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Changes in the gray matter volume during compensation after vestibular neuritis: A longitudinal VBM study

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Abstract.
Purpose: Peripheral vestibular dysfunction following vestibular neuritis (VN) often persists but functional recovery of balance can be variable. The authors compared structural changes in the brain before and after post-VN compensation and related it to the functional recovery.
Methods: Nine patients diagnosed with unilateral VN were included. Brain MRI and clinical observation were performed within 2 days of acute VN diagnosis and were repeated 3 months after the first exam. Voxel-based morphometry (VBM) analysis for longitudinal data was performed using VBM8 toolbox running within SPM8. Changes in local grey matter volume (GMV) were examined using a paired *t*-test and clinical relevance was tested using correlation analyses with functional improvement.
Results: Significant increases in GMV were observed in the vestibular cortex, bilateral hippocampus, visual cortices and the cerebellum. GMV decreased in cerebellar regions, including the vermis, and in the prefrontal cortex. Increases in GMV in visual cortices and cerebellum were associated with the poorest recovery of balance, which might be explained by functional substitution.
Conclusions: The structural layout of vestibular compensation suggests that memory and motor planning are closely related to this process. Vision seems to be a major source of functional substitution, as has been previously demonstrated. This study, however, is the first longitudinal analysis of brain structural changes associated with recovery of balance following unilateral VN.

Keywords: Vestibular neuronitis, neuronal plasticity, voxel-based morphometry, rehabilitation

1. Introduction

Vestibular neuritis (VN) is an acute, peripheral, vestibular syndrome characterized by spontaneous, rotatory vertigo and autonomic symptoms including nausea and vomiting. It does not include hearing impairment, lasts several days, and gradually eases within a few months. Vestibular rehabilitation helps patients recover more quickly through promotion of vestibular compensation (Hillier and McDonnell, 2011). However, most patients will recover without typical treatment and even patients with the same vestibular deficit experience wide variation in its clinical course.

The vestibulo-cerebellar pathway is a crucial central connection for functional recovery after unilateral vestibular loss. Loss of activity from one vestibular end organ produces neural imbalance between bilateral vestibular nuclei, resulting acute vestibular symptoms

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such as, spontaneous nystagmus (SN), ocular tilt reaction, vertigo, postural instability with neurovegetative symptoms (nausea and vomiting). The neural imbalance between both vestibular nucleus complexes progressively diminishes within the first few days or weeks (Dutia, 2010; Lacour and Tighilet, 2010). Static imbalance then fades with resolution of spontaneous nystagmus (SN). However, functional recovery for dynamic vestibular imbalance is still a mystery. Previous functional neuroimaging studies have shown higher central connectivity beyond the cerebellum and distinct cortical vestibular structures. The vestibulo-cortical system, which includes the parieto-insular vestibular cortex (PIVC) activated by vestibular stimulation, is composed of multisensory cortical networks connected with other cortical processing areas, including occulomotor, somatosensory, and visual areas (Dieterich and Brandt, 2008). To cope with unilateral vestibular deafferentation, two different neural compensation mechanisms have been suggested. First, central vestibular compensation could overcome a balance deficit by modulating subcortical/cortical responses to unbalanced peripheral vestibular input in the vestibular network. Second, functional substitution could replace decreased vestibular input by rebalancing sensory components that control posture (i.e., relative strengthening of other balance-related sensory systems such as vision (Brandt et al., 1997; Strupp and Brandt, 2009).

In previous studies, structural changes in grey matter (GM) were related to functional compensation following peripheral vestibular deficits (Brandt et al., 2005; Hüfner et al., 2007; Helmchen et al., 2009; Hüfner et al., 2009; Zu Eulenburg et al., 2010; Helmchen et al., 2011). However, these studies did not determine whether the structural differences were a direct result of central vestibular compensation because they did not investigate differences between acute vestibular failure and functional recovery in the same subjects.

In the present study, we conducted a longitudinal investigation of structural changes in the brain during 3 months following unilateral VN using voxel-based morphometry (VBM), and determined the functional neural compensation mechanism by correlating structural changes and improved clinical scores. Cortical hypertrophy would most likely be associated with compensatory mechanisms versus cortical loss. In areas directly related to the vestibular network, central vestibular compensation may lead to increased cortical volume associated with better functional gain. In areas related to other sensory/cognitive functions that compensate for diminished vestibular components, cortical increase might be inversely related to functional gain.

2. Materials and methods

2.1. Subjects

We included nine right-handed patients (mean age $\pm$ s.d.: 49.2 ± 18.1 years; six males and three females) with acute unilateral VN who were hospitalized in our department. Inclusion criteria were as follows: 1) history of severe, prolonged, acute onset vertigo (onset within 72 h); 2) horizontal SN with a rotational component directed to the unaffected side; 3) no evidence of a central lesion; 4) presence of a catch-up saccade on affected side in head thrust test; and 5) unilateral weakness greater than 25% demonstrated on bithermal alternating caloric test. Patients with a history of vertigo, hearing loss or ear surgery were excluded.

All subjects underwent initial neurotologic examinations including vestibular laboratory tests. Subjective scoring on vertigo-related disability was acquired using the Korean version of the dizziness handicap inventory (K-DHI) (Jacobson and Newman, 1990). In addition, a T1-weighted brain MRI (Philips Achieva 3T, DA Best, The Netherlands) was acquired.

As soon as acute vertigo symptoms became tolerable, patients were instructed to perform a vestibular rehabilitation exercise program, which was a modification of the Cawthorne–Cooksey method (Cooksey, 1946). For 3 months, patients were encouraged to continue the vestibular exercise program while minimizing the use of sedative medications. A second MRI and neurotologic exam, including a questionnaire, were obtained after 12 weeks. All subjects gave written informed consent for participation in the study, which was conducted in accordance with the Declaration of Helsinki. Approval for this study was obtained from the institutional review board of Hallym University Sacred Heart Hospital (IRB No. 2012-1086).

2.2. Korean version of the dizziness handicap inventory

Assessment of subjective symptoms was performed using the K-DHI (Jacobson and Newman, 1990). The DHI includes 25 items with 3 response levels to

ascertain functional, physical, and emotional impacts on disability. For each item, the following scores were assigned: No = 0, Sometimes = 2, and Yes = 4. Scores for each item were added up to obtain a K-DHI score for each individual.

2.3. Neurotologic examinations

The slow phase velocity of SN and immediate head shaking nystagmus (HSN) were measured using a videonystagmography (VNG) system (System 2000; Micromedical, Chatham, IL) in a sitting position. HSN was assessed after 15 s of passive head shaking with neck flexion of 30° at a frequency of 2 Hz.

The bithermal alternating caloric test and rotatory chair test have been described in detail elsewhere (Koo et al., 2011). Briefly, the caloric test was performed using an Aquastar water caloric stimulator (Micromedical, Chatham, IL) in a supine position with the head elevated by 30°. Canal paresis (CP) was determined according to Jongkees' formula, which results in a classification of 'abnormal' when scores exceed 25%.

The rotatory chair test was performed with an earth vertical axis rotation unit (System 2000; Micromedical). The subject's head was positioned and restrained on the headrest with 30° neck flexion. Horizontal vestibulo-ocular reflex was recorded using a VNG system. The rotational stimulus included both impulse acceleration and deceleration (step velocity). The test protocol for step velocity stimulation was an angular acceleration of 100°/s for 1 s, rotation at a constant velocity (100°/s) for 60 s, and then deceleration to 0°/s within 1 s. We used the time constant (TC) of a decrease in nystagmus after impulse acceleration and deceleration as a parameter. The results were considered abnormal when TC was less than 11 s according to our criteria (mean – 2 s.d. of the results of normal subjects using the same rotatory chair in our laboratory).

2.4. Outcome measure during follow-up

Change in subjective and objective vestibular function was calculated as follows: 1) CP improvement = CP at initial – CP at follow-up, 2) TC improvement = ipsilesional TC at follow-up – ipsilesional TC at initial, and 3) K-DHI improvement = K-DHI at initial – K-DHI at follow-up. In all calculations, a higher score means more improvement. Each parameter was used as a covariate for correlation analyses with cortical structural change over time as described in the next section.

2.5. Image acquisition and longitudinal VBM

Each subject underwent two high-resolution T1-weighted MRIs (repetition time 9.3 ms; echo time 4.6 ms; flip angle 8; field of view 230 × 230 mm; matrix 232 × 200/160 slices; slice thickness = 1.0 mm without gap) 3 months apart (initial admission day and last follow-up day). Images were processed using the longitudinal processing pipeline as offered in the VBM8 toolbox (http://dbm.neuro.uni-jena.de/vbm8). The VBM8/new segment toolbox offers a protocol for preprocessing longitudinal data of structural MRIs, which is based on the statistical parametric mapping software package version 8 (SPM8, Wellcome Trust Centre for Neuroimaging, University College London, London, UK; http://www.fil.ion.ucl.ac.uk/spm) run on a Matlab environment (version 7.8, Mathworks Inc., Natick, MA, USA).

The image preprocessing procedures were as follows: 1) calculation of baseline image (mean image) for use as a reference image, 2) correction for signal inhomogeneities with regard to the mean image, 3) estimation of spatial normalization parameters using the segmentations of mean image, 4) adaptation of normalized parameters to the segmentations of the bias-corrected images, and 5) realignment of resulting normalized segmentations (fully automated using the VBM8/new segment toolbox). As the effect of modulation on longitudinal data is rather subtle, it is not included in the longitudinal processing module of the toolbox. Segmented grey matter images were smoothed with 8 mm^3 full width at half maximum and fed into a flexible factorial design with two factors (subject and time). Therefore, differences in local grey matter volume (GMV) between two time points were calculated.

Following our hypothesis of cortical compensation in the vestibular network, we examined GMV increases in the right insula and parietal operculum, where previous studies localized the human primary vestibular cortex (Eulenburg et al., 2012; Lopez et al., 2012). Reported changes in GMV did not survive a more conservative statistical threshold using corrections for multiple comparisons (FWE or FDR correction) and are best explained by the small study population ($n = 9$). We set the statistical threshold at $p = 0.005$, uncorrected, as it was the most stringent threshold to show

the cluster in the right insula. We also applied an extent threshold of k = 35 following the expected cluster size by SPM. These thresholds were maintained for all subsequent analyses.

For clinical correlation, a brain image applying GMV differences between two time points was calculated for each subject. The image reflecting GMV differences were fed into multiple regression analyses using each clinical measure (subjective and objective) as covariates of interest, with age and total intracranial volume as covariates of no interest. All significant clusters from regression analyses are listed in Table 3.

Brain imaging data from patients with different lesion sides were collapsed, in contrast with most previous VBM studies that artificially equalized 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) (Helmchen et al., 2009; Hüfner et al., 2009; Helmchen et al., 2011). Knowing that the brain is systematically asymmetric both in function and structure, we did not do this, as we were focused on the brain's compensatory mechanisms, involving multiple systems such as vision and proprioception (LeMay, 1976; Lancaster et al., 2003). Even in the vestibular network, recent studies advocate hemispheric laterality (Fasold et al., 2002; Dieterich et al., 2003; Janzen et al., 2008; Eulenburg et al., 2012).

3. Results

3.1. Clinical improvement

The detailed clinical profiles of subjects are given in Table 1. All patients showed a typical SN (5–39°/s) and HSN (6–24°/s) with its fast phase toward the lesioned side. Unilateral CP ranged from 29% to 74%. Lesioned TC was between 1 and 6 s, which demonstrates significant unilateral vestibular deficits on initial neurotologic tests. The total score of initial K-DHI ranged from 20% to 58%, suggesting at least mild handicap.

After 3 months of follow-up, SN and HSN diminished over time in all subjects (0 to 5°/s) representing the resolution of static symptoms. In contrast, only six patients (6/9, 67%) showed improvement to normal CP and the remaining three patients still had unilateral vestibular deficits of 31–100%. The K-DHI score decreased to a range of 0–44.

3.2. GMV change during 3 months and clinical correlation

Areas of significant GMV increase were found in the right inferior frontal gyrus, right insula, right superior temporal sulcus, right lingual gyrus, left middle and inferior occipital gyrus, bilateral hippocampi and parahipocampal gyri, left caudate nucleus, bilateral cerebellar hemisphere, and right flocculus. A significant decrease in GMV was found in the right superior medial gyrus, right middle orbital gyrus, cerebellar vermis, and right cerebellar hemisphere (Table 2, Figs. 1–3).

The degree of change in GMV was related to the improvement of clinical scores in many areas. Recovery of CP and TC was positively correlated with GMV change in the right hippocampus and left supplementary motor area (SMA), respectively. An inverse correlation between GMV change and clinical improvement was observed in the left middle occipital

Table 1
Clinical data of vestibular neuritis patients

				Initial				3 months follow-up			
Patient code	Age	Sex	Lesion side	CP (%)	TCW	TCCW	DHI	CP (%)	TCW	TCCW	DHI
VNR01	71	M	R	74	2	6	20	100	2	3	28
VNR02	63	M	R	49	n.a		26	6	10	12	4
VNR03	42	M	R	47	2	10	58	2	9	9	0
VNR04	15	M	R	29	1	11	28	31	10	10	0
VNR05	58	F	R	54	5	10	n.a	43	8	8	44
VNL06	60	M	L	51	6	2	28	15	6	3	0
VNL07	28	F	L	44	8	3	48	2	11	12	0
VNL08	48	F	L	58	10	6	24	9	11	12	0
VNL09	58	M	L	74	10	4	46	11	12	15	6

CP: Canal paresis; DHI: Dizziness Handicap Inventory; P: Physical, E: Emotional, F: Functional; TCW: time constant in the clockwise rotation; TCCW: time constant in the counter-clockwise rotation; R, Right; L, Left; n.a., not available.

Table 2

Areas of significant gray-matter volume changes over the 3-month follow-up period in vestibular neuritis patients (uncorrected $P = 0.005$, extent threshold = 35 voxels, T-score at threshold = 3.36)

Pre > Post	MNI coordinates (x y z)	BA	Cluster size	T	Post > Pre	MNI coordinates (x y z)	BA	Cluster size	T
R superior medial gyrus	4 60 24		37	5.13	R inferior frontal gyrus (pars triagularis)	40 32 6	45	44	5.84
R middle orbital gyrus	32 52 −18		37	4.47					
					R insula	48 8 −3		125	4.58
					R superior temporal sulcus	52 −25 −5		37	4.32
					R lingual gyrus	12 −88 −11	18	118	4.81
					L middle occipital gyrus	−21 −99 19	18	47	4.60
					L inferior occipital gyrus	−20 −90 −12	18	41	4.13
					L hippocampus	−32 −10 −18		78	5.40
					R parahippocampal gyrus	38 −12 −26		40	5.14
					R parahippocampal gyrus	34 4 −39	20	97	6.69
					L parahippocampal gyrus	−22 −4 −29		51	4.41
					L caudate nucleus	−14 −3 18		56	7.44
Cerebellar vermis	−2 −37 −18		176	4.62	R cerebellum (flocculus)	15 −39 −44		62	5.10
R cerebellum (lobule VIIIa Hemisphere)	21 −69 −60		37	4.34	R cerebellum (lobue VIIIa Hemisphere)	30 −45 −47		75	4.82
					L cerebellum (lobule VIIb Hemisphere)	−34 −52 −48		250	6.75

MNI, Montreal Neurological Institute; BA, Brodmann area; L, left; R, right; Pre, acute stage in vestibular neuritis patient; Post, 3-month after symptom onset.

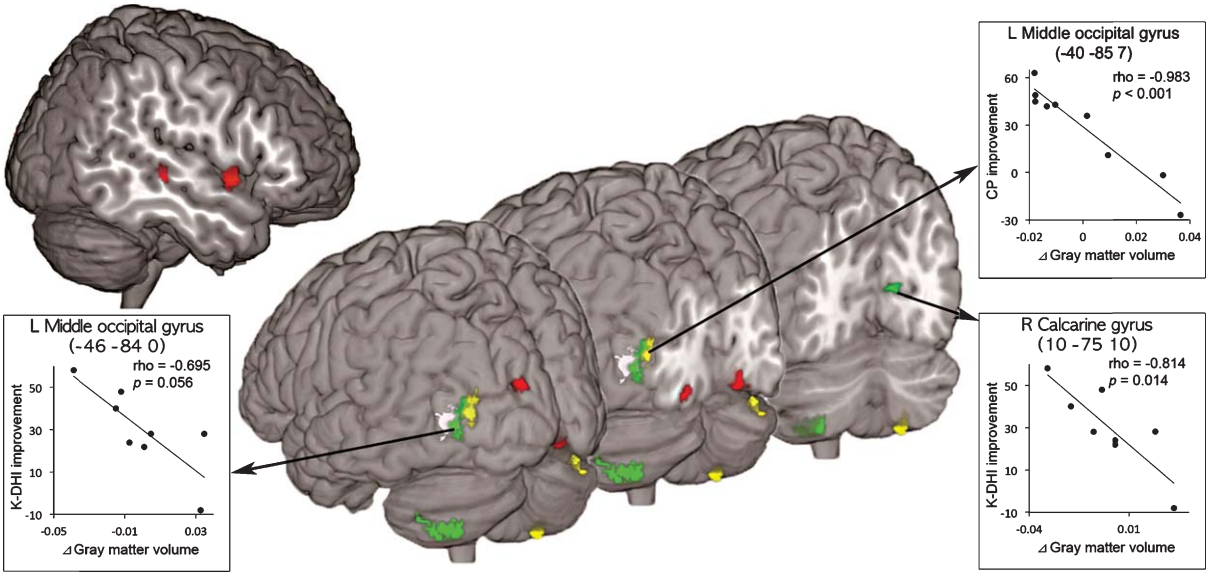

Fig. 1. Areas of GMV increase (red) and clinical correlation in the right insula, the right superior temporal sulcus, and the visual cortex (yellow: negative correlation with CP improvement or TC improvement, green: negative correlation with K-DHI improvement, light gray: V5 ROIs derived from SPM Anatomy toolbox). The *r* values must be interpreted with caution, because such values tend to be overestimated in this kind of analysis (Vul et al., 2009).

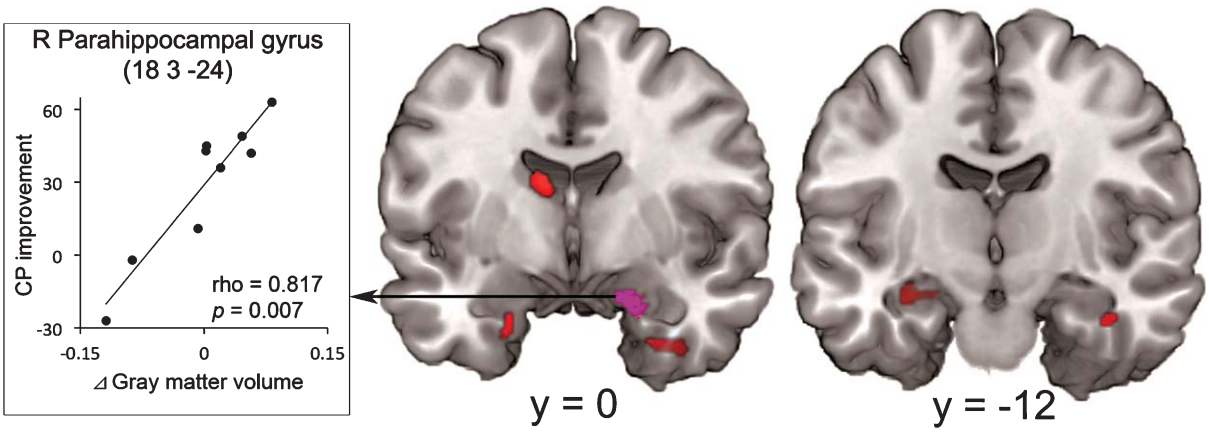

Fig. 2. Areas of GMV increase and clinical correlations in bilateral hippocampi and parahippocampal gyri (red: GMV increase, violet: positive correlation with CP improvement).

gyrus, right calcarine gyrus, and three regions of the cerebellar hemisphere (Table 3, Figs. 1–3). All clusters of clinical correlations were located in the area of cortical hypertrophy except one cluster in the right cerebellum (20, −66, −57) that showed a negative correlation with TC improvement and GMV decrease during the follow-up (Fig. 3).

4. Discussion

Vestibular compensation involves different and parallel plastic processes at various sites in the brain. Static vestibular imbalance following acute unilateral vestibular deafferentation usually ameliorates quite rapidly, modulated by homeostasis of bilateral

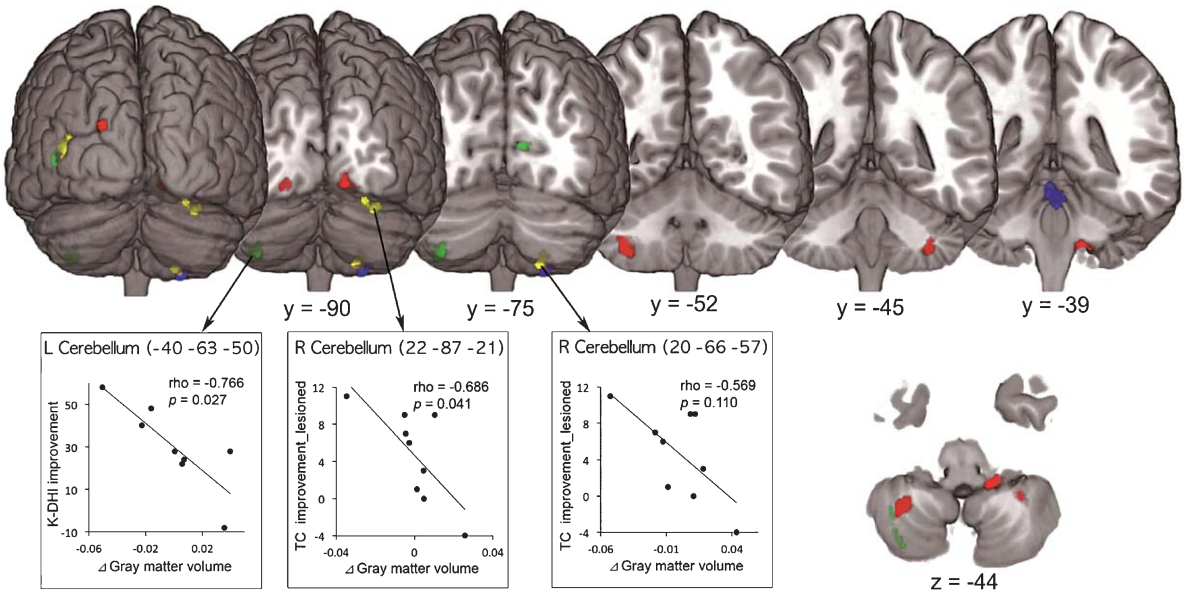

Fig. 3. Areas of GMV changes and clinical correlations in the cerebellum (red: GMV increase, blue: GMV decrease, yellow: negative correlation with CP improvement or TC improvement, green: negative correlation with K-DHI improvement).

excitability of vestibular nuclei in the brainstem. In contrast, persisting dizziness, or oscillopsia, during rapid head movement reflects dynamic vestibular imbalance and persists over months and perhaps years in many cases (Strupp and Brandt, 2009; Dutia, 2010). Compensation for dynamic symptoms is less dependent on rebalancing electrical activity in the vestibular nucleus complex, and is associated with a more prevalent subset of the central nervous system such as motor strategies and sensory substitutions (Lacour and Tighilet, 2010).

Changes in GMV following given interventions or disease processes can arise rather rapidly. In humans, a significant increase in GM following physical training has been found in the visual motion-sensitive area after 1 week and in the motor cortex after a few months (Draganski et al., 2004; Driemeyer et al., 2007). In this study, we examined GMV changes in VN patients during the early period of vestibular compensation (within 3 months) and correlated the change with clinical improvement to tease out the multiple facets of compensatory mechanism in the brain.

4.1. Increases in GMV in the human vestibular cortex

Cortical areas dedicated to vestibular input might play a primary role in the central compensation process through top-down modulation of peripheral vestibular input. The posterior insula, parietal operculum, and superior temporal gyrus have been suggested to be human homologues of the PIVC in monkeys (Dieterich et al., 2003; Eickhoff et al., 2006; Eulenburg et al., 2012; Lopez et al., 2012). In previous VBM studies, changes in grey matter were examined in areas of patients with unilateral vestibular deafferentiation, although the resulting directions of change were controversial. The direction of GM change in patients with vestibular deafferentiation may suggest differential roles in the so-called vestibular cortex. While cortical atrophy (Hüfner et al., 2009; Zu Eulenburg et al., 2010) would indicate dominance of afferent connections receiving peripheral sensory input in the area, cortical hypertrophy (Helmchen et al., 2009; 2011) following peripheral sensory loss would suggest dominance of efferent connections to modulate remaining peripheral input (top-down reinforcement). One previous study reported clinical correlations in these areas that suggest the latter (i.e., degree of GM hypertrophy related to the less prevalent vestibular deficit (Helmchen et al., 2011). Otherwise, increased resting activity in the ipsilesional vestibular nucleus may induce GMV increases in the vestibular cortex, which receives afferents from it (Dieterich et al., 2005). In the present study, cortical hypertrophy was found in regions of the right

Table 3
Areas of significant correlation between GMV changes and clinical improvement over the 3 months (uncorrected $P = 0.005$, extent threshold = 35 voxels, T-score at threshold = 3.36)

	Positive correlation	MNI coordinates (x y z)	BA	Cluster size	T	p	Negative correlation	MNI coordinates (x y z)	BA	Cluster size	T	p
CP improvement												
	R parahippocampal gyrus	18, 3, −24		70	6.60	<0.001	L Middle occipital gyrus	−40, −85 7		59	7.42	<0.001
TC improvement												
	SMA	−15, −3, 63	6	101	9.45	<0.001	R Cerebellum (Lobule VIIa, CrusI, Hemisphere)	22, −87, −21		44	7.53	<0.001
							R Cerebellum (Lobue VIIIa hemisphere)	20 −66 −57		50	4.94	<0.001
K-DHI improvement												
							R Calcarine gyrus	10, −75, 10	17	43	8.61	<0.001
							L Cerebellum (Lobule VIIa CrusII, Hemisphere)	−40 −63 −50		83	8.16	<0.001
							L Middle occipital gyrus	−46, −84, 0		43	5.45	<0.001

MNI, Montreal Neurological Institute; BA, Brodmann area; L, left; R, right; SMA, supplementary motor area, BA; Broadmann area.

insula and the right superior temporal sulcus (Table 2 and Fig. 1). In addition, a positive correlation between GMV increase and CP recovery was found in the left insula (−46, 9, −8), in which cluster size was smaller than our threshold, likely due to a small subject pool.

4.2. Sensory substitution through vision

Vision takes on a major role in vestibular compensation following sensory substitution. As in the vestibular cortex, results of previous VBM studies have reported conflicting findings regarding structural changes in the visual area. While many have reported an increase in grey or white matter in the occipital region, including the motion-sensitive area (MT/V5) (Helmchen et al., 2009, 2011; Zu Eulenburg et al., 2010), studies from one group reported GM atrophy in the left MT/V5 (Hüfner et al., 2007; 2009). In the present study, cortical hypertrophy was examined in regions of the right lingual gyrus and left middle and inferior occipital gyri, suggesting functional substitution by vision (Table 2 and Fig. 1). Clinical correlations found in the visual area support the idea that vision compensates for deficient vestibular sense to improve balance function. Those with larger volumes in regions of the right calcarine gyrus and the left middle occipital gyrus (overlapping with left MT/V5) experienced less recovery of balance function (Table 3, negative correlation). Previous anatomical and functional evidence suggests a visual-vestibular, cross-modal interaction, particularly in the visual motion area. The PIVC in monkeys is tightly connected with the visual temporal sylvian area, which may correspond to the visual motion-sensitive area in humans (Grüsser et al., 1990; Guldin et al., 1992; Eulenburg et al., 2012). Although functional studies have shown activation in the visual motion-sensitive area by vestibular stimulation, the results have been contradictory; both a decrease and an increase in visual motion processing have been reported (Dieterich et al., 2007; Deutschlander et al., 2008; Smith et al., 2012). Our results support the hypothesis of enhanced visual motion processing in VN patients, and evidence of central compensatory mechanisms in other sensory domains reinforce this view. Following the loss of one sensory input, the brain reorganizes its function and structure toward enhancing the remaining senses. These compensatory changes seem to be particularly notable for functions that would normally benefit from convergence with the missing sensory input (e.g., enhanced speechreading in deaf patients). Cortices that receive multimodal inputs are seen to reorganize, not only in the higher cortical areas but also in earlier sensory areas (Bavelier et al., 2006; Noppeney, 2007; Suh et al., 2009).

4.3. Increase of GMV in memory-related areas as a result of rehabilitation

Although hippocampal atrophy associated with impaired spatial memory has been found in patients with bilateral vestibular deficit (Brandt et al., 2005), most volumetric studies on unilateral vestibular loss have not observed significant structural changes in the hippocampus (Hüfner et al., 2007, 2009; Helmchen et al., 2009, 2011). In the present longitudinal study, significant increases in GMV were found in the left hippocampus and bilateral parahippocampal gyri (Table 2, Fig. 2). This increase might be explained in two ways. First, increased volume in these memory-related areas could be considered compensatory in nature, reflecting more need for stored spatial memories. Second, it could be a consequence of vestibular rehabilitation therapy. A positive correlation between GMV increase and CP improvement observed in the right parahippocampal gyrus indicates a compensatory mechanism versus functional substitution. However, the positive correlation in the hypertrophic area cannot be explained by the same mechanism found in the insula. Although a previous study showed activation in the hippocampus by vestibular stimulation (Stephan et al., 2005), that area is not classically considered part of the cortical vestibular network. Thus, our hypothesis is as following: vestibular rehabilitation exercise during follow-up increased the GMV in areas associated with spatial memory, which was then facilitated by recovery of peripheral vestibular input. GMV increases associated with learning have been replicated in the hippocampus, where neurogenesis occurs during adulthood (Zatorre et al., 2012). The discrepancy between this study and previous reports can be explained in two ways. First, previous region of interest-based studies did not include the hippocampus (Helmchen et al., 2009, 2011). Second, other studies measured brain structure years after unilateral vestibular loss (Hüfner et al., 2009; Zu Eulenburg et al., 2010), while our examination was performed 3 months after disease onset with continuing encouragement of vestibular exercise. Training-related cortical hypertrophy may revert back to baseline after training ceases (Draganski et al., 2004; Thomas et al., 2012).

This discrepancy might be eliminated by designing future longitudinal studies with short- and long-term follow-up as well as studies on the effect of vestibular rehabilitation exercise on hippocampal volume.

4.4. *The cerebellum and motor control system for recovery of balance*

Cerebellar vermis and the flocculonodular lobe have reciprocal connections with vestibular nuclei and are important in vision stabilisation. The different directions of GMV change found in these areas suggest a different configuration of vestibular connection: dominance of afferent input in the cerebellar vermis (GM atrophy following loss of peripheral sensory input) and dominance of efferent connection in the flocculus (compensatory hypertrophy following peripheral loss) (Table 2, Fig. 3).

Changes in GMV were also examined in multiple areas of the lateral cerebellum through which inputs and outputs flow between the cerebral cortex and basal ganglia. Clinical correlation in the bilateral cerebellar hemisphere suggests functional substitution (greater increase in GMV with more remaining balance deficit). Cerebellar involvement in vestibular compensation seems natural, considering its function as a centre for fine motor coordination. The lateral cerebellum receives information from premotor cortices and sends neural signals to the motor cortex. It prepares the next movement during the present movement, thus permitting a smooth and coordinated progression from one movement to the next. GMV increase has been examined in an area of the left caudate nucleus, which is involved in motor control, learning, and memory (Grahn et al., 2009). As suggested in the hippocampus, plasticity examined in the motor system may be related to learning vestibular exercise during follow-up. As observed in the right parahippocampal gyrus, positive correlations between GMV increase and peripheral vestibular recovery were examined in the left supplementary motor area, suggesting a boosted training effect for recovery of balance function (Table 3, Fig. 3).

A negative correlation between GMV change and clinical improvement was examined in the right cerebellar hemisphere (20, −66, −57), which is close to the area of GM atrophy (21, −69, −60). In this area, more GM atrophy was associated with better recovery of peripheral vestibular sense (Table 3, Fig. 3). Although speculative, the function subserved by this area seems to be important in VN's earliest stages. As peripheral vestibular function recovers, the functional contribution from this area may decrease and, subsequently, decrease GMV.

These longitudinal results indicate that adaptive changes in the brain vary according to the degree of vestibular functional recovery over time (Choi et al., 2007; Halmagyi et al., 2010). This suggests that functional recovery outcomes would be best using adequate adaptive changes in multisensory cortical areas subserving visual, motor, memory, and cognitive function as well as the vestibular cortex.

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