

Evidence for cortical visual substitution of chronic bilateral vestibular failure (an fMRI study)

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Bilateral vestibular failure (BVF) is a rare disorder of the labyrinth or the eighth cranial nerve which has various aetiologies. BVF patients suffer from unsteadiness of gait combined with blurred vision due to oscillopsia. Functional MRI (fMRI) in healthy subjects has shown that stimulation of the visual system induces an activation of the visual cortex and ocular motor areas bilaterally as well as simultaneous deactivations of multisensory vestibular cortex areas. Our question was whether the chronic absence of bilateral vestibular input (BVF) causes a plastic cortical reorganization of the above-described visual–vestibular interaction. We used fMRI to measure the differential effects of horizontal visual optokinetic stimulation (OKN) on activations and deactivations in 10 patients with BVF and compared their data directly to those of pairwise age- and sex-matched controls. We found that bilateral activation of the primary visual cortex (inferior and middle occipital gyri, Brodmann area BA 17, 18, 19), the motion-sensitive areas V5 in the middle and inferior temporal gyri (BA 37), and the frontal eye field (BA 8), the right paracentral and superior parietal lobule and the right fusiform and parahippocampal gyri was significantly stronger and the activation clusters were larger than that of the age-matched healthy controls. Small areas of BOLD signal decreases (deactivations), located primarily in the right posterior insula containing the parieto-insular vestibular cortex, were similar to those in the healthy controls. No other sensory brain areas showed unexpected activations or deactivations, e.g. the somatosensory or auditory cortex areas. Our finding of enhanced activations within the visual and ocular motor systems of BVF patients suggests that they might be correlated with an upregulation of visual sensitivity during tracking of visual motion patterns. Functionally, these enhanced activations are independent of optokinetic performance, since the mean slow-phase velocity of OKN in the BVF patients did not differ from that in normals. Although psychophysical and neurophysiological tests have provided various examples of how sensory loss in one modality leads to a substitutional increase of functional sensitivity in other modalities, this study presents the first evidence of visual substitution for vestibular loss by functional imaging.

Keywords: optokinetic nystagmus; visual cortex; cortical eye fields; functional magnetic resonance imaging; vestibular cortex; vestibular failure

Abbreviations: BA = Brodmann area; BVF = bilateral vestibular failure; FEF = frontal eye field; fMRI = functional magnetic resonance imaging; MAE = motion aftereffect; OKN = optokinetic nystagmus; PIVC = parieto-insular vestibular cortex

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Introduction

Several separate neural oculomotor subsystems are involved in the visual tracking of a moving target. All have the aim of stabilizing an image on the retina by performing an eye movement in response to the movement of an image. One such subsystem is optokinetic nystagmus (OKN). Distinct from the other subsystems, e.g. smooth-pursuit and saccadic eye movements, OKN is induced by

unidirectional pattern motion and is a reflexive ocular motor response consisting of two rhythmic components: a slow eye movement in the direction of motion stimulation (slow phase) and a quick resetting of the eyes in the opposite direction (quick phase).

Several imaging studies have identified the neural network in the human cortex, which is activated during OKN (Bucher *et al.*, 1997; Brandt *et al.*, 1998;

Dieterich *et al.*, 1998; Galati *et al.*, 1999; Dieterich *et al.*, 2003b; Konen *et al.*, 2005). This network appeared to largely overlap with that elicited during smooth-pursuit eye movements (Petit and Haxby, 1999; O'Driscoll *et al.*, 2000; Tanabe *et al.*, 2002; Konen *et al.*, 2005). Its circuitry shows bilateral activations of the primary visual cortex, the visual motion-sensitive areas in the temporo-occipital cortex, as well as the ocular motor areas, such as the supplementary, frontal and parietal eye fields, and the prefrontal cortex. Simultaneously deactivations are evoked bilaterally in the insular and retroinsular regions, the human equivalent of the parieto-insular vestibular cortex (Brandt *et al.*, 1998; Dieterich *et al.*, 2003b; Konen *et al.*, 2005). Additional deactivations are located in the superior temporal gyrus, inferior parietal lobule, anterior cingulate gyrus, hippocampus and the precentral gyri (Dieterich *et al.*, 2003b). These latter areas belong to the distributed assembly of multisensory vestibular cortex areas, all of which are activated during vestibular stimulation, e.g. by caloric irrigation (Suzuki *et al.*, 2001; Fasold *et al.*, 2002; Dieterich *et al.*, 2003a) or galvanic stimulation of the vestibular nerve (Lobel *et al.*, 1998; Bense *et al.*, 2001; Fink *et al.*, 2003; Stephan *et al.*, 2005). This activation is simultaneously accompanied by a bilateral deactivation of visual and somatosensory cortex areas (Wenzel *et al.*, 1996; Bense *et al.*, 2001; Stephan *et al.*, 2005). Such a robust pattern of activated and deactivated areas supports the hypothesis of a reciprocally inhibitory interaction between the visual and the vestibular systems in healthy subjects (Brandt *et al.*, 1998).

Bilateral vestibular failure (BVF) is a rare disorder of the labyrinth or the eighth cranial nerve which has various aetiologies and often takes a slowly progressive course over several years. BVF causes a loss of peripheral vestibular function bilaterally. The key symptoms are unsteadiness of gait, particularly in the dark and on unlevel ground, combined with blurred vision due to oscillopsia (Brandt, 1996). The diagnosis can be made by the bedside head-impulse test for the deficient vestibulo-ocular reflex, VOR, (Halmagyi and Curthoys, 1988) and by caloric stimulation and rotatory chair testing for absent or severely reduced responses. To compensate for the diminished or missing vestibular input, these patients learn to rely more on somatosensory (Bles *et al.*, 1984b) and visual cues (Gresty *et al.*, 1977; Lacour *et al.*, 1997). Depending on the individual type of behaviour, they depend heavily on vision or not at all (Lacour *et al.*, 1997).

Our question was whether the chronic lack of bilateral vestibular input in BVF patients causes a plastic cortical reorganization of the above-described visual-vestibular interaction. Using functional magnetic resonance imaging (fMRI), we measured the differential effects of visual optokinetic stimulation on activations and deactivations in 10 patients with BVF and compared their data directly to those of pairwise age- and sex-matched

healthy controls subjected to the same stimulation conditions.

Materials and methods

Patients and healthy subjects

Ten right-handed patients (3 f, 7 m; age range 50–80 years, mean age 65.3 ± 14.1 years) with a BVF meeting the criteria of Baloh and Furman (1989) and a slow-phase velocity (SPV) of maximal caloric nystagmus of $<5^\circ/\text{s}$, participated in the study. Their data were compared with that of an age- and gender-matched control group (3 f, 7 m; mean age 61.2 ± 11.7 years). Vestibular failure was evaluated by testing the function of the horizontal semicircular canal by electro-oculography. Semicircular canal function was tested by binaural bithermal caloric irrigation at 30 and 44°C, rotatory testing, as well as caloric irrigation with ice water at 4°C. Mean SPV of maximal caloric nystagmus for the BVP group was $2.1^\circ/\text{s}$ ($\pm 3.8^\circ/\text{s}$), for the age-matched control group $46.8^\circ/\text{s}$ ($\pm 16.8^\circ/\text{s}$). This difference of maximal caloric nystagmus in both groups was highly significant ($F = 87.705$, $df = 1; 25$, $P < 0.001$).

Exclusion criteria were the presence of an acute or chronic central vestibular and central ocular motor disorders, regular intake of medication that affected the CNS, an acute disease of the CNS or an acute malignancy. The modified laterality quotient of handedness according to the 10-item inventory of the Edinburgh test (Chapman and Chapman, 1987) was determined beforehand, since differential effects due to hemispheric dominance had to be considered (Dieterich *et al.*, 2003a). Only completely right-handed control subjects without a history of vestibular, hearing or CNS disorders and right-handed patients participated in the experiment. The study was performed in accordance with the Helsinki Declaration and approved by the local ethics committee. Each participant of this study gave his/her informed written consent.

Optokinetic stimulation and eye tracking

Subjects lay supine with their view directed to a projection surface in front of the scanner bore by a special mirror box of the eye movement recording system (MEyeTrack-LR, SensoMotoric Instruments, SMI, Berlin/Boston; www.smi.com), which was placed on the head coil. A computer-generated stimulus pattern of 14 vertical black-and-white stripes, which remained stationary [i.e. rest condition means stationary visual stimulus (SVS) condition] or moved horizontally with $6^\circ/\text{s}$ velocity in a rightward or leftward direction (stimulation condition A and B), was projected onto this screen by a liquid crystal display projector. The field of view in this setup was restricted to 20° in the horizontal and 15° in the vertical dimensions, i.e. small-field stimulation that did not induce apparent self-motion (vection), but steady optokinetic nystagmus. The subjects were required to look at the target during the whole acquisition time. Both performance of visually induced optokinetic nystagmus and alertness (determined by blink frequency and duration) were monitored and recorded in the control room by the eye-tracking system using real-time image processing. Two-dimensional movement analysis was performed offline on the dominant eye using WinEye software. The calibrated data were low-pass filtered with a digital Gaussian filter having a band width of 20 Hz. Fast phases were automatically detected and removed from the data using a combined velocity-acceleration

criterion in interactive software so that detection errors could be corrected manually (for method see Glasauer *et al.*, 2001). To identify a gaze shift between rest and OKN conditions, the eye position was determined for each block of stimulation (33.6 s) separately. The average eye position was calculated and compared with the average eye position during the preceding rest condition. The order and direction of the stimulations were randomized for each subject.

MRI acquisition

The subjects were positioned in the circularly polarized head coil in a clinical 1.5 T scanner (Siemens Magnetom Vision, Erlangen) using echo-planar imaging (EPI) with a T_2^* -weighted EPI sequence (TR = 4.31 s, TE = 60 ms, FOV = 192–220 mm, image matrix = 64^2 , slice thickness = 4 mm). The protocol included 256 volumes, each consisting of 40 transversal slices that covered the whole brain. Alternating blocks of eight images at rest (looking at the stationary striped target) and eight images during rightward or leftward OKN were acquired in randomized order. To reduce head movements and consequently artificial activation patterns during data acquisition (Friston *et al.*, 1996), the subject's forehead was taped to the coil. Subjects wore ear protection and were asked to lie in a relaxed position with their eyes open for the whole experiment in an otherwise completely darkened scanner room. The images were collected parallel to the AC–PC line. The first three volumes of each session were discarded for reasons of signal quality, e.g. spin saturation effects. Prior to the acquisition of the functional data, a high-resolution sagittal T_1 -weighted image (MPRAGE sequence, 180 slices, slice thickness = 1 mm, image matrix = 256^2 , TR = 9.7 ms, TE = 4 ms) was made for each participant, on which results of the functional data were later superimposed as co-registered images on the image of the individual anatomy.

Data analysis

fMRI data were processed using Pentium IV workstations running on Windows 2000 or XP®. The fMRI data sets were reconstructed offline, and then converted into the file format that was analysed using Statistical Parametric Mapping software (SPM2, Wellcome Department of Imaging Neuroscience, London, 2005). The images were realigned to the first one of each scanning session to correct for subject movement and were then stereotactically normalized into the standard anatomical space defined by the Montreal Neurological Institute (MNI) template by means of linear and non-linear transformation (Friston *et al.*, 1995a). Thus, all stereotactic coordinates given in this paper refer to the MNI coordinate system. During normalization, the image volumes were resampled at a resolution of $2 \times 2 \times 2 \text{ mm}^3$. Prior to statistical analysis, the normalized images were subsequently smoothed with a 3D isotropic Gaussian filter using a 10-mm full-width half-maximum FWHM kernel. A high-pass filter (128 s) was integrated into the design matrix to eliminate low frequency noise. The effect of the different stimulation conditions on regional BOLD responses was estimated according to the general linear model (Friston *et al.*, 1995c). Statistical parametric maps (SPMs) were generated on a voxel-by-voxel basis with a hemodynamic model of the stimulation periods present during the session

(Friston *et al.*, 1995b). SPMs were computed to compare each OKN condition with the SVS, rightward OKN versus SVS, and leftward OKN versus SVS. To account for a probable motion aftereffect, MAE (Taylor *et al.*, 2000; Huk *et al.*, 2001) or an optokinetic afternystagmus immediately after OKN stimulation (Bles *et al.*, 1983), the period of the SVS was further divided into an early (SVS1) and a late phase (SVS2). Separate *t*-contrasts were calculated for SVS1 versus SVS2 for all subjects. This appeared necessary because an optokinetic afternystagmus of healthy subjects under certain stimulation conditions would be significantly reduced or absent in BVF patients due to the missing velocity storage mechanism (Bles *et al.*, 1983, 1984a, b). Thus, the 'rest' conditions (SVS) could have been different in both groups.

Clusters exceeding a threshold of $P \leq 0.001$ and a cluster size threshold of five voxels were considered significant. These condition images were entered into a second-level statistical analysis to test for effects on a between-subject basis. This approach corresponds to a random effects analysis, which extends the scope of inference to the population from which the subjects were initially recruited. Paired *t*-tests for the different sides of OKN stimulation were performed using the linear *t*-contrasts. Two sample *t*-tests were used to compare the patients with the healthy control group. Activations and deactivations were reported (Shmuel *et al.*, 2002). Anatomical localizations of the results were determined using anatomical landmarks, the atlas of Talairach and Tournoux (1988), and the software and parcellation described by Tzourio-Mazoyer and co-workers (Tzourio-Mazoyer *et al.*, 2002).

In a second step, region-of-interest (ROI) analyses were performed bilaterally for the frontal eye fields, the insula, MT/V5 and MST. ROIs were created with MARINA (Walter *et al.*, 2003). The mask for the frontal eye fields was drawn according to the coordinates described by Grosbras and co-workers (2005). For MT/V5 and MST the anatomical landmarks in the works of Smith and co-workers (2006) and Seiffert and co-workers (2003) were used.

Results

Eye movement recording

Analysis of the eye movement recordings demonstrated that the visual stimulation steadily induced OKN, and all subjects were able to accurately perform the task during the whole acquisition time. Post-scanning data analysis revealed no significant differences between the patients and the control group for gaze shift or differences in SPV of the nystagmus during stimulation. Mean SPV of the nystagmus was $7.2^\circ/\text{s} \pm 3.5^\circ/\text{s}$ SD for rightward and $-8.5^\circ/\text{s} \pm 5.6^\circ/\text{s}$ SD for leftward OKN (horizontal mean SPV $7.9^\circ/\text{s} \pm 4.7^\circ/\text{s}$ SD). Post-scanning data analysis further revealed a gaze shift of $2.6^\circ \pm 1.6^\circ$ SD during rightward OKN toward the fast phase (right) and a gaze shift of $-2.7^\circ \pm 1.6^\circ$ SD during leftward OKN toward the left. There were no significant interindividual differences or differences between rightward and leftward OKN. Neither the BVF patients nor the healthy subjects showed an optokinetic afternystagmus.

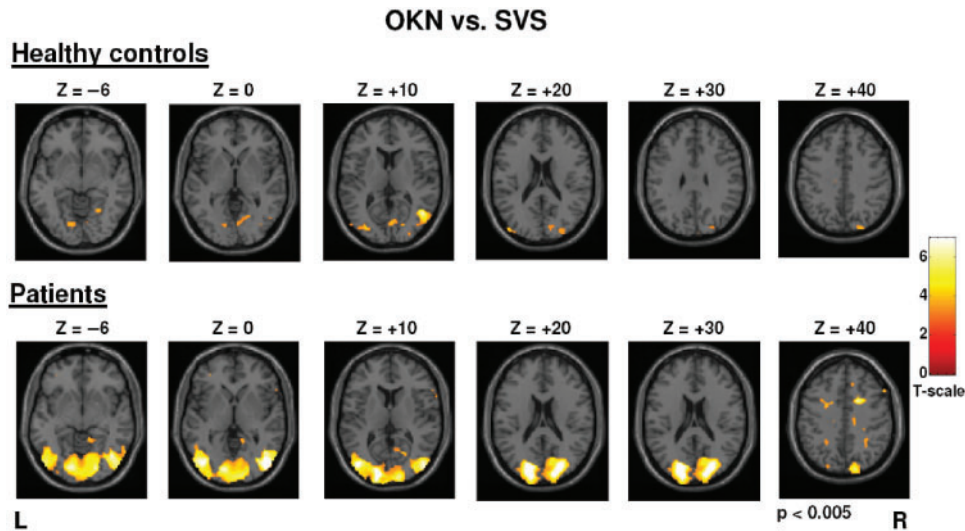


Fig. 1 Head-to-head display of the activation in the *t*-contrast OKN versus SVS in the BVF patients (bottom) and the healthy control group (top).

BOLD signal increases (activations) and decreases (deactivations)

OKN versus SVS in patients with bilateral vestibulopathy

Bilateral activation was found in the middle and inferior occipital gyri (BA 17, 18, 19), the cuneus and precuneus, and MT/V5 in the middle and inferior temporal gyri (BA 37) (Fig. 1). The frontal eye field (FEF, BA 8) was activated in the right hemisphere. A further activation was located in the right paracentral and superior parietal lobule, and in the right fusiform and parahippocampal gyrus. An ROI analysis for the frontal eye fields showed a bilateral activation, again with a stronger response of the right FEF. Relevant deactivations were found in the right posterior inferior vestibular cortex (Fig. 2A).

Patients versus healthy controls for OKN versus SVS

The group comparison showed a significantly stronger bilateral activation of MT/V5 in the inferior and middle temporal gyri in the patients than in the healthy controls (Fig. 2B). Both FEFs were activated significantly more in the patient group than in the control group (Fig. 2C).

No significant deactivations were found in the areas of MT/V5 and FEF. An ROI calculation for the insular cortex revealed no significant deactivation differences in the patients in a two sample *t*-test with the healthy controls.

SVS1 versus SVS2 in patients alone and in comparison to the healthy controls

After subdividing the baseline condition (SVS) into two phases, an early one SVS1 and a late one SVS2, we found a strong motion aftereffect in the patients (Fig. 2D). SVS1 showed significant resonating activation in MT/V5 and MST

bilaterally, the right middle and medial frontal gyrus (BA 6), and the superior and inferior parietal lobule (BA 7, 40) in the right hemisphere. However, the group comparison patients versus healthy controls did not produce any significant differences for this well-known neuropsychological phenomenon (Taylor *et al.*, 2000; Huk *et al.*, 2001).

Correlation analyses for OKN versus SVS in patients with bilateral vestibulopathy

There were no significant correlations of the OKN paradigm with the duration of the post-rotatory nystagmus or with the maximum caloric nystagmus after ice water irrigation (4°C). The duration of BVF symptoms was negatively correlated with the frontal and parietal eye fields. A negative correlation of our stimulus with age was also seen in parts of the visual cortex (correlation coefficient $r = 0.91$; gradient -0.046 in the global maximum) (Fig. 3). The younger the patient, the more activation there was in the lingual and inferior occipital gyri bilaterally, the right middle and superior occipital gyrus (BA 18, 19) and the cuneus. A conjunction analysis (Worsley *et al.*, 1998) revealed no common denominator for the two correlation analyses with age and the duration of symptoms in our BVF patients. A negative correlation of age with parts of the visual or ocular motor systems was also found in our age-matched control group for the frontal eye fields (correlation coefficient $r = 0.84$; gradient -0.0115 ; Fig. 3), but not for visual cortex areas. However, this negative correlation was observed in a larger healthy control group with a broader age range (Bense *et al.*, 2005a). Thus, our negative result for visual cortex areas may be accidental and due to the small number of subjects who were at the upper end of the age span and had higher response variance. Furthermore, older

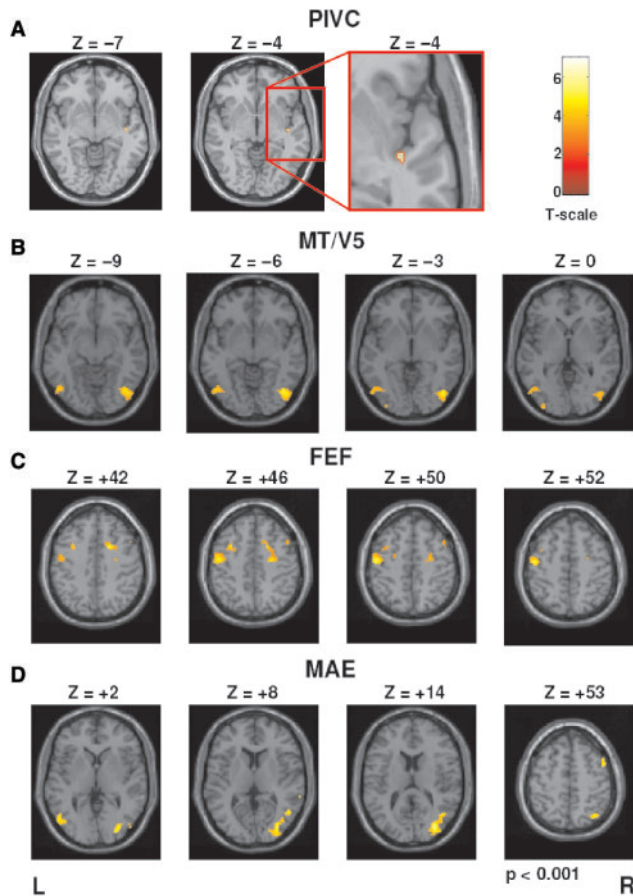


Fig. 2 Deactivation of the right PIVC during OKN stimulation of BVF patients. **(A)** Masked two sample *t*-test for MT/V5 showing a stronger bilateral activation for this area in the inferior and middle temporal gyri in the patients than in the healthy control subjects. **(B)** In another ROI analysis we also found both masked frontal eye fields (FEF) to be more activated in the patients than in the control group. **(C)** 'Normal' motion aftereffect (MAE) during the early phase of SVS with activation of MT/V5 and MST bilaterally in BVF patients subsequent to the optokinetic stimulation. **(D)** Significance threshold of $p < 0.001$ for all rows A–D.

patients showed a decreased *deactivation* in the left posterior insula (insular gyrus V) (negative correlation).

Discussion

The perceptual consequences of chronic BVF are 2-fold. First, self-motion perception is impaired and must be largely substituted by 'increasing sensitivity' to the optic flow. Second, vision is blurred by oscillopsia; it is alleviated by 'decreasing the visual sensitivity' to motion during locomotion. Thus, the visual system apparently has two opposing mechanisms that partially substitute for the absent vestibular function, i.e. upregulation during passive locomotion and downregulation during active locomotion. Psychophysical data on these mechanisms support earlier findings that detection times for single object motion are

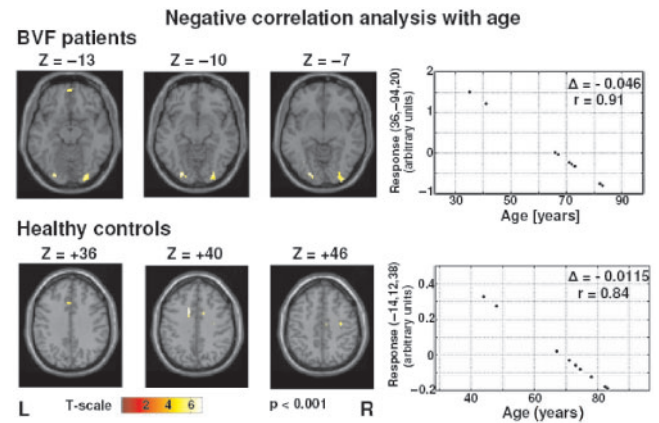


Fig. 3 Comparison of the two negative correlation analyses with age in the BVF patients (upper row) and the healthy control group (lower row). Whereas parts of the visual cortex (MT/V5) showed a diminished activation in the BVF patients with a higher age, only the frontal eye fields showed a comparable correlation at the same threshold in an identical setup for the healthy controls.

increased in patients with BVF (Grünbauer *et al.*, 1998), and thresholds for somatosensory circular vection during 'apparent stepping around' are decreased (Bles *et al.*, 1984b; Bles and de Jong, 1986).

The particular visual motion stimulation condition used in our study, i.e. patients lay stationary and supine during stimulation by a small-field horizontally moving optokinetic pattern, required analysis and tracking of environmental motion rather than suppression of oscillopsia. Under these conditions we found significantly stronger bilateral activations of the primary visual cortex (inferior and middle occipital gyri, BA 17/18/19), the cuneus and precuneus, the motion-sensitive areas MT/V5 in the middle and inferior temporal gyri (BA 37) and the frontal eye field (BA 8), and larger activation clusters than in age-matched healthy controls. The activations of paramedian visual cortex areas, however, were like those in healthy subjects (Bense *et al.*, 2005b), i.e. stronger in the hemisphere contralateral to the slow phase of horizontal OKN (pursuit). This can be attributed to a shift of the mean eye position of gaze (beating field) in the direction of the fast nystagmus phases, causing asymmetrical visual cortex stimulation. Activations of the frontal and parietal eye fields were negatively correlated with the duration of BVF symptoms; activations of visual cortex areas were likewise negatively correlated with symptom duration but also with patient age. These two aspects were combined, although the older patients did not present with the longer duration of disease. Normal controls also showed negative correlations of activations in the frontal eye fields with age, but the correlation coefficient and gradient were higher for the patient data (Fig. 3). Thus, while both older normals and older BVF patients exhibit relevant reductions of the cortical activation pattern in the visual and ocular motor

areas with increasing age, they occur at a higher activation level in the patients.

Small areas of BOLD signal decreases (deactivations) were located primarily in the right posterior insula of patients and were similar to those in healthy controls. No other sensory brain areas showed unexpected activations or deactivations.

Sensory interactions in patients with vestibular loss: substitution by other sensory systems

The enhanced activations in the visual and ocular motor systems of BVF patients appear to reflect an upregulation of visual sensitivity during tracking of visual motion patterns. Functionally, this is independent of optokinetic performance, since the mean SPV of OKN in the BVF patients did not differ from that in normals. It is, however, theoretically possible that the missing otolith input in supine position also plays a role.

Psychophysical and neurophysiological tests have provided various examples of sensory loss in one modality being substituted by increased functional sensitivity in other modalities (e.g. Curthoys and Halmagyi, 1995). Especially the data for patients with vestibular loss indicate involvement of the somatosensory system (e.g. the cervico-ocular reflex) rather than the visual system.

Under purely somatosensory stimulation conditions, i.e. with limb movements, BVF patients exhibited significantly higher gains of cervico-ocular reflexes (Bles *et al.*, 1983) and characteristic abnormalities of arthrokinetic nystagmus: e.g. drastic shortening of latencies, faster build-up of SPV, higher plateau, increased gain and faster decrease of nystagmus and afternystagmus than controls (Bles *et al.*, 1983, 1984a, b). Thus, somatic afferent information receives greater sensory weight. Whereas the gain of the cervico-ocular reflex is low in normals, its importance is significantly enhanced in BVF patients (Kasai and Zee, 1978; Bles *et al.*, 1983; Bronstein and Hood, 1986). Visual information, however, can greatly modify this gain (Heimbrand *et al.*, 1996).

Patients with BVF appear to lack the 'velocity storage' mechanism (i.e. a central phenomenon that preserves the raw vestibular signal), which patients with unilateral vestibular loss still exhibit (Cohen *et al.*, 1973). Rotational testing in patients (Baloh *et al.*, 1984; Böhmer and Fisch, 1993) and monkeys after bilateral neurectomy (Waespe *et al.*, 1992) demonstrated the frequency-dependent gain and the abolished velocity storage mechanism. In the dark, patients with BVF had no or very low gains, whereas when tested with a stationary light or even with imaginary stationary visual targets in the dark their gain could be enhanced to normal values (Möller and Ödkvist, 1989). Furthermore, body sway with eyes open in patients lacking both labyrinths showed a significant and gradual improvement over a 29-month period much more so than

with eyes closed (Bles and de Jong, 1986). This finding holds for both BVF patients and patients with unilateral vestibular loss (Lacour *et al.*, 1997). These findings in humans agree with earlier neurophysiological data in monkeys: physical exercise under visual control accelerated compensation after unilateral and bilateral labyrinthectomy (Igarashi *et al.*, 1975, 1979, 1981). Recent studies show that further substitution of missing vestibular input is achieved by refixation saccades and enhanced smooth pursuit eye movements (Bockisch *et al.*, 2004) as well as by auditory feedback (Möller and Ödkvist, 1989; Hegeman *et al.*, 2005). All these effects are transient and reversible, if the function of the sensory organ is restored or regained, e.g. in patients with *unilateral* vestibular lesions. They persist, if the bilateral vestibular failure persists. In our study the BVF was chronic; the mean duration of disease was 32 months.

Thus, afferent somatosensory as well as visual information have a greater sensory weight when the vestibular deficits are compensated by substitution. The compensating mechanisms, however, seem to be task-specific and dependent on the individual stimulation condition, since some studies found no significantly increased somatosensory sensitivity. For example, the effects of BVF on the podokinetic after-rotation for 30 min were determined and compared to that in controls. The responses of BVF patients differed only within the first 1–2 min (rapid rise in turning velocity), but not for the response decay during minutes 2 to 30 (Earhart *et al.*, 2004). The authors therefore concluded that the absence of vestibular input did not cause a general alteration of podokinetic intensity or decay time constants, and thus somatosensory sensitivity in general was not increased.

Suppression of distressing oscillopsia in patients with vestibular loss

The psychophysical effects on the perception of object motion reflect a decrease in sensitivity (psychophysical studies). Visual motion perception of a single moving target was significantly impaired in BVF patients, even when the head and body remained stationary (Grünbauer *et al.*, 1998). These findings seem to indicate suppression of oscillopsia during self-motion: even under static head and body conditions without involuntary retinal slip by the defective VOR, the system seems in principle downregulated in this task-specific stimulation condition. A similar impairment of object-motion perception was also found in patients with acquired infranuclear ocular motor palsies and supranuclear ocular oscillations such as congenital and downbeat nystagmus (Dieterich and Brandt, 1987).

Since fMRI examinations can only be performed under static body conditions, the deficits of the VOR during head and body movements have not yet been directly examined in BVF patients. Therefore, no human imaging studies have analysed the cortical sensory interactions during head or

Table 1 Data on gender and age of the BVF patients as well as duration, aetiology of the disease and vestibular function (maximum slow-phase velocity of caloric nystagmus after ice water irrigation and mean duration of bilateral postrotatory nystagmus)

Initials	Gender (r)	Age (y)	Aetiology	Duration ^a	Caloric testing (°/s) ^b	Post-rotatory response (s) ^c
AB	f	68	Autoimmune	20 months	3	0
HB	f	71	Idiopathic	36 months	8	0
RE	m	41	Idiopathic	18 months	0	0
HG	m	72	Idiopathic	12 months	6	2
DJ	m	66	Toxic	24 months	6	0
HK	m	73	Idiopathic	60 months	0	10
RM	m	35	Idiopathic	18 months	0	0
FO	f	82	Idiopathic	14 months	0	10
BP	m	83	Ménière's disease	20 months	7	2
WW	m	68	Ménière's disease	21 months	10	0

^aTime period from the first symptoms of the illness to fMRI-testing.

^bMaximum slow phase velocity after ice water irrigation.

^cDuration of post-rotatory nystagmus.

body movements. Future studies will need to determine whether the chronic condition of BVF also leads to a decrease of visual cortex activity during simultaneous stimulation of vision and movements of the head.

Deactivations of the posterior insula

Our finding that the multisensory vestibular cortex in the posterior insula of BVF patients is also deactivated as in the controls was unexpected. One possible explanation could involve the multisensory neurons of this temporo-parietal cortex region, the PIVC and retroinsular areas. Monkey studies have shown that these neurons process signals for head and body orientation in space by responding to vestibular, somatosensory, optokinetic and visual stimulation (Grüsser *et al.*, 1990*a, b*). The absence of vestibular input does not necessarily mean the complete suppression of function in a multisensory cortex area, since input from the other sensory systems can compensate for it.

This 'normal' pattern of deactivation within the posterior insula during visual optokinetic stimulation indicates that cortical interaction between the sensory systems, which is normally reciprocal inhibitory (Brandt *et al.*, 1998), is preserved. Activations of visual cortex areas in a stationary subject are usually combined with a simultaneous deactivation of the multisensory vestibular cortex areas during visual stimulation (Brandt *et al.*, 1998; Dieterich *et al.*, 2003*b*; Konen *et al.*, 2005) and vice versa (Bense *et al.*, 2001; Stephan *et al.*, 2005). Under our visual stimulation conditions of the stationary BVF patients, the different sensory neural networks of the cortex might process information that a significant visual input is combined with no vestibular input (the latter encoded as a deactivation of the vestibular cortex area in the posterior insula). The chronic loss of vestibular function would

indicate that a certain amount of deactivation in the posterior insula is independent of an intact peripheral vestibular function. Thus, the interaction of the sensory systems at cortical level is preserved (even in patients with longer loss of vestibular function). The deactivation of the posterior insula is probably an internal signal induced by the visual stimulus itself, which does not match quantitatively the extent of vestibular function. It also does not match the extent of visual cortex activation, because the enhanced activations of visual cortex areas should be associated with enhanced deactivations of the multisensory vestibular cortex areas, which was not the case in our patients.

Conclusion

The results of this study have raised a number of new questions. One is whether and to what extent the increase in visual cortex activation correlates with increased or decreased visual sensitivity. An age-related investigation is necessary to determine the probable psychophysical consequences. Furthermore, our experimental paradigm was restricted to visual motion stimulation of a stationary subject, and thus it did not allow us to precisely predict the differential effects of visual motion stimulation during head and body motion or optokinetically induced vection. This is a topic for future research.

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