Voxel-Based Morphometry Depicts Central Compensation after Vestibular Neuritis

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Objective: Patients who have had vestibular neuritis (VN) show a remarkable clinical improvement especially in gait and posture >6 months after disease onset.
Methods: Voxel-based morphometry was used to detect the VN-induced changes in gray and white matter by means of structural magnetic resonance imaging. Twenty-two patients were compared an average 2.5 years after onset of VN to a healthy sex-and age-matched control group.
Results: Our analysis revealed that all patients had signal intensity increases for gray matter in the medial vestibular nuclei and the right gracile nucleus and for white matter in the area of the pontine commissural vestibular fibers. A relative atrophy was observed in the left posterior hippocampus and the right superior temporal gyrus. Patients with a residual canal paresis also showed an increase of gray matter in middle temporal (MT)/V5 bilaterally.
Interpretation: These findings indicate that the processes of central compensation after VN seem to occur in 3 different sensory systems. First of all, the vestibular system itself showed a white matter increase in the commissural fibers as a direct consequence of an increased internuclei vestibular crosstalk of the medial vestibular nuclei. Second, to regain postural stability, there was a shift to the somatosensory system due to an elevated processing of proprioceptive information in the right gracile nucleus. Third, there was a bilateral increase in the area of MT/V5 in VN patients with a residual peripheral vestibular hypofunction. This seems to be the result of an increased importance of visual motion processing.

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Vestibular neuritis (VN) is a sudden, usually partial, unilateral failure of the vestibular nerve that impairs communication between the peripheral vestibular organs and the central vestibular nuclei.[1] VN is probably due to a reactivation of herpes simplex virus 1 in the geniculate ganglion or other infectious diseases of the inner ear.[2] Because normal vestibular function depends on continuous bilateral input, an abrupt unilateral peripheral failure leads to an immediate direction-specific imbalance of the bilateral vestibular tone. This causes the following key symptoms: contralateral spontaneous nystagmus (fast phase toward the healthy ear), pathological ipsilateral vestibular ocular reflex (VOR), and postural instability with a tendency to ipsilesional falls along with very disabling autonomic side effects (nausea, vomiting).[3] The patient is usually bedridden for several days. However, despite the abrupt onset of the disease and its disabling character, most patients show a quick recovery and a remarkable clinical outcome <6 months later.[4] The long-term clinical outcome (not of course the response of the ipsilesional VOR) seems to be independent of the actual residual function of the nerve and more a direct result and consequence of the central compensation achieved by the amount of physical training with postural exercises.[5]

Imaging research in VN at first applied positron emission tomography to detect functional responses of patients in the acute stage of the disease compared to their state after recovery.[6] The aim of the current study was to

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analyze by means of voxel-based morphometry (VBM) the structural morphological central nervous system changes involved in central compensation following VN. This kind of analysis after structural magnetic resonance imaging (MRI) is a fairly novel approach in functional neuroscience. The method permits the quantification and localization of changes in the brain through disease and aging. The actual anatomical substrate still remains unclear. It has also been used to demonstrate learning-induced structural plasticity in early and late adulthood.[7,8] Functional imaging studies during vestibular stimulation in healthy volunteers have shown that balance per se and orientation in space are achieved by a multisensory network in the temporoparietal cortex of both hemispheres and that the different sensory systems interact.[9–12]

We addressed the following questions. Could some of the observed changes explain or depict some of the interconnecting sensory pathways that are responsible for the remarkable clinical outcome in our patients? What does central vestibular compensation entail after a unilateral peripheral vestibular dysfunction? So far the basis of the mechanism behind this process of central vestibular compensation is not well established in humans. Which changes, on the other hand, can be seen as distant effects after a vestibular neuritis and are probably the result of a still reduced total amount of peripheral vestibular input due to the disease? Thus, the following questions were of special interest.

- Which brain areas are involved in the process of central compensation after acute peripheral vestibular loss due to VN?
- Do these areas belong solely to the vestibular system or also to other sensory systems such as the visual and somatosensory systems?
- Are these processes dependent on the amount of functional peripheral vestibular loss as measured by neuro-otological testing or do the observed changes correlate with other clinical data of the individual patient?

Subjects and Methods

A total of 22 patients (9 females, 13 males, average age 56.7±10.4 years) who had been confirmed to have unilateral VN (10 right-sided, 12 left-sided) participated >6 months after disease onset (mean 2.5±1.6 years). The modified laterality quotient of handedness and footedness according to the 14-item inventory of the Edinburgh test[13] was determined, because differential effects within the vestibular system due to hemispheric dominance had to be considered.[14] All patients were in fact right-handed and right-footed. The participants were not on any medication other than drugs for hypertension (n = 3) and/or antiplatelet agents (n = 4). Two patients had previously had a minor myocardial infarction; none had suffered a stroke or had a history of cancer. All patients had been treated for vestibular neuritis according to the guidelines of the German Neurological Society in 2005: they had received steroids in tapered dosages for 10 days and had been asked to perform vestibular exercises during the first month until they felt stable again. During the acute stage of the disease, all patients had had a cranial MRI including diffusion-weighted imaging to eliminate the possibility of a lesion in the brainstem or cerebellum mimicking a VN. We did not have to exclude any subjects due to silent lesions of the central nervous system. This study was carried out in accordance with the Helsinki Declaration and was approved by the local ethics committee. We followed the guidelines and principles for reporting VBM studies recently proposed by Ridgway and colleagues.[15]

Neurological and Neuro-otological Examinations

The diagnosis of VN was based on the acute occurrence of the characteristic signs and symptoms, a careful neurological and neuro-otological examination, and an acute canal paresis detected by caloric irrigation of the horizontal semicircular canal during the electro-oculography. Canal paresis was defined as a significant side difference or reduced response according to the formula by Honrubia.[16]

All patients underwent detailed systematic diagnostic procedures during the acute stage of the disease and the follow-up consisting of neurological and neuro-otological examinations including positioning maneuvers, the Underberger stepping test (stepping on place twice for 30 seconds with the eyes closed and arms held forward parallel to the ground), examination with Frenzel glasses, the head-shaking test, and the Halmagyi-Curthoys head-impulse test. Moreover, to detect residual tonic vestibular disorders, fundus photographs, vestibular evoked myogenic potentials (VEMPs), and the average of 6 adjustments of the subjective visual vertical (SVV) under static and dynamic conditions (with a rotating visual background) were used to measure macular dysfunction, as well as binocular electro-oculography, including bithermal caloric and rotatory chair testing to measure semicircular canal dysfunction. All patients filled out the Vertigo Severity Score (VSS) for anxiety and depression and the Vertigo Handicap Questionnaire (VHQ) during the acute stage of the disease and the follow-up.

MRI Acquisition and VBM Data Analysis

A high-resolution sagittal T1-weighted image (MPRAGE sequence; 180 slices; isotropic resolution; slice thickness, 1mm; image matrix, 256^2; TR, 9.7 milliseconds; TE, 4 milliseconds) was obtained for each patient at least 6 months after disease onset as well as for his or her age-and sex-matched control subject in a clinical 1.5T scanner with a circularly polarized head coil (MAGNETOM Vision, Siemens, Erlangen, Germany). The principle of an age-matched control group is a routine approach in VBM.[17,18] After checking for sample homogeneity over all images, a statistical analysis was performed using a workstation running MATLAB 7.4 (The MathWorks, Natick, MA), SPM5

Software (Wellcome Department of Imaging Neuroscience, London, UK), and the additional VBM 5 toolbox by Christian Gaser (Department of Psychiatry, University of Jena, Jena, Germany). Only subjects whose images showed no morphological abnormalities or artifacts on visual inspection were included. Preprocessing of the data involved spatial normalization, unified segmentation, modulation, smoothing using a Gaussian kernel of 8mm, and the application of a Hidden Markov Random Field model.[19–21] Voxel-by-voxel *t* tests using the general linear model were performed to detect regionally specific gray and white matter differences between the groups. Paired *t* tests with the age-and sex-matched controls were performed using only the normalized and modulated images of the segmented gray and white matter. By this means, differences in signal intensities in the modulated images represent underlying volumetric differences. The resulting statistical parametric maps were thresholded at $p < 0.001$ uncorrected, and with a small volume correction of $p < 0.05$ corrected to detect morphological changes within the previously stated sensory systems of interest. Only clusters with >15 voxels were considered significant. Anatomical localizations of the results were determined using anatomical landmarks and the software and parcellation described by Tzourio-Mazoyer and coworkers.[22] For middle temporal (MT)/V5 and medial superior temporal area, the anatomical landmarks in the works of Smith and Seiffert were used.[23,24] Cerebellar structures were named according to Schmahmann et al.[25]

Results

Clinical Data at Follow-up

The static SVV showed a pathological ipsilateral tilt >3° in 4 patients >6 months after VN (for more details including the results of the electrophysiological examinations of the acute stage, see the Supplemental Data Table). Six patients showed a pathological side difference in the dynamic SVV >10°. Twelve patients had a partial residual canal paresis in the electronystagmography during caloric irrigation in the follow-up examination; 5 showed no response at all. Only 1 patient showed a pathological result in VEMPs and only at disease onset. All other VN patients showed no sign of involvement of the inferior branch of the vestibular nerve in the course of the disease. Results for both vertigo scores had returned to baseline >6 months after disease onset. The results for the VSS-Anxiety score went from 11.35 ± 2.31 to 1.6 ± 1.1 during follow-up in our patients and that for the VSS-Severity from 16.42 ± 2.59 to 1.6 ± 0.94. The VHQ declined from 26.42 ± 4.64 during the acute stages of the disease to 2.3 ± 3.86 after more than half a year.

VBM: Patients with Vestibular Neuritis versus Matched Healthy Controls

After at least 6 months following unilateral VN, signal intensities for gray and white matter significantly increased in the medial vestibular nuclei and the adjacent pontine commissural junction bilaterally and in the right gracile nucleus (Fig 1, Table,). Decreases in gray matter intensities were seen in the left posterior hippocampus, the right superior frontal gyrus (Brodmann area [BA] 6) (Fig 2), and the right superior temporal gyrus (BA 22, 42). The VN patients also showed increased white matter signals in the region of the commissural vestibular fibers of the pontine brainstem and decreased signal intensities dorsally to the observed gray matter increases of the medial vestibular nuclei. Restriction of the analysis to VN patients with a residual canal paresis revealed a significant increase in gray matter in the area of MT/V5 bilaterally, with preponderance in the right hemisphere (Fig 3).

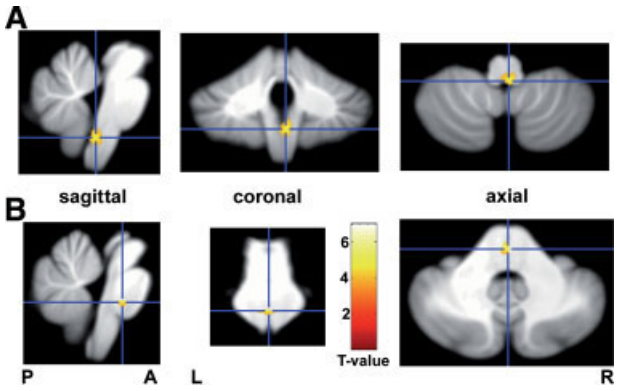

FIGURE 1: (A) Gray matter signal increases of the right gracile nucleus in patients after vestibular neuritis. (B) White matter signal increases in the area of the commissural vestibular fibers in the pons projected onto a brainstem template. Both results illustrate the mechanisms responsible for the profound central vestibular compensation in these patients. P = posterior; A = anterior; L = left; R = right.

VBM: Patients with Right-versus Left-Sided Vestibular Neuritis

A comparison of VN patients with a lesion on the left side with VN patients with a lesion on the right side (VNR) revealed no significant difference in gray matter in our follow-up study. An analysis of the white matter showed signal increases for the patients with right-sided VN in the dorsal left middle temporal gyrus (MT/V5) and in the right middle temporal gyrus (MT/V5) for the left-sided patients. VNR patients tested against their respective controls exhibited a gray matter increase in the MT/V5 bilaterally, but more so in the left hemisphere when only the cluster size was considered.

VBM: Correlation Analyses

The VN patients with a residual semicircular canal paralysis (measured by caloric irrigation) showed a significant, negative correlation for the results of the dynamic SVV with the area of MT/V5 bilaterally and the right semilu-

TABLE: Listing of All Gray and White Matter Signal Changes in VN Patients Compared to a Group of Healthy Age-and Sex-Matched Controls as Well as the Results of the Correlation Analysis

T-Contrast	Brain Area	BA	x, y, z	Cluster Size	*t* Value
Results of group comparisons					
VN patients vs healthy controls					
Gray matter intensities increase	Medial vestibular nucleus bilaterally		−1, −29, −41	78	4.54
	Right gracile nucleus		4, −44, −56	305	4.47
Gray matter intensities decrease	Right superior frontal gyrus	6	19, −2, 70	171	5.2
	Right superior temporal gyrus	22, 42		33	4.55
	Left posterior hippocampus	29	71, −23, 4	80	4.33
White matter increases	Vestibular commissural fibers		5, −46, −55	400	4.88
White matter decreases	Pontomesencephale haube				
VNR vs VNL patients					
White matter increases	Right middle temporal gyrus (MT/V5)		42, −66, 11	65	4.24
	Left inferior parietal lobule	13	−47, −43, 19	92	4.2
White matter decreases	Left middle temporal gyrus (MT/V5)		−32,− 83, 10	72	4.77
VNR patients vs controls					
Gray matter increases	Left middle temporal gyrus (MT/V5)		−35, −79, 9	241	12.89
	Right middle temporal gyrus (MT/V5)		43, −70, 15	141	14.06
White matter decreases	Left precuneus and superior parietal lobule	7	−27, −53, 49	218	7.48
Correlation analysis					
Positive gray matter correlation with duration and degree of canal paresis	Left inferior cerebellar vermis		−8, −55, −56	179	4.67
Negative gray matter correlation with results of dynamic SVV	Left middle temporal gyrus	39	−43, −68, 26	78	4.35
	Right middle temporal and supramarginal gyrus	39, 40	51, −53, 25	198	4.53
	Right posterior cerebellar semilunar lobe		42, −46, −43	312	4.73

$p < 0.001$; cluster size >15 voxels.
VN = vestibular neuritis; BA = Brodmann area; VNR = VN with lesion on right side; VNL = VN with lesion on left side; SVV = subjective visual vertical.

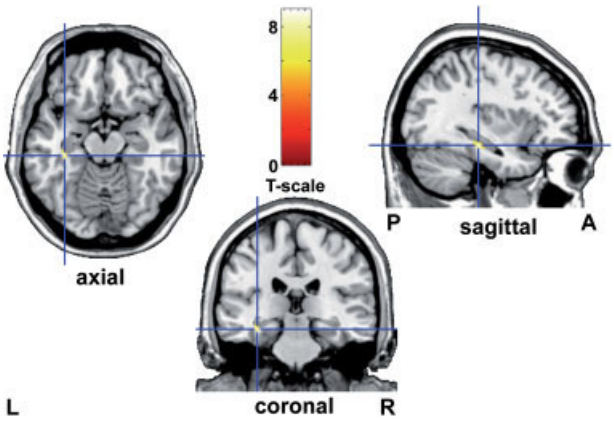

FIGURE 2: A comparison of healthy age-and sex-matched control subjects showed that in the course of vestibular neuritis, the patients exhibit a relative atrophy in the left posterior hippocampus. This finding might indicate an impairment of the memory for orientation in space and navigation. P = posterior; A = anterior; L = left; R = right.

nar lobe of the cerebellum. This means that a larger deviation of the SVV corresponded to less gray matter in MT/V5. There were no significant results for the static SVV, the ipsilateral amplitude of VEMPs, or the pathological side difference after caloric irrigation during electro-oculography, neither with the data from the disease onset nor from the follow-up examination. There was a positive correlation when the duration since disease onset and the degree of residual canal paresis and gray matter intensities in the left inferior cerebellar vermis were compared for all patients.

A methodological control analysis with the parameter age was also performed for all subjects. The result of this negative correlation with gray matter substance can be viewed online in the Supplemental Data.

Discussion

The VBM analysis of all VN patients in a follow-up after >6 months since disease onset (mean 2.5 ± 1.6 years) provided the first evidence that areas in the medial vestibular nuclei and the corresponding commissural fibers in the pontine brainstem as well as in the right gracile nucleus showed volumetric increases. We interpret the increases within the multisensory vestibular network and other sensory systems to be due to the process of central compensation. Signal decreases, conversely, were found in the left posterior hippocampus, the right superior frontal gyrus, and the right superior temporal gyrus. These decreases are probably a result of the still permanently reduced cortical vestibular input after a VN and may reflect the limitations and boundaries of the process of central compensation. Patients with permanently impaired function of the horizontal semicircular canals (detected by caloric irrigation) had increased gray matter in the MT/V5 bilaterally in addition to the aforementioned signal changes. All of these areas belong to a network of the multisensory vestibular (medial vestibular nuclei, posterior hippocampus, superior temporal gyrus) as well as the visual (MT/V5) and somatosensory (gracile nucleus) systems. Such modulations confirm the assumption that central compensation after a unilateral peripheral vestibular nerve deficit is achieved over time due to plasticity in several sensory systems and as a result of the close interaction between these different sensory networks involved in the orientation of the head and body in space. Different processes take place at different sites within 1 sensory system, here the multisensory vestibular system, and cause different volumetric consequences. Whereas the medial vestibular nuclei in the medullary brainstem—the first integration center behind the affected vestibular nerve—show a significant bilateral gray matter increase, the superior temporal gyrus and the posterior hippocampus simultaneously show significant decreases.

Increased Crosstalk between the Vestibular Nuclei

The commissural fibers, which showed a significant signal increase in all of our VN patients independently of the side of the lesion, have been the focus of central vestibular compensation since the early works of Wolfgang Precht in hemilabyrinthectomized cats in 1966.[26,27] He demonstrated that an adaptive change in inhibitory potentials from type II vestibular neurons passes through these com-

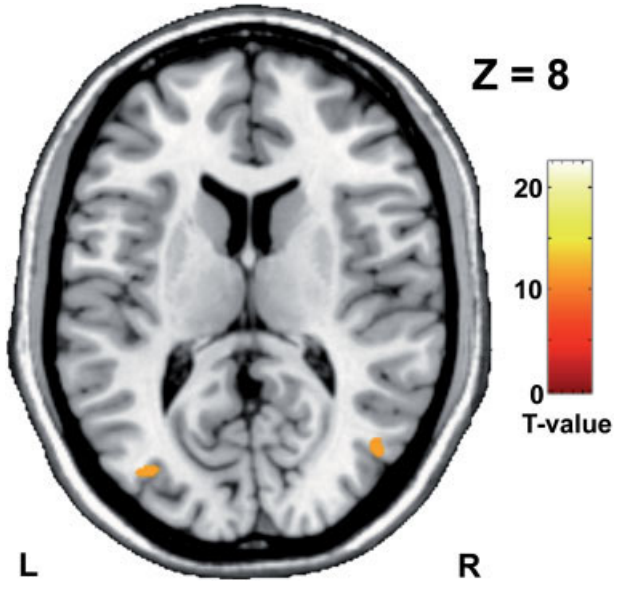

FIGURE 3: Vestibular neuritis patients (n = 14) with a residual canal paresis show a significant increase in the gray matter of middle temporal/V5 bilaterally >2 years after onset. L = left; R = right.

missural fibers to the contralateral vestibular nuclei in the process of central adaption following a unilateral peripheral vestibular loss. After a period of about 40 days, he could not differentiate the field potentials in the vestibular nuclei of a healthy animal from those of a labyrinthectomized cat. In 1 of his later works, Precht proposed that a modification of the synaptic activity and efficacy of the crossed and uncrossed inhibition and excitation via the commissural fibers was the basis of central vestibular compensation in different species.[28] The role of the brainstem commissural pathway in unilateral vestibular hypofunction or loss was further solidified in cats and rats.[29–34] Recently, Bergquist and coworkers showed in mice that elevated levels of gamma-aminobutyric acid in the medial vestibular nuclei ipsilateral to the peripheral vestibular lesion might be the cause for the changes in the firing rate of inhibitory type II vestibular neurons across the commissural pathway.[35,36] Our VBM results in VN patients seem to agree with these animal experiments, because the changes in signal intensity represent either a sprouting or an increased metabolic activity of the inhibitory fibers to the contralateral medial vestibular nucleus. The ipsilateral ascending pathways of the unaffected side of patients with an acute unilateral vestibular loss could take part in the relaying of vestibular information to the cortical level.

Atrophy after a Vestibular Neuritis

The loss or reduction of sensory function obviously leads to a volume reduction in some areas within the affected system, for example, vestibular cortex areas such as the left posterior hippocampus and the right superior temporal gyrus. We consider these changes to be effects possibly due to a reduction of the total amount of vestibular input after an incident of VN. The asymmetric findings with respect to right hemisphere suggest that it plays a leading role in the processing of vestibular information, and thus are the first to show a relative atrophy in VN patients, probably due to a permanently reduced or altered vestibular input despite the remarkable process of central compensation.[14] The superior temporal gyrus is an important area within the vestibular network and closely connected to the multisensory parietoinsular cortex, the core region and integration center of the network.[9,10,37,38] The right superior temporal gyrus in particular shows a strong response in this array to all available forms of vestibular activation (galvanic, caloric, and otolith stimulation).[9,38,39] Although its specific role within this network is still being investigated, it seems to be involved in the processing of the coordination of the eyes, head, and body in space.[40]

The posterior hippocampus also belongs to this vestibular network and plays an important role in spatial memory processes and navigation.[41–44] A decrease of volume in this area appears to be the consequence of reduced vestibular input to the cortical areas connected upstream. This has been documented by manual volumetric imaging techniques in patients with bilateral peripheral vestibular failure, thus giving an example for a group of patients with an almost complete reduction in cortical vestibular input.[45] The activation pattern of the multisensory vestibular cortex areas as well as the deactivation pattern of the visual cortex areas were both significantly diminished during vestibular caloric stimulation compared to that of healthy volunteers.[46] This atrophy in patients with a highly selective, reduced sensory input may represent the other side of the coin of cortical plasticity, when compared to normal subjects who have gray matter volume increases in the hippocampus or MT/V5 in response to specific environmental navigational demands (eg, taxi drivers) or train specific processes (eg, juggling, golf).[8,47,48] The relative atrophy, possible due to a reduced inflow of vestibular information, also shows that the process of central compensation certainly cannot alleviate all aspects of a peripheral vestibular disease.

Shift to Other Sensory Systems

Our data give evidence for volumetric increases in the gracile nucleus and in the area of MT/V5 bilaterally, especially when the function of the vestibular nerve is strongly and permanently impaired. These effects were associated with volumetric decreases in the posterior hippocampus and the superior temporal gyrus. Thus, increases within the somatosensory and visual systems are accompanied by decreases in areas of the multisensory vestibular system, and therefore a shift of sensory function occurs toward the visual and somatosensory systems when the peripheral vestibular system undergoes a substantial loss of function. This shift to the other sensory systems is a well-known compensatory strategy of substitution within the central nervous system. It was described earlier by several psychophysical and neurophysiological data and more recently also by functional imaging data. Psychophysical and neurophysiological tests have provided various examples of sensory loss, in which one modality is substituted by increased functional sensitivity of other modalities.[49] Especially the data of patients with bilateral vestibular loss indicate that the somatosensory system (eg, the cervico-ocular reflex) is involved rather than the visual system. Under purely somatosensory stimulation conditions, that is, with limb movements, patients with bilateral vestibular failure exhibited significantly higher gains of cervico-ocular reflexes and characteristic abnormalities of arthrokinetic nystagmus than did controls.[50,51] Thus,

somatic afferent information receives greater sensory weight.

Whereas the gain of the cervico-ocular reflex is low in normal subjects, its importance is significantly enhanced in patients with bilateral vestibular failure.[52,53] Visual information, however, can greatly modify this gain.[54] Body sway with eyes open in patients lacking 1 or both labyrinths showed a significant and gradual improvement over a 29-month period, much more so than with eyes closed.[55] These findings in humans agree with earlier neurophysiological data in monkeys: physical exercise under visual control accelerated compensation after unilateral labyrinthectomy.[56] More recent studies have shown that further substitution of missing vestibular input is achieved by refixation saccades and enhanced smooth pursuit eye movements as well as by auditory feedback.[57–59] All these effects are transient and reversible, if the function of the sensory organ is restored or regained. They persist if the vestibular failure persists, more so in bilateral than in unilateral loss. In our study, the volumetric effects were also stronger when the vestibular deficit was stronger and persistent. Thus, afferent somatosensory as well as visual information assumes a greater sensory weight when the vestibular deficits are compensated by such substitution.

Recently, an functional MRI study of patients with a chronic bilateral vestibular failure reported that activations were enhanced in the visual and ocular motor systems bilaterally during visual optokinetic stimulation.[60] This finding suggests that these enhanced activations might be correlated with an upregulation of visual sensitivity, and gives the first evidence by imaging techniques for cortical visual substitution of chronic bilateral vestibular failure. Our current data are in line with this concept of cortical sensory substitution and show the volumetric consequences of such central compensatory processes in the different sensory systems: the vestibular, visual, and somatosensory systems.

Dynamic SVV and the Role of MT/V5

The analysis revealed a significant negative correlation with the size of MT/V5 in the VN patients for the dynamic SVV. In this stimulation condition, the visual input acquired more sensorial weight over time, thus also demonstrating the shift in motion processing toward the visual system. This means that an abnormal test result for the dynamic (not the static) SVV goes hand in hand with an increase in MT/V5 in our patients. The increase in MT/V5 represents the substitutional compensatory process within the visual system for a reduced vestibular input. After VN, there is probably a shift in motion processing toward the visual system. This may lead to an acquired inability to suppress artificial visual motion like that in the otherwise static setting of a dynamic SVV, a fact that is often reported by patients who watch a large moving scene (train, television).

Interestingly, the increase in MT/V5 was mostly in the area contralateral to the lesion in VN. This might be due to the fact that the acute loss of vestibular input of 1 ear leads to an imbalance between the vestibular nuclei, with the result that the unaffected, contralateral side is more active. Because the ipsilateral pathways are more dominant, the ascending fibers of the unaffected contralateral pathways transfer more information to the multisensory vestibular cortex areas into the contralateral hemisphere.[6] These temporoparietal areas are in close contact with the MT/V5 of the same contralateral hemisphere.

In conclusion, our data clearly show that a simple unilateral cranial nerve lesion can induce a widespread variety of cortical intersensory responses, with gray and white matter changes in different sensory modules as a result of plasticity in the central nervous system. Another approach, such as acquiring several MRIs of the patient over the course of his rehabilitation, might have been even more revealing. The detected morphological alterations, which we interpret to be modifications of intersensory interactions between the vestibular, the somatosensory, and the visual systems, also underline the importance of an intact vestibular system for orientation in space. Our results demonstrate the amount of central nervous system reprocessing and retuning needed to compensate a relatively small but strategic peripheral vestibular lesion.

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Potential Conflicts of Interest

Nothing to report.

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