

## REVIEW ARTICLE

# Functional brain imaging of peripheral and central vestibular disorders

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**This review summarizes our current knowledge of multisensory vestibular structures and their functions in humans. Most of it derives from brain activation studies with PET and fMRI conducted over the last decade. The patterns of activations and deactivations during caloric and galvanic vestibular stimulations in healthy subjects have been compared with those in patients with acute and chronic peripheral and central vestibular disorders. Major findings are the following: (1) In patients with vestibular neuritis the central vestibular system exhibits a spontaneous visual-vestibular activation–deactivation pattern similar to that described in healthy volunteers during unilateral vestibular stimulation. In the acute stage of the disease regional cerebral glucose metabolism (rCGM) increases in the multisensory vestibular cortical and subcortical areas, but simultaneously it significantly decreases in the visual and somatosensory cortex areas. (2) In patients with bilateral vestibular failure the activation–deactivation pattern during vestibular caloric stimulation shows a decrease of activations and deactivations. (3) Patients with lesions of the vestibular nuclei due to Wallenberg’s syndrome show no activation or significantly reduced activation in the contralateral hemisphere during caloric irrigation of the ear ipsilateral to the lesioned side, but the activation pattern in the ipsilateral hemisphere appears ‘normal’. These findings indicate that there are bilateral ascending vestibular pathways from the vestibular nuclei to the vestibular cortex areas, and the contralateral tract crossing them is predominantly affected. (4) Patients with posterolateral thalamic infarctions exhibit significantly reduced activation of the multisensory vestibular cortex in the ipsilateral hemisphere, if the ear ipsilateral to the thalamic lesion is stimulated. Activation of similar areas in the contralateral hemisphere is also diminished but to a lesser extent. These data demonstrate the functional importance of the posterolateral thalamus as a vestibular gatekeeper. (5) In patients with vestibulocerebellar lesions due to a bilateral floccular deficiency, which causes downbeat nystagmus (DBN), PET scans reveal that rCGM is reduced in the region of the cerebellar tonsil and flocculus/paraflocculus bilaterally. Treatment with 4-aminopyridine lessens this hypometabolism and significantly improves DBN. These findings support the hypothesis that the (para-) flocculus and tonsil play a crucial role in DBN. Although we can now for the first time attribute particular activations and deactivations to functional deficits in distinct vestibular disorders, the complex puzzle of the various multisensory and sensorimotor functions of the phylogenetically ancient vestibular system is only slowly being unraveled.**

**Keywords:** vestibular system; vestibular disorder; functional imaging; fMRI; PET

**Abbreviations:** fMRI = functional magnetic resonance imaging; PET = positron emission tomography; BC = brachium conjunctivum; PIVC = parieto-insular vestibular cortex; VOR = vestibulo-ocular reflex; CVTT = central ventral tegmental tract; INC = interstitial nucleus of Cajal; MLF; medial longitudinal fasciculus; NPH = nucleus prepositus hypoglossi; PPRF = paramedian pontine reticular formation; Vce = nucleus ventrocaudalis externus; Vim = nucleus ventro-oralis intermedius; Dc = nucleus dorsocaudalis; Vci = nucleus ventrocaudalis internus; VPLo = nucleus ventroposterior lateralis oralis; PMT = nucleus of the paramedian tract; DBN = downbeat nystagmus; rCGM = regional cerebral glucose metabolism

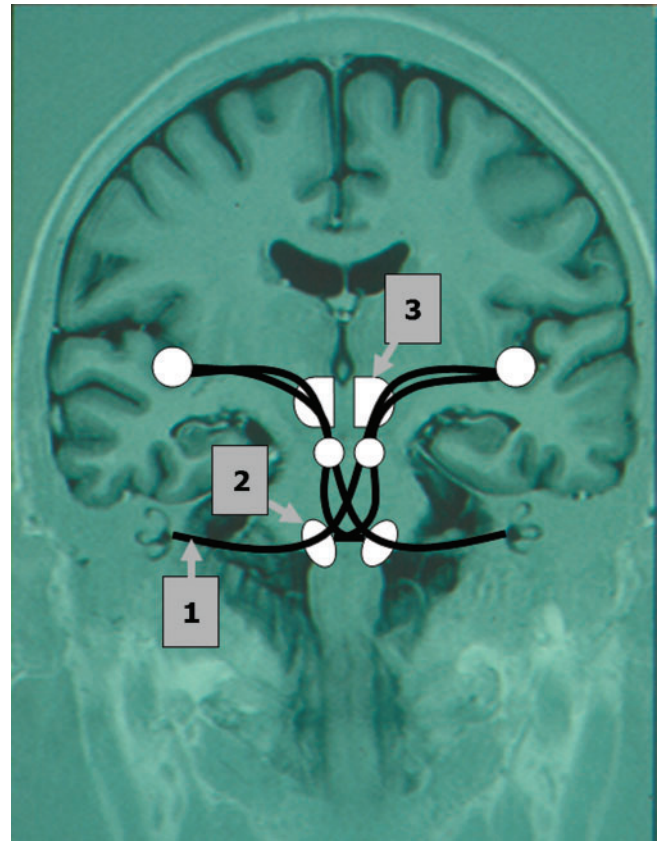
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## Introduction

Experimental stimulation of the intact vestibular system by caloric irrigation or galvanic currents elicits vertigo with signs and symptoms similar to those of clinical vertigo syndromes which manifest with disorders of the labyrinth, the eighth nerve or the central vestibular pathways. Thanks to their improving spatial resolution, PET and fMRI brain activation studies now provide a tool for imaging central connectivity and interactions of different sensory systems. These methods are quite reliable for determining cortical and subcortical as well as cerebellar activation patterns, but still limited when it comes to brainstem structures. When combined with vestibular stimulation in normal subjects, a specific cortical pattern of activations and deactivations is elicited in the sensory systems which will be modified in patients with lesions of peripheral and central vestibular structures. In the following we review current understanding from brain activation studies of the interconnections of vestibular structures, their activations and interactions with other sensory modalities, the correlations of perceptual and motor functions in normal humans, and the changes that result from strategic unilateral peripheral and central vestibular lesions. We first describe the typical cortical activation pattern of unilateral vestibular stimulation in normal subjects, and then show how this pattern is altered in patients with (1) acute unilateral and chronic bilateral peripheral vestibular failure, (2) acute vestibular nuclei lesions (Wallenberg's syndrome), (3) acute lesions of the vestibular posterolateral thalamus relay station and (4) cerebellar disorders of the flocculus [downbeat nystagmus (DBN) syndrome] and nodulus/uvula affecting the vestibulo-ocular reflex (Fig. 1).

The vestibular system is based on the principle of fusion of bilateral sensors, the input of which is distributed in a bilaterally organized neuronal network. The major functions of this system include perceptual, ocular motor, postural and vegetative functions as well as navigation and spatial memory. A neural network with its core circuitry in the brainstem is required to mediate the vestibulo-ocular reflex (VOR). The VOR is not a separate neural and functional system but is imbedded in a complex multisensory system containing numerous ascending and descending pathways that subserve the following major functions. Thus, the vestibular input, which is fed into the VOR structures, is also fed into adjacent but separate fibres for perception and balance control.

- Vestibular *ocular motor* functions are mediated directly by the VOR itself. In its basic version for rapid reflexive ocular motor control, it consists of a three-neuron arc that connects the semicircular canals within both labyrinths via the vestibular nuclei, the ascending tracts (medial longitudinal fasciculus, MLF, central ventral tegmental tract, CVTT, brachium conjunctivum, BC), and the ocular motor nuclei (III, IV, VI) in the ponto-mesencephalic brainstem tegmentum to their



**Fig. 1** Simplified schematic drawing of central structures and pathways involved in the processing of vestibular information. Vestibular input from the labyrinth travels via the vestibular nuclei to the ocular motor nuclei (vestibulo-ocular reflex). Further ascending pathways run from the vestibular nuclei via the posterolateral thalamus to the temporo-insular cortex. Typical sites of lesions within the vestibular circuit are roughly indicated by numbers: vestibular nerve (1), vestibular nucleus in the medullary brainstem (2), posterolateral thalamus (3).

corresponding pair of extraocular eye muscles (for review: Leigh and Zee, 2006). Due to the incorporation of the VOR in a complex multisensory system with ascending and descending pathways—mostly adjacent but separate, in part collaterals of the fibres mediating the VOR—the following additional functions are achieved:

- *Perceptual* functions operate via pathways that run through the lateral and ventroposterior lateral thalamus (nucleus ventro-posterior lateralis, VPL; nucleus ventro-orialis intermedius, Vim) to a number of temporo-parietal cortex areas such as the strongly interconnected area 2v, area 3aV and the temporo-parietal vestibular cortex (PIVC), as well as retroinsular areas, superior temporal gyrus, inferior parietal lobule (Ödkvist *et al.*, 1974; Büttner and Henn, 1976; Büttner *et al.*, 1977; Büttner and Büttner, 1978; Akbarian *et al.*, 1992; Guldin and Grüsser, 1996; Klam and Graf, 2003a, b; Hegemann *et al.*, 2004; Lackner and DiZio, 2005). These areas are all multisensory, i.e. their neurons respond to

several stimuli (somatosensory, vestibular and/or visual optokinetic) and form a multisensory cortical neural network. Other pathways reach areas such as the anterior insula and adjacent inferior frontal gyrus, hippocampus, anterior cingulate cortex and precuneus that were found to be activated in human functional imaging studies (Vitte *et al.*, 1996; De Waele *et al.*, 2001; Dieterich *et al.*, 2003a; Miyamoto *et al.*, 2007). The vestibular projections to the cerebral cortex presumably carry information for spatial orientation, but they also are involved in other aspects of vestibulo-ocular control such as cerebral influences on vestibular adaptation and context or anticipation of specific motor responses (Ventre-Dominey *et al.*, 2003; for review: Leigh and Zee, 2006).

- The *postural control* of head and body is mediated via the descending tracts, e.g. the medial vestibulo-spinal tract to the cervical cord for head position in space and the lateral vestibulo-spinal tract to the thoracic spinal cord for head and body position in space (Nathan *et al.*, 1996).
- *Vegetative functions* are conveyed by pathways from the vestibular nuclei to the locus coeruleus, nucleus of the solitary tract, area postrema and the central nucleus of the amygdale (Pompeiano *et al.*, 2002) as well as the parabrachial nucleus, infralimbic cortex and hypothalamus (Balaban and Thayer, 2001; Balaban, 2004). Close connections between the vestibular system and vegetative functions and respiration were described not only in animal studies but also in humans (Radtko *et al.*, 2000).
- *Navigation* seems to be mediated by ‘head direction cells’ in the thalamus (for review see: Taube *et al.*, 1996) and ‘place cells’ in the hippocampus (O’Mara *et al.*, 1994; Wiener *et al.*, 1995). Various anatomical connections have been proposed to join the vestibular nuclei to the hippocampus, e.g. connections via the thalamus, the dorsal tegmental nucleus (i.e. the ‘head direction pathway’) or the pedunculopontine tegmental nucleus (i.e. the ‘theta pathway’) (Smith, 1997; Horii *et al.*, 2004). Indeed, using functional MRI, Vitte and co-workers (1996) demonstrated that vestibular caloric stimulation even activates the hippocampal formation in humans.

Furthermore, multisensory visual and somatosensory functions receive a major vestibular input due to the convergence of the ascending systems at different levels, beginning at the vestibular nuclei (Angelaki *et al.*, 1993) and the ocular motor nuclei (Baker *et al.*, 1973; Schwindt *et al.*, 1973).

Additional neural assemblies with strong vestibular representation are imbedded in this multisensory network. They include the interstitial nucleus of Cajal (INC), the rostral interstitial nucleus of the MLF (riMLF), the paramedian pontine reticular formation (PPRF) and the nucleus prepositus hypoglossi (NPH) in the brainstem, the flocculus, uvula, nodulus, fastigial and dentate nucleus

of the cerebellum, all of which mainly control eye movements and eye–head coordination. The multisensory vestibular structures above the level of the rostral midbrain tegmentum mainly subserve perception of self-motion, spatial orientation and navigation. These structures include the posterolateral ‘vestibular’ thalamus (containing the subnuclei ventroposterior lateralis, VPLo; ventrocaudalis externus, Vce; ventro-oralis intermedius, Vim; dorsocaudalis, Dc; ventrocaudalis internus, Vci), the multiple temporo-parietal cortex areas and the hippocampus and parahippocampal formation. The interaction and cooperation of the separate and distinct multisensory neural assemblies are mediated in the brainstem by reciprocal interconnections like the MLF, CVTT and Deiter’s tract, which can be excitatory as well as inhibitory. The floccular Purkinje cells can serve as an example of this process: they send their inhibitory efference to the vestibular nuclei for vestibular function and to the pontine nuclei for ocular motor function, especially vertical gaze control by means of different transmitters such as gabaergic or glutaminergic substances.

Thus, the theme of this review is the attempt to correlate signs and symptoms of vestibular disorders with the patterns of spontaneous activity and changes in activity in brain imaging as distinct from normal controls during unilateral vestibular stimulation. The selection of conditions was based on typical and circumscribed lesions along the neuronal vestibular input chain from the peripheral labyrinth and vestibular nerve [vestibular neuritis, bilateral vestibular failure (BVF)] to disorders of the two major nuclei (vestibular nuclei, vestibular thalamus) which convey and distribute bilateral vestibular information about motion and orientation via ascending pathways to multisensory temporo-parietal vestibular cortex areas. Special emphasis has been put on the differential effects of unilateral and bilateral cortical activity of vestibular and visual areas in order to disclose the ascending pathways, the correlate of vertigo due to an acute vestibular tonus imbalance, and the cortical visual substitution of a bilateral vestibular loss. Brain activation studies allow us to elucidate and differentiate the gross activity and hemispherical asymmetry of vestibular cortical function in patients suffering from acute and chronic peripheral and central vestibular disorders. Bilateral cerebellar floccular disorders with impairment of inhibitory Purkinje cell activity of vertical vestibular and ocular motor function have been imaged by fMRI and PET before and after treatment, as a first demonstration of medically altered activity of vestibular neuronal assemblies by PET.

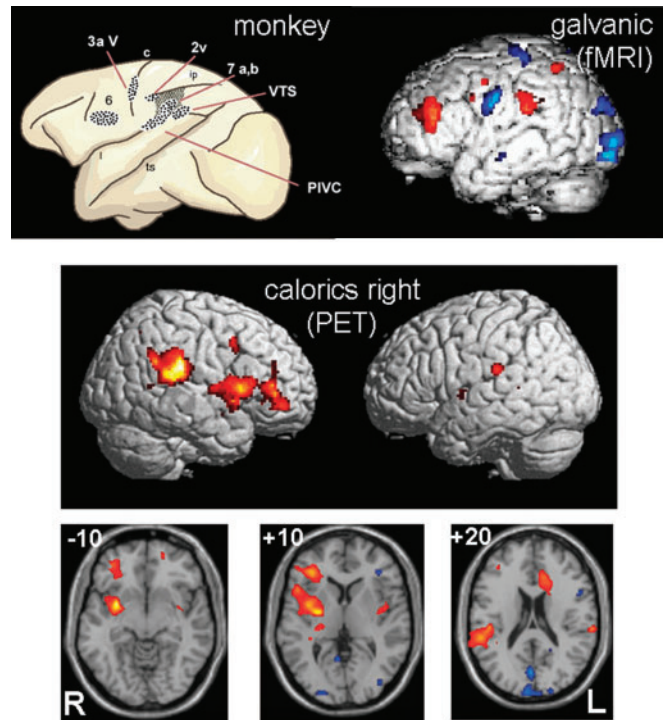
### Brain activations and deactivations during vestibular stimulation in healthy subjects

Imaging studies in humans have confirmed the existence of several separate and distinct cortical areas identified earlier by tracer and electrophysiological studies in animals, especially in monkeys. The most robust cortical structures



involved were the parieto-insular vestibular cortex (PIVC), the visual temporal sylvian area (VTS) in the retroinsular cortex, the superior temporal gyrus (STG), the inferior parietal lobule (IPL), the anterior cingulum, the hippocampus and area 6a. All belong to a multisensory (vestibular) cortical circuit. The PIVC seems to be a dominant multi-modal vestibular cortex area in monkeys closely connected to the other areas and to the opposite hemisphere; it is considered the ‘core region’ within this network (Guldin and Grüsser, 1996). Recent studies have further defined the roles of the ventral-intraparietal area, VIP, and periarculate cortex in the frontal lobes in this cortical vestibular circuit (Bremmer *et al.*, 2002; Ebata *et al.*, 2004; Schlack *et al.*, 2005). During the last 10 years functional imaging studies using vestibular, somatosensory, and visual optokinetic stimulation have suggested that such multisensory vestibular cortical areas are located and connected in similar sites in humans. Indeed, a complex network of areas predominantly in the temporo-insular and temporo-parietal cortex were delineated in both hemispheres of healthy subjects during caloric (Bottini *et al.*, 1994, 2001; Suzuki *et al.*, 2001; Fasold *et al.*, 2002; Naito *et al.*, 2003; Dieterich *et al.*, 2003a; Emri *et al.*, 2003) and galvanic (Bucher *et al.*, 1998; Lobel *et al.*, 1998; Bense *et al.*, 2001; Bremmer *et al.*, 2001; Stephan *et al.*, 2005) vestibular stimulation. The areas in humans were located in the posterior insula (first and second long insular gyri) and retroinsular regions [representing the PIVC and the posterior adjacent visual temporal sylvian area, VTS (Guldin and Grüsser, 1996) in the monkey], the superior temporal gyrus, the parts of the inferior parietal lobule representing area 7 in the monkey, deep within the intraparietal sulcus representing monkey area VIP, the postcentral and precentral gyrus, the anterior insula and adjacent inferior frontal gyrus, the anterior cingulate gyrus, the precuneus and the hippocampus, most often bilaterally (Fig. 2). Activation of this cortical network during vestibular stimulation is not symmetrical in the two hemispheres. Rather, it depends on three determinants that were defined in a study investigating healthy right- and left-handers (Dieterich *et al.*, 2003a). The determinants were first, the subject’s handedness, second, the side of the stimulated ear and third, the direction of the induced vestibular nystagmus. Activation was stronger in the non-dominant hemisphere (right hemisphere in right-handers, left hemisphere in left-handers), in the hemisphere ipsilateral to the stimulated ear, and in the hemisphere ipsilateral to the slow phase of vestibular caloric nystagmus (Dieterich *et al.*, 2003a; Bense *et al.*, 2003; Naito *et al.*, 2003; Dieterich *et al.*, 2005a).

Deactivations of areas within the visual and somatosensory systems of both hemispheres have been observed to occur simultaneously with activations (Wenzel *et al.*, 1996; Bense *et al.*, 2001; Naito *et al.*, 2003). Since opposite activation–deactivation patterns were found during visually induced self-motion perception [for example, activations of



**Fig. 2** Illustration of the normal activation–deactivation pattern during unilateral vestibular stimulation in healthy volunteers (activations in yellow-red, deactivations in blue). For comparison a schematic drawing of a monkey brain with the neurophysiologically determined multisensory vestibular areas 6, 3aV, 2v, 7a, b, PIVC and VTS is given (top left). Note that the locations of the activated areas during galvanic stimulation of the vestibular nerve (fMRI; top right) are similar in humans. During caloric irrigation of the right ear in healthy right-handers, activations ( $H_2^{15}O$ -PET) occur in temporo-parieto-insular areas of both hemispheres, but there is a dominance of the non-dominant right hemisphere (middle: surface view of the right and left hemispheres; bottom: transverse sections  $Z = -10, +10, +20$  mm). Deactivations are located in areas of the visual cortex bilaterally (modified after Dieterich *et al.*, 2003a).

occipital and parietal visual areas co-occur with deactivations of the multisensory vestibular cortex, e.g. the PIVC (Brandt *et al.*, 1998; Dieterich *et al.*, 2003b)], it was assumed that a reciprocal inhibitory cortical interaction occurred between the two sensory systems, the visual and the vestibular systems (Brandt *et al.*, 1998). This interaction provides a powerful means for shifting the dominant sensorial weight from one modality to the other for resolving conflicts between incongruent sensory inputs. These findings prompted the hypothesis that reciprocal inhibitory interactions between the sensory systems are a fundamental mechanism of the central nervous system (Brandt and Dieterich, 1999). Such interactions were also seen between other sensory modalities, e.g. the somatosensory and nociceptive, the nociceptive and the vestibular, the tactile sensory and visual and the visual and auditory systems (Bense *et al.*, 2001; Laurienti *et al.*, 2002; Maihöfner *et al.*, 2006; Merabet *et al.*, 2007). The psychophysical consequences were shown for example by investigation of

high-resolution visual mental imagery and mental rotation tasks which were significantly impaired during vestibular caloric stimulation in healthy subjects (Mast *et al.*, 2006). Not only was the interaction between different systems disturbed, but also that within the visual system (visuo-visual interaction). The fMRI finding that coherent motion stimulation of the right or left visual hemifield produced negative signal changes (deactivations) in the primary visual cortex and the lateral geniculate nucleus contralateral to the stimulated hemisphere (Brandt *et al.*, 2000) was psychophysically evaluated to determine the functional significance of this contralateral inhibition of the visual system. In fact, mean detection times for horizontal and vertical object motion were significantly prolonged during concurrent motion pattern stimulation in the contralateral hemifield (Brandt *et al.*, 2003). These data support the interpretation that the deactivation of neural activity in the visual system measured by fMRI and PET may be associated with a functional decrement in sensitivity needed to perceive motion and orientation. This may reflect transcallosal attentional shifts between the two hemispheres, i.e. considerable ‘cross-talk’ between the two cerebral hemispheres to resolve sensory conflicts. Indeed, negative functional MRI responses correlated with decreases in neural activity in the monkey visual area V1 (Shmuel *et al.*, 2006). Thus, deactivations in PET and fMRI studies also seem to represent decreases of function at the neural level.

### **Vestibular nerve (vestibular neuritis) Signs and symptoms of a unilateral vestibular failure**

An acute unilateral vestibular failure due to, for example, a typical vestibular neuritis, induces a tonus imbalance of the bilateral peripheral vestibular input, which normally stabilizes eyes, head and body in an upright position. An acute imbalance of ocular motor, perceptual and postural functions results in rotatory vertigo and apparent tilt, spontaneous nystagmus (with the slow nystagmus phase toward the lesioned ear), ipsilateral torsion of both eyes, ipsilateral tilts of the perceived vertical, and an instability of stance and gait with ipsilateral falls (Curthoys *et al.*, 1991; Curthoys and Halmagyi, 1994). This imbalance improves gradually within the subsequent 4 to 6 weeks due to central compensation, so that many signs and symptoms fade away even when the loss of peripheral vestibular function continues to be complete. However, some functions remain asymmetrical after unilateral loss of vestibular function, especially during head movements in the higher frequency range (Aw *et al.*, 2001; Borel *et al.*, 2002; Lopez *et al.*, 2005). Similar signs and symptoms can also be elicited by acute unilateral lesions along the ascending vestibular pathways of the brainstem, for example, of the vestibular nucleus, the MLF, and the interstitial nucleus of

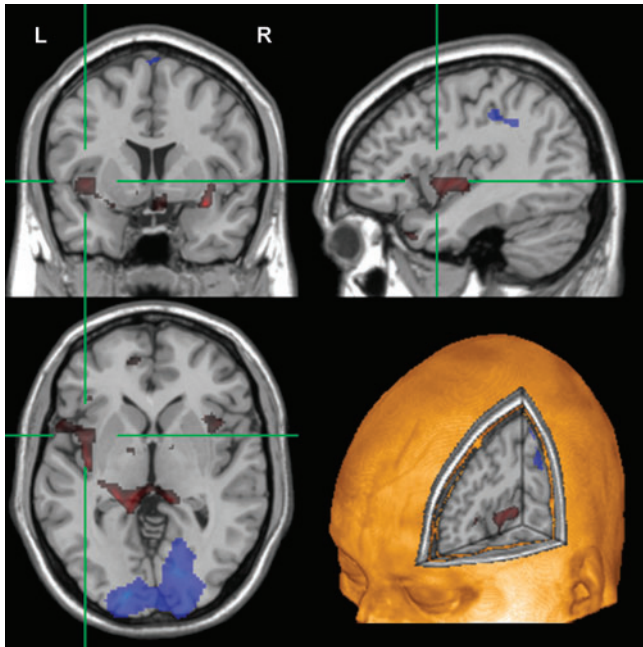
Cajal (integration centre for torsional and vertical eye position in roll and pitch planes) (Dieterich and Brandt, 1993a).

### **Functional imaging in patients with unilateral peripheral vestibular lesions**

Does the acute lesion-induced vestibular tonus imbalance between the two labyrinths in vestibular neuritis lead to a modulation of neural activity within the thalamo-cortical vestibular system and, if so, is this activation pattern asymmetrical and thus reflects the perceptual correlate of the tonus imbalance at the cortical level? To answer this question the cortical activation pattern in the patients with unilateral lesions were compared to that described earlier in the functional imaging data of healthy volunteers during unilateral caloric (Suzuki *et al.*, 2001; Fasold *et al.*, 2002; Dieterich *et al.*, 2003a; Naito *et al.*, 2003) or galvanic (Lobel *et al.*, 1998; Bense *et al.*, 2001; Fink *et al.*, 2003) stimulation. Both unilateral vestibular stimulation, on the one hand, and unilateral failure of the vestibular endorgan, on the other, should create a vestibular tonus imbalance, which, however, occurs at different levels of activity of the vestibular system. A unilateral lesion reduces the resting discharge input, whereas a unilateral stimulation increases the resting discharge input from one endorgan. Furthermore, the direction of lesion signs and symptoms of conduction block and excitation are opposite in direction.

During the acute stage of vestibular neuritis (mean: 6.6 days after symptom onset) it was indeed possible to demonstrate that the central vestibular system exhibited a visual-vestibular activation–deactivation pattern similar to that described earlier in healthy volunteers during unilateral vestibular stimulation. Right-handed patients with a right-sided vestibular neuritis were investigated by FDG-PET in the acute stage and 3 months later after central vestibular compensation when the patients were symptom-free (Bense *et al.*, 2004a). RCGM was significantly increased during the acute stage in multisensory vestibular cortical and sub-cortical areas (PIVC in the posterior insula, posterolateral thalamus, anterior cingulate gyrus, ponto-mesencephalic brainstem, hippocampus) (Fig. 3). Thus, FDG-PET could image a cortical activation pattern of the vestibular system, which was induced by unilateral peripheral vestibular loss and may reflect the tonus imbalance. Simultaneously, there was a significant decrease of regional glucose metabolism in the visual and somatosensory cortex as well as in parts of the auditory cortex (transverse temporal gyrus). These decreases were very similar to those in the visual and somatosensory systems during vestibular stimulation in healthy subjects (Bense *et al.*, 2001; Naito *et al.*, 2003; Stephan *et al.*, 2005). This pattern probably reflects a non-specific inhibition of other sensory areas in response to vestibular activation.

The details, however, also revealed certain differences from the activation–deactivation pattern during



**Fig. 3** Statistical group analysis of five patients with vestibular neuritis of the right ear versus the control condition 3 months later (eyes closed, without stimulation). A significant increase (red) of rCGM is seen in the contralateral left vestibular cortex, left superior temporal gyrus, hippocampus, thalamus bilaterally; it is also pronounced in the anterior cingulate gyrus. Simultaneous rCGM decreases (blue) are located in the visual and somatosensory cortex bilaterally. For illustrative purposes, voxels above a threshold of  $P \leq 0.005$ , uncorrected, are shown.

experimental vestibular stimulation in healthy volunteers. In these patients, the activation of the vestibular cortex in the posterior insula (PIVC) was not bilateral with a dominance of the right side, but unilateral and contralateral (left) to the right labyrinthine failure. This asymmetry of activations within the posterior insula, PIVC, can be explained by assuming that the more dominant ipsilateral right-sided ascending projections to the right insular cortex were depressed by the right vestibular neuritis, because the tonic endorgan input was absent (resting discharge). An additional explanation might be that the vestibular tonus imbalance at vestibular nuclei level mimics a left-sided vestibular excitation due to a higher resting discharge rate of the unaffected left vestibular nuclei complex. This would be compatible with activation of the pontine and ponto-mesencephalic brainstem and left temporo-insular vestibular cortex areas (dominance of ipsilateral pathways) as well as the concurrent deactivation of the visual and somatosensory cortex areas. These suggestions are in line with recent animal data on vestibular neuronal excitability and molecular mechanisms of neural and synaptic plasticity in the vestibular nuclei during vestibular compensation that follows deafferentation of one rat labyrinth (Yamanaka *et al.*, 2000; Guilding and Dutia, 2005; Bergquist *et al.*, 2006). Rapid compensatory changes in GABA receptor efficacy in medial vestibular nucleus neurons lead to a

downregulation in the ipsilesional and a simultaneous upregulation in contra-lesional neurons. Furthermore, examinations of the histaminergic and glycinergic modulation of GABA release in the medial vestibular nuclei of normal and labyrinthectomised rats showed a profoundly downregulated GABA release on both sides for at least 3 weeks after unilateral labyrinthectomy, which could be restored to normal only on the contralateral side by stimulation of histamine H(3) receptors.

Correlation analyses in patients with vestibular neuritis have, furthermore, shown that some of the 'secondary' vestibular cortex areas such as the superior temporal gyrus, inferior parietal lobule and precuneus seem to be involved in special aspects of vestibular function or dysfunction (Bense *et al.*, 2004a). First, the amount of spontaneous nystagmus during the acute stage of vestibular neuritis positively correlated with the increase of glucose metabolism in the area of the superior temporal gyrus bilaterally (BA 22) as well as with that of an ocular motor area in the right inferior medial frontal gyrus (BA 9/44) that includes the frontal eye field. Second, the index of vestibular failure measured as the caloric asymmetry between the affected and unaffected ears positively correlated with an area in the left inferior parietal lobule (BA 40) known to represent a multisensory (vestibular) cortex area that is also involved in the modulation of gain and time constants of the VOR (Ventre-Dominey *et al.*, 2003).

In conclusion, the typical cortical activation–deactivation pattern during vestibular stimulation of normal subjects was modified in patients with unilateral peripheral vestibular lesions, most likely due to adaptive substitution or compensation within the central vestibular system of the unaffected side. The beneficial result was the suppression of input from the affected modality and the restoration of adequate spatial orientation by the unaffected vestibular nucleus complex.

## Vestibular nerve (BVF)

### Signs and symptoms of BVF

BVF is a rare chronic disorder of the labyrinth or the eighth cranial nerve with various aetiologies (Baloh *et al.*, 1989; Rinne *et al.*, 1998; Zingler *et al.*, 2007). Its key symptoms are unsteadiness of gait, particularly in the dark and on unlevel ground, combined with blurred vision due to oscillopsia (Brandt, 1996; Baloh and Halmagyi, 1996). Oscillopsia, the apparent motion of the visual scene, is caused by involuntary retinal slip due to an insufficient VOR.

### Functional imaging in patients with bilateral peripheral vestibular lesions

One major difference from vestibular neuritis is that patients with BVF do not usually have a vestibular tonus imbalance, and their signs and symptoms can only be



elicited by locomotion and head movements. The differential effects of caloric irrigation in right-handed patients with complete and incomplete BVF were of special interest. They exhibited no caloric vestibular nystagmus and perceived no apparent self-motion or vegetative sensations due to caloric irrigation. Their activation–deactivation patterns during vestibular caloric stimulation showed a decrease of activations as well as deactivations ( $H_2^{15}O$ -PET: Bense *et al.*, 2004b) with the major findings as follows: (i) The activation pattern showed only a small area of activation in the PIVC contralateral to the irrigated ear; there was no significant activation on the side of the irrigated ear. This is relevant, because in healthy right-handers the activation was bilateral but the activation on the ipsilateral right side was stronger. (ii) Bilateral deactivation of the visual cortex was largely absent in these patients. (iii) There was no evidence of common nonvestibular (e.g. auditory, somatosensory) responses in other cortex areas. This general absence of bilateral deactivation of the visual cortex suggests that it depends on a ‘normal’ activation of the vestibular cortex, which is not the case in BVF patients. One can speculate that because vestibular input is reduced in these patients, causing reduced or absent vestibular nystagmus and consecutive oscillopsia, there is no need for a ‘protective’ reduction of visual cortex functions. BVF might cause the sensorial weight in the patients to be permanently shifted to the visual system, because no valid vestibular information can be generated. On the other hand, there was obviously no shift of the sensorial weight to the somatosensory or auditory modalities, since no signal changes in other sensory cortex areas were found during vestibular stimulation.

Indeed, a study on visual optokinetic stimulation in BVF patients provides first evidence by functional imaging of visual substitution for vestibular loss (Dieterich *et al.*, 2007). In these BVF patients visual optokinetic stimulation induced a significantly stronger activation and larger activation clusters of the primary visual cortex bilaterally (inferior and middle occipital gyri, 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 compared to that of age-matched healthy controls. Functionally, the enhanced activations were independent of optokinetic performance, since the mean slow phase velocity of optokinetic nystagmus in the BVF patients did not differ from that in normals. Furthermore, small areas of BOLD signal decreases (deactivations), located primarily in the right posterior insula containing the PIVC, were similar to those in the healthy controls. The 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. So far 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 (e.g. Bles *et al.*, 1983, 1984; Curthoys and Halmagyi, 1994). This is now complemented by functional brain imaging techniques.

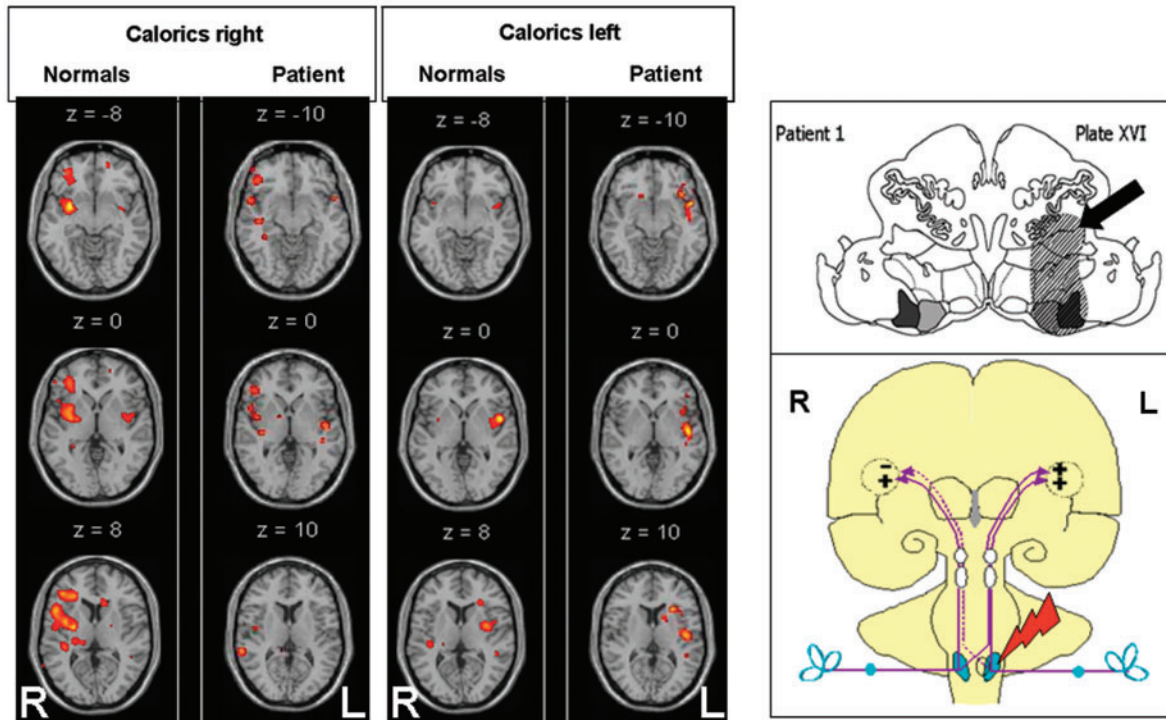
In conclusion, these results of BVF patients are compatible with the concept of a reciprocal inhibitory interaction between the vestibular and visual systems, which normally act together for orientation in space and perception of motion. This interaction appears to be preserved in BVF patients at a significantly lower level during vestibular stimulation, that is, with less activations and less deactivations, and at an enhanced level during visual stimulation within the visual cortex probably representing visual substitution of vestibular loss.

### **Vestibular nucleus (infarction of the dorsolateral medulla, Wallenberg’s syndrome) Signs and symptoms of a unilateral lesion of the vestibular nucleus**

Vestibular nucleus lesions due to an infarction of the dorsolateral medulla (Wallenberg’s syndrome) affect the medial and/or superior vestibular subnuclei, thus causing a central vestibular disorder. This central vestibular syndrome is characterized by static vestibular signs such as ipsiversive cyclorotation of one or both eyes (82%), skew deviation with the ipsilateral eye lowermost (44%), complete ocular tilt reaction (33%), tilts of perceived vertical in most patients (94%), dynamic vestibular signs such as ipsilateral lateropulsion of eyes and body (Dieterich and Brandt, 1992, 1993a), and torsional nystagmus and dysmetria of saccades and limbs (Kommerell and Hoyt, 1973; Morrow and Sharpe, 1988). Additional vestibular signs such as torsional spontaneous nystagmus and an impaired head-impulse test regularly occur. Other neurological deficits are Horner’s syndrome, impairment of facial pain and temperature sensation, paralysis of the pharynx and larynx with dysphagia and dysphonia, and contralateral impairment of pain and temperature sensation over the trunk and limbs.

### **Functional imaging in patients with an acute infarction of the dorsolateral medulla oblongata affecting the vestibular nucleus (Wallenberg’s syndrome)**

Caloric irrigation of the ears in Wallenberg’s patients elicited asymmetrical activations at the cortical level as it does in patients with vestibular neuritis. Patients with Wallenberg’s syndrome and the typical signs of acute unilateral vestibular dysfunction (i.e. transient rotatory vertigo with vomiting at the onset, ipsiversive body and ocular lateropulsion, and a complete ocular tilt reaction with tilts of the subjective visual vertical) were examined during warm-water caloric vestibular stimulation



**Fig. 4** Activated areas during caloric vestibular stimulation of the right or left ear in a right-handed patient who had an acute posterolateral medullary infarction left (Wallenberg's syndrome) and right-handed normals projected onto standard MRI template brain (group analysis). The lesion site of the infarction (arrow, shaded area) is documented by a projection of the lesion in MRI onto the appropriate section (Plate XVI; top right) of the brainstem atlas of Olszewski and Baxter (1982). The infarction affects the medial and superior vestibular subnuclei (gray and black on both sides). In healthy volunteers activations are found in a cortical network within the temporo-parieto-insular cortex areas bilaterally, and there is a dominance of the right hemisphere during caloric irrigation right and of the left hemisphere during caloric irrigation left. Note that the activation pattern during calorics right appears 'normal' in the patient, whereas that during calorics of the left ear ipsilateral to the infarction showed a 'normal' activation of the ipsilateral left temporo-insular cortex but no activation or reduced activation within the contralateral right hemisphere. The conclusion is depicted in a drawing of the ascending vestibular pathways from the endorgans to the vestibular cortex (bottom right): the left-sided infarction mainly affects the crossing pathways to the contralateral right hemisphere and spares the ipsilateral left pathways. Therefore, the activity is reduced (–+, dashed line for affected pathway) in the right temporo-insular cortex and normal (++, bold line for normal pathway) in the left.

( $H_2^{15}O$ -PET: Dieterich *et al.*, 2005b). Their activation pattern was typically changed from that of healthy volunteers. During caloric irrigation of the ear ipsilateral to the side of the lesion, they showed no activation or significantly reduced activation in the contralateral hemisphere, whereas the activation pattern in the ipsilateral hemisphere appeared 'normal' (Fig. 4). These results are compatible with the existence of bilaterally ascending vestibular pathways from the vestibular nuclei (especially the medial vestibular subnucleus) to vestibular cortex areas, in which only the contralateral tract is affected. The novel finding was that the activation patterns were compatible with the assumption that only the fibres crossing from the medial vestibular subnucleus to the contralateral MLF were lesioned, whereas the ipsilateral vestibular thalamo-cortical projections via the superior vestibular subnucleus were spared (Fig. 4).

Further results comparable to those in patients with vestibular neuritis were reported recently in right-handed patients with an acute unilateral medullary infarction (six right, six left) (FDG-PET: Bense *et al.*, 2006a). The patients were examined twice without any stimulation,

(I) in the acute phase on day 7 as a mean after symptom onset and (II) again 6 months later after recovery. There were widespread *decreases* of regional glucose metabolism not only in the visual cortex (BA 17–19) bilaterally, including the motion-sensitive areas MT/V5 and merging into the secondary visual areas in the upper occipital cortex (BA 19/37), but also in the multisensory temporo-parietal areas of the medial and STG and the IPL. Interestingly, no relevant activations were seen at the cortical level as distinct from patients with vestibular neuritis. On the other hand, the findings for deactivations in visual cortex areas parallel the data for vestibular neuritis. This means that the concept of a reciprocally inhibitory interaction between the vestibular and visual systems is modified by the type of central vestibular lesion: areas became deactivated (GTS, IPL), which were normally activated during vestibular stimulation conditions in healthy subjects.

As a fundamental finding, Wallenberg's patients showed signal increases in the acute phase of disease, which were located mainly in the medulla and cerebellar peduncle contralateral to the infarction, and also in the vermis and



widespread in both cerebellar hemispheres (Bense *et al.*, 2006a). These signal increases seem to represent an essential circuit for the central compensation in unilateral central vestibular lesions (Wallenberg's syndrome), since such relevant cerebellar activations were not observed in the patients with unilateral or bilateral vestibular lesions.

In conclusion, these recent data suggest that central compensatory processes of vestibular imbalance during the acute phase after medullary infarctions take place mainly in brainstem-cerebellar loops (upregulation), not only or predominantly at the cortical level. The visual cortical system—primary visual areas as well as secondary visual cortex areas and even multisensory (vestibular) areas—were deactivated at the cortical level (decreases of glucose metabolism) in the acute phase; this probably means it was downregulated. Such downregulation of visual cortex areas would make sense, for in this way visual impairment due to nystagmus-induced oscillopsia and double vision due to misalignment of the eyes could be avoided. Only recently a systematic neurophysiological and fMRI study in macaque monkeys gave evidence that a negative BOLD response correlated significantly with a decrease in neural activity in visual area V1 (Shmuel *et al.*, 2006).

It must, nevertheless, be stressed that the functional relevance of these deactivations at neural levels is still not known, since adequate psychophysical tests for the visual system are rare. Only recently during vestibular caloric stimulation in healthy volunteers—as mentioned earlier—did psychophysical testing of high-resolution visual tasks reveal a significant impairment during caloric nystagmus (Mast *et al.*, 2006). Whether this finding represents a probable impairment or a decrement of neural function within the visual cortex must still be proven in further investigations.

### **Vestibular thalamic nuclei (infarction of the posterolateral thalamus)**

#### **Signs and symptoms of a unilateral lesion of the posterolateral thalamus (i.e. vestibular thalamus)**

Unilateral lesions of the posterolateral thalamus and—at the cortical level—the superior temporal and the insular cortex (including the PIVC) cause vestibular tonus imbalance without ocular motor signs but with perceptual and postural deficits. These are characterized by perceptual disturbances (e.g. deviations of the perceived visual vertical) and an imbalance of stance and gait with lateral falls (Dieterich and Brandt, 1993b; Brandt and Dieterich, 1994; Dieterich *et al.*, 2005a). This type of vestibular imbalance is probably identical to the earlier so-called 'thalamic astasia', a condition of irresistible falls without paresis or sensory or cerebellar signs (Masdeu and Gorelick, 1988).

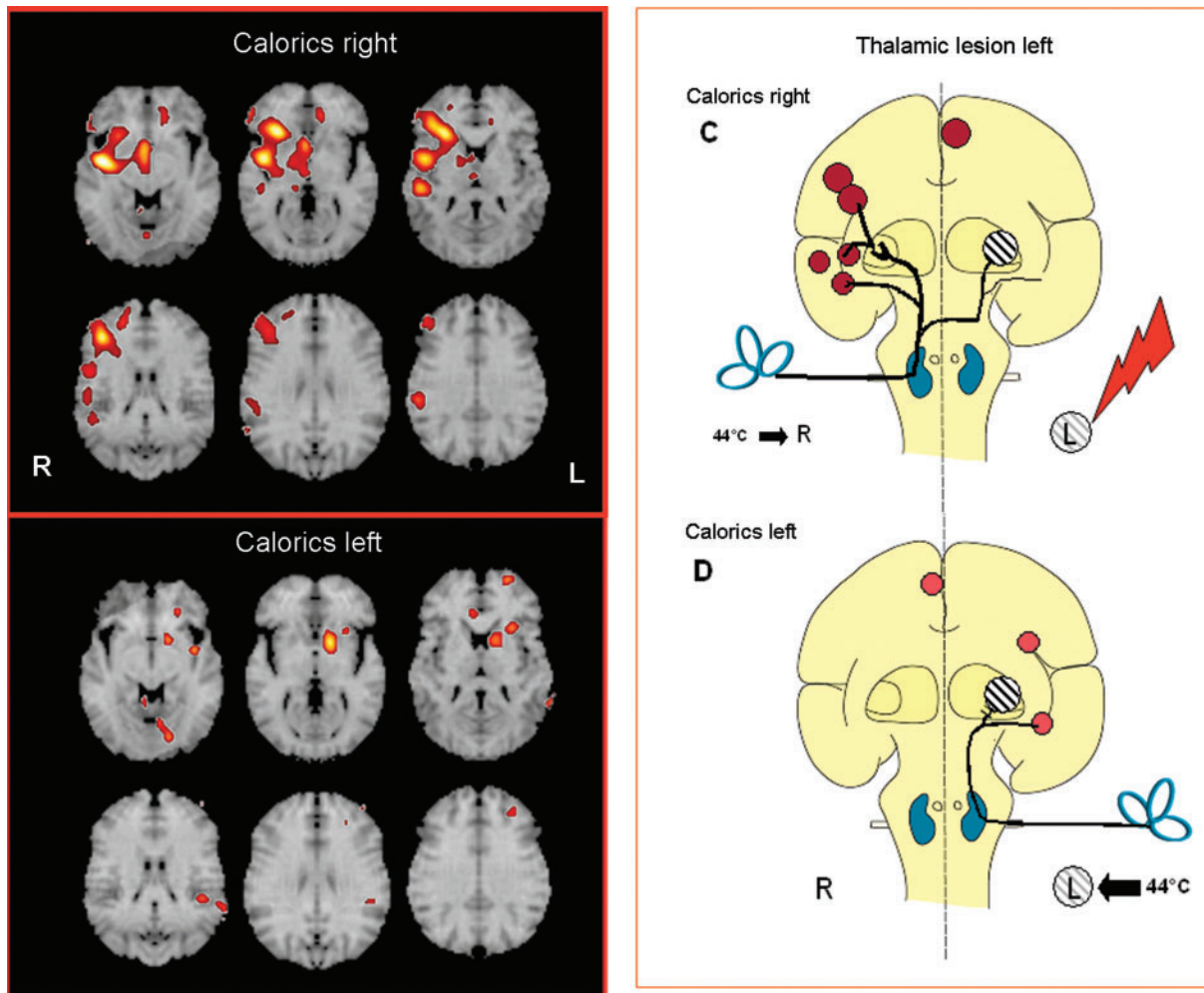
Vestibular stimulation investigations in animal experi-

Henn, 1976) have shown that the posterolateral thalamus—including the subnuclei ventrocaudalis externus (Vce), ventro-oralis intermedius (Vim), dorsocaudalis (Dc), ventrocaudalis internus (Vci) and ventroposterior lateralis (VPLo)—is the afferent relay station for multiple multisensory vestibular cortex areas. Vestibular information in animals reaches several separate and distinct cortex areas via the subnuclei of this relay station: for example, the PIVC in the posterior insula, adjacent retroinsular areas and the granular insular region (Grüsser *et al.*, 1990a, b; Guldin and Grüsser, 1996), the visual temporal sylvian area posterior to PIVC (Guldin and Grüsser, 1996), parts of area 7 in the inferior parietal lobule (BA 40) (Ventre, 1985; Faugier-Grimaud and Ventre, 1989; Ventre-Dominey *et al.*, 2003), the ventral intraparietal area, VIP, in the fundus of the intraparietal sulcus (Bremmer *et al.*, 2002; Klam and Graf, 2003a, b), area 3aV in the central sulcus (Schwarz and Fredrickson, 1971; Ödkvist *et al.*, 1974), and probably area 2v at the tip of the intraparietal sulcus (Schwarz and Fredrickson, 1971; Büttner and Büttner, 1978). From patients with three different types of acute unilateral thalamic infarctions it is known that only posterolateral lesions cause transient vestibular signs and symptoms like perceptual deficits with ipsi- or contralateral tilts of the subjective visual vertical, corresponding deviations of stance and gait, but no ocular motor deficits (Dieterich and Brandt, 1993b).

These signs of thalamic lesions fit earlier findings in electrical stimulation studies of the thalamic subnucleus Vim in humans. Such stimulation elicited a corresponding rotation or spinning of the body, head or eyes in either a counterclockwise (more often) or clockwise direction (Hassler, 1959; Tasker *et al.*, 1982). Vestibular thalamic deficits found in humans (Dieterich and Brandt, 1993b) also agreed with findings of electrophysiological studies on the posterolateral thalamus in non-human primates (Sans *et al.*, 1970; Deecke *et al.*, 1974; Büttner and Henn, 1976).

#### **Functional imaging in patients with lesions of the posterolateral 'vestibular' thalamus (posterolateral infarctions)**

In view of the vestibular thalamo-cortical network in both hemispheres, the question arose as to the consequences of a unilateral lesion of the 'vestibular relay station' in the posterolateral thalamus. Therefore, the differential effects of unilateral caloric vestibular stimulation (right- or left-ear irrigation with warm water) on the cortical and subcortical activation pattern of both hemispheres were analysed in right-handed patients with an acute unilateral stroke of the posterolateral thalamus ( $H_2^{15}O$ -PET: Dieterich *et al.*, 2005a). The major findings of the group analyses were as follows (Fig. 5): (i) activation of the multisensory vestibular cortex was significantly reduced in the ipsilateral hemisphere, if the ear ipsilateral to the thalamic lesion was



**Fig. 5** Left: activated areas during caloric stimulation of the right or left ear in patients with a left-sided posterolateral thalamic lesion (group analyses; each group  $n = 4$ ;  $P < 0.001$ ). Top left: activations for the left-sided lesions during right calorics (non-affected side) occur as large clusters in the posterior and anterior insula, inferior frontal gyrus, superior temporal gyrus, inferior parietal lobule, and superior parts of the parietal lobe, hippocampus, paramedian thalamus, and midbrain, nucleus ruber, putamen, medial and superior frontal gyrus, and cerebellar vermis of the right hemisphere. Activations of the left hemisphere are found in only the anterior cingulate gyrus, and diagonal frontal gyrus. Caloric irrigation of the affected left side (bottom left) is associated with smaller activations, predominantly within the left hemisphere, anterior and median parts of the insula, inferior frontal gyrus, putamen, caudate nucleus, superior frontal gyrus, medial temporal gyrus/inferior parietal lobule and lingual gyrus. Activations within the right hemisphere occur only in the anterior cingulate gyrus and cerebellar vermis. Right: schematic drawing of hypothetical ascending bilateral vestibular pathways from the vestibular nerve via the vestibular nuclei of the medullary brainstem through the midbrain and posterolateral thalamus to the temporo-insular region. Projections from the vestibular nuclei to the PIVC of the posterior insula are known to be stronger on the ipsilateral side (thicker line). Schematic depiction of the most consistent activations in the temporo-parieto-insular regions during caloric irrigation. The schematic coronal section through the insula summarizes all activations in the anterior–posterior direction from the frontal to parietal lobe. Note: activation in the affected hemisphere is reduced or missing for both stimulation sides (ipsilateral and contralateral stimulation) and also in the contralateral hemisphere, when the ear ipsilateral to the lesioned side is stimulated (modified after Dieterich *et al.*, 2005a).

stimulated; (ii) activation of multisensory vestibular cortex areas of the hemisphere contralateral to the irrigated ear was also diminished, but to a lesser extent; (iii) the earlier described right hemispheric dominance in right-handers was preserved in patients with right and left thalamic lesions. Thus, these data demonstrated the functional importance of the posterolateral thalamus as a gatekeeper, of the dominance of ipsilateral ascending pathways, and of the right hemisphere in right handedness.

This cortical asymmetry of the pattern of activation during calorics was neither associated with directional asymmetry of caloric nystagmus nor of motion perception for the entire group (Dieterich *et al.*, 2005a). There was only a trend of the caloric nystagmus to be stronger during stimulation of the ear contralateral to the lesion side and a striking contrast between the significant hemispheric differences in the mediation of vestibular input (activations) and the minimal vestibular signs and symptoms of the patients. The finding that the caloric nystagmus was not

significantly influenced by the vestibular thalamic lesion is not trivial, as there are cortical areas such as the suprasylvian cortex in cats and monkeys, particularly area 7, corresponding to an area at the occipito-temporo-parietal junction in humans, which influence VOR symmetry in terms of directional preponderance of VOR gain and VOR time constant and nystagmus frequency (Ventre, 1985; Faugier-Grimaud and Ventre, 1989; Tusa *et al.*, 1989; Ventre-Dominey *et al.*, 2003). Since activation of the multisensory vestibular cortex ensemble was found to be significantly reduced in the ipsilateral hemisphere during stimulation of the ear ipsilateral to the thalamic lesion, the diminished activation of the occipito-temporo-parietal region could have modulated the VOR symmetry and thereby reduced the caloric nystagmus.

Vestibular stimulation—as mentioned earlier—in healthy volunteers not only activates vestibular cortex areas but at the same time deactivates visual cortex areas bilaterally (Wenzel *et al.*, 1996; Bense *et al.*, 2001, Stephan *et al.*, 2005). In the patients with posterolateral thalamic infarctions deactivations of the visual cortex areas were generally found in only one hemisphere, namely in the hemisphere contralateral to the stimulated ear and contralateral to activated vestibular cortex areas (Dieterich *et al.*, 2005a), suggesting a crossed inhibition. Thus, the normal interaction between the two sensory systems, the vestibular and the visual, described earlier as a reciprocal inhibitory interaction in both hemispheres (Brandt *et al.*, 1998), was disturbed in these patients: their ipsilateral hemisphere was ‘functionally disconnected’.

In conclusion, the calorically induced vestibular nystagmus appeared to be mainly mediated by a subthalamic brainstem VOR circuitry and the vestibular cerebellum rather than by thalamo-cortical structures. This was also reflected in the absence of spontaneous vestibular nystagmus and rotational vertigo in the patients with acute and subacute lesions of the vestibular thalamus. Moreover, the ipsilateral hemisphere did not show activations, and the contralateral hemisphere did not show deactivations. Thus, the inhibitory interaction between the visual and the vestibular systems may be organized by pathways that cross the hemispheres.

### **Vestibulocerebellar lesions: cerebellar flocculus/paraflocculus (DBN syndrome by cerebellar degeneration)**

#### **Symptoms of a DBN syndrome**

The DBN syndrome is often associated with a vestibulocerebellar lesion of the flocculus and paraflocculus. There is evidence that the cerebellar flocculus plays an important role in VOR adaptation and in recovery of function after unilateral labyrinthine loss; this was proposed in Ito's flocculus hypothesis (Ito, 1993, 2002; for review: Leigh and Zee, 2006).

DBN is characterized by a fixational nystagmus, which is frequently acquired, beats downward in primary gaze position, and is exacerbated on lateral gaze and in head-hanging position. It is accompanied by a combination of visual and vestibulo-cerebellar ataxia with a tendency to fall backward and past-pointing upward as well as vertical deficits of smooth pursuit eye movements downward more than upward (Baloh and Spooner, 1981). DBN is often the result of a bilateral cerebellar lesion of the flocculus or paraflocculus or is caused by a lesion at the bottom of the fourth ventricle (Zee *et al.*, 1981). Accordingly, it is mostly due to craniocervical junction anomalies, cerebellar degeneration, drug-induced dysfunction or is congenital.

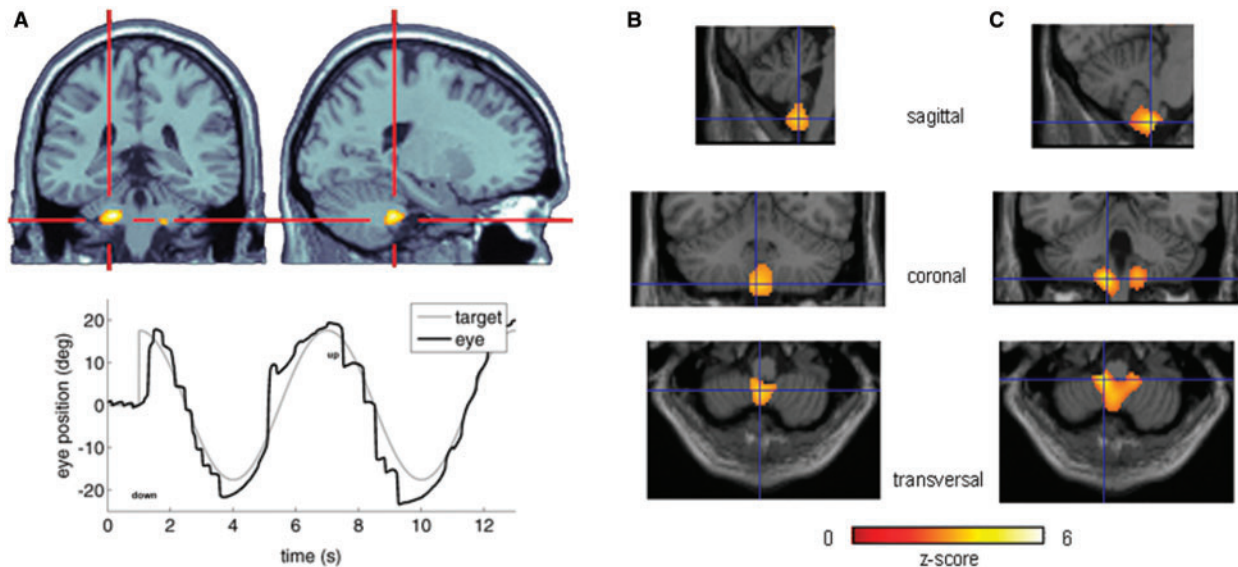
Various mechanisms have been proposed for DBN: a vertical vestibular tonus asymmetry (Baloh and Spooner, 1981; Pierrot-Deseignilly and Milea, 2005; Leigh and Zee, 2006), an upward shift of the eyes' null position for vertical gaze holding, or an imbalance of vertical smooth-pursuit signals due to floccular deficiency (Glasauer *et al.*, 2003).

### **Functional imaging of cerebellar flocculus lesions**

A patient with downbeat nystagmus syndrome was examined once while off and twice while on successful treatment with 4-aminopyridine (4-AMP), a potassium channel blocker that significantly improves the syndrome (FDG-PET: Bense *et al.*, 2006b). All PET scans of the patient showed a reduced cerebral glucose metabolism bilaterally, but only in the region of the cerebellar tonsil and flocculus/paraflocculus when compared with a normal database of the whole brain (Fig. 6). An additional region-of-interest analysis revealed that 4-aminopyridine treatment lessened the hypometabolism. This finding supports the hypothesis that the cerebellar (para-) flocculus and tonsil play a crucial role in DBN. Hypometabolism itself might indicate that the inhibition of the circuits to the vestibular nuclei is reduced, or even disinhibited, thus causing DBN. It is, however, also possible that this hypometabolism is a consequence of disturbances in the brainstem mechanisms, which do not induce measurable signal changes or do not reach spatial resolution in PET. The improvement of hypometabolism during treatment with 4-AMP probably indicates that the cerebellar inhibition is improved. This might be due to the functioning of cerebellar pathways, which mediate gaze holding by improving the excitation of the cerebellar Purkinje cells of the tonsil and flocculus. Further studies on a larger number of DBN patients need to address this question.

The bilateral floccular activity was also significantly lowered in four patients with DBN compared to healthy controls when they performed downward but not upward pursuit in fMRI (Kalla *et al.*, 2006). This supports the view that a functional deficiency of the flocculi causes the downward pursuit deficit in DBN. Recently, voxel-based-morphometry in patients with idiopathic DBN revealed





**Fig. 6** (A) Results obtained by region of interest analysis in controls versus four patients with DBN during downward smooth pursuit (contrast DOWN-FIXMID). Downward but not upward smooth pursuit eye movements are impaired; shown in the original search-coil recording (bottom). fMRI activity of both flocculi is significantly diminished during downward but not during upward pursuit in DBN. Results of the fluorodeoxyglucose-positron emission tomography scanning without (B) and with (C) effective treatment of the DBN. Cerebellar areas with statistical differences from the normal database versus patients are identified as hypometabolism of tonsil and (para)flocculus bilaterally (modified after Bense *et al.*, 2006b; Kalla *et al.*, 2006).

localized gray matter atrophy in the lateral cerebellar hemisphere (lobule VI) and the dorsal ‘ocular motor vermis’ but not in the flocculus/paraflocculus (Hüfner *et al.*, 2007). fMRI, however, showed reduced function in the parafloccular lobule and the pontomedullary brainstem, when these patients performed downward pursuit. The authors hypothesized that various forms of DBN result from a disinhibition within a final common pathway of the superior vestibular nuclei neurons and the  $\gamma$ -group in the brainstem (Marti *et al.*, 2002; Hüfner *et al.*, 2007). The site of the lesion can be the (para)flocculus itself or possibly the ‘ocular motor vermis’ which plays a crucial role in smooth pursuit eye movements. The latter is in line with the finding that the ‘ocular motor vermis’ – similar to the flocculus/paraflocculus – contains Purkinje cells which fire more with downward than upward pursuit (Shinmei *et al.*, 2002). Lesions of the gaze-holding pathway in the pontomedullary brainstem affecting the PMT in non-human primates can also cause DBN (Nakamagoe *et al.*, 2000), probably by a consecutive hypofunction of the (para)flocculus.

Furthermore, a positioning DBN was found in patients with a circumscribed tumorous lesion of the cerebellar uvula and nodulus; they also benefited from 3,4-diaminopyridine (Helmchen *et al.*, 2007).

In summary, fMRI and PET studies in humans have proven useful for investigating (1) the differential effects on the spontaneous activation–deactivation patterns of the multisensory vestibular network in acute unilateral peripheral and central vestibular lesions (vestibular neuritis,

Wallenberg’s syndrome, posterolateral thalamus infarctions) and (2) the effects of unilateral and bilateral vestibular lesions on the mediation of vestibular stimuli such as caloric and galvanic stimulation. Although first attributions can be made for the particular activations and deactivations in certain locations, a complete understanding of the multisensory and sensorimotor functions of the physiologically ancient vestibular system in humans is still in its infancy.

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