RESEARCH ARTICLE | Sensory Processing

Idiiothetic signal processing and spatial orientation in patients with unilateral hippocampal sclerosis

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Submitted 8 January 2018; accepted in final form 8 June 2018

Anagnostou E, Skarlatou V, Mergner T, Anastasopoulos D. Idiothetic signal processing and spatial orientation in patients with unilateral hippocampal sclerosis. J Neurophysiol 120: 1256–1263, 2018. First published June 13, 2018; doi:10.1152/jn.00016.2018.—The role of the hippocampus in spatial navigation and the presence of vestibular-responsive neurons in limbic areas are well-established from animal experiments. However, hippocampal spatial processing in humans is not fully understood. Here, we employed real whole body and head-on-trunk rotations to investigate how vestibular signals, either alone or in combination with neck-proprioceptive stimulation, shape the spatial frame of reference in patients with unilateral hippocampal sclerosis (HS). Patients were asked to point in darkness with a light spot, moved on a cylindrical screen by means of a joystick, into their visual straight-ahead direction (VSA), to remember this direction in space, and to revert back to this point after the rotations. Estimates in patients with HS were compared with those of healthy controls and of patients with epilepsy without hippocampal involvement. All groups produced similar errors after low-frequency vestibular stimuli. These errors were eliminated when rotations involved concurrent neck stimulation. Significantly increased variability was observed, however, in both the VSA and reposition estimates after the rotations in patients with HS compared with controls. These results suggest that cognitive processing of idiiothetic signals for self-motion perception is inaccurate in patients with HS. Importantly, however, the responses of patients with HS showed no spatial lateralization with regard to right or left HS, suggesting that the underlying neuronal loss attenuates the precision of head-direction signal decoding in a nondirectional manner. Hence, patients are unable to use these signals as efficiently as normal subjects in the construction of a stable head-centric spatial frame of reference.

NEW & NOTEWORTHY Spatial perception relies on combined processing of various idiiothetic (vestibular and proprioceptive) and allothetic (visual and auditory) sensory signals. Despite the established knowledge of rodent vestibular-hippocampal interactions, human data are lacking. We investigated idiiothetic orientational processing in subjects with unilateral hippocampal sclerosis using various combinations of vestibular and proprioceptive stimuli. Hippocampal impairment leads to less accurate, noisy decoding of the signal related to idiiothetic orientation. However, patients did not show any lateralized deficits of visual straight-ahead perception or of target/self-displacement perception after idiiothetic stimulation.

INTRODUCTION

Spatial perception and orientation constitute a complex sensory and cognitive function based on a combination of various idiiothetic (vestibular and proprioceptive) and allothetic (visual and auditory) sensory signals. Under naturalistic (as opposed to virtual) conditions, the continuous vestibular inflow, linked to the stimulation of the semicircular canals and the otoliths and subsequent activation of the vestibular nerve, represents a crucial idiiothetic information source for accurate self-motion perception (Beritoff 1966; Hitier et al. 2014).

However, the labyrinths are fixed in the head, which can move relative to the body. Neck-proprioceptive information is thus also important for human perception of self-motion in space. Furthermore, integration of visually derived signals with vestibular and neck-proprioceptive signals is necessary for coordinate transformations, i.e., processing of neuronal activity not only in retinal, but also in the head-centered and spatial frame of reference.

With the use of various psychophysical techniques, researchers have established that humans are able to sense angular velocity and angular displacement (Guedry 1974). Performance in tasks requiring subjects to reproduce the location of a visual object in extrapersonal space in the absence of allothetic landmarks requires an accurate psychophysical measure of idiiothetic orientation processing. This procedure is intimately related to the psychophysical measure of the “subjective straight-ahead” or the “visual straight-ahead” (VSA), which reflects the combined result of idiiothetic inputs (Anastasopoulos et al. 1998; Bridgeman and Graziano 1989; Mergner et al. 1991). In normal subjects, VSA judgements in the dark are aligned with the midsagittal plane of the body. When head and trunk orientations are dissociated from each other, the VSA then coincides well with the head rather than the trunk midsagittal plane offset (Maurer et al. 1997). This alignment changes in pathological conditions such as acute and chronic peripheral vestibulopathy and cervical dystonia (Anastasopoulos et al. 1998; Friedmann 1970; Saj et al. 2013).

It has been long known that navigation in rodents is tightly coupled to activity patterns of the so-called place cells and
head-direction (HD) cells that reside in the mesial temporal lobe, including the hippocampus. Place cells fire preferentially when the animal visits specific areas within an arena, whereas HD cell activity is correlated with certain horizontal head directions in relation to a landmark. Thus place cells encode information about the perceived spatial location of the animal in the environment, whereas HD cells change their firing rate as a function of the head direction, independent of the animal’s location and ongoing behavior. The complementary information provided by these neurons and a number of further, more recently identified cells in interconnected limbic areas is crucial for spatial orientation and accurate navigation (reviewed in Grieses and Jeffery 2017). Spatial neural representations must be constantly updated by various idiothetic and allocentric inputs.

Accumulating evidence suggests that the hippocampus and other mesial temporal lobe circuits are interconnected with the principal vestibular processing sites. The exact pathways that convey angular velocity and linear motion signals from the labyrinth to the hippocampus are still a matter of debate (Biazoli et al. 2006; Cullen and Taube 2017; O’Mara et al. 1994; Wiener and Berthoz 1993). Nonetheless, it is clear that primate and rodent hippocampal neurons are modulated by vestibular stimuli (Cuthbert et al. 2000; O’Mara et al. 1994), whereas experimental vestibular lesions have been shown to disrupt HD cell activity (Stackman and Taube 1997; Taube 2007).

Human studies dealing with the issue of hippocampal-vestibular interactions are still rare. Two studies from the same research group addressed for the first time the functional linkage of vestibular system and hippocampus in human patients with acquired peripheral vestibular pathology (Brandt et al. 2005; Hübner et al. 2007). The authors tested spatial memory and navigation ability in subjects with chronic unilateral and bilateral vestibulopathy (UV and BV, respectively). Patients with BV exhibited specific spatial memory and navigation deficits, whereas general memory deficits were not observed. No significant deficits in spatial memory and navigation could be demonstrated in the patients with left UV, whereas patients with right UV showed a tendency to perform worse on the respective tests. Moreover, subjects with BV displayed a reduction of hippocampal volume on both sides. This was not observed in any of the patients with UV. The spatial task used was a virtual Morris water-maze task, e.g., a purely visual task employed on a computer monitor.

Here, we test the hypothesis that hippocampal atrophy may impede processing of vestibular and neck-proprioceptive spatial information needed for updating of body orientation in space after body and head rotations. We applied such stimuli to subjects with unilateral (right or left) hippocampal sclerosis (HS) and intact labyrinthine function who were sitting on a Bárány chair in complete darkness and asked them to redirect a visual target (“light spot”) in the previously set and memorized VSA direction (space-centric direction updating). With combined analyses of prerotation straight-ahead judgments and space-centric updating estimates after whole body and head-only rotations, we investigated whether 1) updating of object and self-location in space after the rotational stimuli is disregarded in patients, 2) there is a differential weighting of isolated vs. combined idiothetic inputs within the hippocampal circuit, and 3) the unilateral lesions are reflected in lateralized spatial perception impairment patterns.

Should hippocampal function be lateralized, as research on human spatial cognition has suggested (Hübner et al. 2007; Iglói et al. 2010), bias and deficiencies may be expected to be more prominent in one of the two groups of patients with HS.

MATERIALS AND METHODS

Subjects. Ten patients with HS (age: 38.9 ± 14.8 yr, eight women, four with left and six with right hippocampal sclerosis, disease duration range 1–11 yr), five patients with epilepsy without HS (age: 37.4 ± 9.0 yr, three women, disease duration range 3–10 yr), and eleven normal control subjects (age: 36.4 ± 13.9 yr, eight women) gave their written, informed consent to the study, and the protocol was approved by the Human Research Ethics Committee of the University of Athens in accordance with the Declaration of Helsinki. All participants had a complete neurological examination before the study. None had cerebellar or other neurological signs. Both patients with HS and non-HS patients were under antiepileptic treatment. The non-HS epileptic group was included to minimize the possibility of confounding effects of antiepileptic drug intake or the epileptic condition itself on statistical comparisons. Patients with lesions in or near the mesial temporal lobe (including the hippocampus) or the so-called vestibular cortex in the posterior insula (“parietoinsular vestibular cortex”) were excluded. HS was diagnosed based on the simultaneous presence of 1) unilaterally increased intensity of the hippocampus on fluid-attenuated inversion recovery (FLAIR)-weighted MRI images and 2) unilateral hippocampal atrophy (Menzler et al. 2010). Diagnosis was made by neuroradiologists operating 1.5-T MRI scanners. Hippocampal signal intensity was evaluated on angled coronal FLAIR sequences, whereas atrophy was judged on both FLAIR- and T1-weighted scans. Ambiguous cases were not included in the study. Volumetric measurements were not possible because scans originated from several different laboratories and were often only available as films. MRIs were obtained within the last 3 mo before the measurement. Intact vestibular function (at least regarding the horizontal semicircular canal) was documented by caloric irrigation of the labyrinth and after 180°/s velocity steps on a Bárány chair (laboratory normal values for gain and time constant of the slow phase component are 0.55–0.72 and 14.3–17.0 s, respectively). All participants were screened with the Mini-Mental State Examination before inclusion in the study and scored ≥28. All subjects were right-handed as assessed with the Edinburgh Handedness Inventory. Clinical details and demographics are given in Table 1.

Apparatus and stimuli. Subjects were seated on a position-controlled Bárány chair in the center of a cylindrical screen of 0.8-m radius. Their heads were stabilized by means of a dental bite board attached to a head holder (head gear). The head holder was affixed to the chair but could be rotated by a servomotor independently of the chair in the horizontal plane. A light spot, subtending 0.2° of visual angle, could be projected at eye level onto the screen and moved horizontally by means of a mirror galvanometer. The axes of the galvanometer, the turning chair, and the head gear were collinear. During measurements, care was taken to align the head with respect to the trunk. Whole body rotation (turning the chair alone) was used to generate the vestibular stimulus (VEST). Isolated neck stimulation (NECK) was obtained by rotating both the head gear and the turning chair about the same angle, but counter to each other, so that the head remained stationary in space. The dynamics of chair and head rotation devices were matched to each other under computer control. Rotation of only the head gear, resulting in head rotation on the stationary trunk, was used to produce a vestibular-neck stimulus combination (VEST + NECK). The rotation trajectories were derived by integration of a “raised cosine velocity” envelope, which is known to resemble the bell-shaped velocity profile of natural head and extremity movements: \( \gamma(t) = -A \cdot f \cdot \cos(2\pi f t) + A \cdot f \), where \( t \) is time, \( A \) is angular...
displacement, and \( f \) is frequency (Anastasopoulos et al. 2003). Angular displacement was kept constant at 16°, whereas stimulus duration was varied (10, 5, and 1.25 s; measured peak angular velocity amounted to 4, 8, and 18°/s, respectively). These stimuli were designed to contain the dominant frequencies 0.1, 0.2, and 0.8 Hz with the aim to relate the present findings to the known dynamic characteristics of the vestibular and neck systems, which are usually given in the frequency domain. The mirror galvanometer received two inputs. One input was generated by a computer and shifted the light spot in steps of 10° to either side (probe stimulus), and the other was produced by a joystick, which was handled by the subjects during the psychophysical procedure. The performance of the subjects during the experimental tasks was continuously checked by means of an infrared video camera.

Instructions and experimental procedure. The following instruction was given at the beginning of the experiment: "... set the spot in the straight ahead direction and, when it is stepped to one or the other side, restore its location as fast as possible. Remember this location in space. After application of the rotational stimulus, restore the remembered location of the spot in space" (“space task”). Trials consisted of three parts (see Fig. 1). 1) Baseline: after turning off the room lights, a probe stimulus sequence was dispensed with four steps of the light spot in either direction (interstep interval 5 s; step direction changed after each second step; Fig. 1). The subject had to bring the light spot in the direction of his or her subjective straight-ahead (visual straight-ahead, VSA) after each step (see below). 2) Stimulus: a rotational test stimulus (VEST, NECK, or VEST+NECK) was applied in complete darkness. 3) Response: 2 s after stimulus termination, a second, identical probe sequence consisting again of offsetting the spot first by two steps to the left and then by two steps to the right was presented to evaluate the extent to which subjects were able to reproduce their prestimulus estimation of the VSA direction. This is only possible if spatial information derived from the rotational stimulus can be used appropriately to calculate self-displacement (“update self-orientation”). Here, subjects had to set the spot after each step in the remembered direction they chose when estimating VSA direction before the application of the rotational stimulus. Thereafter, head and trunk were returned to their starting positions in the dark, and the subject was given a 30-s break with the room lights turned on, during which the bite bar was maintained. Thus the subject was asked to memorize the space direction perceived as her/his straight-ahead during baseline adjustments and point to this direction after head rotation when presented with successive probe steps of the spot. The test of 18 such trials [3 stimulus durations \( \times 2 \) directions (right/left) \( \times 3 \) different test stimuli (VEST, NECK, and VEST+NECK)] in random order lasted 30–40 min. Rest periods of several minutes were allowed after 6 trials. Before these experiments, an “objective” baseline value was obtained by asking control subjects to point under visual control (i.e., in the illuminated laboratory) in the direction of the head/trunk midsagittal. Objective baseline values from control subjects differed by <1° and coincided on average with the midsagittal plane of the head holder/gear, which was consequently taken as the objective head/trunk midsagittal (0°).

Data acquisition and analysis. Position readings of the 2 galvanometer inputs, of the galvanometer output, of chair and head-holder potentiometers and of the on-off signal of the light beam, were sampled at 100 Hz and stored in a laboratory computer for offline analysis. The last 20 data points that preceded each step displacement of the light spot (i.e., a time interval when the joystick was not moved by the subject) were marked with an interactive computer program (Fig. 1) and were stored as response displacement values, i.e., the adjustment on the immediately previous light spot step. They were later referenced to the objective head/trunk midsagittal position, i.e., to the fixed direction of the head holder/gear midsagittal. Equal numbers of rightward and leftward steps were analyzed. The mean of the 2nd to 5th response to probe step sequences of the spot before rotations (i.e., responses to 2 steps in either direction) is defined as the baseline (i.e., the direction VSA). The mean of the 2nd to 5th response to probe steps after the whole body (VEST) and head-only (VEST+NECK) rotations was, in turn, referenced to the baseline (difference between the 2 mean values) and defined as the stimulus response or space-centric updating estimate of the previously set VSA direction. Means were calculated over both left and right spot displacements. Perceptual underestimation of head rotation is expected to lead to increasingly larger updating estimates approaching 16° when subjects try to reproduce the initial setting of the VSA. Estimates after isolated neck-proprioceptive stimulation (NECK) are not reported and compared in the following because they are contaminated in normal subjects by a variable head movement illusion if the instruction does not specifically direct spatial attention either to head or trunk motion (Mergner et al. 1991). We wanted to formulate the instruction as simply as possible and refrained from complicating it. Baseline variability was defined as the value of the standard deviation across the 2nd to 5th responses to the step sequences before a rotational stimulus, and its mean value across the 18 trials is taken as an accuracy measure for subjects’ internal notion of their visual straight-ahead (intertrial variability of the baseline). Variability of space updating estimates was defined as the value of the standard deviation across the 2nd to 5th responses to the step sequences after a rotational stimulus. It is taken as a measure of the sensorimotor matching performance (Anastasopoulos et al. 2003).
**Statistical analysis.** Unless otherwise stated, linear mixed-effects analysis was performed to outline the relationship between dependent variable of interest $y$ ("space-centric updating estimates of the previously set VSA direction” or variability thereof) and patients vs. controls (group) because multiple correlated measurements were made on each subject. Random intercept models were used with intercepts for subjects being entered as random effects ($u$). As fixed effects ($\beta$), direction (rightward/leftward), frequency (0.1–0.2–0.8 Hz), and group were entered into the model with or without interaction terms. In matrix notation:

$$y = X\beta + Zu + \varepsilon,$$

where $y$ is the $n \times 1$ vector of responses, $X$ is a $n \times p$ design/covariate matrix relating the responses to the fixed effects $\beta$, and $Z$ is the $n \times q$ design/covariate matrix relating the responses to the random effects $u$.

The $n \times 1$ vector of errors $\varepsilon$ is assumed to be multivariate normal with mean 0 and variance matrix $\sigma^2R$.

Because of the small sample size, $\chi^2$-values were rescaled to $F$ ratios. Statistical significance could be directly derived after adjusting the denominator degrees of freedom by fitting the model in Stata SE 14.2 (StataCorp):

$$\text{mixed \ } y \ \text{i.direction i.frequency i.group} \ || \ \text{subject;} \ \text{dfmethod(repeated)} \ (2)$$

Additional proof of significance was gathered by likelihood ratio (lr) tests comparing the full model (Eq. 2) with the effect of a fixed term (i.e., group) against the reduced nested model (Eq. 3) without the effect of the same term,

$$\text{mixed \ } y \ \text{i.direction i.frequency} \ || \ \text{subject;} \ \text{dfmethod(repeated)} \ (3)$$

$$\text{Eq. 2}$$

$$\text{Eq. 3}$$
 Significant difference between the likelihood of these two models, as judged by $\chi^2$ and $P$ value of the comparison, would confirm that this fixed term affects the dependent variable $Y$. Deviations from homoscedasticity were estimated by visual inspection of residuals vs. fitted values plots.

**RESULTS**

The subjective VSA direction, which served as baseline for the space task, averaged $3.1^\circ$ (4.6) for normal subjects, $-4.1^\circ$ (8.1) for patients with epilepsy without HS [means (SD)], showing no significant difference between the groups (minus sign stands for left, plus sign for right). Driftlike increases or decreases in subjects' directional estimates were frequent in all groups. They typically changed over time and trials in the same subject, and they did not show any particular direction in the patient group. Intertrial variability of the baseline was $\geq 300\%$ larger in both patients with right and left HS compared with normal subjects [2.7 (0.8) and 2.4 (0.3) vs. 0.7$^\circ$ (0.3) in controls and 0.9$^\circ$ (0.3) in patients with epilepsy without HS, 1-way ANOVA, $F(3,22) = 29.9$, $P < 0.0001$; compare representative baseline traces in Fig. 1A]. Significant pairwise differences (Scheffé post hoc analysis) were found between patients with left HS and controls ($P < 0.001$), patients with right HS and controls ($P < 0.001$), patients with left HS and patients with epilepsy without HS ($P < 0.01$), and patients with right HS and patients with epilepsy without HS ($P < 0.001$). There was no significant difference between patients with epilepsy without HS and controls or between patients with right and left HS.

The controls' and patients with HS' responses on whole body (VEST) and head-only (VEST+NECK) rotations are shown in Figs. 2A and 3A, respectively. Following the VEST+NECK stimulus, repositioning to the memorized VSA direction before rotations was almost ideal after correction for the individual baseline errors for all three frequencies in all groups (i.e., close to the perceived subjective straight-ahead direction set before the rotation). Near-ideal updating was also possible on VEST at 0.8 Hz (Fig. 2A). At lower stimulus frequencies of whole body rotation, however, the subjects underestimated the rotations so that their responses showed a driftlike increase or decrease. Driftlike increases or decreases in subjects' directional estimates were frequent in all groups. They typically changed over time and trials in the same subject, and they did not show any particular direction in the patient group. Intertrial variability of the baseline was $\geq 300\%$ larger in both patients with right and left HS compared with normal subjects [2.7 (0.8) and 2.4 (0.3) vs. 0.7$^\circ$ (0.3) in controls and 0.9$^\circ$ (0.3) in patients with epilepsy without HS, 1-way ANOVA, $F(3,22) = 29.9$, $P < 0.0001$; compare representative baseline traces in Fig. 1A]. Significant pairwise differences (Scheffé post hoc analysis) were found between patients with left HS and controls ($P < 0.001$), patients with right HS and controls ($P < 0.001$), patients with left HS and patients with epilepsy without HS ($P < 0.01$), and patients with right HS and patients with epilepsy without HS ($P < 0.001$). There was no significant difference between patients with epilepsy without HS and controls or between patients with right and left HS.

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Variability of space-centric updating estimates, i.e., the standard deviation of estimates after a rotational stimulus, amounted on average to $<1^\circ$ in normal subjects (Figs. 2B and 3B). Patients with right HS showed an approximately two- to threefold increased performance variability both after vestibular $[F(4,15) = 64.4$, $a = 2.5 \pm 0.3$ SE, $P < 0.0001$; lr test: $\chi^2 = 26.6$, $P < 0.0001$; $a$ denotes the predicted coefficient of the fixed-effect group $\pm$ standard errors] and after combined vestibular-neck stimulation $[F(4,15) = 16.3$, $a = 2.2 \pm 0.6$ SE, $P < 0.0001$; lr test: $\chi^2 = 11.4$, $P < 0.0007$]. Similar results were obtained in patients with left HS [VEST: $F(4,13) = 116.7$, $a = 1.8 \pm 0.2$ SE, $P < 0.0001$; lr test: $\chi^2 = 28.8$, $P < 0.0001$; VEST+NECK: $F(4,13) = 48.8$, $a = 1.6 \pm 0.2$ SE, $P < 0.0001$; lr test: $\chi^2 = 22.2$, $P < 0.0001$]. The effect of group was prominent for both rightward and leftward rotations and at all rotation frequencies for patients with both right and left HS. Comparisons between the levels of the fixed terms frequency and direction were nonsignificant. Variability of space-centric updating estimates in patients with epilepsy without HS was normal (Figs. 2A and 3A). Furthermore, response variability after whole body rotations (VEST) was increased compared with baseline variability both in patients with HS and control subjects [patients with HS:
stimuli is preserved in patients with unilateral hippocampal damage, 2) within the range of the applied stimulation amplitude and frequencies, the weighting and interaction of vestibular- and neck-idiiothetic inputs of patients with HS are similar to those of normal controls, 3) there is no lateralized offset of the VSA direction in patients with left vs. right HS, and 4) unexpectedly, we observed a marked association of unilateral hippocampal atrophy with increased variability of visual straight-ahead and the postrotational recovery of this direction.

Previous investigations that examined vestibular-hippocampal interactions employed virtual setups (Brandt et al. 2005; Maguire et al. 1996). However, the importance of real movement of the animal in the environment was recently demonstrated by Terrazas et al. (2005), who showed that when the entire visual arena was rotated around the immobile rat, place cells lost their spatial selectivity in comparison with rotations involving actual self-motion. Only a single human study previously employed natural vestibular stimuli in patients with hippocampal damage (Wiest et al. 2000). These authors used whole body rotations, and the subjects’ task was to rotate themselves back to the initial position. Different rotation frequencies and independent movements of head and trunk were not tested. In comparison with controls, the patients’ responses were slightly but significantly hypometric. The authors’ interpretation was that patients with HS underestimate vestibular stimuli, resulting in erroneous path integration whenever subjects rely solely on vestibular cues.

In the present study, analysis of the static (baseline) condition showed that patients did not produce abnormal estimates of the VSA, and this was true for both right and left HS. This suggests that, in the absence of a foregone vestibular or combined vestibular and neck-propioreceptive stimulus, unilateral HS does not introduce directional shifts in VSA processing. After isolated vestibular and combined vestibular-neck-propioreceptive stimulation, patients’ performance, again, did not differ significantly from that of normal controls (Figs. 2A and 3A). Whenever the rotational stimuli included a displacement of the trunk in space at low rotational frequency (whole body rotation), both patients and healthy subjects incorrectly pointed in the direction of the trunk rotation. Rotations at higher frequency (0.8-Hz dominant frequency) and velocity yielded improved, almost veridical, estimates in both patients and controls. The “trunkward shift” at lower frequencies suggests a systematic, physiological underestimation of rotation amplitudes. The frequency-dependent error of the vestibular contingent recovery of the light spot direction in space reflects the high-pass characteristics of the corresponding self-motion perception.

These results are in line with previous studies from this laboratory, which included normal subjects and patients with cervical dystonia (Anastasopoulos et al. 1998, 2003; Mergner et al. 2001). Similar to the previous data, patients with HS and normal controls also showed near-ideal performance when the vestibular and neck-propioreceptive inputs were combined during head-on-trunk rotations. The trunk is then perceived as stationary in space independently of head rotation frequency, which thus facilitates the detection of any relative target motion. Hence, patients with HS and normal controls tend to shift the direction of the previously estimated VSA toward the trunk movement, independent of the side of the affected hippocampus, and errors become smaller at higher rotation...
frequency. When rotating the head on the trunk, performance in both control subjects and patients with HS approaches veridical estimation, i.e., concurrent neck-proprioceptive stimulation modifies spatial perception similarly in both groups.

In conclusion, chronic unilateral hippocampal dysfunction does not result in erroneous processing of vestibular or combined vestibular and neck-proprioceptive signals when these are employed for estimating self-motion in space-centric orientation tasks. These findings are compatible with the notion that vestibular and neck-proprioceptive projections are bilateral (Brandt et al. 2005; Hufner at al. 2007). Indeed, vestibular-responsive HD cells, directionally tuned for rightward or leftward rotations, are located in both cerebral hemispheres (Basset et al. 2007; Stackman and Taube 1997) so that the remaining place and HD cells in the unaffected hippocampus may theoretically still preserve a veridical directional sensing (Leutgeb et al. 2000). Similarly, a human functional neuroimaging study showed simultaneous activation of both hippocampi during imagined left or right turns (Ghaem et al. 1997).

Maguire et al. (1996) conducted one of the few studies on the role of hippocampal disease in spatial orientation in humans. The authors demonstrated topographical disorientation in temporal lobe patients using sophisticated topographical tasks testing route proximity, distance judgements, and other route knowledge parameters. The differences were mainly between normal controls and patients but not between right and left temporal lobe patients. It is worth noting, however, that the participants of this study were patients with intractable epilepsy after resections of large parts or the whole temporal lobe, which renders the comparison with our patients with HS difficult. Moreover, Maguire et al. (1996) mention that before surgery, these patients had no difficulties in way-finding in environments or in any other real-world topographical tasks. This may be in line with the reported unimpaired orientation and navigation of our patients under everyday conditions. The lack of directional impairments contrasts with the well-established directional bias seen in patients with right temporoparietal junction, superior temporal, or insular damage who exhibit a marked right-sided compression of perceptual and motor space, known as spatial hemineglect (Karnath and Dieterich 2006).

A major result of our study is the increased estimate variability in patients with HS. This phenomenon was evident both in the baseline condition as well as after immediate idiothetic stimulation. This impairment might be interpreted as increased noise in the setting of the VSA and is found in about the same magnitude in patients with right and left HS (Figs. 2B and 3B). The reduction of the number of intact hippocampal and parahippocampal neurons, which is the hallmark of HS neuropathology, appears to be important in certain computational models of hippocampal function (Burgess and O'Keefe 2011; Jensen and Lisman 1996; Tsodyks et al. 1996). As the reconstruction of a precise head-direction signal is generally thought to depend on the number of neurons tuned by such a signal (as computed, for example, by Fisher information analysis; see Pouget et al. 1998), it might become clear why sparse cell loss, as it occurs in HS, leads to less accurate, more noisy directional estimates. In this respect, our data are comparable with the study of Wiest et al. (2000), who found hypometric come-back errors in the patient group. These errors may have indeed reflected a strategy to deal with perceptual uncertainty. Unfortunately, no statistics on variability were provided in the article. From the presented data (numbers in Table 2 of Wiest et al. 2000), one may, however, infer higher standard deviation values in the performance of patients with HS. Notably, although these authors also used real body rotations, differences in their procedure render straightforward comparisons difficult: 1) the subjects’ ability to rotate themselves back to the initial position was measured, and 2) feedback given after each trial introduced clear learning effects.

As mentioned above, we also demonstrated increased estimates variability in the baseline condition, before the application of any rotational stimulus. Baseline performance is still a multisensory task that also requires matching of all spatial senses (including vestibular inputs). Horizontal deviation ($\approx 10^\circ$) of the visual straight-ahead is a common finding in patients with unilateral peripheral vestibulopathy with preserved vision (Strupp et al. 1998). Hence, increased baseline variability in patients with HS might arise, at least in part, from deficiencies in processing (noisy) vestibular input, which is conveyed to the brain even at rest (in terms of bilateral vestibular tone). Alternatively, a precise internal representation of straight-ahead may be formed through the immediate past history of convergent idiothetic and allothetic signals. Since HS appears to produce a nonlateralized spatial inaccuracy, we predict that bilateral HS would lead to increasingly variable estimates. Of course, actual measurements are required to provide definite proof of this hypothesis.

One limitation of our study is the lack of quantification of hippocampal volume loss. The included patients with HS were, however, unambiguous cases with severe atrophy and increased signal in T2 MRI sequences (and a compatible epileptic syndrome). Volumetric measurements would still have been useful to correlate performance with the degree of hippocampal atrophy statistically. Another drawback of our study is the fact that participants were not subjected to a comprehensive neuropsychological and allothetic testing, apart from the Mini-Mental State Examination. Hence, any association of performance variability with other cognitive factors is unknown and remains to be evaluated. Possible further confounds, such as the noise of the actuated devices, have been, however, carefully eliminated. Our experimental setup has been repeatedly tested with normal subjects and has yielded consistent results (Maurer et al. 1997; Mergner et al. 1991, 2001).

Our data leave unexplored the extent to which the response scatter in HS scales up with increasing rotational amplitudes. Furthermore, it is still an open question why our subjects with HS, as well as patients with HS from previous studies, do not experience difficulties in daily activities requiring ambulation in simple or complex environments. A possible explanation is that visual-vestibular interactions and/or allothetic landmarks in everyday life suffice to compensate for the scattered VSA judgments found in our experiments. Studies designed to employ various combinations of idiothetic and allothetic stimuli may help to increase our understanding of the function of the human hippocampus in the manifold of ecological situations.
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