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ORIGINAL ARTICLE

Sequential [^{18}F]FDG μPET whole-brain imaging of central vestibular compensation: a model of deafferentation-induced brain plasticity

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Abstract Unilateral inner ear damage is followed by a rapid behavioural recovery due to central vestibular compensation. In this study, we utilized serial [^{18}F]Fluorodeoxyglucose ([^{18}F]FDG)-μPET imaging in the rat to visualize changes in brain glucose metabolism during behavioural recovery after surgical and chemical unilateral labyrinthectomy, to determine the extent and time-course of the involvement of different brain regions in vestibular compensation and test previously described hypotheses of underlying mechanisms. Systematic patterns of relative changes of glucose metabolism (rCGM) were observed during vestibular compensation. A significant asymmetry of rCGM appeared in the vestibular nuclei, vestibulocerebellum, thalamus, multisensory vestibular cortex, hippocampus and amygdala in the acute phase of vestibular imbalance (4 h). This was followed by early vestibular compensation over 1–2 days where rCGM re-balanced between the vestibular nuclei, thalami and temporoparietal cortices and bilateral rCGM increase appeared in the hippocampus and amygdala. Subsequently over 2–7 days, rCGM increased in the ipsilesional spinal trigeminal nucleus and later (7–9 days) rCGM increased in the vestibulocerebellum bilaterally and the hypothalamus and persisted in the hippocampus. These systematic dynamic rCGM patterns during vestibular compensation, were confirmed in a second rat model of chemical unilateral labyrinthectomy by serial [^{18}F]FDG-μPET. These findings show that deafferentation-induced plasticity after unilateral labyrinthectomy involves early mechanisms of re-balancing predominantly in the brainstem vestibular nuclei but also in thalamo-cortical and limbic areas, and indicate the contribution of spinocerebellar sensory inputs and vestibulocerebellar adaptation at the later stages of behavioural recovery.

Keywords Vestibular compensation · μPET · Rat · Unilateral labyrinthectomy

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Introduction

Ablation of one inner ear causes severe ocular motor and postural symptoms like spontaneous nystagmus, head tilt, posturing, barrel rolling and circular walking, as well as persistent hearing loss (Precht et al. 1966). Remarkably, the initial vestibular symptoms rapidly improve over days to

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weeks through a process of central vestibular compensation. This process is attributed to neuronal plasticity that takes place mainly in the brainstem and cerebellum (Curthoys and Halmagyi 1995; Dieringer 1995; Vibert et al. 1999; Darlington and Smith 2000; Dutia 2010; Peusner et al. 2012; Beraneck and Idoux 2012).

In the past, most studies used electrophysiological and histological techniques to examine the compensatory processes in distinct brain regions during central vestibular compensation (Kaufman et al. 1992; Smith and Curthoys 1988; Ris et al. 1995; Beraneck et al. 2003; Dutheil et al. 2009; Shao et al. 2012). Most recent concepts of vestibular compensation emphasize the importance of the commissural connections between the vestibular nuclei, the vestibulocerebellar pathways, the multisensory thalamocortical networks and the stress-axis activation (Curthoys and Halmagyi 1995; Strupp et al. 1998; Bergquist et al. 2008; zu Eulenburg et al. 2010; Shao et al. 2012; Saman et al. 2012). Changes in the intrinsic membrane properties, receptor expression and synaptic transmission already appear in the vestibular nuclei during early vestibular compensation (Cameron and Dutia 1997; Yamanaka et al. 2000; Vibert et al. 2000; Bergquist et al. 2008; Lim et al. 2010; Shao et al. 2012). Reactive neurogenesis and receptor-dependent functional differentiation of newborn cells may possibly improve long-term functional compensation (Dutheil et al. 2009, 2013). Extravestibular sensory signals and motor efference copy information might help to substitute the missing output from the vestibular nuclei to compensate static and dynamic symptoms of vestibular imbalance (Strupp et al. 1998; Sadeghi et al. 2010; Jamali et al. 2013). It is thought that the vestibulocerebellum is most likely involved in consolidating vestibular compensation (Darlington and Smith 2000; Beraneck et al. 2008). All in all, successful vestibular compensation must be seen as a process involving multiple, synergistic adaptations in neuronal networks in various areas of the brain (Dutia 2010; Beraneck and Idoux 2012).

To experimentally test this integrative view and relate this to previously described hypotheses on vestibular compensation, we used the non-invasive and in vivo technique of sequential μPET with [^{18}F]Fluoro-deoxyglucose ([^{18}F]FDG) to investigate the process of vestibular compensation, at a whole-brain level and over time in the same animal. The observed changes in relative glucose metabolism in various brain areas during compensation were correlated with the time-course of behavioural recovery in two rat models of unilateral labyrinthectomy. We hypothesized that re-balancing of activity of the brainstem vestibular nuclei will be observed early during vestibular compensation and followed by mechanisms of sensory substitution and vestibulocerebellar adaptation over the following time course.

Methods

Animals

All experiments were approved by the government of Upper Bavaria and performed in accordance with the guidelines for the use of living animals and the German Law on Animal Experimentation. A total of 36 male Sprague–Dawley rats (mean 360 ± 15 g, age 3 months, Charles River Ltd, UK) were housed two animals per cage in a temperature- and humidity-controlled room with a 12 h light/dark cycle, with free access to food and water.

Unilateral labyrinthectomy

Surgical labyrinthectomy (n = 12)

Animals were anaesthetized with 1.5 % isoflurane, delivered at 1.2 l/min via a mask, and injected with 1.5 mg/kg meloxicam s.c. for postsurgical analgesia. After local anaesthesia with 1 % lidocaine hydrochloride, a left paramedian incision was made to expose the lamboidal ridge and the external ear canal. The external ear canal was opened just anterior to the exit point of the facial nerve. The tympanic membrane was opened at its caudal hemicircumference. To expose and fenestrate the most anterior part of the horizontal semicircular canal, a 0.7 mm drill bit was used to drill into the caudal wall of the medial ear lateral and superior to the oval window close to the ceiling of the facial nerve canal. The opened horizontal canal was followed anteriorly and ventrally into the orifice of the vestibulum, the epithelial lining was mechanically removed with a 30-gauge needle, with which all the contents were aspirated. Then 99 % ethanol, which had been aspirated before the bone was covered with fascia, was instilled, and the skin was subsequently sutured.

Chemical labyrinthectomy (n = 12)

Animals were anaesthetized with 1.5 % isoflurane delivered up to 1.2 l/min via a mask. For surgical analgesia 1.5 mg/kg meloxicam was injected s.c. before and 3 days after surgery. After local anaesthesia with 1 % lidocaine hydrochloride, a left paramedian incision was made to expose the lamboidal ridge and the external ear canal. The external ear canal was opened just anterior to the exit point of the facial nerve. With a 26-gauge needle the tympanic membrane was perforated caudally to the hammer shaft, and about 0.150 ml of a 20 % bupivacaine solution was instilled into the tympanic cavity. After about 1 min the bupivacaine solution was aspirated and again slowly instilled. This procedure was repeated three times. After the local anaesthesia was instilled, the same procedure was repeated with 0.150 ml of a

10 % solution of p-arsanilic acid, to irreversibly desensitize the primary sensory cells of the inner ear (Vignaux et al. 2012). After the last thorough aspiration, the wound was closed by skin suture and 2 mg/kg marbofloxacine were injected s.c. for 3 days to prevent antibiosis.

Sham treatment (n = 12)

After anaesthesia (see above) the laboidal ridge and external ear canal were exposed by a left paramedian incision and the skin was sutured afterwards.

Behavioural scoring

Behavioural scoring focussed on the static compensation of ocular motor and postural symptoms, which is initially most prevalent after unilateral labyrinthectomy. Aspects of dynamic compensation were addressed by testing the influence of perturbations on postural control. The following behavioural symptoms were scored after unilateral vestibular ablation by two experienced raters: nystagmus, postural asymmetry in static conditions, and postural asymmetry during somatosensory perturbation. Each component had a maximum score of 10.

Nystagmus was visually observed with the animal recumbent in the cage. Intensity of spontaneous nystagmus was scored with 6–10 points, with one point for every 60 beats per minute (bpm). In the absence of spontaneous nystagmus at rest, the animal was either picked up or given a gentle airpuff over the head. Nystagmus evoked during these conditions was scored 1–5 points, with 1 point for every 60 bpm.

Postural asymmetry in static conditions was scored as follows: spontaneous barrel rolling, 10 points; barrel rolling evoked by light touch or air-puff, 9 points; recumbent position on lesioned side without leg support, 8 points; some ipsilesional leg support, 7 points; moving around on one side or using ipsilesional legs for recumbent support, 6 points; moving around with bilateral leg support, 5 points; moving around with occasional falls to the ipsilesional side, 4 points; moving around leaning towards the ipsilesional side, 3 points; hardly noticeable asymmetry, 2 points, postural asymmetry only noticeable when picked up, 1 point (Bergquist et al. 2008).

Postural asymmetry during somatosensory perturbation was examined by the elevation tail test. Animals were picked up from the ground by their tails for 30 s and body rotation was estimated in degrees and scored; 10 points were given for more than 360°, 8 points for 180–360°, 6 points for 90–180°, 4 points for less than 90° and 2 points for no relevant rotation.

Subsequent identical behavioural scoring was done at baseline, 4 h, 1, 2, 3, 7, 9, 15 days post-unilateral labyrinthectomy in all rats prior to μPET scans and directly after awakening from anaesthesia for μPET scans (Fig. 1a).

μPET imaging

Short-term anaesthesia was induced with isoflurane (2.5 %, administered in an acrylic container), and a cannula was placed in a tail vein before each radiotracer injection. Small samples of blood were taken, and the glucose concentration was measured by a commercial procedure (Glucometer Elite, Bayer HealthCare, Leverkusen, Germany). After awakening from anaesthesia, a [^{18}F]FDG (50 MBq) bolus was injected (in 1 ml saline, over 10 s), the cannula was removed and animals were allowed to move freely for 20 min. Afterwards anaesthesia was reinduced with isoflurane (2.5 %) and maintained throughout the μPET scan with 1.5 % isoflurane, delivered at 1.2 l/min via a mask. Animals were positioned in the aperture of a Siemens Inveon P120 PET scanner (Siemens Medical Solutions, Munich, Germany) and were kept warm with a heating pad. To minimize head movement, the head position was fixed using a custom-made head holder. A 30 min-long emission recording was initiated 30 min after [^{18}F]FDG bolus injection, which was followed by a transmission scan by using a rotating [^{57}Co] point source. Rats were then removed from the tomograph and, upon recovery from anaesthesia, returned to their home cages (Fig. 1b). Subsequent identical μPET recordings were done at baseline, 4 h, 1, 2, 3, 7, 9 days post-unilateral labyrinthectomy in all rats (Fig. 1a).

Image processing and statistical analysis

Image processing was performed as described previously (la Fougere et al. 2010). In brief, PET data were reconstructed by means of an OSEM-3D iterative reconstruction algorithm, which includes scatter and attenuation correction (Siemens Medical Solutions Munich, Germany). For attenuation correction, the corresponding transmission measurements at the end of the emission scan were used. The voxel dimensions of the reconstructed images were $0.59 \times 0.59 \times 0.79$ mm^3. [^{18}F]FDG uptake was calculated in units of percentage of total injected [^{18}F]FDG dose per gram (% ID/g) and normalized to body weight. Further data processing and statistical analysis were performed by means of custom-made toolboxes implemented in statistical parametric mapping software SPM5 (Wellcome Department of Cognitive Neurology, London). All the individual [^{18}F]FDG μPET images were stereotactically normalized to a custom-made [^{18}F]FDG template (average of 20 healthy rats), which was manually coregistered to a digital high-resolution cryosection-based atlas of rat brain (Toga et al. 1995; Rubins et al. 2003), using automated algorithms implemented in SPM5. All scans were analyzed after normalization to

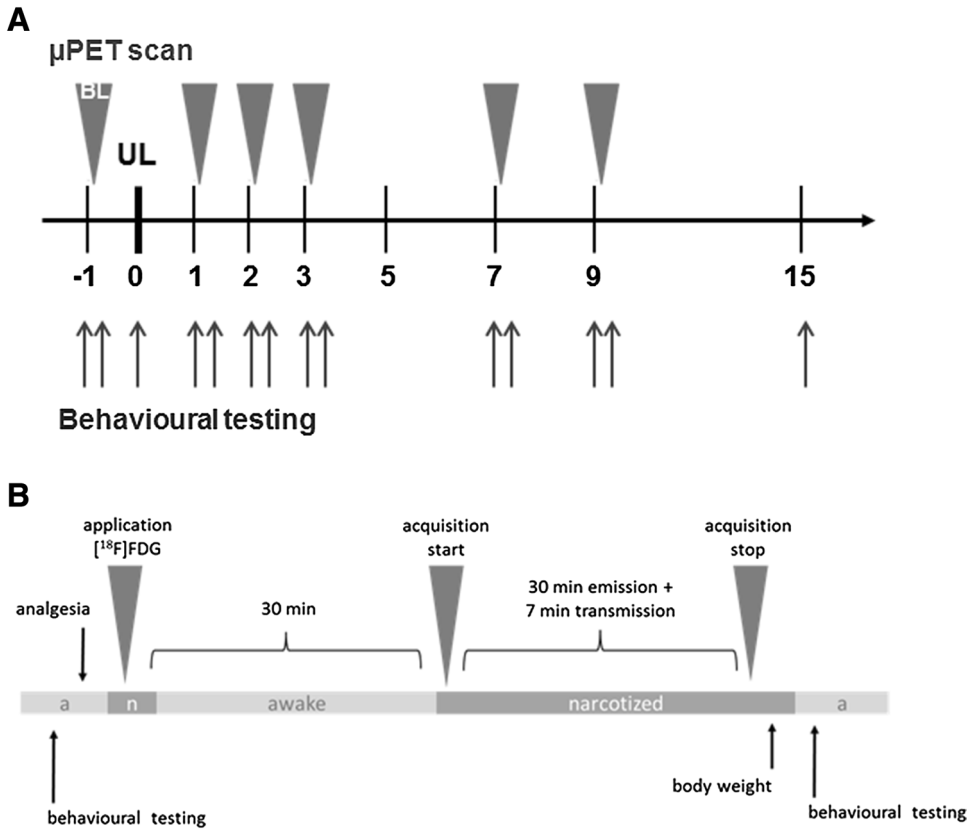

Fig. 1 **a** Study design and time course of longitudinal μPET scanning and behavioural testing. **b** At the respective time points after behavioural testing, anaesthesia was induced with isoflurane and [^{18}F]FDG was injected. After awaking, animals were allowed to move freely until anaesthesia was induced again with isoflurane for the μPET scan. The scan was started 30 min after [^{18}F]FDG injection. A 30 min emission recording was initiated followed by a 7 min transmission scan. After awaking from anaesthesia behavioural testing was done again. *BL* baseline, *UL* unilateral labyrinthectomy, *a* awake, *n* narcotized

whole brain. The normalization prior to voxel-based statistics was done with a whole brain anatomic mask, which was used for all subjects, to remove the effects of the differences in the overall count. Images after UL were compared with those of the baseline condition in a voxel-wise manner using SPM5 for group analysis. Both relative rates of glucose-metabolism increases and decreases (rCGM) were calculated. Changes were considered significant for $p < 0.01$ and $p < 0.001$ if applicable (uncorrected).

Results

Behavioural compensation after surgical unilateral labyrinthectomy

After surgical unilateral labyrinthectomy all animals showed severe symptoms of vestibular imbalance including barrel rolling, circular walking and postural instability (Fig. 2), whereas no signs of vestibular dysfunction were observed after sham treatment (data not shown). In the surgical unilateral labyrinthectomy group ocular motor and postural deficits gradually improved over time, indicating vestibular compensation. Spontaneous nystagmus significantly decreased within 3 days, postural asymmetry at static conditions within 3–15 days and during somatosensory perturbation within 7–15 days. Compared to the prior status, postural asymmetry transiently worsened following anaesthesia (for 1–3 min) up to 7 days after surgical unilateral labyrinthectomy but did not change significantly after this time point (Fig. 2).

Central vestibular compensation after surgical unilateral labyrinthectomy

Significant asymmetries or changes in relative rates of cerebral glucose metabolism (rCGM) were found at none of the time points in the sham group compared to baseline (data not shown). In contrast, characteristic patterns of rCGM changes were observed for the surgical unilateral labyrinthectomy group during vestibular compensation:

Compared to baseline, rCGM was asymmetric in the vestibular nuclei 4 h after surgical unilateral labyrinthectomy; there was a decreased rCGM in the ipsilesional vestibular nucleus (Fig. 3a, I). Further asymmetries were found in the vestibulocerebellum (contralesional increase) (Fig. 4a, I), posterior thalami (contralesional decrease) (Fig. 4b, I), hippocampus (ipsilesional increase) (Fig. 4c, I) and multisensory vestibular cortical areas (ipsilesional increase) (Fig. 4d, I). The asymmetric pattern of rCGM coincided with severe ocular motor and postural symptoms of vestibular imbalance.

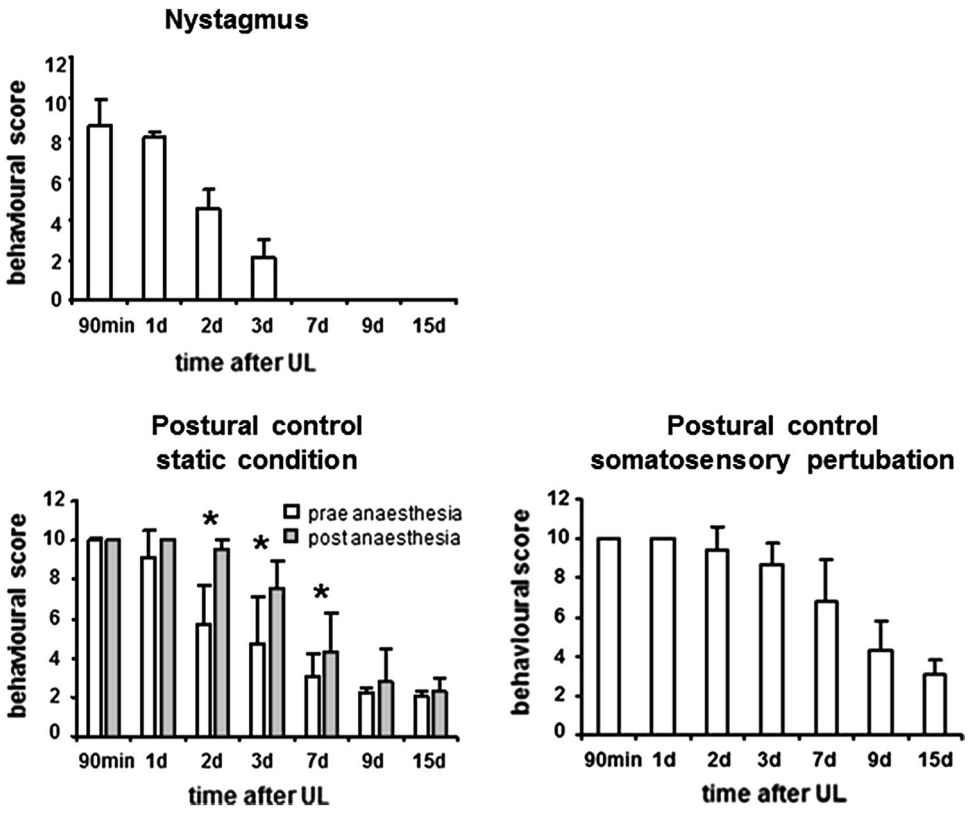

Fig. 2 Behavioural compensation after surgical unilateral labyrinthectomy. In the surgical unilateral labyrinthectomy group ocular motor and postural deficits gradually improved over time, indicating vestibular compensation. Spontaneous nystagmus significantly decreased until 3 days after unilateral labyrinthectomy. Postural asymmetry during the static condition gradually improved over 15 days, but could be transiently re-induced by short-term anaesthesia especially between 2 and 7 days. Postural asymmetry during somatosensory perturbation indicated a prolonged course of dynamic compensation with a significant increase of postural stability after 7 days. *Asterisk* significant difference between pre and post anaesthesia testing ($p < 0.05$), *UL* unilateral labyrinthectomy

On days 1 and 2 after surgical unilateral labyrinthectomy, asymmetry in the vestibular nuclei decreased mostly due to an increase of rCGM in the ipsilesional vestibular nucleus (Fig. 3b, I). On day 1, rCGM was slightly higher in the contralesional vestibular nucleus (Fig. 3b, I). On day 2, the asymmetry of rCGM in the posterior thalamus (Fig. 4b, III) or multisensory vestibular cortices (Fig. 4d, III) disappeared. An ipsilesional increase in rCGM was seen in the vestibulocerebellum on day 2 (Fig. 4a, III). A bilateral increase of rCGM appeared in the hippocampus and amygdala on days 1 and 2 (Fig. 4c, II/III). Parallel to these changes, the intensity of nystagmus and postural asymmetry was markedly reduced (by 43 and 15 % after 2 days vs. 4 h, respectively). However, postural decompensation could be induced by anaesthesia.

Two days after surgical unilateral labyrinthectomy, no further dynamics of rCGM in the vestibular nuclei were observed (Fig. 3b, II/III/IV/V). However, there was a prominent increase of rCGM in the ipsilesional spinal trigeminal nucleus (visible from day 2 to 9, maximum on day 3) (Fig. 4a, III/IV/V/VI).

Starting on day 7 after surgical unilateral labyrinthectomy, rCGM increased in the vestibulocerebellum bilaterally (Fig. 4a, V/VI). The increase of rCGM persisted in the amygdala, day 3, predominantly ipsilesional (Fig. 4c, IV); day 7, contralesional (Fig. 4c, V) and in the hippocampus bilateral (days 3 and 9) (Fig. 4c, IV/VI). The hypothalamus showed a significant rCGM increase on day 9 (Fig. 4c, VI). Behavioural scoring for vestibular imbalance on day 7 indicated a normalization of nystagmus and improvement of postural asymmetry (by 69 % of peak symptoms after 4 h). Somatosensory perturbation as well as anaesthesia induced a significant deterioration of postural control (compared to the unmodified condition) until day 7. Remarkably, after day 9, anaesthesia did not cause a significant decompensation of postural control, suggesting structural consolidation of vestibular compensation.

Central auditory processing after surgical unilateral labyrinthectomy

Surgical labyrinthectomy also causes collateral damage to the cochlea. Therefore, changes in central auditory pathways over time were examined to determine the potential central compensatory mechanisms of hearing loss. Compared to baseline at 4 h after surgical unilateral labyrinthectomy, a significant decrease in rCGM was found in the contralesional inferior colliculus (Fig. 5a, I) and the auditory cortex (Fig. 5b, I). This pattern did not change significantly until day 9 (Fig. 5a/b, II/III/IV/V/VI), and therefore gave no clear indication of central auditory compensation. As a summary, Table 1 shows all significant

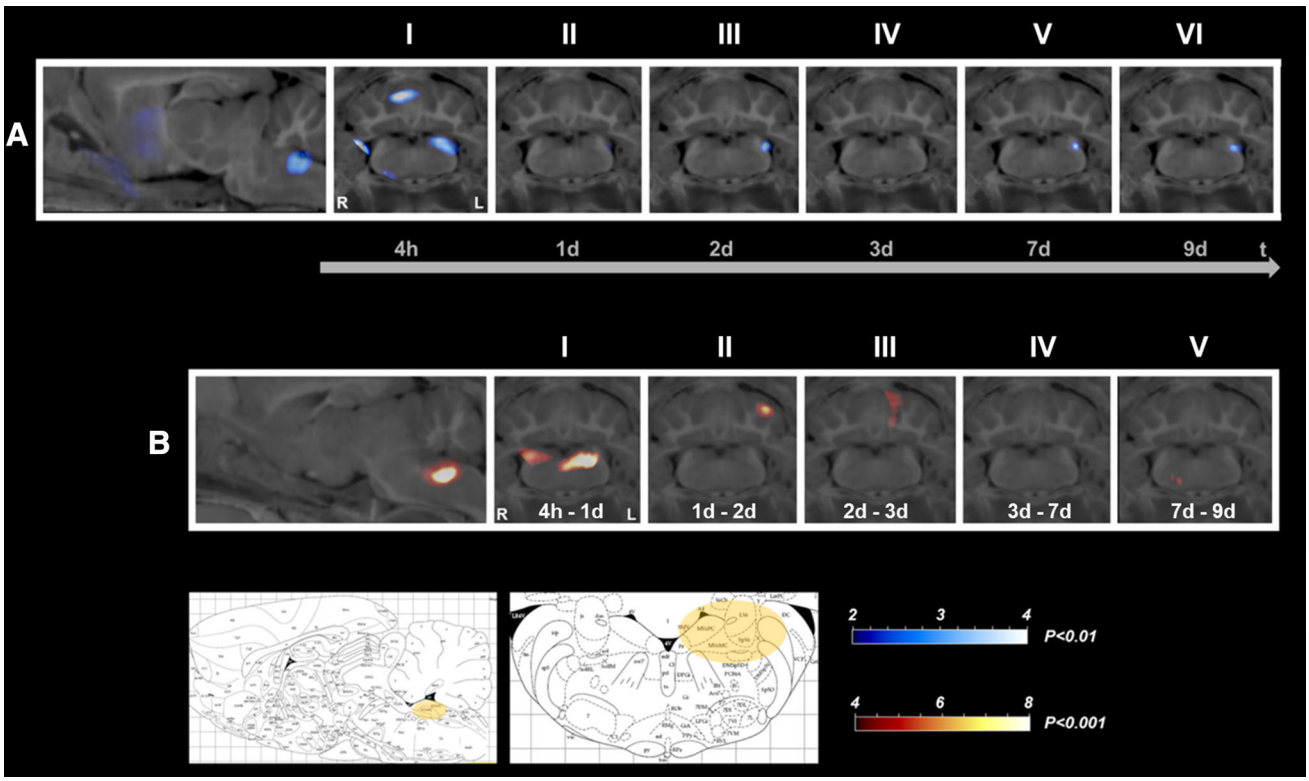

Fig. 3 Sequential [^{18}F]FDG μPET dynamics in the vestibular nuclei after left surgical unilateral labyrinthectomy. **a** Changes of rCGM in the vestibular nuclei over time compared to baseline (prior unilateral labyrinthectomy); **b** relative changes of rCGM in the vestibular nuclei between time points of measurement. Compared to baseline, an asymmetry in rCGM occurred 4 h after unilateral labyrinthectomy in the vestibular nuclei, and there was a decreased rCGM of the ipsilesional vestibular nucleus (**a** *I*). On day 1 asymmetry in the vestibular nuclei decreased (**a** *II*) due to the increase of rCGM in the ipsilesional vestibular nucleus (**b** *I*). RCGM in the contralesional vestibular nucleus was slightly higher (**b** *I*). After 2 days, no further dynamics of rCGM were observed in the vestibular nuclei (**b** *II*/*III*/*IV*/*V*). Localisation of the vestibular nuclei is indicated on sagittal and transversal slices of a brain atlas. *L* left side, *R* right side

rCGM changes following surgical unilateral labyrinthectomy for all relevant anatomic regions as a function of time.

Central vestibular compensation after chemical unilateral labyrinthectomy

To test the hypotheses derived from the surgical model and to determine whether dynamic patterns during vestibular compensation were independent of the specific features of the surgical unilateral labyrinthectomy model, a second rat model of chemical unilateral labyrinthectomy was investigated using behavioural testing and serial μPET scanning. After chemical unilateral labyrinthectomy all animals exhibited severe signs of vestibular imbalance including nystagmus and postural instability (peak score on day 2). Nystagmus disappeared within the first 5 days post-chemical unilateral labyrinthectomy; the postural imbalance score decreased significantly after day 9 (data not shown). As in the surgical unilateral labyrinthectomy model, a decrease in rCGM was found in the contralesional inferior colliculus at all examined time points (data not shown). Four hours after chemical unilateral labyrinthectomy, there was a decrease in rCGM in the ipsilesional vestibular nucleus (Fig. 6 I). The symmetry between the vestibular nuclei was restored on day 1 by the rCGM increase more in the ipsilesional than in the contralesional vestibular nucleus (Fig. 6 II). After day 7 an rCGM increase appeared in the ipsilesional spinal trigeminal nucleus (Fig. 6 III), and on day 9, in the ipsilesional vestibulocerebellum (Fig. 6 IV). Table 2 summarizes all significant rCGM changes in the chemical unilateral labyrinthectomy model by anatomic region and time.

Discussion

Central vestibular compensation—a multimodal and multiphasic process of plasticity

The identification of the neural substrates of vestibular compensation constitutes a challenge, because vestibular compensation involves adaptations in various vestibular-

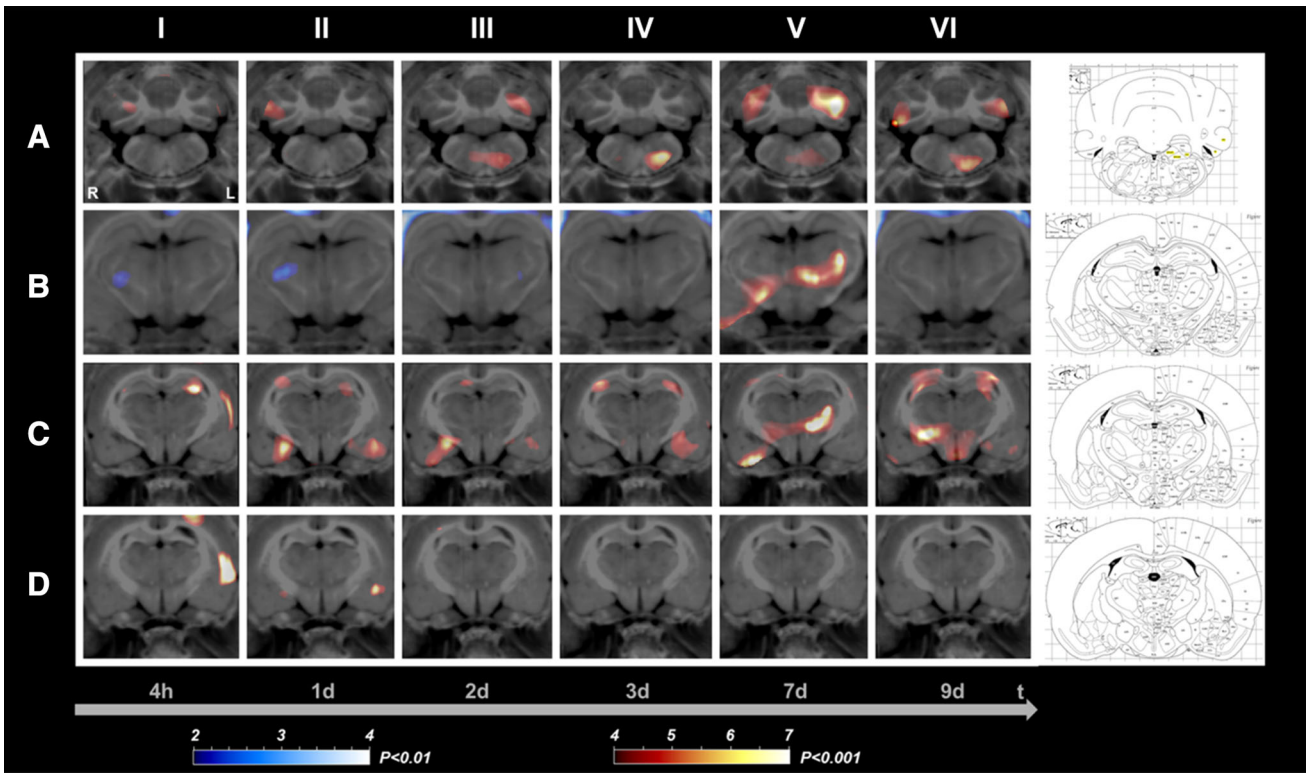

Fig. 4 Sequential whole brain [^{18}F]FDG μPET dynamics after left surgical unilateral labyrinthectomy. **a** Changes of rCGM compared to baseline (prior unilateral labyrinthectomy) in the medulla oblongata and vestibulocerebellum over time. A prominent increase of rCGM appeared in the ipsilesional spinal trigeminal nucleus (maximum after 3 days) (**a** *III*/*IV*/*V*/*VI*). In the vestibulocerebellum rCGM increased contralesionally after 1 day (**a** II), ipsilesionally after 2 days (**a** III) and bilaterally after 7 days (**a** *V*/*VI*). **b** Changes of rCGM compared to baseline in the thalamus. rCGM was reduced in the contralesional posterior thalamus after 1 day (**b** *II*), than adjusted to baseline (**b** *III*) and increased in the ipsilesional posterior thalamus after 7 days (**b** *V*). **c** Changes of rCGM in the hippocampus and amygdala. An increase of rCGM was found in the hippocampus ipsilesionally after 4 h (**c** *I*) and bilaterally after 1, 3 and 9 days (**c** *II*/*IV*/*VI*). The amygdala was activated after 1, 2, 3 and 7 days (**c** *II*/*III*/*IV*/*V*), the hypothalamus after 9 days (**c** *VI*). **d** Changes of rCGM compared to baseline in the multisensory vestibular cortex. RCGM was asymmetric in the multisensory vestibular cortices (activation ipsilesionally) after 4 h and less after 1 day (**d** *I*/*II*) and then became symmetric at baseline level (**d** *III*–*VI*). Corresponding transversal slices of a brain atlas are shown on the *right side*. *L* left side, *R* right side

related structures throughout the brain. In-vitro studies have helped to clarify the molecular mechanisms involved in vestibular compensation, but systematic investigations of the effects of unilateral labyrinthectomy on whole brain vestibular-related networks and their changes during vestibular compensation are lacking. Here we used μPET as a non-invasive imaging technique to investigate temporo-spatial rCGM changes during vestibular compensation and thereby test previously described hypotheses on vestibular compensation in a whole brain in vivo model. In the following, the discussion of rCGM dynamics during vestibular compensation is guided by mechanisms of deafferentation-induced plasticity.

Acute vestibular imbalance

It has been proposed that the initial vestibular syndrome following unilateral labyrinthectomy results from severe imbalance during the resting activity of neurons in the vestibular nuclei (Precht et al. 1966). The initial decrease of the firing rate of ipsilesional second-order vestibular neurons has been attributed to deafferentation-induced disfacilitation and increased inhibition via the vestibular commissural system (Smith and Curthoys 1988; Ris et al. 1995; Bergquist et al. 2008). Indeed, rCGM of the ipsilesional vestibular nucleus decreased in our study 4 h post-unilateral labyrinthectomy. Further rCGM asymmetries were found in the vestibulocerebellum, thalamus, multisensory cortex and hippocampus, all of which are part of vestibular-related networks (Dieterich and Brandt 2001; Smith et al. 2005; Zwergal et al. 2009). These findings illustrate that an acute vestibular lesion affects ocular motor and postural functions as well as higher-order processing of verticality perception, spatial orientation and multimodal integration (Dieterich and Brandt 2008).

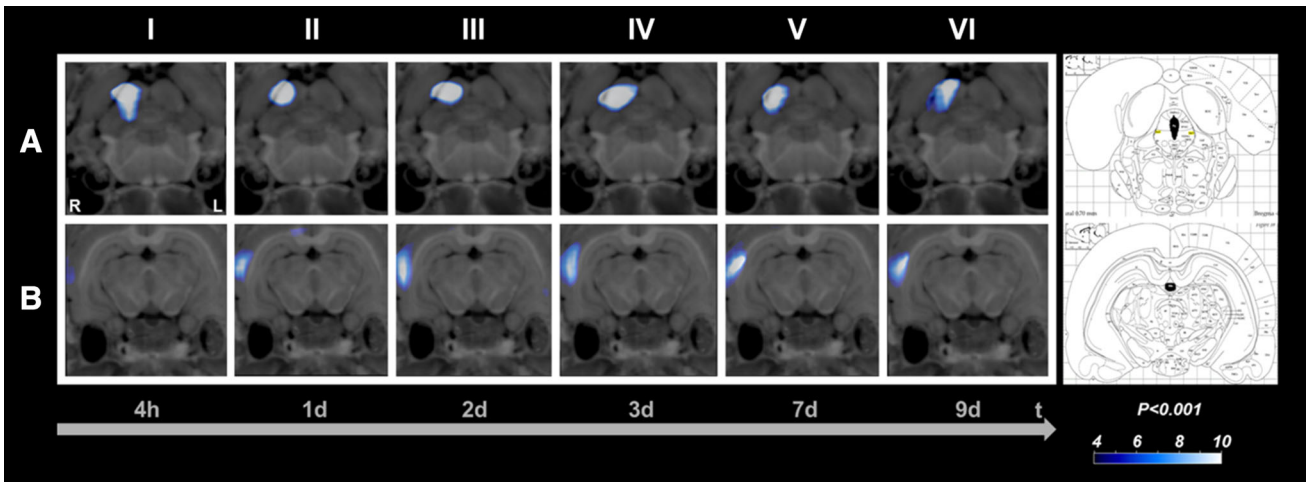

Fig. 5 Sequential [^{18}F]FDG μPET dynamics in the central auditory system after left surgical unilateral labyrinthectomy. **a** Changes of rCGM in the inferior colliculi over time compared to baseline (prior unilateral labyrinthectomy); **b** changes of rCGM in the auditory cortices over time compared to baseline. Four hours after unilateral labyrinthectomy there was a significant decrease in rCGM in the contralesional inferior colliculus (**a** *I*) and the auditory cortex (**b** *I*). This pattern did not change significantly after the consecutive time point until after 9 days (**a** *II–VI*; **b** *II–VI*), therefore giving no clear indication for central auditory compensation within this time interval. Corresponding transversal slices of a brain atlas are shown on the *right side*. *L* left side, *R* right side

Table 1 shows all significant rCGM changes following surgical unilateral labyrinthectomy for all relevant anatomic regions as a function of time

Decrease of rCGM is depicted in Italic, increase in Bold

L left side, *R* right side

The significance of the clusters is depicted by *t*-values at a *p* value of 0.001 or 0.01 (the latter indicated by *)

	Surgical unilateral labyrinthectomy					
	4 h	1 day	2 day	3 day	7 day	9 day
Vestibular nucleus	*3,5 (L)**					
Trigeminal nucleus			**5,1 (L)**	**6,5 (L)**	**3,2 (L)**	**5,8 (L)**
Vestibulocerebellum	**4,0 (R)**	**4,6 (R)**	**5,1 (L)**		**7,2 (L)**	**5,3 (L)**
					6,4 (R)	**4,6 (R)**
Thalamus	*2,9 (R)**	*3,1 (R)**			**6,5**	
Vestibular cortex vMSC	**6,7 (L)**					
Hippocampus	**6,4 (L)**			**5,2 (L)**		**6,2 (L)**
				5,8 (R)		**5,9 (R)**
Amygdala		**5,2 (L)**	**5,7 (R)**	**4,7 (L)**	**6,5 (R)**	
		5,8 (R)				
Cochlear nucleus	*3,4 (L)**	*1,9 (L)**	*3,3 (L)**	*1,8 (L)**	*3,6 (L)**	*3,3 (L)**
Inferior colliculus	*9,1 (R)*	*9,4 (R)*	*9,5 (R)*	*10,1 (R)*	*8,9 (R)*	*8,6 (R)*
Auditory cortex	*4,8 (R)*	*6,2 (R)*	*6,4 (R)*	*6,1 (R)*	*7,3 (R)*	*7,0 (R)*

Vestibular nuclei re-balancing

It has been reported that during the initial phase of vestibular compensation (4–24 h post unilateral labyrinthectomy) a restoration of spontaneous activity of ipsilesional second-order vestibular neurons and bilateral re-balancing of resting firing rates occurs which is due to changes in membrane properties (Precht et al. 1966; Smith and Curthoys 1988; Cameron and Dutia 1997; Guilding and Dutia 2005; Bergquist et al. 2008; Lim et al. 2010; Shao et al. 2012). This intrinsic hyperactivity may be related to firing rate potentiation or rapid down-regulation of GABA receptors (Yamanaka et al. 2000; Nelson et al. 2003; Bergquist et al. 2008). In our study, a significant increase of rCGM in the ipsilesional and a less significant increase in the contralesional vestibular nucleus 1 day after unilateral labyrinthectomy resulted in symmetry between the vestibular nuclei. This result agrees with a previous 2-desoxyglucose autoradiography study in unilateral labyrinthectomy rats, which showed a rapid decrease of initial asymmetry in the vestibular nuclei within 48 h (Luyten et al. 1986).

Extravestibular sensory substitution

The intrinsic cellular mechanisms underlying rebalancing of activity in the vestibular nuclei are not permanent and

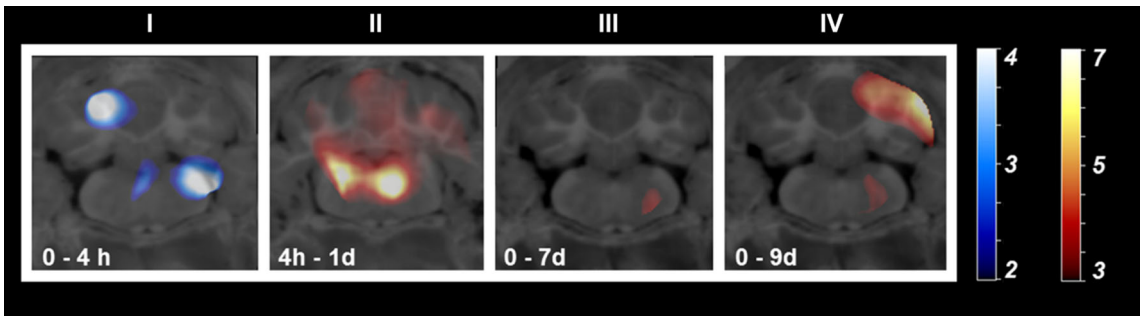

Fig. 6 Sequential [^{18}F]FDG μPET dynamics after left chemical unilateral labyrinthectomy. The decrease in rCGM in the ipsilesional nucleus 4 h after chemical unilateral labyrinthectomy was very similar to that in the surgical UL model (*I*). The symmetry between the vestibular nuclei was restored after 1 day via a larger rCGM increase in the ipsilesional than in the contralesional vestibular nucleus (*II*). After 7 days an rCGM increase appeared in the ipsilesional spinal trigeminal nucleus (*III*), after 9 days in the ipsilesional vestibulocerebellum (*IV*)

Table 2 summarizes all significant rCGM changes in the chemical unilateral labyrinthectomy model by anatomic region and time

Decrease of rCGM is depicted in Italic, increase in Bold

L left side, *R* right side

The significance of the clusters is depicted by t-values at a p value of 0.001 or 0.01 (the latter indicated by *)

	Chemical unilateral labyrinthectomy					
	4 h	1 day	2 day	3 day	7 day	9 day
Vestibular nucleus	*4,1 (L)**	*3,5 (L)**				
Trigeminal nucleus					**3,6 (L)**	**4,4 (L)**
Vestibulocerebellum		**4,2 (R)**		**4,7 (L)**	**3,5 (L)**	**6,5 (L)**
					3,1 (R)	
Thalamus	*3,4 (L)**					
Vestibular cortex vMSC	**5,7 (L)**	**4,3 (L)**				
Hippocampus	**7,2 (L)**		**4,1 (R)**	**4,4 (R)**	**6,4 (R)**	
	6,8 (R)					
Amygdala			**6,7 (R)**	**6,2 (L)**	**2,6 (R)**	**5,3 (R)**
				5,8 (R)		
Cochlear nucleus	*4,1 (L)**	*3,2 (L)**	*2,5 (L)**	*2,6 (L)**	*2,2 (L)**	*2,0 (L)**
Inferior colliculus	*12,1 (R)*	*10,9 (R)*	*8,2 (R)*	*8,9 (R)*	*7,2 (R)*	*10,1 (R)*
Auditory cortex	*9,2 (R)*	*7,4 (R)*	*6,3 (R)*	*7,1 (R)*	*6,4 (R)*	*9,0 (R)*

from 2 days on are followed by changes of spontaneous activity that depend on synaptic inputs (Guilding and Dutia 2005). The vestibular nuclei are embedded in sensorimotor networks, through which proprioceptive information reaches the vestibular nuclei from the central cervical and spinal trigeminal nucleus (Sato et al. 1997). After unilateral labyrinthectomy, proprioceptive inputs to the vestibular nuclei are unmasked and enhanced (Sadeghi et al. 2011; Beraneck and Idoux 2012; Jamali et al. 2013). Patients with vestibular neurititis displayed an enhanced sensitivity to ipsilesional neck vibration and a gray matter volume increase of the gracile nucleus (Strupp et al. 1998; zu Eulenburg et al. 2010). Our study shows an rCGM increase in the ipsilesional spinal trigeminal nucleus 2–9 days after surgical and 7–9 days after chemical unilateral labyrinthectomy. This most likely indicates a re-weighting of proprioceptive signals from the face and neck. In line with our finding, Sadeghi et al. showed that neck proprioceptive signals contribute to vestibular nucleus firing rates, maximally in the first week post-unilateral labyrinthectomy. This is an important finding, since sensory re-weighting may be a potential focus of future rehabilitation programs for acute vestibular disorders.

Cerebellar sensorimotor adaptation

The contribution of sensory substitution to vestibular compensation decreases over weeks and is augmented by additional integration of motor efference copy signals at the vestibular nucleus level later on (Sadeghi et al. 2010; Beraneck and Idoux 2012). The cerebellum substantially contributes to motor learning in the vestibular system (Boyden et al. 2004). In our study, rCGM increases in the vestibulocerebellum mainly after 7 days in the surgical and after 9 days in the chemical UL model. We can only speculate on whether this effect represents motor memory storage, reorganization of

synaptic connectivity or neurogenesis (Goto et al. 2002; Dutheil et al. 2009). The lack of postural decompensation post-anaesthesia 7 days after surgical unilateral labyrinthectomy suggests mechanisms that contribute to the structural plasticity and consolidation of vestibular compensation. Previous evidence shows that the vestibulocerebellum is critical for late vestibular compensation. Ablation of the vestibulocerebellum or disruption of climbing fibre inputs severely disturbed vestibular compensation (Kitahara et al. 1997; Darlington and Smith 2000). Cerebellum-deficient transgenic mice showed no further restoration of the vestibulo-ocular reflex 5 days post-UL (Beraneck et al. 2008).

Stress-axis regulation

The stress-axis is activated by acute vestibular dysfunction via connections from the vestibular nuclei to the hypothalamic paraventricular nucleus (Balaban 2002; Saman et al. 2012). The expression of hypothalamic corticotrophin-releasing hormone increases after 1 day and persists up to 30 days after unilateral labyrinthectomy (Tighilet et al. 2009). Previous studies suggested that stress-axis activation facilitates vestibular compensation by promoting synaptic and neuronal plasticity via the action of glucocorticoids or other stress-related neuroactive substances (Cameron and Dutia 1999). Our study shows an rCGM increase in the amygdala, which reaches a maximum on day 1 and persists up to 9 days. This most likely reflects the arousal with aversion and lack of control in the acute vestibular syndrome. The temporal dynamics of amygdala activation parallels behavioural recovery. Hypothalamic rCGM increases after 9 days, indicating a long-lasting modulation of the stress-axis following unilateral labyrinthectomy. This process may be beneficial in long-term consolidation of vestibular compensation, but it may also facilitate development of anxiety disorders after acute vestibular disease (Eckhardt-Henn et al. 2008).

Hippocampal plasticity

Vestibular information reaches the hippocampus by various multisynaptic pathways to augment spatial orientation (Smith et al. 2005). In uni- and bilateral vestibulopathy hippocampal dysfunction occurs (Brandt et al. 2005; Zheng et al. 2006, 2007). Following unilateral labyrinthectomy, hippocampal electrophysiological and neurochemical changes are more complex (Stackman et al. 2002; Zheng et al. 2003). In our study, hippocampal rCGM is asymmetric 4 h after unilateral labyrinthectomy due to ipsilesional increase, which may reflect the spatial disorientation in the acute vestibular syndrome. In the following days, the hippocampal rCGM increases symmetrically—possibly by upregulating bilateral projections from the intact labyrinth. The functional relevance of this effect is, however, unclear. Furthermore, it must be noted that hippocampal plasticity evolves over several months following unilateral labyrinthectomy (Zheng et al. 2003).

Central auditory compensation?

Previous studies have shown plasticity of the central auditory system following cochlear lesions (Syka 2002). It has been proposed that the main mechanism is the reorganization of cortical projection maps via strengthening of input from the intact ear and loss of collateral inhibition. Less is known about changes in subcortical auditory pathways. A μPET study in the rat model reported a decreased rCGM in the contralesional inferior colliculus 14 days after UL (Hsu et al. 2009). Our study also shows contralesional deactivation of the inferior colliculus and auditory cortex early after collateral auditory damage due to UL. Interestingly, this asymmetry persists up to 9 days. On the basis of rCGM dynamics, we therefore found no indication of plasticity in the central auditory system within the first week after unilateral labyrinthectomy. Likewise plastic changes in the auditory system take several weeks (Syka 2002). This is in contrast to the rapid rebalancing occurring in the central vestibular system and indicates there are differential modes of plasticity in the sensory systems.

Methodological strengths and limitations

The strengths of the method of applying serial μPET to study vestibular compensation are that it allows visualization of rCGM in vivo, on a whole-brain level and over time. RCGM is a sensitive measure for depicting metabolic changes, but it does not allow conclusions about the underlying mechanisms (e.g., changes in fire rate, synaptic input or structural plasticity). μPET was shown to be suitable for repeated measurements in small animals (Lou et al. 2007). The methodological challenges are related to the limited spatial resolution of about 1–2 mm that complicates the exact delineation of subcortical and brainstem structures (Coello et al. 2011). To overcome these problems in the present study an observer-independent whole-brain analysis was implemented using the reliable stereotactic normalization procedure of SPM. This allows quantitative voxel-based statistical analysis between time points and within groups (Prieto et al. 2011). In future studies, accuracy of spatial localization may be controlled by application of autoradiography. The current study used two different rat models of unilateral labyrinthectomy to account for a potential bias due to specific features of the methods. The basic rCGM patterns during vestibular compensation were shown in both models. The minor differences in time dynamics can be explained by the

slightly variable time courses of behavioural compensation between the models.

Conclusion

In this study, serial [^{18}F]FDG-μPET was used to investigate dynamic cerebral plasticity during vestibular compensation after unilateral labyrinthectomy. The findings indicate that vestibular compensation results from a systematic sequence of adaptations in brain areas concerned with sensorimotor processing and spatial cognition. Partial re-balancing of activity in the brainstem vestibular nuclei is an important mechanism of early vestibular compensation, accompanied by adaptations in the activity of thalamocortical and limbic areas including the hypothalamus and amygdala. Subsequently, up-regulation of sensory synaptic inputs, involving in particular the spinal trigeminal nucleus, and the bilateral activation of the vestibulocerebellum, add to consolidation of vestibular compensation. Stress-axis activation accompanies behavioural recovery. Understanding these respective mechanisms, acting in parallel with different starting points and time courses, is likely to be important for the treatment of patients with acute vestibular disorders.

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Conflict of interest The authors declare no competing financial interests.

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