HIPPOCAMPUS 17:471–485 (2007)

Spatial Memory and Hippocampal Volume in Humans With Unilateral Vestibular Deafferentation

Katharina Hüfner,[1*] Derek A. Hamilton,[2] Roger Kalla,[1] Thomas Stephan,[1] Stefan Glasauer,[1,3] Jun Ma,[4] Roland Brüning,[4] Hans J. Markowitsch,[5] Kirsten Labudda,[5] Christian Schichor,[6] Michael Strupp,[1] and Thomas Brandt[1,3]

ABSTRACT: Patients with acquired chronic bilateral vestibular loss were recently found to have a significant impairment in spatial memory and navigation when tested with a virtual Morris water task. These deficits were associated with selective and bilateral atrophy of the hippocampus, which suggests that spatial memory and navigation also rely on vestibular input. In the present study 16 patients with unilateral vestibular deafferentation due to acoustic neurinoma were examined 5- to 13-yrs post-surgery. Volumetry of the hippocampus was performed in patients and age- and sex-matched healthy controls by manually tracing the structure and by an evaluator-independent voxel-based morphometry. Spatial memory and navigation were assessed with a virtual Morris water task. No significant deficits in spatial memory and navigation could be demonstrated in the patients with left vestibular failure, whereas patients with right vestibular loss showed a tendency to perform worse on the respective tests. Impairment was significant only for one computed measure (heading error). The subtle deficiencies with right vestibular loss are compatible with the recently described dominance of the right labyrinth and the vestibular cortex in the right hemisphere. Volumetry did not reveal any atrophy of the hippocampus in either patient group.

KEY WORDS: hippocampus; navigation; unilateral vestibular deafferentation; vestibular system

INTRODUCTION

The human hippocampal formation is known to have an important function in various aspects of memory, such as early encoding, consolidation, and retrieval (Scoville and Milner, 1957; Manns et al., 2003a,b). Several studies in patients with hippocampal lesions have demonstrated its role in spatial memory, that is, remembering where a location is and how to get there (Smith and Milner, 1981; Maguire et al., 1996; Kessels et al., 2001; Spiers et al., 2001; Astur et al., 2002). These findings were confirmed in healthy volunteers by imaging techniques (PET and fMRI) that showed activation, especially of the right hippocampus, during the imagination of navigation (Ghaem et al., 1997; Maguire et al., 1997), as well as wayfinding in a virtual environment, a navigation task defined as "finding novel paths between locations" (Maguire et al., 1998; Gron et al., 2000; Hartley et al., 2003).

The ability of an individual to accurately navigate in space is thought to also depend on vestibular input (Etienne, 1980; Matthews et al., 1989; Stackman et al., 2002a; Horii et al., 2004). This concept is supported by studies demonstrating that vestibular stimulation in the absence of vision modulates hippocampal neuronal activity in rats (Gavrilov et al., 1995, 1998) and primates (O'Mara et al., 1994). Various anatomical connections have been proposed to exist between the vestibular nuclei and the hippocampus: the thalamo-cortical route passing through the thalamus, the parietal cortex, and the ento- or perirhinal cortex to the hippocampus; the θ-generating pathway leading from the pontine reticular formation via the supramammillary nucleus and medial septum to the hippocampus; or the head-direction system passing through the dorsal tegmental nucleus, lateral mammillary nucleus, and anterodorsal thalamic nucleus to the hippocampus (for an overview: Smith, 1997; Bland and Oddie, 1998; Russell et al., 2003b; Hopkins, 2005; Smith et al., 2005). Many of these polysynaptic connective pathways suggest a bilateral representation of vestibular signals in the hippocampus of rodents (Cuthbert et al., 2000; Zheng et al., 2003). In humans fMRI studies have provided evidence for hip-

[1] **Department of Neurology, Ludwig-Maximilians University, Munich, Germany;** [2] **Department of Psychology, University of New Mexico, Albuquerque, New Mexico;** [3] **Bernstein Center for Computational Neuroscience, Munich, Germany;** [4] **Department of Neuroradiology, Ludwig-Maximilians University, Munich, Germany;** [5] **Department of Physiological Psychology, University of Bielefeld, Bielefeld, Germany;** [6] **Department of Neurosurgery, Ludwig-Maximilians University, Munich, Germany**
Grant sponsor: BMBF; Grant number: BCCN Munich 01GQ0440.
Abbreviations used: ANOVA, analysis of variance; ANCOVA, analysis of covariance; BVD, bilateral vestibular deafferentation; CSF, cerebrospinal fluid; HPC, hippocampus; UVD, unilateral vestibular deafferentation; VBM, voxel-based morphometry; VMWT, virtual Morris water task.
Jun Ma is currently at Department of Neuroradiology, Tiantan Hospital, Beijing, China.
Roland Brüning is currently at Department of Radiology, Asklepios Klinik Barmbek, Hamburg, Germany.
*Correspondence to: Katharina Hüfner, MD, Department of Neurology, Ludwig-Maximilians University, Klinikum Grosshadern, Marchioninistr. 15, 81377 Munich, Germany.
E-mail: katharina.huefner@med.uni-muenchen.de
Accepted for publication 13 February 2007
DOI 10.1002/hipo.20283
Published online 30 March 2007 in Wiley InterScience (www.interscience.wiley.com).

pocampal activation during vestibular stimulation, but predominantly ipsilateral to the vestibular stimulus (Vitte et al., 1996; Suzuki et al., 2001).

In rodents unilateral vestibular deafferentation (UVD) leads to biochemical changes in the ipsilateral and contralateral hippocampus; some effects persist for weeks (Zheng et al., 2001; Liu et al., 2003a,b) after surgery. Other studies in rodents have shown that unilateral vestibular damage results in bilateral changes in electrical excitability of the CA1 region of the hippocampus (Zheng et al., 2003) and in deficits in spatial navigation (Chapuis et al., 1992). It was shown recently that rats are impaired on a food foraging task following UVD and that this impairment resolved 6 months after the lesion. Deficits did, however, persist in animals with bilateral vestibular deafferentation (BVD) (Zheng et al., 2006). In a different study UVD did not impair the exploration and recognition of unfamiliar objects in rats; both functions were compromised in animals with BVD (Zheng et al., 2004).

In humans BVD (patients with neurofibromatosis Type II) caused significant deficits in spatial memory and navigation (Brandt et al., 2005). Neurofibromatosis Type II is a disease caused by mutations in the *NF2* gene located on the long arm of chromosome 22. The presentation of this disease is characterized by bilateral acoustic neurinomas (Seizinger et al., 1986). When tested in a virtual Morris water task BVD patients showed significant deficits in spatial memory and navigation, although their overall general memory performance was comparable with that of controls. The observed deficits were associated with bilateral hippocampal atrophy (16.9% hippocampal volume decrease relative to controls). Overall brain volume was, however, not altered (Schautzer et al., 2003; Brandt et al., 2005). Based on these studies and the above-described animal experiments on hippocampal changes following UVD, we conducted a study on patients with chronic UVD due to acoustic neurinoma. Unilateral acoustic neurinomas are sporadic tumors originating from the Schwann cells of the vestibular nerve. Loss of the structural integrity of the vestibular nerve due to tumor growth in all of these patients was confirmed by the surgeon during microneurosurgical tumor removal via a retrosigmoidal approach. Our aim was to determine the effect on spatial and general memory performance and hippocampal volumes. We were also interested in whether the side of the vestibular lesion (right or left) has differential effects on the function and morphology of the hippocampus, since the right hippocampus is primarily involved in human spatial navigation (Maguire et al., 1997; Gron et al., 2000; Hartley et al., 2003), and the vestibular organ and the vestibular cortex show a dominance in the right hemisphere in right-handed subjects (Bense et al., 2001; Dieterich et al., 2003).

MATERIALS AND METHODS

Subjects

Sixteen patients (four women and four men with left-sided vestibular lesion (left UVD group), Pat 1L to Pat 8L (mean age ± SD = 58.0 ± 4.9 yr) and four women and four men with right-sided vestibular lesion (right UVD group), Pat 1R to Pat 8R (55.4 ± 5.6 yr)) with unilateral vestibular failure due to acoustic neurinoma participated in the study (Table 1). All patients had undergone surgery 5–13 yr before the test (left-sided vestibular lesion 9.9 ± 2.8 yr, right-sided vestibular lesion 8.9 ± 2.4 yr). Only those patients were included, whose tumor growth extended beyond the inner ear canal into the cerebellopontine angle without significantly compressing the brainstem. The surgeon confirmed loss of vestibular nerve integrity due to tumor growth intraoperatively in all of these patients. All tumors were removed via a retrosigmoidal approach, which allows microscopic evaluation of the brainstem, cranial nerves, and inner ear canal. At the time of the study all patients had unilateral hearing loss. Eight patients also had facial palsy, and four also had mild facial nerve deficit. The facial nerve was not affected in the remaining four. All patients underwent caloric irrigation to confirm unilateral vestibular unresponsiveness and orthoptic examination to exclude central ocular motor and vestibular disorders. Lesion volumes due to neurinoma growth or removal, located in the cerebellar hemispheres, did not depend on the time since the operation ($r = -0.01$, $P > 0.05$) and did not lead to clinical symptoms per se. There was, however, a correlation between the extent of the lesion and the occurrence of facial palsy ($r = 0.52$, $P < 0.05$). The lesion volumes did not differ significantly between the patients with left or right-sided lesions. None of the patients required additional surgery or had received radiation therapy. Sixteen sex- and age-matched subjects (57.4 ± 5.5 yr) with no known neurological history served as a control population (control group). All subjects were right-handed. Patients and controls were also matched for years of school education (patients: 10.3 ± 1.7 yr and controls: 10.6 ± 1.5 yr) and computer experience (controls 8/16 with some or extensive computer experience, patients 9/16 with some or extensive computer experience). The study was conducted in accordance with the principles described in the Declaration of Helsinki. All subjects gave their informed consent prior to the study.

MRI Volumetry

Acquisition protocol

All 16 patients and 16 controls were examined with a 1.5-T scanner and a circular polarized head coil (Magnetom Vision®, Siemens Medical Systems, Germany). T2-weighted images (TR/TE = 4,150/119 ms at flip angle 180° field of view 210 mm, 3-mm slice, 0.9-mm gap, matrix size 512/384) and matched T1-inversion-recovery images (TR/TE = 6,336/60 ms, TI = 400 ms, flip angle 180°, field of view 230 mm, 3-mm slice, 0.9-mm gap, matrix size 512/384) with identical slice positions were obtained in the oblique coronal orientation perpendicular to the long axis of the hippocampus. Additionally, a 3D gradient-echo sequence was measured (MPRAGE, TR/TE = 11.4/4.4 ms, flip angle 15°, with a voxel size of $1.00 \times 1.00 \times 1.00$ mm^3). The total measurement time was

TABLE 1.

Characteristics of Patients and Control Subjects Included in the Study

Patient	G	Age (yr)	Lesion	Time since operation (yr)	Computer exp.	Education (yr)	Subject	G	Age (yr)	Computer Exp.	Education (yr)
Pat 1L	f	61	L	8	none	9	NP 1	m	60	none	9
Pat 2L	f	64	L	9	none	9	NP 2	f	52	some	10
Pat 3L	m	58	L	5	extensive	10	NP 3	m	49	extensive	13
Pat 4L	f	59	L	8	none	9	NP 4	f	56	extensive	13
Pat 5L	m	53	L	12	extensive	13	NP 5	f	56	none	10
Pat 6L	m	49	L	13	some	13	NP 6	m	57	none	10
Pat 7L	m	58	L	12	none	9	NP 7	m	50	extensive	9
Pat 8L	f	62	L	12	none	9	NP 8	f	61	some	10
Pat 1R	m	50	R	7	extensive	9	NP 9	m	52	extensive	10
Pat 2R	f	52	R	12	extensive	13	NP 10	f	56	some	10
Pat 3R	m	47	R	10	extensive	10	NP 11	m	53	extensive	9
Pat 4R	f	56	R	12	extensive	10	NP 12	f	68	none	13
Pat 5R	f	56	R	9	none	13	NP 13	m	61	none	13
Pat 6R	m	61	R	8	extensive	10	NP 14	f	64	none	10
Pat 7R	f	64	R	8	none	9	NP 15	m	64	none	10
Pat 8R	m	57	R	5	some	9	NP 16	f	60	none	10

G, gender; computer exp., degree of computer experience (extensive: subject has used computer for games or at work for several years; some: subject knows how to turn on computer, type, and save simple documents; none: subject has never used a computer without help).

about 25 min per patient. One patient in the left UVD group was excluded from further analysis due to motion artifacts.

MRI data postprocessing

Image data for the manual hippocampal volume measurements were processed as described previously (Brandt et al., 2005). In brief, image data processing was performed on a remote Linux workstation, using FSL and MedX 3.4 (Medical Numerics, Sterling, VA). Both the T1-inversion-recovery-weighted and the T2-weighted data sets were determined by manually tracing the outlines of the hippocampus on reformatted, successive 1-mm coronal slices. The evaluator (J.M.) was blinded as to patient status or side of lesion. In some cases blinding was not possible, since patient status was evident in view of surgery lesions on the traced coronal slices. The hippocampus was segmented manually according to recently described protocols (Bernasconi et al., 2003) using the anatomical landmarks described there; the entorhinal (Bernasconi et al., 1999), perirhinal, and parahippocampal cortex (Insausti et al., 1998) were not included. The Sienax Protocol (Version 2.2) was used on the 3D data set to estimate total brain volume (Smith et al., 2002). The volumes computed included right hippocampal volume (right HPC), left hippocampal volume (left HPC), total hippocampal volume (total HPC = right HPC + left HPC), total white matter (WM), total gray matter (GM), total brain volume (GM + WM), and cerebrospinal fluid (CSF) volume. Analysis of variance (ANOVA) was performed on hippocampal volumes normalized to whole brain volume using GROUP (left UVD, right UVD, control) and SEX (male, female) as between-subject factors and using SIDE (left HPC volume vs. right HPC volume) as within-subject factors.

Voxel-Based Morphometry

An optimized voxel-based morphometry (VBM) protocol was followed to analyze the MPRAGE data sets. Images from the patients with right-sided lesions were flipped and analyzed together with the data from the patients with left-sided lesions. Data were analyzed using SPM2 (Wellcome Department of Cognitive Neurology, London, UK, http://www.fil.ion.ucl.uk/spm) and Matlab (MathWorks, Natick, MA). The various automated preprocessing steps implicit in VBM, such as brain extraction, spatial normalization, segmentation, modulation, and smoothing were performed as described elsewhere (Ashburner et al., 1997, 1999, 2000, 2001; Good et al., 2001). In brief, a customized symmetrical template of gray and white matter was constructed in stereotactic space using data from the patients and controls. Data were spatially normalized to this template, segmented into GM, WM, and CSF, modulated to preserve tissue volume within a voxel (Good et al., 2001), and then smoothed with a 12-mm isotropic Gaussian kernel. Modulated images were analyzed using statistical parametric mapping software (SPM2) and a general linear model. A voxel-wise statistical parametric map was created, which identified brain regions containing significant differences of local gray matter vol-

ume in both groups (Wright et al.,1995; Ashburner et al., 1997). An estimate of whole brain volume (GM + WM) was used as a confounding covariate in the analysis of covariance (ANCOVA). Anatomical structures were named according to the automated anatomical labeling atlas (Tzourio-Mazoyer et al., 2002) and the Tailarach stereotactic atlas (Talairach and Tournoux, 1988).

Memory and Memory-Influencing Functions

A German-language adaptation of the national adult reading test of Nelson was selected to estimate premorbid intelligence. The Wechsler memory scale-revised was primarily used in full, since it constitutes the most universally employed memory test battery and allows calculation of several indices (general memory, attention/concentration, visual memory, verbal memory, delayed recall). The Doors subtest of the Doors and People Test (Baddeley et al., 1994) was used. This test provides a measure for visual recognition memory. All tests were administered to all 16 patients using computer-screen-based visual instructions to avoid a bias due to impaired hearing after UVD and to provide comparability with the data of the BVD patients (Brandt et al., 2005).

Virtual Morris Water Task

The Morris water task is considered the gold standard for testing spatial learning, spatial memory, and navigation in rodents. Rats are trained to navigate to an escape platform in a circular pool of water. The escape platform is made invisible by submerging it just below the surface of the opaque water. Normal rats are nevertheless capable of directly navigating to the platform location from several release points after training. It is generally agreed that this behavior is related to ambient visual cues in the extramaze environment which remain in a fixed spatial location to the platform throughout the training (Morris, 1984).

The virtual version of this test and its validation in determining human spatial learning, spatial memory, and navigation abilities have been described in detail elsewhere (Hamilton et al., 2002; Driscoll et al., 2003). In brief, the basic features of the environment consisted of a circular pool located in the center of a room with a square floor plan. Four conspicuous cues of equal size were placed around the distal walls. The cues were positioned so that one cue was on each of the four distal room walls, and the platform could not be encountered by simply moving toward a single cue from any release point. The platform was positioned in the center of one quadrant (N/E) and occupied ~2% of the pool area. A first-person view of the virtual environment was displayed on a 17-in. PC monitor with a 45° field of view. The observer's position was always slightly above the surface of the water, and forward movement was controlled by the UP (↑) arrow key on the keyboard. Rotation was controlled by the LEFT (←) and RIGHT (→) arrow keys. Backward navigation or up-down movement within the pool was not possible. A full 360° rotation in the absence of forward movement required ~2.5 s to complete, and the direct path from a release point to the opposite side of the pool took ~4 s.

The human subjects were given written instructions prior to the testing, explaining in detail the testing procedures. Training and testing were done in three phases that required a total of ~30 min to complete. During Phase I, participants completed five hidden platform training blocks, each consisting of four trials. Starting locations during Phase I were sampled pseudorandomly without replacement from four locations that corresponded to the cardinal compass points. The latency and cumulative distance required to navigate to the hidden platform were measured for each trial (latency was measured from the time the first movement was made until the platform was found; cumulative distance was determined by summing up the distance from the platform 10 times per second until the platform was found and dividing the resulting value by the pool diameter such that a value of one indicates a cumulative distance equivalent to the pool diameter). The heading error (deviation from a direct path to the platform location in degrees) was also determined and computed after patients or controls had traveled a distance equal to the radius of the pool. A maximum of 60 s was allotted to locate the platform during Phase I trials. If the platform was found during the allotted time, the words "platform found" appeared on the screen, and the subject was moved to a new starting location. If the platform was not reached in the required time, the platform was made visible by raising it above the surface of the water. The number of trials per training block in which subjects did not find the platform (number of trials in which the platform became visible) was determined for each block. Phase II consisted of a single 45-s probe trial during which the platform was removed from the environment. The starting location for the probe trial was selected pseudorandomly from the two starting locations furthest from the platform location. Six measures were recorded for the probe trial: (1) latency to enter the platform quadrant, (2) cumulative distance to the former platform location, (3) percentage of navigation time spent in the platform quadrant, (4) percentage of distance traveled in the platform quadrant, (5) heading error, and (6) number of times participants crossed the platform location. During Phase III the platform was slightly raised above the surface of the water for two blocks consisting of four trials each. Starting locations were determined as in Phase I, and the latencies, cumulative distance, and heading error were measured. ANOVA was performed using a general linear model, and values with $P < 0.05$ were considered significant. AGE was included as a continuous predictor in all analyses.

Patients were also specifically asked if they had difficulties in daily life activities such as reading maps of unknown towns, finding their car in a big parking lot, or taking shortcuts they had never used before. Only one patient with right-sided vestibular lesion reported a subjective difference

between his pre- and postoperative performance in the above-mentioned tasks.

RESULTS

Spatial Memory and Navigation

The VMWT was used to assess spatial memory and navigation in the described patient population (left UVD, right UVD) and controls (control). ANOVA was performed to test for differences between the groups. SEX (female, male) and GROUP (right UVD, left UVD, control) were used as between-subject factors and REPETITION (where applicable) as within-subject factor. AGE was used as a continuous predictor in all analyses.

Phase I: Place learning

Figure 1 shows the performance of left UVD patients, right UVD patients, and controls during the Phase I place learning trial blocks. Subjects completed five hidden platform training blocks, each consisting of four trials. The mean latency to navigate to the platform for each block was calculated for each group (Table 2, Fig. 1A). There was no statistically significant effect of the factors GROUP ($F(2,25) = 0.99$; $P > 0.05$), and AGE ($F(1,25) = 3.06$; $P > 0.05$), or significant interaction between the factors GROUP × REPETITION ($F(8,100) = 1.11$; $P > 0.05$), SEX × REPETITION ($F(4,100) = 0.22$; $P > 0.05$), or GROUP × SEX × REPETITION ($F(8,100) = 0.73$; $P > 0.05$). The factor REPETITION was, however, significant, indicating that latencies decreased with training of the subjects ($F(4,100) = 9.42$; $P < 0.001$). The factor SEX was also significant ($F(1,25) = 9.09$; $P < 0.001$), which was due to higher latencies for females compared with males.

The cumulative distance to navigate to the platform for each block was also calculated (Table 2, Fig. 1B). There was no statistically significant effect of the factors GROUP ($F(2,25) = 0.56$; $P > 0.05$) or AGE ($F(1,25) = 3.98$; $P > 0.05$) or significant interaction between the factors GROUP × REPETITION ($F(8,100) = 1.33$; $P > 0.05$), SEX × REPETITION ($F(4,100) = 0.49$; $P > 0.05$), or GROUP × SEX × REPETITION ($F(8,100) = 0.67$; $P > 0.05$). The factor REPETITION was, however, significant ($F(4,100) = 15.59$; $P < 0.00001$), indicating a decrease in cumulative distance as the training progressed. The factor SEX ($F(1,25) = 8.81$; $P < 0.01$) was significant: males performed better than females.

Analysis of the heading error during the place learning trial blocks 1–5 showed no statistically significant effect of the factors GROUP ($F(2,25) = 2.52$; $P > 0.05$), AGE ($F(1,25) = 0.14$; $P > 0.05$), SEX ($F(1,25) = 0.34$; $P > 0.05$), or REPETITION ($F(4,100) = 1.28$; $P > 0.05$) and no significant interaction between the factors GROUP × REPETITION ($F(8,100) = 0.99$; $P > 0.05$) and SEX × REPETITION ($F(4,100) = 1.19$; $P > 0.05$). The GROUP × SEX × REPETITION interaction was, however, significant ($F(8,100) = 2.34$; $P < 0.05$): males with right-sided UVD and females with left-sided UVD showed a smaller decrease in heading errors compared with the other subgroups.

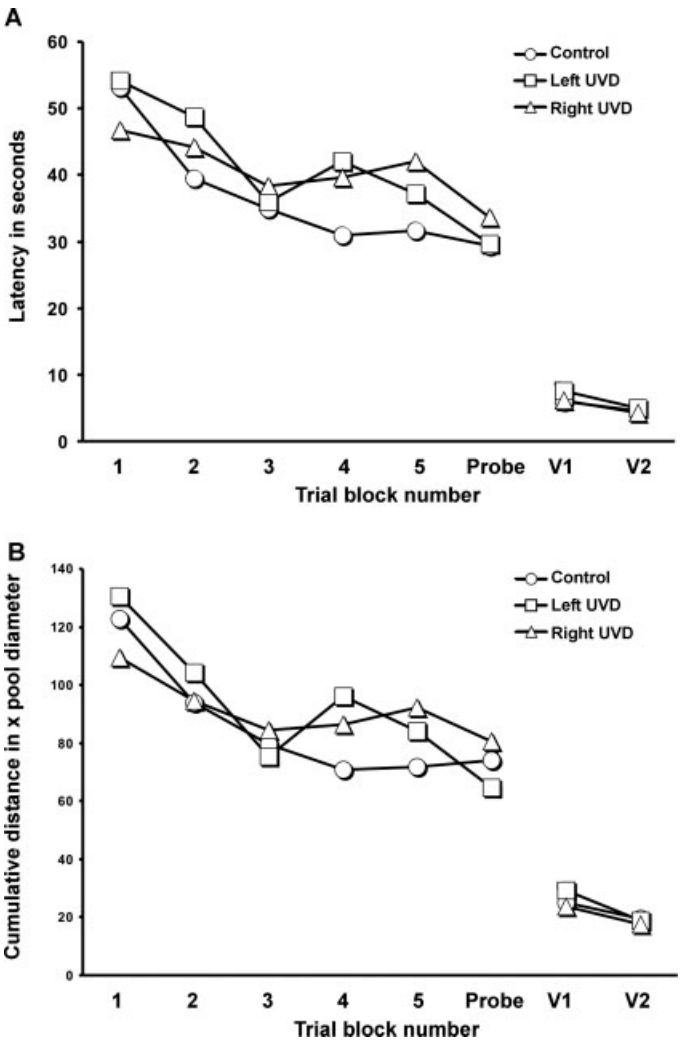

FIGURE 1. Results of spatial memory and navigation in the VMWT. Mean latencies (A) and cumulative distance (B) during Phase I for control (circle), left UVD (square), and right UVD (triangle) groups to navigate to the platform during the 20 place-learning trials (hidden platform; blocks 1–5, each consisting of four trials), Phase II no-platform trial (Probe), and two visible platform trials (V1, V2 consisting of four trials each). Latency was measured from the time of the first movement until the platform was found; it is given in seconds. The cumulative distance was determined by summing up the distance from the platform until the platform was found and dividing by the pool diameter such that a value of one indicates the distance is equivalent to the pool diameter. During Phase I latencies and cumulative distance significantly decreased during place learning, but there was no GROUP effect. Standard deviations are given in Table 2; they were not plotted.

The number of trials in which the platform became visible during each training block decreased in all groups during the training (REPETITION ($F(4,100) = 5.30$; $P < 0.001$). The factor GROUP ($F(2,25) = 0.99$; $P > 0.05$) was not significant, whereas AGE ($F(1,25) = 4.73$; $P < 0.05$) and SEX ($F(1,25) = 14.57$; $P < 0.001$) were significant. Females per-

TABLE 2.

Latencies and Cumulative Distance From the Platform for Patients and Controls in the Virtual Morris Water Task

Trial	1	2	3	4	5	Probe	V1	V2
Latency to platform[a]								
Left UVD	54.16 (9.92)	48.67 (16.08)	35.96 (15.28)	42.07 (19.56)	37.23 (20.15)	29.67 (15.94)	7.54 (3.24)	5.00 (1.29)
Right UVD	46.74 (18.58)	44.19 (23.41)	38.36 (21.84)	39.69 (19.12)	42.06 (17.15)	33.59 (10.42)	6.08 (2.54)	4.33 (0.92)
Control	53.19 (18.76)	39.47 (16.35)	15.20 (34.85)	30.95 (10.78)	31.64 (14.68)	29.34 (12.19)	6.02 (3.40)	4.59 (1.25)
Cumulative distance from the platform[b]								
Left UVD	130.55 (30.49)	104.24 (29.65)	75.22 (25.60)	96.21 (40.39)	84.03 (42.45)	64.74 (39.44)	29.17 (10.86)	18.92 (4.55)
Right UVD	109.37 (45.17)	94.64 (51.62)	84.31 (50.62)	86.40 (46.89)	92.32 (40.83)	80.70 (32.13)	23.67 (7.20)	17.47 (4.51)
Control	122.87 (42.69)	93.90 (35.12)	79.62 (34.31)	70.70 (25.73)	71.93 (25.73)	73.90 (29.47)	24.85 (10.02)	19.47 (4.46)

[a]Mean latencies for left UVD, right UVD and controls in the virtual Morris water task to navigate to the hidden platform during the training blocks (1–5), the no-platform trial (probe), and the visible platform trials (V1, V2). Values are given in seconds (±SD).
[b]Cumulative distance from the platform for left UVD, right UVD, and controls to navigate to the hidden platform during the training blocks (1–5), the no-platform trial (probe), and the visible platform trials (V1, V2). Values are given in multiples of the pool diameter (±SD).

formed less well than men, and older subjects less well than younger ones. There were no significant interactions between the factors analyzed.

Although group differences for the latencies, cumulative distance, and heading error were not significant, inspection of the individual "swim" paths taken by each participant suggested that right UVD patients were less likely to navigate to the platform on a direct path. A rater blind to group membership and not involved in the generation or evaluation of the data otherwise characterized the swim paths during Phase I as either "direct" or "indirect." A total of 12 of the 16 control participants (75%) were classified as using direct paths, 6 of 8 left UVD patients (75%) used direct paths, and 2 of 8 right UVD patients (25%) used them. χ^2 statistics showed this difference to be significant (for right UVD vs. controls $P < 0.05$). Individual swim paths for the probe trial are shown in Figure 2 to demonstrate how different subjects solved the task (Fig. 2C).

Phase II: Probe trial

When the latencies to enter the former platform quadrant during Phase II in the so-called no-platform trial (probe) were evaluated no significant effect of the factors GROUP ($F(2,25) = 0.28$; $P > 0.05$; Table 2, Fig. 1A), AGE ($F(1,25) = 0.07$; $P > 0.05$), or SEX ($F(1,25) = 0.01$; $P > 0.05$), or interaction of the factors GROUP × SEX ($F(2,25) = 2.43$; $P > 0.05$) was observed. For the cumulative distance from the former platform location there was no significant effect of the factors GROUP ($F(2,25) = 0.55$; $P > 0.05$), SEX ($F(1,25) = 0.01$; $P > 0.05$) or AGE ($F(1,25) = 0.17$; $P > 0.05$), or interaction of the factors GROUP × SEX ($F(2,25) = 2.45$; $P > 0.05$; Table 2, Fig. 1B). However, for both measures right UVD patients performed worse than left UVD patients or controls. During the probe trial the left UVD and control group spent about equal percentages of their navigation time and navigation distance searching in the former platform quadrant, while the right UVD group spent less time and distance searching in the correct quadrant (Table 2, Fig. 2A). This effect did not, however, reach statistical significance, neither for time in the correct quadrant ($F(2,25) = 0.71$; $P > 0.05$) nor for the distance in the correct quadrant ($F(2,25) = 0.76$; $P > 0.05$). The main effects and interactions involving the SEX factor were not significant for either of the measures.

The analysis of heading errors revealed a significant GROUP effect ($F(2,25) = 5.66$; $P < 0.01$; Fig. 2A). A post hoc Fisher's LSD comparison of group means confirmed that the right UVD patients had a higher heading error than left UVD ($P = 0.003$) or control participants ($P = 0.013$). This effect was more pronounced in right UVD females than males; the GROUP × SEX interaction term was, however, not significant ($F(2,25) = 3.33$; $P = 0.052$), nor was the SEX main effect significant ($F(1,25) = 0.00$; $P > 0.05$).

The number of times each participant crossed the former platform location during the probe trial was also analyzed. No significant effect of the factors GROUP ($F(2,25) = 0.43$; $P > 0.05$) or SEX ($F(1,25) = 0.43$; $P > 0.05$) or interaction of the factors GROUP × SEX ($F(2,25) = 1.23$; $P > 0.05$) was observed. It is noteworthy that again right UVD patients performed worse (mean number of times former platform location was crossed 0.62) than left UVD or controls (mean number of times former platform location was crossed 1 and 0.94, respectively).

Phase III: Cued navigation

In Phase III the navigation to the visible platform was measured in two blocks consisting of four trials each (V1, V2). Navigation to the visible platform revealed no differences in latency related to SEX ($F(1,25) = 0.80$; $P > 0.05$), GROUP ($F(2,25) = 0.90$; $P > 0.05$), or AGE ($F(1,25) = 0.77$; $P > 0.05$). The factor REPETITION was significant ($F(1,25) = 11.80$; $P < 0.005$) with decreased latencies in V2. The interaction GROUP × SEX × REPETITION was also significant ($F(2,25) = 4.03$; $P < 0.05$); left UVD females performed worse than the other groups during the first but not the second visible platform trial (Table 2, Fig. 1A). The same held true

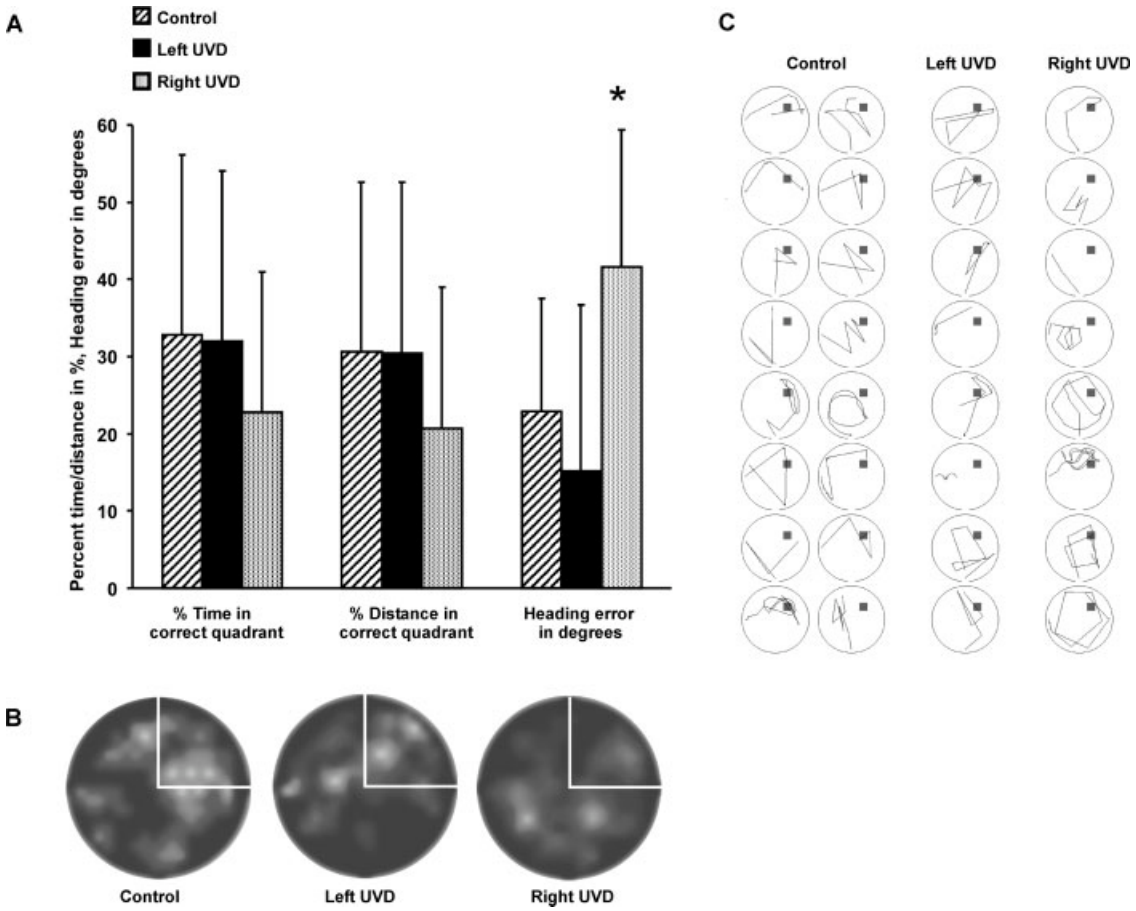

FIGURE 2. Results of spatial memory and navigation: probe trial. (A) Mean percentage of search time and search distance spent by each group in the platform quadrant during the no-platform (probe) trial of Phase II as well as heading errors during this trial (control (striped bars), left UVD (black bars), and right UVD (dotted bars)). Values of search time and search distance are given in % with their respective standard deviations. The heading error is shown in degrees with standard deviation (SD). Although right-lesioned patients seemed to spend less time and distance searching in the platform quadrant, the measures did not reach statistical significance. The heading error was significantly higher (indicated by the asterisk) in right UVD patients compared with left UVD patients and controls. (B) Dwell time for the controls, left UVD, and right UVD patients during the no-platform (probe) trial of Phase II. Lighter gray indicates regions where a relatively large amount of time was spent, and black regions where a relatively small amount of time was spent searching for the platform. The platform quadrant is demarcated by the white lines. Controls and left UVD patients seem to spend more time searching in the correct location, although this measure did not reach statistical significance. (C) Sample paths for controls, left UVD, and right UVD groups during the probe trial. Left UVD patients and controls were rated by an independent observer to employ more direct paths to the platform location than right UVD patients.

when cumulative distance was evaluated for the visible platform trials: no significant effect of the factors SEX ($F(1,25) = 2.93$; $P > 0.05$) or GROUP ($F(1,25) = 0.36$; $P > 0.05$) was found. The factor REPETITION was again significant ($F(1,25) = 26.85$; $P < 0.001$), and the factor AGE was also significant ($F(1,25) = 4.70$; $P < 0.05$; Table 2, Fig. 1B). For the heading error only the factor AGE ($F(1,25) = 6.94$; $P < 0.05$) was significant.

Premorbid Intelligence and Nonspatial Memory

The premorbid intelligence was assessed by a German version of the national adult reading scale "Mehrfach-Wahl-Wortschatztest B" and was found to be above average or average in 15/16 patients; only one patient had a verbal IQ below average. Quantitative data on memory and attention/concentration of the patients as assessed by the Wechsler memory scale-revised are presented in Table 3. All patients performed average or above on all tests. Only the attention/concentration index was below average in 3/16 patients and visual recognition memory, as measured by the Doors Test, was impaired in 4/16 patients.

Manually Computed Hippocampal Volumes

ANOVA was performed by using GROUP (control, left UVD, right UVD) and SEX (male, female) as between-subject factors and SIDE (left HPC volume and right HPC volume), where applicable, as a within-subject factor. MRI volumetry revealed no change in normalized total hippocampal volume in patients with unilateral vestibular failure (total HPC/whole

TABLE 3.

Results of Behavioral Tests of Memory and Intelligence[a]

	Nelson test	Wechsler memory scale, revised					Doors test
Patient	Verb IQ (IQ)	GenM (index)	VerbM (index)	VisM (index)	Att/conc (index)	DelRecall (index)	RecogM (percentile)
Pat 1L	136	111	102	124	91	108	75–90
Pat 2L	104	90	94	86	95	88	25
Pat 3L	124	114	120	97	108	111	50–75
Pat 4L	*82*	100	105	91	*80*	91	*1*
Pat 5L	104	115	114	111	129	118	75
Pat 6L	145	123	132	98	119	90	50
Pat 7L	94	110	106	114	102	108	25
Pat 8L	89	100	103	93	92	95	*5*
Pat 1R	97	113	120	98	*83*	120	75
Pat 2R	136	138	140	107	90	134	75
Pat 3R	136	140	140	117	99	140	25–50
Pat 4R	112	121	125	105	89	126	*5*
Pat 5R	112	115	124	91	97	106	*10–25*
Pat 6R	100	94	97	89	99	104	50
Pat 7R	101	102	91	119	92	98	90
Pat 8R	104	98	104	86	*84*	101	25

[a]Test results below average are marked in italics.
Att/conc, Attention/concentration Index; DelRecall, delayed recall index; GM, general memory index; IQ, intelligence quotient; RecogM, recognition memory; VisM, visual memory index; VerbM, verbal memory index.

brain) compared with the healthy age- and sex-matched controls by ANOVA ($F(2,25) = 1.09$; $P > 0.05$; Table 4). The factor SEX was significant with females, who had larger normalized HPC volumes than males ($F(1,25) = 7.94$; $P = 0.007$). ANOVA using right HPC/whole brain, left HPC/whole brain (within-subject factor SIDE) as dependent variables showed no interaction of the measures SIDE × GROUP ($F(2,25) = 3.35$; $P > 0.05$). The only significant effects obtained through ANOVA were related to SEX, with females having larger normalized hippocampal volumes ($F(1,25) = 7.94$; $P = 0.009$), as expected from the analysis of the whole hippocampal volume, and to SIDE, with the ratio of right HPC/whole brain being larger than the left side ($F(1,25) = 14.83$; $P < 0.001$). Since the ANOVA on normalized volumes depends on the normalization factor (here: whole brain volume), the occurrence of side differences was also analyzed inde-

TABLE 4.

Brain Volumes in Patients and Controls[a]

	Left UVD[b]	Right UVD	Control
Right HPC (cm^3)	2.88 (0.31)	3.12 (0.36)	2.71 (0.44)
Left HPC (cm^3)	2.80 (0.29)	2.74 (0.21)	2.59 (0.36)
Total HPC (cm^3)	5.68 (0.58)	5.86 (0.54)	5.30 (0.75)
Gray matter (cm^3)	532.36 (65.47)	518.17 (51.21)	529.44 (63.00)
White matter (cm^3)	614.43 (113.93)	612.10 (60.84)	583.82 (74.65)
Whole brain (cm^3)	1146.79 (175.76)	1130.27 (105.90)	1113.26 (132.60)
CSF (cm^3)	170.23 (17.64)	172.19 (30.16)	182.79 (29.81)
Right HPC/whole brain	0.26 (0.06)	0.28 (0.03)	0.24 (0.03)
Left HPC/whole brain	0.25 (0.05)	0.24 (0.02)	0.23 (0.04)
Total HPC/whole brain	0.51 (0.11)	0.52 (0.06)	0.48 (0.07)

[a]Mean hippocampal volumes in left UVD, right UVD patients, and controls as determined by MRI manual volumetry. An estimate of gray matter, white matter, cerebrospinal fluid, and whole brain volume (±SD) is also given.
[b]Measures could not be computed for one female patient with left-sided lesion due to movement artifacts.

pendently of normalization (right hippocampus larger or smaller than left hippocampus) on a binomial scale by logit ANOVA. This analysis revealed a significant effect of GROUP (likelihood Type 3 test, $P < 0.05$), with a side difference between the hippocampi being especially evident in the right UVD group and in controls (right UVD: right HPC > left HPC in 7/7 cases; control: right HPC > left HPC in 12/16 cases; left UVD: right HPC > left HPC in 4/8 cases).

Correlation analysis revealed no correlation between normalized HPC volumes and the time since the lesion occurred (right HPC/whole brain: $r = -0.11$; left HPC/whole brain: $r = -0.05$; total HPC/whole brain: $r = -0.09$; $P > 0.05$), nor was there a correlation between the patient's IQ and hippocampal volume, as was expected from other studies in the field (Maguire et al., 2003b) (right HPC/whole brain: $r = -0.24$; left HPC/whole brain: $r = -0.29$; total HPC/whole brain: $r = -0.27$; $P > 0.05$). Normalized HPC volumes did not correlate with the subject's age (right HPC/whole brain: $r = 0.17$; left HPC/whole brain: $r = 0.34$; total HPC/whole brain: $r = 0.26$; $P > 0.05$).

Voxel-Based Morphometry of Gray Matter Volumes

Gray matter volumes of the different groups were compared using VBM (Wright et al., 1995; Ashburner et al., 2000; Critchley et al., 2003). Images of the right UVD group were flipped and analyzed in one group with the images of left UVD patients. The contrast controls–patients did not exhibit any differences in hippocampal volume at a threshold of $P < 0.05$, corrected for multiple comparison, FDR. The patients compared with the control group showed, however, a significant reduction of gray matter volume in the cerebellar hemisphere on the affected side due to lesions induced by the neurinoma growth or removal (Fig. 3). Further areas of gray matter reduction in the patient group compared with the control group included the contralateral mesencephalon, thalamus, and an area in the ipsilateral middle occipital gyrus (Fig. 3). The ipsilateral parietal cortex showed a loss of volume in the area of the somatosensory cortex and in the supramarginal gyrus in the patient group compared with the controls. When the VBM results of the contrast controls–patients were viewed at a less conservative threshold, there was still no area of gray matter changes in the hippocampus. At lower thresholds the above-described clusters consisted of more voxels, but did not include the hippocampus, nor did any significant new areas of volume loss appear. When left UVD and right UVD data sets were tested separately against controls, the only difference was an area of gray matter volume loss in the ipsilateral cerebellar hemisphere ($P < 0.001$, uncorrected; data not shown).

Correlation of Navigation Performance and Hippocampal Volumes

To test for a possible dependence of navigation performance on hippocampal, or more specifically right hippocampal volumes, a correlation analysis was performed over all subjects between normalized right HPC volume, left HPC volume, and total HPC volume and navigation parameters of the no-platform probe trial. No correlation was detected between the latency to enter the platform quadrant, the heading error, the percent time in correct quadrant, the percent distance in correct quadrant, and the number of platform crosses of the probe trial ($P > 0.05$). The only statistically significant correlation was a negative one between the total HPC/whole brain and the cumulative distance from the putative platform location ($r =$

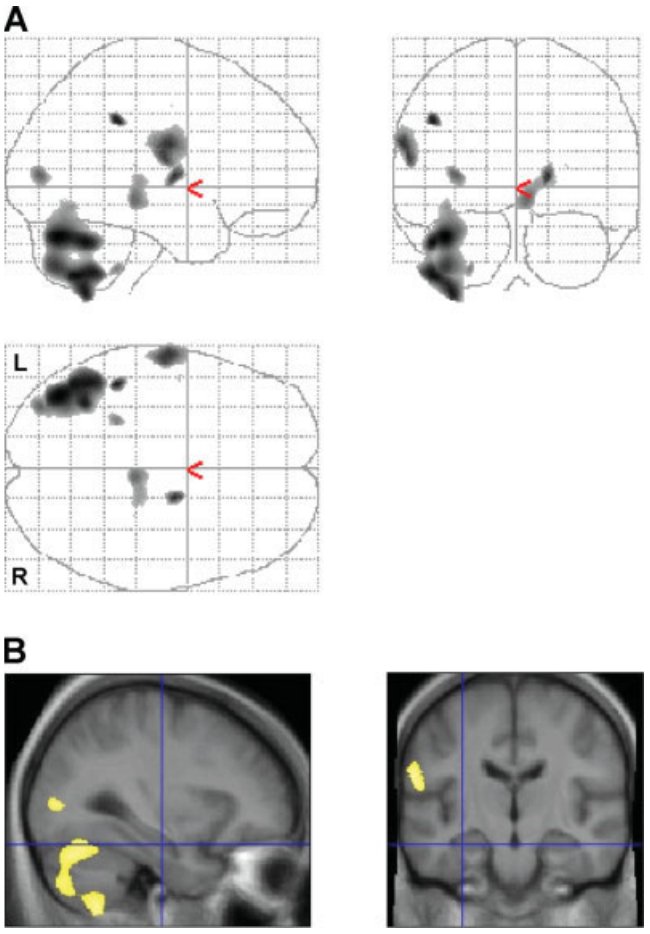

FIGURE 3. Results of VBM comparing UVD patients and controls. (A) "Glass brain" presenting the results of VBM ($P < 0.05$ after correction for multiple comparison). The brain volumes of UVD patients (data sets of right UVD patients were flipped prior to analysis) were compared with healthy, age- and sex-matched controls. No gray matter atrophy was observed in the hippocampus of the UVD patients. Areas of volume loss include the cerebellar hemisphere due to lesions induced by the neurinoma growth or removal. Further areas of gray matter reduction in the patient group compared with the control group were in the contralateral mesencephalon and thalamus, in the ipsilateral middle occipital gyrus, possibly within the area MT/V5, and in the ipsilateral parietal lobe. (B) Results of VBM projected on an averaged T1 template generated from the data sets of patients and controls. The crosshairs are centered through the left hippocampus, which did not show any gray matter volume loss. Volume loss in the cerebellar hemisphere as well as loss in the middle occipital gyrus are depicted on the sagittal section; the atrophy in the parietal lobe is visible on the coronal section.

-0.37; $P < 0.05$); however, for left HPC/whole brain and right HPC/whole brain this correlation was not significant.

DISCUSSION

Spatial Navigation in Rodents and Humans

Our study measured place learning and spatial navigation ability in UVD subjects using identical tests under the same conditions as applied previously to BVD patients (Schautzer et al., 2003; Brandt et al., 2005). Furthermore, hippocampal volumes were manually calculated by the same investigator as for BVD patients (J.M.). This provided us with comparable data for the two patient populations. Contrary to the deficits seen in patients with BVD, patients with UVD were not consistently impaired in spatial memory and navigation when tested on a VMWT. Left UVD patients performed as well as controls, while patients with right UVD showed a trend towards performing worse in some computed measures. These deficits were even significant for the heading error during the no-platform probe trial. The hippocampal volume in right and left UVD patients did not significantly differ from that of an age- and sex-matched control group. Thus, the vestibular input from one intact labyrinth appears to be sufficient to maintain spatial memory and navigation abilities as well as the gross volume of the hippocampus in humans. There were, however, differences in right and left UVD with respect to performance in the VMWT. These subtle differences were compatible with the recently described dominance of the right labyrinth and the vestibular cortex in the right (nondominant) hemisphere; it must be kept in mind that all of our subjects were right-handed (Bense et al., 2001; Dieterich et al., 2003).

Post-BVD rodents have shown deficits in spatial navigation in several independent experimental settings (Matthews et al., 1989; Stackman et al., 2002b; Wallace et al., 2002; Russell et al., 2003a). In a recent study BVD rats were consistently shown to be impaired in a food foraging task, while UVD animals were only impaired in performing the task in the dark at 3 months after the lesion, however, this impairment disappeared later (Zheng et al., 2006). BVD in rodents also disrupts object recognition, which is not impaired after UVD (Zheng et al., 2004). These studies clearly demonstrate that BVD causes different behavioral deficits than UVD.

UVD in rodents is known to lead to long-term changes in neurochemical and electrophysiological properties of the hippocampus, and some effects have been observed bilaterally (Zheng et al., 2001; Liu et al., 2003a,b). However, behavioral data on UVD that correlate with these findings are limited. Chapuis et al. (1992) examined the behavioral effects of UVD in rodents and demonstrated that UVD leads to an impairment in spatial memory and navigation. In their study two groups of healthy guinea pigs were trained to find a hidden goal; one group was provided with a visual cue (colored card). Tested up to 1 month after unilateral labyrinthectomy in their respective tasks, the animals were significantly impaired only in the task without conspicuous cues. Zheng et al. (2006) tested UVD rats on a food foraging task in light and dark 3 and 6 months following UVD. Deficits were found after 3 months only when tested in the dark. This impairment had resolved after 6 months following UVD.

There is also only limited evidence about the effect of UVD on spatial navigation in humans. Peruch et al. (1999) tested patients with Menière's disease in nonvisual and visual navigation tasks prior to and after vestibular nerve section. Menière's disease is thought to be caused by endolymphatic hydrops and is characterized by recurrent attacks of vertigo, tinnitus, and hearing loss. In intractable cases some centers perform vestibular nerve section. The patients' performance was impaired only in the acute stage of vestibular nerve section and only in tasks requiring place learning. It had returned to normal 1 month after the procedure. The deficits observed in the described study were thus most likely due to the acute vestibular imbalance after vestibular nerve section. Long-term effects of UVD on spatial memory and navigation were not determined. Borel et al. (2004) examined a similar group of patients before and up to 3 months after vestibular nerve section due to intractable Menière's disease. The patients were instructed to walk straight ahead at two speeds, either with their eyes open or closed. UVD patients continued to deviate to the lesioned side in the eyes-closed condition for up to 3-months post-surgery (the last time point evaluated in the study). In contrast to the study by Borel et al. (2004), Cohen (2000) reported that patients with acoustic neurinoma who were tested on a similar task before and 1 and 3 weeks postoperatively performed as well as presurgery when tested 3 weeks afterwards. These data are, however, not comparable with ours, since the task of walking in a straight line might test for path integration, but does not clearly test for spatial memory and navigational abilities. In another study in humans, Glasauer et al. (2002) examined three patients with bilateral vestibular failure and two patients with UVD while walking a triangular path blindfolded. The three BVD and two UVD patients failed to turn correctly around corners, although their overall path length was comparable with that of controls. This impaired performance of UVD patients could be due to the combined lack of visual and unilateral vestibular input.

The Virtual Morris Water Task

The suitability of the VMWT for detecting deficits in spatial memory and navigation in humans has been questioned. The Morris water task is considered the standard test to assess spatial memory and navigation in nonhumans (Morris, 1984), and there have been reports validating the virtual version of the test in assessing human navigation (Astur et al., 1998, 2002, 2004; Hamilton et al., 2002; Driscoll et al., 2003, 2005; Brandt et al., 2005). Although there is no vestibular input in the virtual version which can help during navigation, this test is still suitable for detecting deficits in spatial memory and navigation (Astur et al., 2002; Schautzer et al., 2003; Brandt et al., 2005). Patients with lesions in the

hippocampus proper have been shown to be impaired in navigation tasks when tested by the VMWT (Astur et al., 2002). In the study by Astur et al. (2002) this deficit was unrelated to the side of hippocampal lesion, whereas other studies in which patients with similar lesions were examined, reported a marked difference of performance related to the side of the lesion (Abrahams et al., 1997; Spiers et al., 2001). In the study by Spiers et al., patients with right hippocampal lesions performed worse on tests of spatial memory, and patients with left hippocampal lesions were impaired in context-dependent episodic memory. The study by Spiers et al., however, used a more complex visual environment than the one used in the VMWT. In our study we did not consistently observe a statistically significant difference between the right UVD and the left UVD group. The absence of a clear laterality effect is probably due to the bilateral representation of vestibular input in the hippocampus. It is, however, noteworthy that right UVD patients showed a tendency to perform worse than their left-lesioned counterparts or controls. Also, fewer of the right UVD patients tended to navigate to the platform using a direct path compared with left UVD patients or controls. These differences in navigation strategy were not as apparent in the quantitative data, perhaps owing to the age of the participants, which was in the range in which normal decline in performance has been observed (Driscoll et al., 2003, 2005; Moffat et al., in press). Thus, variability in spatial navigation performance in our sample could possibly be related to factors other than spatial learning success per se (Hamilton et al., 2004). Although we acknowledge that the deficits observed in the right UVD patients are not nearly as robust as those observed in BVD patients, it is particularly important to note that, consistent with previous reports of age-related decline in VMWT performance, control performance in the VMWT was substantially worse than is typically observed in younger subjects. This alone makes detecting significant UVD-related spatial learning impairments difficult. Thus, the fact that some significant right UVD deficits were obtained and the right UVD group was consistently worse than that of left UVD patients or controls across a range of measures should be considered when evaluating the present findings. The effect of laterality can be explained by considering three previously made observations related to the laterality of perceptual systems: first, the right and left vestibular labyrinth predominantly project to the ipsilateral hemisphere; second, the right hemisphere shows a cortical vestibular dominance (Dieterich et al., 2003); and third, the right hippocampus is thought to be more involved in spatial memory and navigation (Maguire et al., 1997; Gron et al., 2000; Hartley et al., 2003). Right-hemispheric dominance (in right-handed subjects) has also been observed during studies of visuospatial attention (Mapstone et al., 2003), ocular motor paradigms (Dieterich et al., 1998), and shape discrimination (Petrides et al., 1993). More generally this laterality can be summarized as a right-sided dominance (in right-handed subjects) for attention as well as for representing and exploring space. This becomes apparent in clinical practice when examining patients with neglect who usually have right-hemispheric lesions (Mesulam, 1999).

Hippocampal Volumes

Hippocampal volumes were compared both by manually tracing the outlines on subsequent coronal MRI slices as well as with a semiautomated process that tests for differences in volume and concentration in each voxel of a 3D MPRAGE data set (VBM). Voxel-based morphometry is more advantageous than manual tracing, because it is an automated process that is insensitive to observer bias and considers the whole brain rather than specific regions of interest. It has been shown to be sensitive to structural hippocampal changes in healthy subjects as well as patients (Gadian et al., 2000; Maguire et al., 2000; Good et al., 2001). The bilateral representation of vestibular signals might prevent hippocampal atrophy in UVD patients. Slightly larger normalized right HPC volumes compared with the left HPC volumes were reported in healthy volunteers (Szabo et al., 2001). It has also been observed previously that with normal aging hippocampal volumes decline in males, whereas they remain relatively constant in females. This leads to larger hippocampal volumes in females than in males in older individuals (Pruessner et al., 2001). Bilateral polysynaptic vestibular input to both hippocampi has been demonstrated by electrophysiological experiments in guinea pigs. Electrical stimulation of the right labyrinth evoked field potentials over the hippocampal formation bilaterally (Cuthbert et al., 2000). In agreement with these findings, Zheng et al. (2003) reported that UVD leads to changes in hippocampal CA1 fields ipsilateral and contralateral to the lesion in rats. FMRI and PET studies confirmed this concept in humans (Suzuki et al., 2001; Bense et al., 2004). In the latter report patients with vestibular neuritis were examined in a PET experiment in which the hippocampus, among other regions, was activated bilaterally.

Using VBM we compared gray matter volumes of patients with that of controls. Areas of reduced extrahippocampal gray matter volume in the patients compared with the controls were in the ipsilateral cerebellar hemisphere secondary to the tumor growth or surgical neurinoma removal. Several additional areas of volume loss were identified in the patient population compared with controls; their significance remains speculative. The volume loss in the tegmentum of the mesencephalon and the thalamus, both contralateral to the side of vestibular nerve section, could be due to the lack of vestibular and/or auditory input, the latter crosses in the corpus trapezoideum at the brainstem level. The small area of volume change in the middle occipital gyrus ipsilaterally might correspond to the MT/V5, a region thought to depend, among others, on vestibular information and to be motion sensitive (Zeki et al., 1991). The reason for the gray matter volume loss in the ipsilateral parietal cortex remains unclear. Although this area is associated with vestibular input, the core region of the vestibular system is the parietoinsular cortex (Brandt and Dieterich, 1999; Bense et al., 2001; Stephan et al., 2005), which showed no gray matter loss in our study.

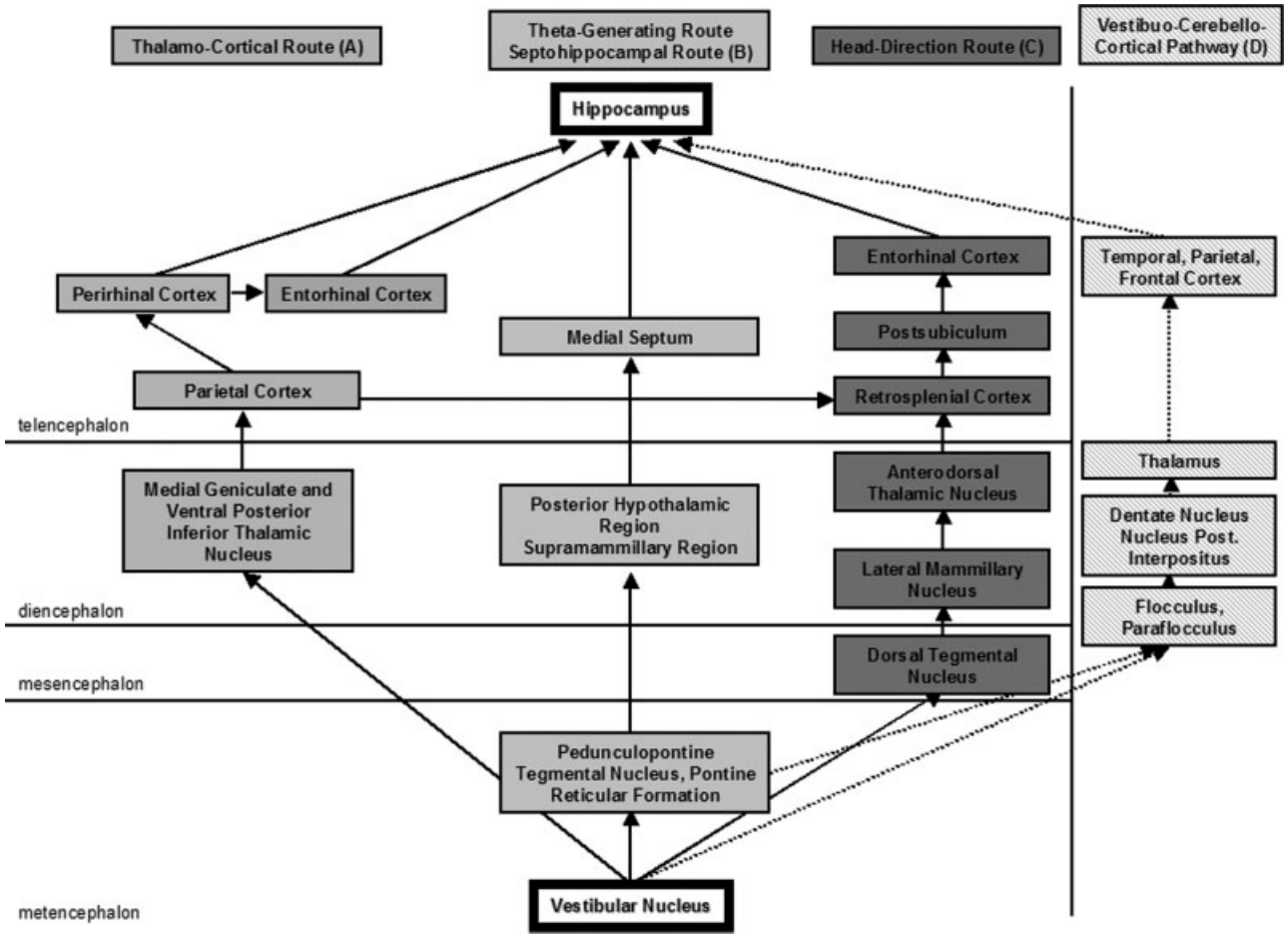

FIGURE 4. Vestibulo-hippocampal connections. Putative pathways through which vestibular information could reach the hippocampus and thus contribute to spatial memory and accurate navigation in humans. Pathways were mostly adopted from electrophysiological and tracer studies in rodents. Only ascending pathways were depicted for clarity (see Discussion section for details).

Hippocampal Volumes and Spatial Navigation Performance

We could not detect any correlation between the volume of the right HPC and the individual performance in the VMWT. This seems at first glance to contradict the data by Maguire et al., who found an enlarged hippocampus in London taxi drivers, i.e., subjects with extensive navigational expertise. The size of the hippocampus also correlated positively with the time spent driving a taxi (Maguire et al., 2000). Similarly studies on birds reported that food-storing birds have larger hippocampi than nonstorers (Biegler et al., 2001). In a further study, Maguire et al. investigated the association between navigation performance and hippocampal gray matter volume using VBM in normal nontaxi drivers. No correlation between hippocampal volume and navigation ability could be detected in nontaxi drivers (Maguire et al., 2003a). In an additional VBM study no increase in hippocampal volume was observed in subjects with generalized, superior memory abilities (Maguire et al., 2003b). De Toledo-Morrell et al. (2000) examined spatial and verbal memory in patients with Alzheimer's disease and matched controls. Various brain volumes were measured including right and left hippocampal volumes. The authors found a correlation between spatial memory and right hippocampal volume in patients with Alzheimer's disease. This correlation, however, did not hold for the healthy controls. Our data are in line with their findings: we also did not detect any correlation between navigational performance and right HPC volume.

Vestibular-Hippocampal Connections in Animals and Possibly also in Humans

The above-discussed data as well as the present study suggest a role of the hippocampus in vestibular orientation. At least three distinct pathways have been proposed to connect the vestibular nuclei to the hippocampus (Fig. 4): the thalamo-cortical route passing through the thalamus, the parietal cortex and the ento- or perirhinal cortex to the hippocampus (A); the theta-generating pathway originating in the pontine reticular forma-

tion and passing through the supramammillary nucleus and medial septum to the hippocampus (B); and the head-direction system passing through the dorsal tegmental nucleus, lateral mammillary nucleus, and anterodorsal thalamic nucleus to the hippocampus (C; for an overview: (Smith, 1997; Bland and Oddie, 1998; Russell et al., 2003b; Hopkins, 2005; Smith et al., 2005). It is also possible that the vestibulo-cerebello-cortical pathway (Fukushima, 2003; D) transports vestibular information to the hippocampus, although this has not been extensively investigated. These pathways were mostly adopted from electrophysiological and tracer studies in rodents. Which of them is the most important for vestibular orientation and place navigation remains to be determined.

Acknowledgments

We thank the patients and control subjects for participating in the study. Furthermore we appreciate the help of M. Glaser, C. Karch, and N. Rettinger with the orthoptic examinations. We also thank Tim Wesemann for help with MRI measurements and Judy Benson for critically reading and editing the manuscript.

REFERENCES

Abrahams S, Pickering A, Polkey CE, Morris RG. 1997. Spatial memory deficits in patients with unilateral damage to the right hippocampal formation. Neuropsychologia 35:11–24.

Ashburner J, Friston K. 1997. Multimodal image coregistration and partitioning—A unified framework. Neuroimage 6:209–217.

Ashburner J, Friston KJ. 1999. Nonlinear spatial normalization using basis functions. Hum Brain Mapp 7:254–266.

Ashburner J, Friston KJ. 2000. Voxel-based morphometry—The methods. Neuroimage 11:805–821.

Ashburner J, Friston KJ. 2001. Why voxel-based morphometry should be used. Neuroimage 14:1238–1243.

Astur RS, Ortiz ML, Sutherland RJ. 1998. A characterization of performance by men and women in a virtual Morris water task: A large and reliable sex difference. Behav Brain Res 93:185–190.

Astur RS, Taylor LB, Mamelak AN, Philpott L, Sutherland RJ. 2002. Humans with hippocampus damage display severe spatial memory impairments in a virtual Morris water task. Behav Brain Res 132:77–84.

Astur RS, Tropp J, Sava S, Constable RT, Markus EJ. 2004. Sex differences and correlations in a virtual Morris water task, a virtual radial arm maze, and mental rotation. Behav Brain Res 151:103–115.

Baddeley A, Emslie H, Nimmo-Smith I. 1994. Doors and People Test. Bury St. Edmunds, England: Thames Valley Test.

Bense S, Stephan T, Yousry TA, Brandt T, Dieterich M. 2001. Multisensory cortical signal increases and decreases during vestibular galvanic stimulation (fMRI). J Neurophysiol 85:886–899.

Bense S, Bartenstein P, Lochmann M, Schlindwein P, Brandt T, Dieterich M. 2004. Metabolic changes in vestibular and visual cortices in acute vestibular neuritis. Ann Neurol 56:624–630.

Bernasconi N, Bernasconi A, Andermann F, Dubeau F, Feindel W, Reutens DC. 1999. Entorhinal cortex in temporal lobe epilepsy: A quantitative MRI study. Neurology 52:1870–1876.

Bernasconi N, Bernasconi A, Caramanos Z, Antel SB, Andermann F, Arnold DL. 2003. Mesial temporal damage in temporal lobe epilepsy: A volumetric MRI study of the hippocampus, amygdala and parahippocampal region. Brain 126:462–469.

Biegler R, McGregor A, Krebs JR, Healy SD. 2001. A larger hippocampus is associated with longer-lasting spatial memory. Proc Natl Acad Sci USA 98:6941–6944.

Bland BH, Oddie SD. 1998. Anatomical, electrophysiological and pharmacological studies of ascending brainstem hippocampal synchronizing pathways. Neurosci Biobehav Rev 22:259–273.

Borel L, Harlay F, Lopez C, Magnan J, Chays A, Lacour M. 2004. Walking performance of vestibular-defective patients before and after unilateral vestibular neurotomy. Behav Brain Res 150:191–200.

Brandt T, Dieterich M. 1999. The vestibular cortex. Its locations, functions, and disorders. Ann N Y Acad Sci 871:293–312.

Brandt T, Schautzer F, Hamilton DA, Bruning R, Markowitsch HJ, Kalla R, Darlington C, Smith P, Strupp M. 2005. Vestibular loss causes hippocampal atrophy and impaired spatial memory in humans. Brain 128:2732–2741.

Chapuis N, Krimm M, de WC, Vibert N, Berthoz A. 1992. Effect of post-training unilateral labyrinthectomy in a spatial orientation task by guinea pigs. Behav Brain Res 51:115–126.

Cohen HS. 2000. Vestibular disorders and impaired path integration along a linear trajectory. J Vestib Res 10:7–15.

Critchley HD, Good CD, Ashburner J, Frackowiak RS, Mathias CJ, Dolan RJ. 2003. Changes in cerebral morphology consequent to peripheral autonomic denervation. Neuroimage 18: 908–916.

Cuthbert PC, Gilchrist DP, Hicks SL, MacDougall HG, Curthoys IS. 2000. Electrophysiological evidence for vestibular activation of the guinea pig hippocampus. Neuroreport 11:1443–1447.

de Toledo-Morrell L, Dickerson B, Sullivan MP, Spanovic C, Wilson R, Bennett DA. 2000. Hemispheric differences in hippocampal volume predict verbal and spatial memory performance in patients with Alzheimer's disease. Hippocampus 10:136–142.

Dieterich M, Bucher SF, Seelos KC, Brandt T. 1998. Horizontal or vertical optokinetic stimulation activates visual motion-sensitive, ocular motor and vestibular cortex areas with right hemispheric dominance. An fMRI study. Brain 121:1479–1495.

Dieterich M, Bense S, Lutz S, Drzezga A, Stephan T, Bartenstein P, Brandt T. 2003. Dominance for vestibular cortical function in the non-dominant hemisphere. Cereb Cortex 13:994–1007.

Driscoll I, Hamilton DA, Petropoulos H, Yeo RA, Brooks WM, Baumgartner RN, Sutherland RJ. 2003. The aging hippocampus: Cognitive, biochemical and structural findings. Cereb Cortex 13: 1344–1351.

Driscoll I, Hamilton DA, Yeo RA, Brooks WM, Sutherland RJ. 2005. Virtual navigation in humans: The impact of age, sex, and hormones on place learning. Horm Behav 47:326–335.

Etienne AS. 1980. The orientation of the golden hamster to its nest-site after the elimination of various sensory cues. Experientia 36: 1048–1050.

Fukushima K. 2003. Roles of the cerebellum in pursuit-vestibular interactions. Cerebellum 2:223–232.

Gadian DG, Aicardi J, Watkins KE, Porter DA, Mishkin M, Vargha-Khadem F. 2000. Developmental amnesia associated with early hypoxic-ischaemic injury. Brain 123:499–507.

Gavrilov VV, Wiener SI, Berthoz A. 1995. Enhanced hippocampal theta EEG during whole body rotations in awake restrained rats. Neurosci Lett 197:239–241.

Gavrilov VV, Wiener SI, Berthoz A. 1998. Discharge correlates of hippocampal complex spike neurons in behaving rats passively displaced on a mobile robot. Hippocampus 8:475–490.

Ghaem O, Mellet E, Crivello F, Tzourio N, Mazoyer B, Berthoz A, Denis M. 1997. Mental navigation along memorized routes activates the hippocampus, precuneus, and insula. Neuroreport 8:739–744.

Glasauer S, Amorim MA, Viaud-Delmon I, Berthoz A. 2002. Differential effects of labyrinthine dysfunction on distance and direction during blindfolded walking of a triangular path. Exp Brain Res 145:489–497.

Good CD, Johnsrude IS, Ashburner J, Henson RN, Friston KJ, Frackowiak RS. 2001. A voxel-based morphometric study of ageing in 465 normal adult human brains. Neuroimage 14:21–36.

Gron G, Wunderlich AP, Spitzer M, Tomczak R, Riepe MW. 2000. Brain activation during human navigation: Gender-different neural networks as substrate of performance. Nat Neurosci 3:404–408.

Hamilton DA, Driscoll I, Sutherland RJ. 2002. Human place learning in a virtual Morris water task: Some important constraints on the flexibility of place navigation. Behav Brain Res 129:159–170.

Hamilton DA, Rosenfelt CS, Whishaw IQ. 2004. Sequential control of navigation by locale and taxon cues in the Morris water task. Behav Brain Res 154:385–397.

Hartley T, Maguire EA, Spiers HJ, Burgess N. 2003. The well-worn route and the path less traveled: Distinct neural bases of route following and wayfinding in humans. Neuron 37:877–888.

Hopkins DA. 2005. Neuroanatomy of head direction cell circuits. In: Wiener SI, Taube JS, editors. Head Direction Cells and the Neural Mechanisms of Spatial Orientation. Cambridge, London: MIT press. pp 17–39.

Horii A, Russell NA, Smith PF, Darlington CL, Bilkey DK. 2004. Vestibular influences on CA1 neurons in the rat hippocampus: An electrophysiological study in vivo. Exp Brain Res 155:245–250.

Insausti R, Juottonen K, Soininen H, Insausti AM, Partanen K, Vainio P, Laakso MP, Pitkanen A. 1998. MR volumetric analysis of the human entorhinal, perirhinal, and temporopolar cortices. AJNR Am J Neuroradiol 19:659–671.

Kessels RP, de Haan EH, Kappelle LJ, Postma A. 2001. Varieties of human spatial memory: A meta-analysis on the effects of hippocampal lesions. Brain Res Brain Res Rev 35:295–303.

Liu P, Zheng Y, King J, Darlington CL, Smith PF. 2003a. Long-term changes in hippocampal *n*-methyl-D-aspartate receptor subunits following unilateral vestibular damage in rat. Neuroscience 117:965–970.

Liu P, Zheng Y, King J, Darlington CL, Smith PF. 2003b. Nitric oxide synthase and arginase expression in the vestibular nucleus and hippocampus following unilateral vestibular deafferentation in the rat. Brain Res 966:19–25.

Maguire EA, Burke T, Phillips J, Staunton H. 1996. Topographical disorientation following unilateral temporal lobe lesions in humans. Neuropsychologia 34:993–1001.

Maguire EA, Frackowiak RS, Frith CD. 1997. Recalling routes around London: Activation of the right hippocampus in taxi drivers. J Neurosci 17:7103–7110.

Maguire EA, Burgess N, Donnett JG, Frackowiak RS, Frith CD, O'Keefe J. 1998. Knowing where and getting there: A human navigation network. Science 280:921–924.

Maguire EA, Gadian DG, Johnsrude IS, Good CD, Ashburner J, Frackowiak RS, Frith CD. 2000. Navigation-related structural change in the hippocampi of taxi drivers. Proc Natl Acad Sci USA 97:4398–4403.

Maguire EA, Spiers HJ, Good CD, Hartley T, Frackowiak RS, Burgess N. 2003a. Navigation expertise and the human hippocampus: A structural brain imaging analysis. Hippocampus 13:250–259.

Maguire EA, Valentine ER, Wilding JM, Kapur N. 2003b. Routes to remembering: The brains behind superior memory. Nat Neurosci 6:90–95.

Manns JR, Hopkins RO, Reed JM, Kitchener EG, Squire LR. 2003a. Recognition memory and the human hippocampus. Neuron 37: 171–180.

Manns JR, Hopkins RO, Squire LR. 2003b. Semantic memory and the human hippocampus. Neuron 38:127–133.

Mapstone M, Weintraub S, Nowinski C, Kaptanoglu G, Gitelman DR, Mesulam MM. 2003. Cerebral hemispheric specialization for spatial attention: Spatial distribution of search-related eye fixations in the absence of neglect. Neuropsychologia 41:1396–1409.

Matthews BL, Ryu JH, Bockaneck C. 1989. Vestibular contribution to spatial orientation. Evidence of vestibular navigation in an animal model. Acta Otolaryngol Suppl 468:149–154.

Mesulam MM. 1999. Spatial attention and neglect: Parietal, frontal and cingulate contributions to the mental representation and attentional targeting of salient extrapersonal events. Philos Trans R Soc Lond B Biol Sci 354:1325–1346.

Moffat SD, Kennedy KM, Rodrigue KM, Raz N. Extrahippocampal contributions to age differences in human spatial navigation. Cereb Cortex (in press).

Morris R. 1984. Developments of a water-maze procedure for studying spatial learning in the rat. J Neurosci Methods 11:47–60.

O'Mara SM, Rolls ET, Berthoz A, Kesner RP. 1994. Neurons responding to whole-body motion in the primate hippocampus. J Neurosci 14:6511–6523.

Peruch P, Borel L, Gaunet F, Thinus-Blanc G, Magnan J, Lacour M. 1999. Spatial performance of unilateral vestibular defective patients in nonvisual versus visual navigation. J Vestib Res 9:37–47.

Petrides M, Alivisatos B, Evans AC, Meyer E. 1993. Dissociation of human mid-dorsolateral from posterior dorsolateral frontal cortex in memory processing. Proc Natl Acad Sci USA 90:873–877.

Pruessner JC, Collins DL, Pruessner M, Evans AC. 2001. Age and gender predict volume decline in the anterior and posterior hippocampus in early adulthood. J Neurosci 21:194–200.

Russell NA, Horii A, Smith PF, Darlington CL, Bilkey DK. 2003a. Bilateral peripheral vestibular lesions produce long-term changes in spatial learning in the rat. J Vestib Res 13:9–16.

Russell NA, Horii A, Smith PF, Darlington CL, Bilkey DK. 2003b. Long-term effects of permanent vestibular lesions on hippocampal spatial firing. J Neurosci 23:6490–6498.

Schautzer F, Hamilton D, Kalla R, Strupp M, Brandt T. 2003. Spatial memory deficits in patients with chronic bilateral vestibular failure. Ann N Y Acad Sci 1004:316–324.

Scoville WB, Milner B. 1957. Loss of recent memory after bilateral hippocampal lesions. J Neurol Neurosurg Psychiatry 20:11–21.

Seizinger BR, Martuza RL, Gusella JF. 1986. Loss of genes on chromosome 22 in tumorigenesis of human acoustic neuroma. Nature 322:644–647.

Smith ML, Milner B. 1981. The role of the right hippocampus in the recall of spatial location. Neuropsychologia 19:781–793.

Smith PF. 1997. Vestibular-hippocampal interactions. Hippocampus 7 :465–471.

Smith PF, Horii A, Russell N, Bilkey DK, Zheng Y, Liu P, Kerr DS, Darlington CL. 2005. The effects of vestibular lesions on hippocampal function in rats. Prog Neurobiol 75:391–405.

Smith SM, Zhang Y, Jenkinson M, Chen J, Matthews PM, Federico A, De SN. 2002. Accurate, robust, and automated longitudinal and cross-sectional brain change analysis. Neuroimage 17:479–489.

Spiers HJ, Burgess N, Maguire EA, Baxendale SA, Hartley T, Thompson PJ, O'Keefe J. 2001. Unilateral temporal lobectomy patients show lateralized topographical and episodic memory deficits in a virtual town. Brain 124:2476–2489.

Stackman RW, Clark AS, Taube JS. 2002a. Hippocampal spatial representations require vestibular input. Hippocampus 12:291–303.

Stackman RW, Herbert AM. 2002b. Rats with lesions of the vestibular system require a visual landmark for spatial navigation. Behav Brain Res 128:27–40.

Stephan T, Deutschlander A, Nolte A, Schneider E, Wiesmann M, Brandt T, Dieterich M. 2005. Functional MRI of galvanic vestibular stimulation with alternating currents at different frequencies. Neuroimage 26:721–732.

Suzuki M, Kitano H, Ito R, Kitanishi T, Yazawa Y, Ogawa T, Shiino A, Kitajima K. 2001. Cortical and subcortical vestibular response to caloric stimulation detected by functional magnetic resonance imaging. Brain Res Cogn Brain Res 12:441–449.

Szabo CA, Xiong J, Lancaster JL, Rainey L, Fox P. 2001. Amygdalar and hippocampal volumetry in control participants: differences regarding handedness. AJNR Am J Neuroradiol 22:1342–1345.

Talairach J, Tournoux P. 1988. Co-Planar Stereotactic Atlas of the Human Brain. Stuttgart, NewYork: Thieme. 122 p.

Tzourio-Mazoyer N, Landeau B, Papathanassiou D, Crivello F, Etard O, Delcroix N, Mazoyer B, Joliot M. 2002. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. Neuroimage 15:273–289.

Vitte E, Derosier C, Caritu Y, Berthoz A, Hasboun D, Soulie D. 1996. Activation of the hippocampal formation by vestibular stimulation: A functional magnetic resonance imaging study. Exp Brain Res 112:523–526.

Wallace DG, Hines DJ, Whishaw IQ. 2002. Quantification of a single exploratory trip reveals hippocampal formation mediated dead reckoning. J Neurosci Methods 113:131–145.

Wright IC, McGuire PK, Poline JB, Travere JM, Murray RM, Frith CD, Frackowiak RS, Friston KJ. 1995. A voxel-based method for the statistical analysis of gray and white matter density applied to schizophrenia. Neuroimage 2:244–252.

Zeki S, Watson JD, Lueck CJ, Friston KJ, Kennard C, Frackowiak RS. 1991. A direct demonstration of functional specialization in human visual cortex. J Neurosci 11:641–649.

Zheng Y, Horii A, Appleton I, Darlington CL, Smith PF. 2001. Damage to the vestibular inner ear causes long-term changes in neuronal nitric oxide synthase expression in the rat hippocampus. Neuroscience 105:1–5.

Zheng Y, Kerr DS, Darlington CL, Smith PF. 2003. Unilateral inner ear damage results in lasting changes in hippocampal CA1 field potentials in vitro. Hippocampus 13:873–878.

Zheng Y, Darlington CL, Smith PF. 2004. Bilateral labyrinthectomy causes long-term deficit in object recognition in rat. Neuroreport 15:1913–1916.

Zheng Y, Darlington CL, Smith PF. 2006. Impairment and recovery on a food foraging task following unilateral vestibular deafferentation in rats. Hippocampus 16:368–378.