


ORIGINAL ARTICLE

Reorganization of sensory networks after subcortical vestibular infarcts: A longitudinal symptom-related voxel-based morphometry study

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Abstract

Background and purpose: We aimed to delineate common principles of reorganization after infarcts of the subcortical vestibular circuitry related to the clinical symptomatology. Our hypothesis was that the recovery of specific symptoms is associated with changes in distinct regions within the core vestibular, somatosensory, and visual cortical and subcortical networks.

Methods: We used voxel- and surface-based morphometry to investigate structural reorganization of subcortical and cortical brain areas in 42 patients with a unilateral, subcortical infarct with vestibular and ocular motor deficits in the acute phase. The patients received structural neuroimaging and clinical monitoring twice (acute phase and after 6 months) to detect within-subject changes over time.

Results: In patients with vestibular signs such as tilts of the subjective visual vertical (SVV) and ocular torsion in the acute phase, significant volumetric increases in the superficial white matter around the parieto-opercular (retro-)insular vestibular cortex (PIVC) were found at follow-up. In patients with SVV tilts, spontaneous nystagmus, and rotatory vertigo in the acute phase, gray matter volume decreases were located in the cerebellum and

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the visual cortex bilaterally at follow-up. Patients with saccade pathology demonstrated volumetric decreases in cerebellar, thalamic, and cortical centers for ocular motor control. **Conclusions:** The findings support the role of the PIVC as the key hub for vestibular processing and reorganization. The volumetric decreases represent the reciprocal interaction of the vestibular, visual, and ocular motor systems during self-location and egomotion detection. A modulation in vestibular and ocular motor as well as visual networks was induced independently of the vestibular lesion site.

KEYWORDS

compensation, PIVC, SBM, stroke, VBM, vestibular network

INTRODUCTION

Ischemic infarcts that affect the central vestibular and ocular motor pathways lead to disabling vertigo or dizziness, and imbalance of stance and gait, partly with double vision and falls. A gradient of decreasing symptom severity and a change of symptom character (from rotational vertigo to swaying dizziness and unsteadiness) can be observed after infarcts in the upper brainstem, the thalamus, and the vestibular cortical areas [1,2]. This can be explained by the sensory integration of vestibular signals that is used (i) to transform the vestibular head velocity to a head position signal; and (ii) to integrate head and trunk position to compute and supply reference frames for ocular motor control, for egomotion processing including self-location for spatial orientation, and for spatial cognition and navigation [1,3–5]. Because vestibular signals are integrated with other sensory input for a common percept of egocentric orientation, it has been suggested that cortical vestibular areas are multimodal areas that receive “redundant” vestibular information about head position rather than a primary sensory cortex [6]. Based on this hypothesis, vestibular reorganization would not be necessary for recovery in the cortical vestibular representations [6]. Recently, however, diverging patterns of compensatory volumetric changes following pontomedullary, pontomesencephalic, and cerebellar infarcts were demonstrated in the cerebral cortex in comparison with healthy controls [7,8].

Here, we studied whether common areas for vestibular and sensory processing show adaptation that is based on clinically defined vestibular deficits rather than the location of the lesion within the vestibular network. Based on our prior work, we hypothesized that recovery would be accompanied by structural reorganization in the core vestibular cortical areas (volumetric increases in the parieto-occipital (retro-) insular vestibular cortex (PIVC) and adjacent white matter (WM) and in primary visual and/or somatosensory areas based on the concepts of reciprocal interaction and multisensory integration [8,9]. Volumetric increases would argue for a functional specialization of the PIVC for processing of vestibular information (i.e., a “distinct” vestibular cortex), rather than only providing reference copy signals for other sensory functions. Additional compensatory changes in brainstem infarcts might be detected in the cerebellum, given its close interaction with the vestibular nuclei.

METHODS

Patients

We included 42 patients with a first ever unilateral subcortical or infratentorial ischemic stroke who presented at our tertiary referral center with vestibular and/or ocular motor symptoms (University Hospital, Ludwig Maximilian University of Munich, recruiting period 2012–2019). Patients received a full clinical, neuro-otological, and radiological workup in the acute stage (M0) and chronic stage after 6 months (M6; mean time to follow-up = 7.8 ± 2.3 months). The magnetic resonance imaging (MRI) at M0 serves as the individual baseline before structural adaptation to the infarct has occurred; the changes between M0 and M6 can then be considered the individual structural response to the infarct. Inclusion criteria were unilateral subcortical infarct (thalamus or below) confirmed by imaging, ability to complete the detailed neuro-otological (vestibular and ocular motor) examination in the acute stage and after 6 months, and completion of follow-up imaging. Subcortical infarcts were chosen because we expected compensatory changes to be subtle. Widespread cortical volume loss, as could be expected if cortical infarcts would have been included, would have reduced the chances to detect these subtle effects on structural reorganization. Exclusion criteria were absence of an ischemic lesion on diffusion MRI, bilateral or multifocal infarcts, cortical cerebral infarcts, prior stroke, tumor, cerebral hemorrhage, vascular malformation, edema (i.e., compression of cerebrospinal fluid space, shift of midline structures), severe WM hyperintensities (WMH; Fazekas grade >1 for periventricular WMH and deep WMH), cortical involvement, and inability of patients to complete the neurological and neuro-otological examination due to cognitive impairment or impaired vigilance [10]. The sample was part of a localization-centered analysis in which we compared patients with healthy controls [7,8].

Clinical examination

All patients received a thorough neurological and neuro-orthoptic and clinical examination. The neuro-orthoptic examination included spontaneous eye position (skew deviation, ocular torsion) and eye

movements (nystagmus), smooth pursuit, saccades, optokinetic nystagmus, and fixation suppression of the vestibulo-ocular reflex (VOR). The VOR was tested clinically with the head impulse test (vestibular semicircular canal function) [11]. Falls as a presenting symptom were recorded in all patients. Measurements of perceptual deficits were performed by the subjective visual vertical (SVV) to evaluate vestibular graviceptive function (otoliths and vertical semicircular canals). For the SVV, a mean deviation of $>\pm 2.5^\circ$ over seven measurements was considered pathological [12].

Imaging

All patients received high-resolution structural MRI on a 3-T MRI scanner: T1 fast spoiled gradient-echo, 1 mm³ isotropic, 176 slices, repetition time (TR) = 6.63 ms, echo time (TE) = 3.15 ms (GE Signa Excite HD); or T1 magnetization-prepared rapid acquisition gradient echo, 1 mm³ isotropic, 192 slices, TR = 2500 ms, TE = 4.37 ms (Magnetom Verio or Skyra, Siemens Healthineers). Twenty patients received MRIs in the GE scanner and 22 patients in the Siemens Verio or Skyra in the context of the Determinants of Dementia after Stroke study [13]. The follow-up MRI after 6 months (M6) was performed on the same scanner as the baseline for each patient.

Lesion segmentation

The infarcts were delineated on the chronic stage (M6) T1 sequence using MRICron (<https://www.nitrc.org/projects/mricron>). Lesion maps were then normalized to $1 \times 1 \times 1$ mm³ Montreal Neurological Institute (MNI) space using the Clinical Toolbox in Statistical Parametric Mapping (SPM; <https://www.fil.ion.ucl.ac.uk/spm/>) [14].

Voxel-based morphometry

Data quality estimation, preprocessing, and analysis were performed using the CAT12 toolbox, version 1739 (Gaser & Dahnke, Department of Psychiatry, University of Jena; <http://www.neuro.uni-jena.de/cat>) within SPM12, version 7771 (Wellcome Department of Cognitive Neurology; <https://www.fil.ion.ucl.ac.uk/spm/>), using MATLAB R2017b (MathWorks) after standard preprocessing including an 8-mm Gaussian smoothing kernel. The modulated gray matter (GM) and WM images were used for the volumetric analysis. Sample homogeneity analysis revealed an excellent correlation within the sample.

Surface-based morphometry: Cortical thickness

The CAT12 toolbox contains a fully implemented and validated processing pipeline for surface-based morphometry [15]. We

employed its established algorithm for extracting the thickness of the cortical surface [16,17]. The T1-weighted images underwent tissue segmentation to estimate WM distance. Local maxima were then projected onto other GM voxels by using a neighbor relationship, described by the WM distance. These values equal cortical thickness. This projection-based method also includes partial volume correction, sulcal blurring, and sulcal asymmetries without sulcus reconstruction. Topological correction was performed using an approach based on spherical harmonics. For interparticipant analysis, an algorithm for spherical mapping of the cortical surface was included [16,17]. An adapted volume-based diffeomorphic DARTEL algorithm was then applied to the surface for spherical registration. Central cortical surfaces were created for both hemispheres separately. Surface reconstructions of the cortical values for each hemisphere were resampled to the 164k mesh template space (FreeSurfer) after merging and then smoothed with a 14-mm Gaussian filter.

Statistical analysis

We examined changes in GM volume (GMV), WM volume (WMV), and the dedicated surface parameters using the longitudinal design option implemented in the CAT12 toolbox. The timepoints M0 and M6 were included in a longitudinal flexible factorial model in SPM12. Total intracranial volume, age, and time to follow-up in days were used as covariates of no interest for the volumetric analysis. Patients were divided into groups based on the specific symptoms at first presentation. We focused on vestibular and ocular motor symptoms (tilts of the SVV, ocular torsion, spontaneous nystagmus, vertigo, falls, dysmetric saccades, saccadic smooth pursuit). As a control condition, we studied patients with sensory deficits induced by the ischemic infarct. *T*-statistics were estimated for the contrasts M0 > M6 (volume loss over time) and M6 > M0 (volume increases). Nonparametric permutation testing (threshold free cluster enhancement *TFCE*) was applied, calculating 10,000 permutations [18,19]. All results were corrected for multiple comparisons on the cluster level using familywise error (FWE) correction; results exceeding a threshold of $p < 0.05$ were considered significant. Changes in GMV and WMV were projected onto an MNI152 template brain using MRICRO GL (<https://www.mccauslandcenter.sc.edu/mricro/gl/>). Results are shown with their peak *t*-score intensities.

Standard protocols and procedures

The study was performed in accordance with the 1964 Declaration of Helsinki (latest applicable revision, Fortaleza 2013) and approved by the institutional review board of the Ludwig Maximilian University of Munich, Germany. All patients gave informed written consent to participate in the study.

TABLE 1 Demographic and clinical data of the 42 patients with vestibular or ocular motor symptoms at presentation

Characteristic	Value ^a
Age, median years (IQR)	65.0 (22)
Handedness	
Right	41 (97.6)
Left	1 (2.4)
Gender	
Female	20 (47.6)
Male	22 (52.4)
Lesion distribution	
Cerebellar	7 (16.7)
Pontomedullary	15 (35.7)
Pontomesencephalic	9 (21.4)
Thalamic	11 (26.2)
Lesion side	
Left	25 (59.5)
Right	17 (40.5)

Clinical test	M0		M6	
	n	%	n	%
Vestibular				
Pathological SVV score	25	59.6	3	7.1
Mean SVV, ° (SD)	4.22 (±3.71)		1.54 (±1.5)	
Skew deviation	10	23.8	0	0
Ocular torsion	11	26.2	0	0
Head tilt	7	16.7	0	0
Nystagmus, horizontal	9	21.4	0	0
Nystagmus, DBN/UBN	10	23.8	0	0
Lateropulsion	5	11.9	0	0
Pathological VOR, Halmagyi	1	2.4	1	2.4
Rotational vertigo/dizziness	19	45.2	0	0
Ocular motor				
Cranial nerve palsy, III, IV, VI	3	7.2	2	4.8
Gaze evoked nystagmus	19	45.2	3	7.1
Saccade pathology, dysmetria, slowing	16	38.8	3	7.1
Saccade palsy	11	26.2	0	0
Pathological optokinetic reflex	9	21.4	0	0
Disturbed fixation suppression of VOR	8	19.0	3	7.1
INO	8	19.0	0	0
Saccadic smooth pursuit	35	83.3	17	40.5
Double vision	15	35.7	2	4.8
Motor				
Paresis	16	38.8	4	9.5
Ataxia	12	28.6	5	11.9
Dysarthria	15	35.7	0	0
Falls	19	45.2	3	7.1

TABLE 1 (Continued)

Clinical test	M0		M6	
	n	%	n	%
Other				
Sensory deficits ^b	22	52.4	7	16.7
Slowing of speech	2	4.8	0	0
Visual field defect	1	2.4	1	2.4
Spatial neglect	1	2.4	0	0
Contraversive pushing	0	0.0	0	0

Abbreviations: DBN, downbeat nystagmus; INO, internuclear ophthalmoplegia; IQR, interquartile range; SVV, subjective visual vertical; UBN, upbeat nystagmus; VOR, vestibulo-ocular reflex.

^a Values are given as n (%) unless otherwise noted.

^b Hemihyesthesia (n = 14), hypesthesia of face and arm (n = 8), additional thermoception deficits (n = 4).

RESULTS

Demographic

Median age at presentation was 65 years (range = 28–86 years). Most patients (41/42, 97.6%) were right-handed, 20 (47.6%) were female. Infarcts were left-sided in 25 cases (59.5%). The mean time from symptom onset to first MRI was 2.4 days (±2.2 days); the time from symptom onset to the first ocular motor examination was 3.5 days (±2.3 days). Follow-up visits were carried out after approximately 6 months (mean time to follow-up = 7.8 ± 2.3 months).

Clinical

Acute phase

The most common finding was saccadic smooth pursuit (n = 35, 83.3%) and tilts of the SVV (n = 25, 59.5%). Additional somatosensory deficits were present in 22 patients (52.4%). Vertigo/dizziness was reported in 19 patients (45.2%) and double vision in 15 (35.7%). Horizontal rotatory spontaneous nystagmus was present in nine patients (21.4%), downbeat nystagmus in seven patients (16.7%), and upbeat nystagmus in three patients (7.1%). Mean tilt of the SVV was 4.22° (SD = ±3.71°). A detailed account with frequency of the clinical symptoms is given in Table 1.

Chronic phase

All patients with nystagmus recovered fully over the period of 6 months, and SVV tilts were compensated (mean = 1.54° ± 1.5°). Equally, no patient reported vertigo or dizziness related to a vestibular tone imbalance at follow-up. Ocular motor symptoms were improved in almost all patients (three patients (7.1%) with persistent gaze-evoked nystagmus, dysmetric saccades, and disturbed fixation suppression of the VOR). Double vision persisted in two patients with cranial nerve palsies. In contrast, limb ataxia persisted in five of 12 patients (9.5% of the overall sample) and somatosensory deficits

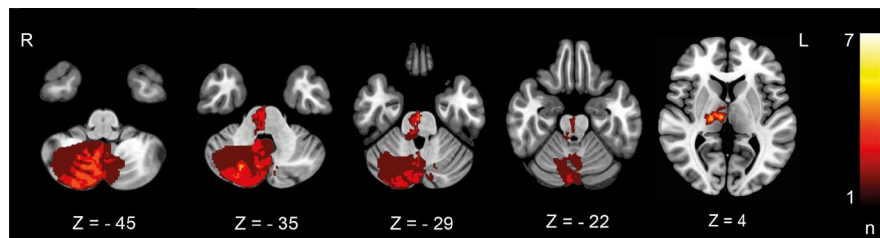


FIGURE 1 Lesion distribution is demonstrated on representative slices for different hubs of vestibular and ocular motor processing in the cerebellum, pontomedullary and pontomesencephalic brainstem, and thalamus. All lesions were flipped to the right to create the overlap image. L, left; R, right

in seven patients (16.7%). Six of the seven patients with persistent somatosensory deficits had posterolateral thalamic infarcts.

Imaging

Lesion distribution

The lesions were distributed along the central vestibular circuitry. Fifteen patients (35.7%) had pontomedullary infarcts, and seven (16.7%) had pontomesencephalic brainstem infarcts. Thirteen patients (31%) had thalamic infarcts: seven posterolateral (ventral posterior lateral/medial and ventral lateral nuclei) and six paramedian (mediodorsal, central median, and intralaminar nuclei, including the parafascicular nucleus). Cerebellar infarcts were detected in seven (16.7%) patients. Lesion distribution is shown in representative slices in Figure 1.

Voxel-based morphometry related to signs and symptoms

Spontaneous nystagmus

In patients with spontaneous nystagmus, GMV decreases were found in the primary visual cortex of both hemispheres extending along the ventral visual stream (centered around area MT+). Further clusters were located in the right inferior parietal lobule and the left subiculum as well as primary somatosensory and motor cortex (areas 1, 3b) in the right hemisphere (Figure 2a). Additional GMV decreases were located in the cerebellum (deep cerebellar nuclei: dentate nucleus, right and left crus I and II, lobule VIIB, right IX). WMV decreases reflected most strongly the GMV in the visual cortex, namely area MT+ (Figure 2b).

Rotatory vertigo

GMV reductions in patients with rotatory vertigo showed a similar pattern including the cerebellum (vestibular lobules IX and X, motor lobules V and VII) and area MT+ of the temporal lobe. An additional cluster was located around the lateral intraparietal (LIP) and ventral intraparietal (VIP) areas in the left hemisphere (Figure 2c). A WMV reduction was found in the splenium of the corpus callosum (Figure 2d).

Deviations of the SVV

When considering all patients with pathological SVV scores at first presentation ($n = 25$, nine [36.0%] pontomedullary, seven [28%] pontomesencephalic, five [20%] thalamic, four [16%] cerebellar; 12 right-sided, 13 left-sided lesions), a GMV reduction was observed in the cerebellum (ocular motor vermis: lobules VI, VII, and VIIIab; vestibular lobules nodulus/uvula: lobule IX; cerebellar hemispheres: left VI, VIIIa, crus II; right V) and in the visual cortex (Figure 3a). Volumetric increases were found in the superficial WM around the right PIVC only (cytoarchitectonic areas OP2, long insular gyri, TE1.1; Figure 3b).

Ocular torsion

We did not detect unique GMV changes in the patients with ocular torsion ($n = 11$). Clusters of volumetric increases were found in the WM around the PIVC (area OP2) in both hemispheres (Figure 3c).

Saccade pathology

Patients with saccade pathologies (dysmetria, slowing, saccade palsy) at first presentation showed volume loss in the cerebellum (ocular motor vermis [OMV] in vermal lobules V–VII, motor cerebellum, hemispheric lobules crus I and II), the medial thalamus (MD nucleus, medial pulvinar), the putamen, the PIVC, area 6d (likely reflecting the frontal eye fields [FEF]), the parietal cortex (LIP area), and the visual cortex (Figure 4a).

Falls

In patients with falls as the initial symptom, GMV decreases were restricted to the cerebellum (lobules V, VIIB/VIIA, crus I, fastigial nucleus; Figure 4b).

Somatosensory deficits

Patients with somatosensory deficits (sensory loss of arms, legs, face) showed a WMV increase around the primary sensory cortex (areas 1, 2) in the right hemisphere (Figure 4c).

Surface-based morphometry

In patients with tilts of the SVV at first presentation, we observed a reduction of cortical thickness (CT) after 6 months in area 2 and the posterior parietal cortex (areas 7AL, 7PC) of the right

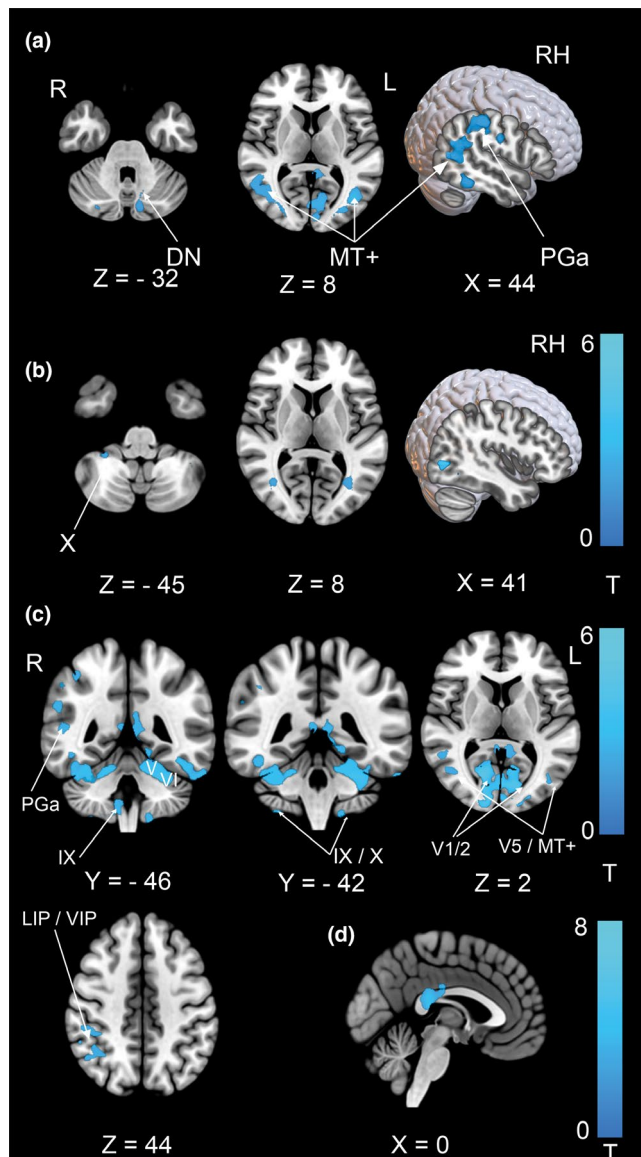


FIGURE 2 (a) Gray matter volume decreases in patients with spontaneous nystagmus were located in the cerebellum (midline cerebellum around lobule VIIIB, Crus I, II, lobule X and the dentate nucleus), along the ventral visual stream including motion sensitive temporal area MT+, dorsal visual stream, and inferior parietal lobule (PGa). (b) White matter volume (WMV) reductions were found in the cerebellum (lobule X) and around area MT+ bilaterally. (c) Patients with rotatory vertigo at presentation showed a similar pattern of volumetric decreases in the vestibular (lobules IX and X) and motor representations (lobules V and VI) of the cerebellum as well as primary and higher order visual cortex including area MT+ bilaterally. (d) A WMV decrease was found in the splenium of the corpus callosum. All results thresholded at $p < 0.05$, familywise error corrected after calculating 10,000 permutations using threshold free cluster enhancement. DN, dentate nucleus; L, left; LIP, lateral intraparietal area; PGa anterior angular gyrus of the intraparietal lobule; R, right; RH, right hemisphere; VIP, ventral intraparietal area, T t-score intensity

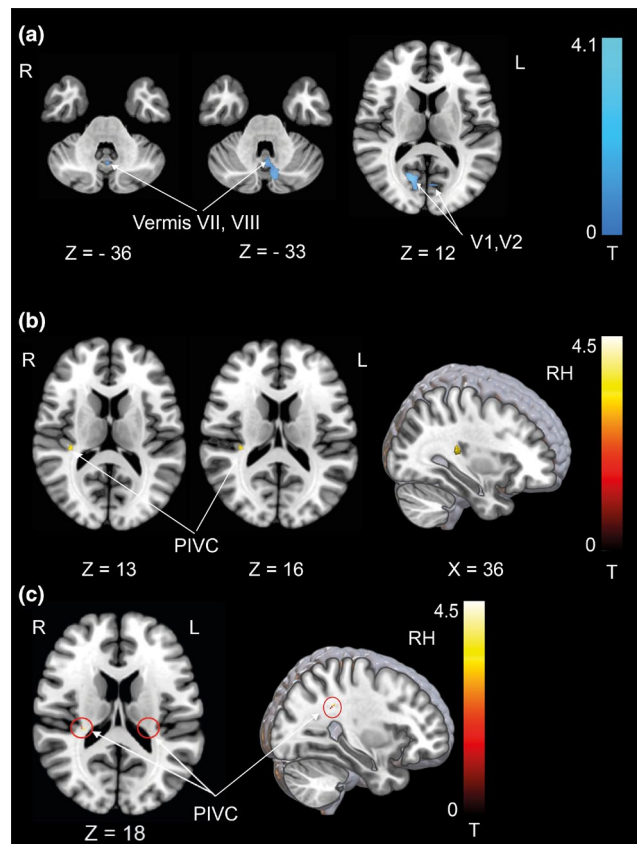


FIGURE 3 (a) Patients with tilts of the subjective visual vertical also showed gray matter volume decreases in the visual and midline cerebellar cortex. (b) White matter volume increases were found in the superficial white matter around the parieto-opercular (retro-) insular vestibular cortex (PIVC) in the right hemisphere. (c) Similarly, patients with ocular torsion at presentation showed volumetric increases over time around the PIVC in both hemispheres. All results thresholded at $p < 0.05$, familywise error corrected after calculating 10,000 permutations using threshold free cluster enhancement. L, left; R, right; RH, right hemisphere, T t-score intensity

hemisphere. In patients with dysmetria of saccades, we found a reduction of CT centered around the visual cortex and the right > left frontal and parietal eye fields (FEF and LIP areas, also multisensory VIP area; Figure 5).

DISCUSSION

The main findings can be summarized as follows. (i) Structural reorganization after subcortical infarcts with vestibular and ocular motor symptoms involves vestibular, visual, and multisensory cortical and cerebellar areas. (ii) Volumetric decreases were detected in the cerebellar representations for vestibular processing (IX, X), postural control (fastigial nucleus), and saccadic eye movements (cerebellar

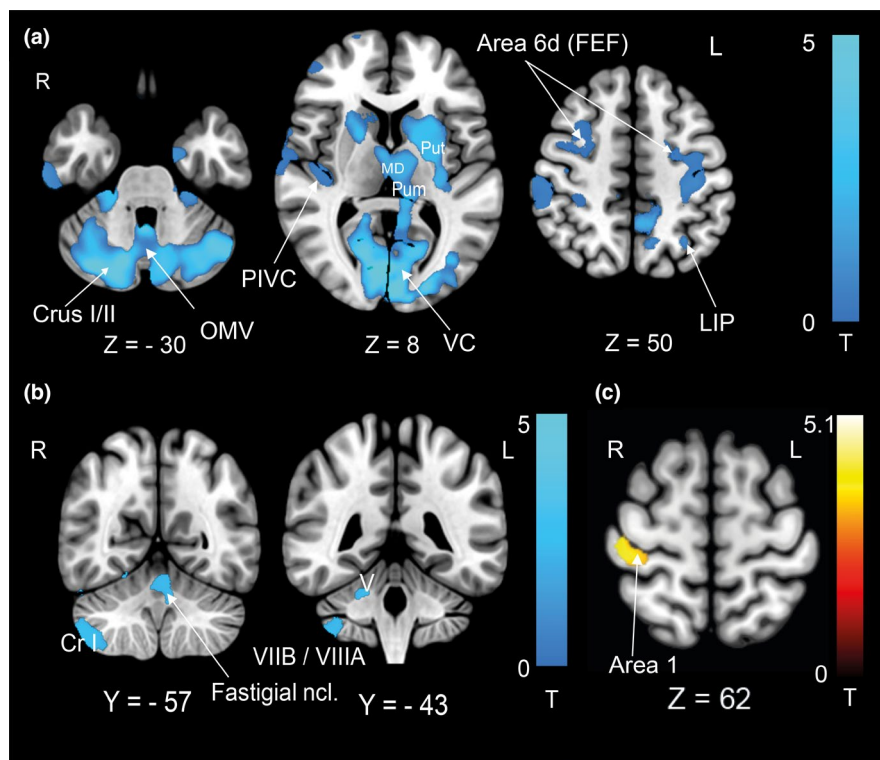


FIGURE 4 (a) Patients with saccade pathologies showed gray matter volume (GMV) decreases in the cerebellar (vermal lobules V–VII), subcortical (mediodorsal nucleus of the thalamus [MD], medial pulvinar [Pum], putamen [Put]) and cortical centers for ocular motor controls (FEF [frontal eye fields] and LIP [lateral intraparietal] areas). (b) GMV decreases were found in the cerebellum (V, VIIB/VIIIA, crus [Cr] I, fastigial nucleus [ncl.]) in patients with falls as their presenting symptom. (c) Patients with initial somatosensory deficits showed white matter volume increases in the superficial white matter around the primary somatosensory cortex (area 1). All results thresholded at $p < 0.05$, familywise error corrected after calculating 10,000 permutations using threshold free cluster enhancement. L, left; OMV, ocular motor vermis; PIVC, parieto-opercular (retro-)insular vestibular cortex; R, right; VC visual cortex; T t-score intensity

vermal lobules V–VII, i.e., OMV). (iii) In patients with spontaneous nystagmus and associated rotatory vertigo, cortical volumetric decreases could be detected in the integration centers for the detection of self- versus object motion (MT+), the primary visual cortex, and multisensory integration centers (area VIP). (iv) In patients with saccade pathologies, volume decreases were distributed along the subcortical and cortical centers for visual processing and ocular motor control (OMV of the cerebellum, MD and medial pulvinar nuclei of the thalamus, primary visual cortex, and areas LIP and FEF). (v) In patients with vestibular signs, volumetric increases were found in the superficial WM surrounding the PIVC only; in patients with sensory loss, volumetric increases were located in the primary sensory cortex.

Recovery of vestibular function

Vestibular and ocular motor symptoms after subcortical infarcts along the vestibular and ocular motor pathways were compensated at the time of follow-up after 6 months [7,8,20]. Recovery is thought to be a process including recovery of function and compensation of deficits. This involves reorganization of the central vestibular pathways and also a high degree of multisensory

integration of different signals to establish a congruent perception of head velocity, direction, self-location, and egomotion [21–24]. With the present data, we provide evidence that the superficial WM around the human PIVC is a key area involved in structural reorganization for vestibular and eye–head-centered processing (SVV and ocular torsion). A role for the PIVC in the compensation of verticality perception has been suggested recently using lesion symptom mapping in patients with cortical infarcts that presented with tilts of the SVV in the acute phase [25]. We also observed volumetric increases over time in the primary somatosensory cortex. Apart from vestibular cortical reorganization, a stronger reliance on sensory signals might compensate for the loss of vestibular input to the cortex (i.e., substitution). In contrast to the bilateral volumetric decreases in the visual system, volumetric increases in patients with SVV tilts were observed in the PIVC of the right hemisphere only. Although the majority of the ischemic infarcts were left-sided and in right-handers, the dichotomy of volumetric increases in the PIVC and somatosensory cortical areas supports a prominent role of the right hemisphere in right-handers in the integration of somatosensory and vestibular signals for self-location and spatial orientation [26]. The bilateral changes in patients with ocular torsion point toward a more eye-centered (bilateral) cortical representation of this specific symptom.

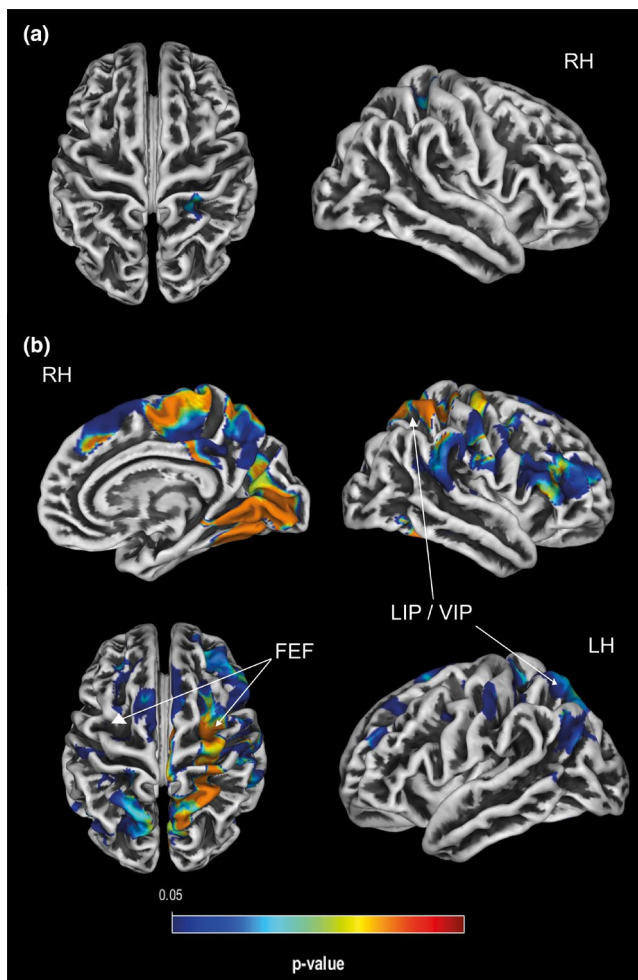


FIGURE 5 (a) Decrease in cortical thickness in patients with tilts of the subjective visual vertical in the right parietal lobe (areas 1, 2, 7PC). (b) Decrease in cortical thickness in the patients with saccade pathologies. The decrease includes the cortical ocular motor and vestibular representations (lateral intraparietal area [LIP] and ventral intraparietal area [VIP]) in the intraparietal sulcus as well as the frontal eye fields (FEF) bilaterally. Statistical overlays are depicted with logarithmic *p*-value scales FWE corrected for TFCE after 10,000 permutations. LH, left hemisphere; RH, right hemisphere

Interaction of the visual and vestibular systems

Another key finding of the present study is the profound volume loss over time in the visual cortex in patients with vestibular and ocular motor symptoms at first presentation. This was especially evident for ocular motor disorders and patients presenting with spontaneous nystagmus. A close interaction between the vestibular and visual systems has been proposed, a concept known as reciprocal inhibitory visual–vestibular interaction [9]. For a stable perception of the surroundings, vestibular and visual signals have to be congruent. If a strong vestibular stimulation occurs, visual cortex activation is downregulated; the sensory weight of the vestibular input prevails, which guarantees accurate perception of motion of the head relative to the surroundings and vice versa

as well as a reduction of oscillopsia due to disturbing nystagmus. Here, we could demonstrate that an asymmetry in the vestibular system due to an acute tone imbalance leads to concurrent structural changes in the visual system. This was true in the primary visual cortex bilaterally and in particular for the motion-sensitive visual temporal areas MT+ in patients with rotatory vertigo and spontaneous nystagmus.

Additionally, WMV reductions were found after 6 months in the splenium of the corpus callosum in the patients with rotatory vertigo at first presentation. This nicely fits with the interhemispheric diffusion tensor imaging tractography analysis of vestibular pathways in healthy volunteers that identified the antero-caudal splenium (region V of the Witelson classification) for the interhemispheric projection [27]. With the present data, we provide further evidence for the role of the splenium in interhemispheric connectivity of the vestibular system.

Structural adaptation in the ocular motor system

In patients with saccade pathologies, volume loss in key subcortical and cortical centers for saccadic eye movements was demonstrated. Volumetric decreases involved the cerebellum (including the OMV), the medial thalamic nuclei (MD and medial pulvinar), the putamen, and the cortical centers for saccadic eye movements in the frontal (area 6d, corresponding to the FEF) and parietal lobe (LIP area, the putative human homologue of the parietal eye field) [28–31].

In prior studies on vestibular brainstem strokes, we detected structural adaptation over time compared to a group of healthy age-matched controls [8]. In comparison to the former, in the current study, patient groups were evaluated based on a specific vestibular or ocular motor symptom regardless of the lesion site along the vestibular circuitry. In addition, here we used a strict longitudinal approach, that is, within-subject comparison over time. This allowed us to expand our knowledge of the structural multisensory reorganization after ischemic infarcts. Some differences in this longitudinal study design compared to earlier studies have to be discussed. In the current study, the volumetric increases were smaller and located only in the vestibular cortical core region (around PIVC) in patients with vestibular symptoms. These findings provide more evidence for and underline the importance of the PIVC as the core region for vestibular processing along the vestibular circuitry for all stages of disease, acute and chronic, and for all lesion sites within the vestibular circuitry. The heterogeneity of the infarcts (at different levels of the vestibular processing route) might be the reason other hubs for vestibular processing did not emerge in the analysis apart from its core region PIVC. Volumetric increases were found in the superficial WM around the PIVC. The structural architecture and functional specialization of the superficial WM areas are distinct from the deep WM and the adjacent cerebral cortex and have been related to plasticity [32]. We are aware that the resolution of the current analysis does not allow a clear distinction between superficial and deeper layers of

the subcortical WM to be made. Nonetheless, the observation of the WM volumetric increases suggests a role in adaptation to vestibular deficits after ischemic infarcts.

Limitations

The use of different scanners presents a possible limitation of our study. Patients were evenly distributed over the MRI machines, and all patients received both of their MRI scans on the same scanner. Lesion volumes did not differ between the two scanner groups. The T1-based tissue segmentations were harmonized during preprocessing via denoising and bias field correction. The data quality estimates over the entire sample showed good to very good signal homogeneity for the different tissue types. In addition, we used a methodologically conservative approach with a strict within-subject design and extensive permutation testing and FWE correction to control for false positives. Based on this, we are confident that it did not bias our results in any way.

The distribution of lesion locations might have influenced the sensitivity to detect all cortical vestibular hubs involved in structural adaptation. With this sample, we aimed to provide evidence for a common cortical response to specific clinical deficits within subcortical vestibular and ocular motor hubs of a shared network. The current approach is complimentary to prior work [7,8]. With the site-based approach, we were able to detect differences in structural reorganization over time that reflect the increasing integration of vestibular signals in the upper brainstem, and also the cerebellum. With the lesion-based approach applied in this study, we show the common denominator of structural reorganization after infarcts with vestibular symptoms on all stages of the central vestibular circuitry.

It should be taken into account that vestibular and ocular motor symptoms were significantly improved or fully resolved at follow-up after about 6 months. We cannot distinguish whether the localized volumetric increases around the PIVC represent adaptive (neuroplastic) changes, but the findings provide a further piece of evidence that the PIVC is involved in structural reorganization of the vestibular network at all stages after lesion onset. This further emphasizes its function as a core region within the vestibular cortical network.

CONCLUSIONS

The study demonstrates structural reorganization after ischemic infarcts with vestibular and ocular motor symptoms. The findings highlight the role of the subcortical WM around the PIVC as a core region for structural reorganization of cortical vestibular processing. Structural adaptation to vestibular and ocular motor disorders is accompanied by bilateral volumetric loss in the visual cortex and in the cerebellar, subcortical, and cortical centers for ocular motor control. On this basis, noninvasive brain stimulation of the parietal

operculum or intensive visual training could aid rehabilitation in patients with incomplete compensation of vestibular and ocular motor disorders.

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CONFLICT OF INTEREST

None of the authors has any conflict of interest to disclose.

AUTHOR CONTRIBUTIONS

Julian Conrad: Conceptualization (lead), formal analysis (lead), investigation (lead), methodology (lead), software (lead), visualization (lead), writing—original draft (lead). **Maximilian Habs:** Data curation (supporting), investigation (supporting), writing—review & editing (supporting). **Ria Maxine Ruehl:** Investigation (supporting), visualization (supporting), writing—review & editing (supporting). **Rainer Boegle:** Investigation (supporting), methodology (supporting), software (supporting), writing—review & editing (supporting). **Matthias Ertl:** Investigation (supporting), software (supporting), writing—review & editing (supporting). **Valerie Kirsch:** Investigation (supporting), writing—review & editing (supporting). **Ozan Emre Eren:** Investigation (supporting), writing—review & editing (supporting). **Sandra Becker-Bense:** Conceptualization (supporting), funding acquisition (supporting), investigation (supporting), methodology (supporting), project administration (supporting), supervision (supporting), writing—review & editing (supporting). **Thomas Stephan:** Investigation (supporting), methodology (supporting), software (supporting), writing—review & editing (supporting). **Frank Arne Wollenweber:** Conceptualization (lead), funding acquisition (lead), investigation (lead), writing—review & editing (supporting). **Marco Duering:** Conceptualization (lead), funding acquisition (lead), investigation (lead), writing—review & editing (supporting). **Marianne Dieterich:** Conceptualization (lead), funding acquisition (lead), methodology (lead), project administration (lead), supervision (lead), writing—review & editing (lead). **Peter zu Eulenburg:** Formal analysis (lead), methodology (lead), software (lead), supervision (lead), writing—review & editing (lead).

DATA AVAILABILITY STATEMENT

The lesion maps are publicly available (<https://osf.io/2nmcf/>). The structural imaging patient data are not publicly available due to European privacy laws and lack of consent for data sharing by the patients.

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