand [29]. These mechanisms are reflected by increased activity within brain areas responsible for processing of vestibular information and integration of multisensory information [22]. The sustained increased activity in parts of the TPN and the attentional demand reduce the activity within the DMN. In turn, the DMN compensates by decreasing the amount of information that is received from the task positive network, leading to decreased connectedness [29]. Furthermore, the involvement of the DMN in this pathology is further supported by findings of difficulties with cognitive skills such as reading, arithmetic and concentration suggesting a decreased ability to engage the task positive networks [73].

Final overview

The vestibulo-cortical system, which includes the PIVC activated by vestibular stimulation, is composed of multisensory cortical networks connected with other cortical and subcortical processing areas, including oculomotor, somatosensory, visual areas and cerebellar sub-regions.

The present review clearly reveals that sudden UVF may induce a wide variety of cortical intersensory responses, with changes in different, sensory modules as a result of acute plasticity in the central nervous system.

Interestingly, during the acute phase of disease perfusional and metabolic studies demonstrated such rCGM changes in the so-called "vestibular cortex", decreased resting-state activity in the contralateral IPS – close to the human equivalent of PIVC – and a decreased inter-network connectivity between the DMN and multiple other networks. Simultaneously, a neural cascade of acute plasticity related events was found in the visual and multisensory cortex as well as in those areas (enthorinal, SMG) involved in spatial navigation.

Overall, findings from imaging and neuropsychological studies can disclose two side of the same coin for which the acute dissociation of sensory inflow was pinpointed, highlighting phenomena of emotional and orientation impairment.

Finally, we hope the present review can serve as a framework of the intricate puzzle represented by multi-scale brain changes involved in the acute phases of VN and can provide additional considerations for future acute VN studies.

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