

Christian Hölscher · Wolfgang Jacob ·
Hanspeter A. Mallot

Learned association of allocentric and egocentric information in the hippocampus

Received: 6 June 2003 / Accepted: 7 March 2004 / Published online: 7 April 2004
© Springer-Verlag 2004

Abstract Single-cell recording was conducted in the hippocampus of rats that performed a spontaneous alternation task in a modified T-maze. In the central arm of the maze, 4 out of 45 cells (8%) were found that fired selectively depending on which turn the animals would take. This result is in disagreement with a previous study in which two-thirds of cells (22 out of 33) showed a clear bias for direction of turns. The interpretation was that the cells coded information of episodic memory. Our results do not support this hypothesis. Interestingly, over the course of training, an increasing number of cells were found that fired in correlation with the rats' movements. It is proposed that these cells associate egocentric motor information with allocentric spatial information rather than encode episodic memory.

Keywords Place cells · Single neuron · Spatial · Memory · Orientation · Area CA1 · Area CA3 · Electrophysiology

Introduction

The hippocampus is considered to be involved in memory processes. Hippocampal lesions or the application of receptor blockers to impair neuronal functionality in the hippocampus seem to affect short-term or episodic memory (Rawlins 1985; Zola-Morgan et al. 1986; Butelman 1990; Bolhuis and Reid 1992; Hölscher and Schmidt 1994; Tulving et al. 1994; Floresco et al. 1997) while information learned before the lesion appeared to be less affected (Rasmussen et al. 1989; Shapiro and Caramanos 1990; Vnek and Rothblat 1996). In single-cell recordings from freely moving rats, however, neuronal activity has

been found that is very stable and related to the location of the animal in space ('place cells'). Numerous experiments have been conducted to characterise the information used in constructing such place cells and what role they might play in information processing and memory mechanisms (O'Keefe 1979; Nadel and Eichenbaum 1999; Shapiro and Eichenbaum 1999; Fenton et al. 2000; Redish et al. 2001). This apparent contradiction between the seemingly very stable place-cell activity over time and few modulations of neuronal activity over time that could be correlates of memory process has puzzled many scientists. A number of studies have addressed this issue, and it was found that place-cell activity is not as static as assumed and can be influenced. For example, it was shown that landmarks that are observed by the rat to be mobile will have much less effect on place-cell firing properties than stationary landmarks (Jeffery 1998; 2001). Also, place-cell activity can be related to the movements that the animal anticipates and can be interpreted as a correlate of memory. In this case, no changes in the distal cues or landmarks occur, yet neuronal activity is dependent on the animals' actual movements, or intentions of movement, or perhaps attention towards selective cues (Frank et al. 2000; Wood et al. 2000; Hollup et al. 2001). In one of these studies, 22 of 33 cells that fired in the centre arm of a modified T-maze were found to do so in a movement-specific way. Some neurons would fire when the animal was about to turn right at the end of the centre arm and fire very little when the animal was about to turn left (Wood et al. 2000). These modulations of neuronal activity have been initially interpreted as correlates of episodic memory since they cannot be explained by changes in the environment or other external cues that could induce remapping of place fields (Eichenbaum 2000; Moser and Paulsen 2001). The neurons would store the information on which arm the animal had visited in the previous run so that it can decide to visit the alternate arm. However, in a lesion study it has been shown since that animals can perform this modified T-maze task even without the hippocampus (Ainge and Wood 2003). Therefore, the experiment has been repeated in a similar modified T-maze

C. Hölscher (✉) · W. Jacob · H. A. Mallot
Department of Cognitive Neuroscience, Faculty of Biology,
Tübingen University,
Auf der Morgenstelle 28,
72076 Tübingen, Germany
e-mail: christian.hoelscher@uni-tuebingen.de
Tel.: +49-7071-2974605
Fax: +49-7071-292891

to analyse what factors determine the neuronal activity of the cells observed by Wood et al. (2000) and what information these cells might encode.

Material and methods

Subjects

Five naive male Long-Evans rats (300–350 g at implantation stage) were housed individually in large transparent perspex cages with food and water available ad libitum. Animals were kept on a reversed 12-h/12-h light/dark schedule and were tested in the dark phase.

All experiments in this study were licensed under German and European Community Law (Genehmigung ZP 1/01 nach Tierschutzgesetz BGBl. S. 1105).

Electrode implantation

Tetrodes (O'Keefe and Recce 1993) were made of four twisted 25- μ m heavy formvar-coated platinum–iridium (90%/10%) wires (Cal-Wire Company, Vernon, CA, USA). Electrodes were soldered to a headstage that allowed controlled lowering of tetrodes after implantation. The impedance of electrodes was 500–800 k Ω .

Animals were anaesthetised with 75 mg/kg ketamine (Ketamin; WDT, Garbsen, Germany) plus 5 mg/kg xylazine (Rompun; Bayer, Leverkusen, Germany) administered subcutaneously. A local injection of lidocaine was given into the scalp, and the skin was cut and pulled back. Animals were mounted in a stereotaxic frame. A 1.5-mm diameter hole was drilled into the skull (4 mm post bregma, 3 mm lateral to midline) to allow the positioning of a microdrive with four tetrodes above the dorsal hippocampus. Four 1-mm stainless steel screws were inserted into the skull. One of the screws served as a ground electrode. The microdrive was fixed to the screws by dental acrylic cement. The sides of the scalp skin were treated with antibiotics. Animals were given 1 week to recover before any recording was started.

Apparatus

A figure-of-eight-shaped maze (Fig. 1) was constructed of wooden runways 16 cm wide without any walls. The floor was painted grey. The central runway was 150 cm long and the width of the maze was 130 cm long. A black well was located for the food reward at the end of the choice arms. The maze was elevated 55 cm from the ground on wooden blocks. It was located in a sound-attenuated recording room with white walls. The recording room contained a cupboard, one table with a computer, and various other clearly visible cues. The whole room was illuminated by four 20-W halogen lamps that were located in each corner of the room.

Behavioural training

Rats were trained to perform a continuous alternation task for 30 min each day. Each rat was placed at the base of the central arm of the apparatus, facing the choice arms. Only if the animal entered the arm not entered in the previous run was it rewarded with a Choco Krispie (Kellogg's). After a wrong choice the rat was required to continue along the connection arm, enter again the central arm, and make the correct choice on the following trial. This procedure was repeated, using a cardboard barrier to direct the animal's traverses over the central arm and to alternate entries into the choice arms, until the animals ran the pattern consistently. After 4 weeks of training the animals continued to run in a figure-of-eight-

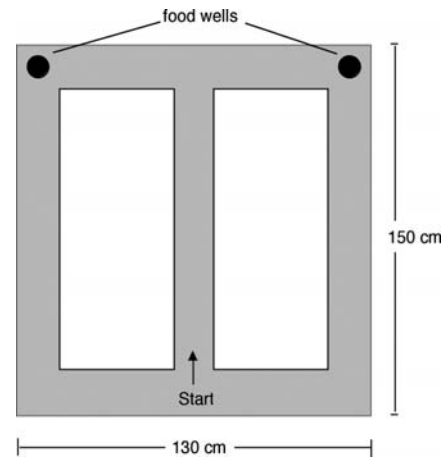


Fig. 1 The modified T-maze. Rats performed a continuous alternation task in which they traversed the central arm of the maze on each trial and then alternated between left and right turns at the upper junction. Rewards for correct alternations were provided in black food wells on the end of each choice arm. The rat returned to the starting position via connecting arms, and then entered the central arm again on the next trial. The maze was elevated 55 cm above the floor. *Arrow* indicates the direction in which the animal started the run

like pattern without barriers present. The rats were allowed to run 30–50 continuous trials. After recovering from surgery (4 days), the animals were running in the maze for 15 min a day as done prior to the surgery. Recording sessions consisted of 30–40 trials composed of an equal number of right-turn and left-turn trials. Each session lasted 300 s.

Recording procedure

The animal was connected to a headstage preamplifier (Axona, St. Albans, UK), which also contained three light-emitting diodes that were used by the tracking system to identify the location of the animal. The amplifier was connected via cables to a main AC-coupled amplifier (10,000 to 25,000 amplification) and to the recording system (Axona). The cables were suspended by rubber bands to prevent the animals trailing the wires during runs. Signals from each electrode were passed through bandpass filters, 600 Hz to 6KHz for the spike channels, and lowpass filtered >200 Hz for the electroencephalographic (EEG) channel. Each channel of the tetrodes was recorded differentially to the reference electrode on the skull and to a different tetrode nearby. Signals that crossed a pre-set trigger threshold were recorded. Waveforms were sampled at 48 kHz, time stamped and stored for offline analysis. A video tracker recorded the position of the rat during the trial. The coordinates were stored offline for later analysis. Positions were sampled at 47 Hz.

Animals were given trial runs through the maze in order to identify neurons. Tetrodes were advanced about 50 to 300 μ m to optimise recording or to record from different cells.

Spike isolation and analysis

Spikes were separated according to principal analysis using a software program (TINT; Axona). The slopes of waveforms recorded from each channel of a tetrode were compared with another channel. 'Clusters' of waveforms with similar upward slopes were identified and analysed further according to temporal and waveshape criteria (Harris et al. 2000; Hölscher et al. 2003). Interneurons were identified and distinguished from pyramidal cells by the duration of the extracellular action potential (>0.3 ms for

pyramidal cells), firing patterns (complex spikes) temporal firing patterns (autocorrelation analysis of firing frequencies, eg. theta firing patterns) and low firing average outside of the place field. The quality of isolation was tested by autocorrelation.

Average firing rate was expressed as the total number of spikes divided by the total length of the recording period. Cells with a firing rate of >1 Hz were not used for analysis. The peak firing rate was found by dividing the maze surface into 48×48 bins. Spike rates

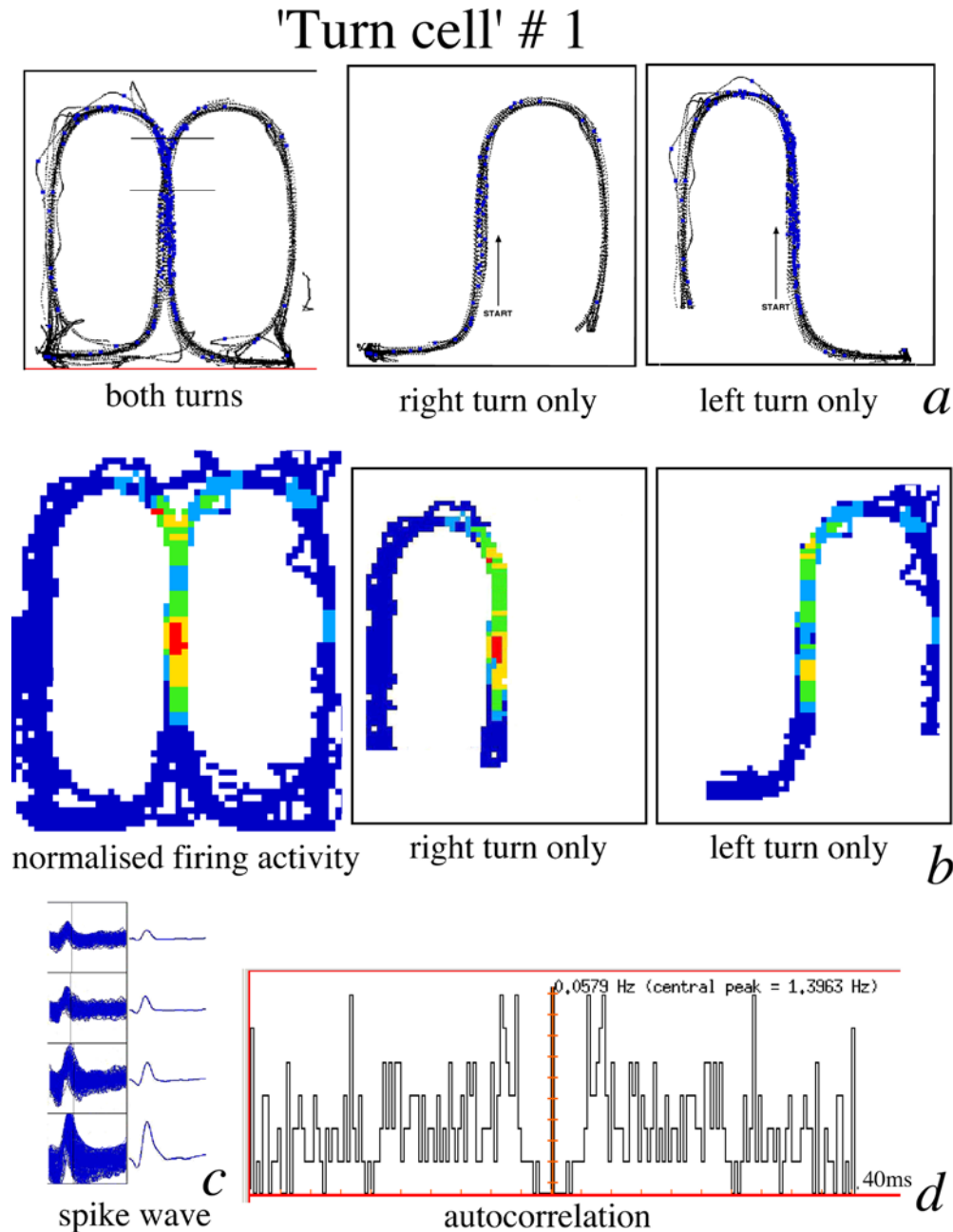


Fig. 2a–g Examples of ‘turn-sensitive cells’ or ‘episodic cells’ as described by Wood et al. (2000). **a** Tracks of the animal in the maze with neuronal spikes indicated as *blue dots*. In panel showing *both turns*, more activity is seen when the animal turned left (mean \pm SEM: left 10.3 ± 2.6 vs right 2.6 ± 1.3 , $p < 0.01$). This panel was used for the comparison of firing rates. Other panels in **a** show data for *right turn only* and *left turn only* with respective neuronal activity. **b** Cell activity for left and right turns normalised for number of spikes per time to avoid a bias introduced by changes of travelling speed. Both turns and only left or only right turns are shown separately. Activity rates were separated into five groups, 0–20% of firing rate (*blue*), 20–40% (*light blue*), 40–60% (*green*), 60–80% (*yellow*), and 80–100% (*red*) of the maximum firing rate (7.1 Hz). **c** Spike waves as recorded on a tetrode, shown as summation (*left*) and average of

all waves (*right*). **d** Autocorrelation demonstrating that the cell is not contaminated with spikes from other cells, since the shortest spike interval is not below the absolute refractory period. **e** A second turn-sensitive cell. Cell activity for left and right turns were normalised for number of spikes per time to avoid a bias introduced by changes of travelling speed and represented as in **b** (mean activity \pm SEM: left 0.3 ± 0.1 vs right 5.1 ± 1.3 , $p < 0.01$). Two *horizontal lines* mark the section where the animal travelled across the same location on the left or right turn run. This section was used for the comparison of firing rates. **f** Autocorrelation demonstrating that the cell is not contaminated with spikes from other cells. **g** Spike waves of this turn-sensitive cell, shown are all four channels of the tetrode as summation (*left*) and average of all waves (*right*)

unit were extracted. For normalisation, the number of spikes in each bin was normalised for the time spent by the rat in this bin. The values in this array were smoothed by replacing each value with the average of this value and those of the adjacent eight neighbours. The peak rate was then taken as the maximum smoothed firing rate in any bin. Spike rates were separated into five groups, 0–20% of firing rate, 20–40%, 40–60%, 60–80%, and 80–100% of the maximum firing rate.

When analysing the directionality of cells, the firing activity of a give cell in the upper section of the central arm of the maze was analysed (see Fig. 2b). In this section, animals were in the same location when turning left or when turning right. this restriction was needed to ensure that the spatial coordinates were identical for the left and the right turn. In the middle section of the central arm, animals were not always in the same location when turning left compared to turning right. Here, a difference in firing activity of the cell when turning left in comparison with that when turning right could be due to a difference in the location of the rat in the place field.

We assigned the cells into three subgroups. The first group consists of ‘place cells’, which were defined as those with firing fields that did not exceed a length of 25 cm of an arm. Neurons that fired along the length of the arm were not defined as place cells but as ‘extended firing field cells’. Cells that fired in a biased way for a turn left or right were defined as ‘turning cells’.

Statistics

Firing rates for runs along the central arm were compared. A *U*-test was used to analyse differences between left and right firing rates of neurons. For analysis of numbers of extended firing field cells over time, regression statistics were employed. Analysis of variance (ANOVA) was used for the analysis of standard deviations of residuals from the regression line (InStat statistics program; GraphPad, San Diego, CA, USA).

Histology

Animals were anaesthetised with urethane and the brains removed. The brains were fixed in a buffered 8% paraformaldehyde solution for 12 h. Brains were cut on a cryostat, mounted, and stained with cresyl violet. Sections were then examined under a light microscope to identify the localisations of the tetrodes. All cells were located in area CA1.

Results

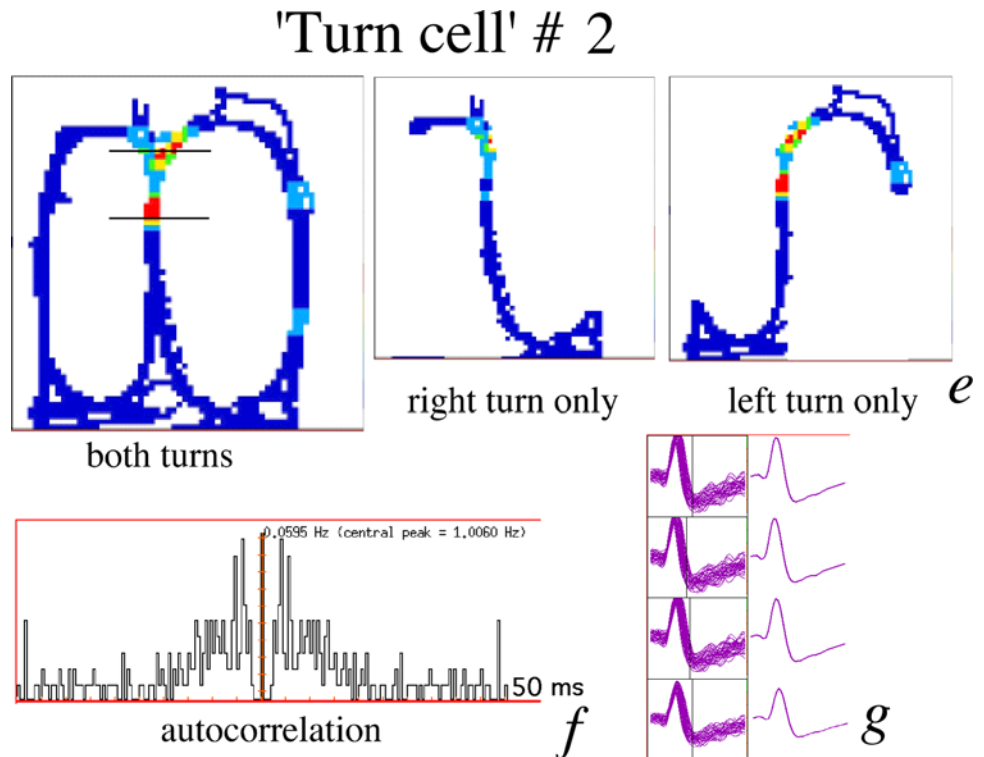
Hippocampal complex-spike cells were recorded as animals alternated continuously in a modified T-maze. All four rats acquired the task in 20–40 training sessions (4 weeks daily training) and reached the criterion of a 70% success rate. Over the following recording trials, the animals further improved to 87% correct trials ($p < 0.01$, *t*-test), indicating that the animals learned further.

Firing fields were found in all parts of the maze pathways. In this paper we included only cells with isolated firing fields in the central arm. The total number of recording days was 19, and the number of detected cells was 114. Of these neurons, 45 had firing fields in the middle stem of the maze.

It was found that 4 of the 45 cells showed a bias for turn direction (Fig. 2). Values (\pm SEM) for each cell in a *U*-test when comparing firing rates left with right turns were: cell 1, 7.45 ± 1.1 vs 4.78 ± 0.4 , $p < 0.036$; cell 2, 2.71 ± 0.4 vs 1.4 ± 0.2 , $p < 0.023$; cell 3, 10.3 ± 2.6 vs 2.6 ± 1.3 , $p < 0.01$; cell 4, 3.4 ± 0.3 vs 1.2 ± 0.2 , $p = 0.038$.

The remaining 41 cells showed no significant difference between left and right turns. Of these cells, 22 were

Fig. 2a–g (continued)



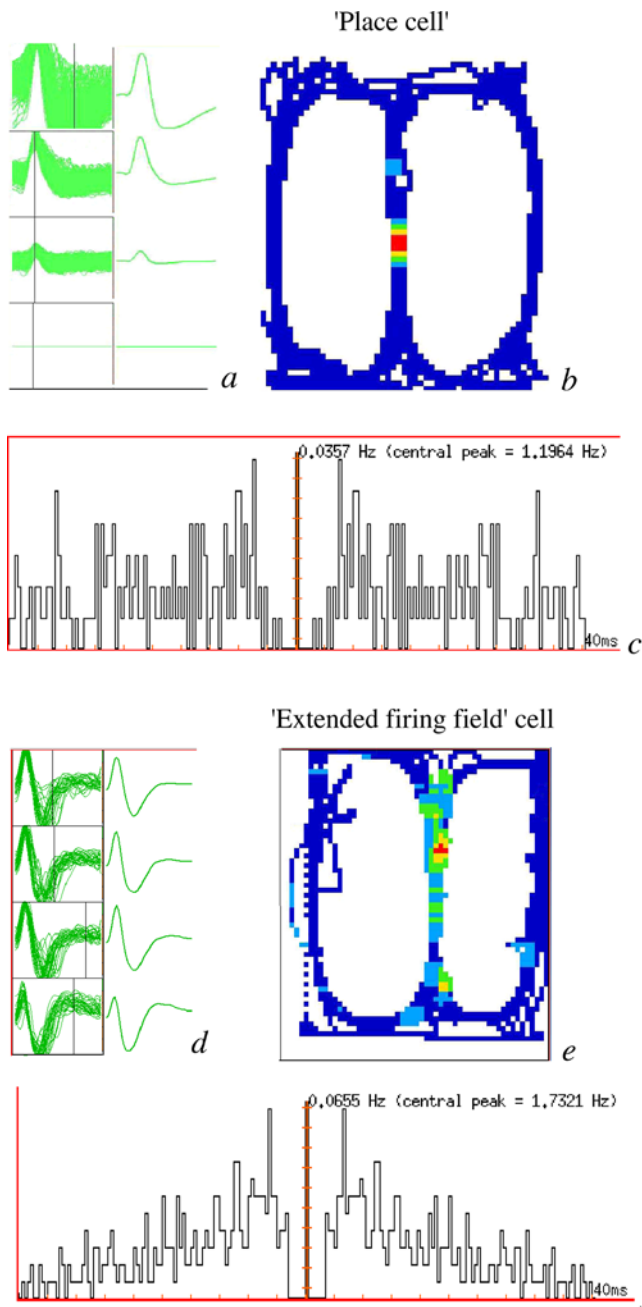


Fig. 3a–f Example of a ‘place cell’ and of a ‘extended firing field cell’. **a** Spike waves (*left* summation, *right* average of all traces) of the place cell. Channel 4 was the lowpass filtered EEG channel and did not contain spike data. **b** Cell activity normalised for spikes per time to avoid a bias introduced by changes of traveling speed. Activity rates were separated into five groups, 0–20% of firing rate (*blue*), 20–40% (*light blue*), 40–60% (*green*), 60–80% (*yellow*), and 80–100% (*red*) of the maximum firing rate (4.2 Hz). A clearly demarked place field can be seen in the centre arm. **c** Autocorrelation demonstrating that the cell is not contaminated with spikes from other cells. **d** Spike waves of the extended firing field cells. These cells did not discriminate between right or left turns of the animal. **e** Autocorrelation demonstrating that the cell is not contaminated with spikes from other cells. **f** Cell activity within the central arm of the maze. Activity rates were separated into five groups represented as in **b**

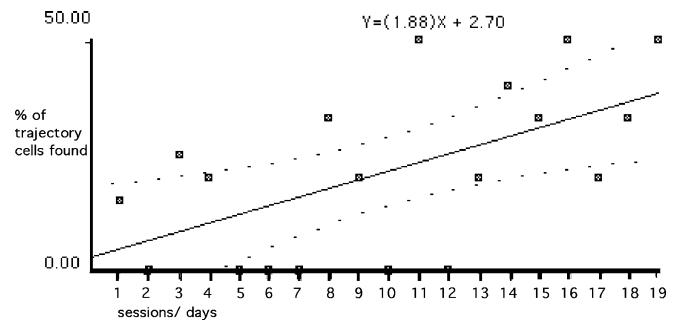


Fig. 4 Increase of numbers of extended firing field cells (plus the four ‘turn-sensitive cells’) over the course of the recording sessions. The percentage of cells in this category significantly increased over time as shown by a linear regression analysis, with $r=0.546$ and standard deviation of residuals from line $=0.841$ (ANOVA F -value $=7.222$, $p=0.015$)

considered place cells as their firing field was no larger than 25 cm and there was only one firing field in the maze (Fig. 3). Nineteen cells were considered extended firing field cells since their firing field stretched along the length of the arm (Fig. 3).

When analysing the number of extended firing field cells during the course of the experiment, a significant increase of numbers over time was found. Since the turning cells are similar to the extended firing field cells, with the exception of the bias for turns, they were included in the analysis. The number of cells in this category increased over time, as shown by a linear regression analysis with $r=0.546$, standard deviation of residuals from line $=0.841$, and F -value (ANOVA) $=7.222$, $p=0.015$ (Fig. 4).

Discussion

In this study, 114 cells were isolated, and 45 of these cells fired in the central arm of the maze. Only 4 of these 45 cells showed increased activity when the animal was about to turn into one of the two arms (left or right) but reduced activity when the animal was about to turn the other way.

These results stand in sharp contrast to the results observed by Wood et al. (2000). In that study, 22 of 33 cells were active in the central arm of the modified T-maze. The results found in our study are comparable to those reported in a study that recorded neuronal activity in rats that were trained in a Y-maze. In that study, firing activity of neurons was not dependent on left or right turn choices at all (Lenck-Santini et al. 2001). Also, in a different study in which a similar set-up as in the present study was used, no neurons that were turn-selective have been reported (Barnes et al. 1997). How can such differences be explained?

A recent study investigated the effect of different training techniques on the development of place cell or ‘turn cell’ activity. It was shown that when teaching the animals a similar route-learning task as was done in the present study, the result was dependent on the technique that was used to initially train the animals. When blocking

the pathway for the animals to prevent them from taking a wrong turn, more turning cells were found than when not blocking the arms and thereby giving the animals a choice of visiting arms (Bower et al. 2002). In the study by Wood et al. (2000), blocks were used initially in the training procedure to prevent the animals from taking the wrong turn (E.R. Wood, personal communication), and many turning cells were found. In the study presented here, animals were mostly free to choose the arms, but were gently moved back if a wrong turn was chosen, and few such cells were found. Hence, in agreement with the interpretation given by Bower et al. (2002), it appears that the version of the task with blocks is actually a different task in which the animals learn a different strategy than in the unblocked ‘free choice’ version. If there is no true choice in the arms taken, animals might be encouraged to learn a routine motor program, and turn cells evolve, whereas in the version with choices, animals have to decide which arm to take, preventing the acquisition of a stereotypic motor program. This is very likely since we know that the task can be performed by animals even without the hippocampus (Ainge and Wood 2003). It has been shown that rats will learn a routine motor program (basal ganglia dependent) in repetitive tasks, whereas they will learn a cognitive allocentric strategy (dependent on hippocampal function) if a decision has to be made during the task (McDonald and White 1994; for a detailed discussion of these processes see Packard and Knowlton 2002).

In conclusion, at the present stage of knowledge we cannot make any assessments of what type of information is encoded in such turn-sensitive cells. It was argued that in a T-maze during an alternation task, the animals have to keep in memory which arm they had visited previously in order to be able to visit the alternate arm. If this was the case, the animals in the present study should not have been able to perform well in the task, as their neuronal activity did not reflect turns to the same percentage as was found in the studies by others (Wood et al. 2000; Lenck-Santini et al. 2001; Bower et al. 2002). It makes little sense that, in some studies, no such turning cells were observed at all, whereas in others up to 66% of all cells did show this type of activity, yet the performance of the animals is good in all of these studies. More importantly, the modified T-maze task that is used in these studies is most likely not an episodic memory task due to its change of design. In a standard T-maze, the animals will have to remember which arm had been visited in the previous run in order to be able to alternate arm visits in the next run. In the modified T-mazes used by Wood et al. (2000) and in the present study, the animals can return to the starting position themselves. This makes the maze a figure-of-eight-type of maze, in which the animal will run continuously. In such a maze, the animal will not have to remember which arm it had visited in the previous run the way it would have to in a T-maze. It is sufficient for the animal to learn a simple motor pattern in order to perform such a task. This algorithm is ‘when coming from the lower left side (see Fig. 1), turn left to enter the central arm and right at the top. After

turning around to the lower right side, turn right to enter the central arm and left at the top’. The rule is left–right, then right–left. Once this algorithm has been rehearsed extensively and ‘automated’, there is no true decision involved when performing the task, in contrast to an ordinary T-maze where the animal cannot use such an algorithm. This could explain why the task can be performed even without the hippocampus (Ainge and Wood 2003). Interestingly enough, the hippocampectomised rats in the Ainge and Wood (2003) study could perform the task when it was continuous, but were very poor at it when a delay was inserted at the starting arm by keeping the animal in a holding box for some time. Since the delay interrupts the learned motor pattern, the animals now need to remember during the delay the direction from which they had come before the delay. This requires episodic memory. Hence, if the modified T-maze task is not an episodic test at all, we do not know what information the turn-sensitive cells might encode. We do know that these cells appear in a motor task, especially when the animals are trained in an arm-blocked version of the task (as used in Wood et al. 2000 and Bower et al. 2002). This indicates that the cells might encode learned motor programs in repetitive tasks.

A different interpretation of the results, therefore, is that the cells that fire in a direction-biased fashion do not encode episodic memory but motor information in conjunction with information about the location in space (trajectory encoding, turn encoding, or running distance encoding). The observation that the extended firing field cells increase in number over the course of our study (see Fig. 4) suggests that a learning effect takes place. Such cells have been described in many studies, e.g. Gothard et al. (1996) have shown that cells can fire along the entire length of an arm, and that this firing field shortens if the arm is shortened and the animals have to run a shorter distance. Some of these cells are also direction-specific and will not fire on the return journey. In a different study, Frank et al. (2000) found that some neurons fire when the animal is turning in a W-shaped maze, and that those cells also fire when the animal turns in a U-shaped maze. The cells observed by Wood et al. (2000) are similar to the ones observed by Frank et al. (2000) and could well be defined as trajectory encoding cells. We postulate that there is an association between motor activity and orientation in space that serves to guide behaviour and synchronise motor activity with the actual location in space (Foster et al. 1989; McNaughton et al. 1996; see also the review by Gaffan 1998). In support of this postulation it is important to note that place cell activity has been observed in basal ganglia (Lavoie and Mizumori 1994; Ragozzino et al. 2001). Also, a synchronisation of EEG activity in the theta range recorded in the dorsal striatum and in the hippocampus was observed in animals that were performing tasks in a T-maze (Allers et al. 2002; DeCoteau et al. 2002). This indicates that there is functional integration of information processed in the basal ganglia and the hippocampus in order to execute goal-directed movements. Functional integration between the dorsal

striatum and the cortex has been described before (Wise et al. 1996). Also, it has been shown that motor-learning processes are slow and take many days whereas sensory hippocampal-dependent learning is rapid (Packard and Knowlton 2002), suggesting that the observed slow emergence of extended firing fields (see Fig. 4) represents a learning effect that involves motor memory formation. Furthermore, since rats are capable of performing the modified T-maze task without the hippocampus (Ainge and Wood 2003), we could assume that it is a motor-memory task and that learned behavioural patterns are read out from basal ganglia or other motor control brain areas. Neuronal network models that implement Hebbian synaptic plasticity dynamics actually predict that the firing activity of place cells would change after training in accordance with the task to be learned (Gerstner and Abbott 1997; see also McNaughton et al. 1996). Synchronous activity in basal ganglia and the hippocampus could join neuronal networks in different brain areas that encode the learned trajectories by Hebbian mechanisms. Hence, the cells that encode trajectories could be cells that have learned to associate egocentric movement information that is processed in the motor system with allocentric spatial information that is processed in the temporal lobe.

However, further experiments will be necessary to show such a postulated link between the motor system (e.g. basal ganglia) and the hippocampus, and to shed more light on what type of information the turn-selective and the extended firing field cells actually encode.

References

- Ainge JA, Wood E (2003) Excitotoxic lesions of the hippocampus impair performance on a continuous alternation T-maze task with short delays but not with no delay. Society for Neuroscience 24th Annual Meeting, New Orleans, Program no. 91.1. Society for Neuroscience, Washington DC. Available online via 2003 Abstract Viewer/Itinerary Planner: <http://sfn.scholarone.com/tin2003/>
- Allers K, Ruskin D, Bergstrom D, Freeman L, Ghazi L, Tierney P, Walters J (2002) Multisecond periodicities in basal ganglia firing rates correlate with theta bursts in transcortical and hippocampal EEG. *J Neurophysiol* 87:1118–1122
- Barnes CA, Suster MS, Shen J, McNaughton BL (1997) Multistability of cognitive maps in the hippocampus of old rats. *Nature* 388:272–275
- Bolhuis JJ, Reid IC (1992) Effects of intraventricular infusion of the *N*-methyl-D-aspartate (NMDA) receptor antagonist AP5 on spatial memory of rats in a radial arm maze. *Behav Brain Res* 47:151–157
- Bower M, Euston D, Roop R, Gebara N, McNaughton B (2002) How an ambiguous sequence is learned determines how the hippocampus encodes it. Society for Neuroscience Meeting, Orlando Neurosci 23rd Annual Meeting, Orlando, Program no. 678.13. Society for Neuroscience, Washington DC. Available online via 2002 Abstract Viewer/Itinerary Planner: <http://sfn.scholarone.com/tin2002/>
- Butelman ER (1990) The effect of NMDA antagonists in the radial arm maze task with an interposed delay. *Pharmacol Biochem Behav* 35:533–536
- DeCoteau W, Courtemanche R, Kubota Y, Graybiel A (2002) Anti-phase theta-range oscillations in striatum and hippocampus recorded in rats during T-maze task performance. Society for Neuroscience 23rd Annual Meeting, Orlando, Program no. 765.6. Society for Neuroscience, Washington DC. Available online via 2002 Abstract Viewer/Itinerary Planner: <http://sfn.scholarone.com/tin2002/>
- Eichenbaum H (2000) A cortical–hippocampal system for declarative memory. *Nat Rev* 1:41–50
- Fenton AA, Csizmadia G, Muller RU (2000) Conjoint control of hippocampal place cell firing by two visual stimuli. I. The effects of moving the stimuli on firing field positions. *J Gen Physiol* 116:191–209
- Floresco SB, Seamans JK, Phillips AG (1997) Selective roles for hippocampal, prefrontal cortical, and ventral striatal circuits in radial-arm maze tasks with or without a delay. *J Neurosci* 17:1880–1890
- Foster TC, Castro CA, McNaughton BL (1989) Spatial selectivity of rat hippocampal neurons: dependence on preparedness for movement. *Science* 244:1580–1582
- Frank LM, Brown EN, Wilson M (2000) Trajectory encoding in the hippocampus and entorhinal cortex. *Neuron* 27:169–178
- Gaffan D (1998) Idiopathic input into object-place configuration as the contribution to memory of the monkey and human hippocampus: a review. *Exp Brain Res* 123:201–209
- Gerstner W, Abbott L (1997) Learning navigational maps through potentiation and modulation of hippocampal place cells. *J Comput Neurosci* 4:79–94
- Gothard KM, Skaggs WE, McNaughton BL (1996) Dynamics of mismatch correction in the hippocampal ensemble code for space: interaction between path integration and environmental cues. *J Neurosci* 16:8027–8040
- Harris K, Henze D, Csicsvari J, Hirase H, Buzsáki G (2000) Accuracy of tetrode spike separation as determined by simultaneous intracellular and extracellular measurements. *J Neurophysiol* 84:401–414
- Hollup SA, Molden S, Donnett JG, Moser MB, Moser EI (2001) Accumulation of hippocampal place fields at the goal location in an annular watermaze task. *J Neurosci* 21:1635–1644
- Hölscher C, Schmidt WJ (1994) Quinolinic acid lesion of the rat entorhinal cortex pars medialis produces selective amnesia in allocentric working memory (WM), but not in egocentric WM. *Behav Brain Res* 63:187–194
- Hölscher C, Jacob W, Mallot H (2003) Reward modulates neuronal activity in the hippocampus of the rat. *Behav Brain Res* 142:181–191
- Jeffery KJ (1998) Learning of landmark stability and instability by hippocampal place cells. *Neuropharmacology* 37:677–687
- Jeffery K (2001) Plasticity of the hippocampal cellular representation of space. In: Hölscher C (ed) *Neuronal mechanisms of memory formation: concepts of long term potentiation and beyond*. Cambridge University Press, Cambridge, Chapter 4
- Lavoie A, Mizumori S (1994) Spatial, movement- and reward-sensitive discharge by medial ventral striatum neurons of rats. *Brain Res* 638:157–168
- Lenck-Santini, P, Save, E, Poucet, B (2001) Place-cell firing does not depend on the direction of turn in a Y-maze alternation task. *Eur J Neurosci*, 13:1055–1058
- McDonald RJ, White NM (1994) Parallel information processing in the water maze: evidence for independent memory systems involving dorsal striatum and hippocampus. *Behav Neural Biol* 61:260–270
- McNaughton B, Barnes C, Gerrard J, Gothard K, Jung M, Knierim J, Kudrimoti H, Qin Y, Skaggs W, Suster M, Weaver K (1996) Deciphering the hippocampal polyglot: the hippocampus as a path integration system. *J Exp Biol* 199:173–185
- Moser EI, Paulsen O (2001) New excitement in cognitive space: between place cells and spatial memory. *Curr Opin Neurobiol* 11:745–751
- Nadel L, Eichenbaum H (1999) Introduction to the special issue on place cells. *Hippocampus* 9:341–345

- O'Keefe J (1979) A review of the hippocampal place cells. *Prog Neurobiol*, 13:419–439
- O'Keefe J, Recce ML (1993) Phase relationship between hippocampal place units and the EEG theta rhythm. *Hippocampus* 3:317–330
- Packard MG, Knowlton BJ (2002) Learning and memory functions of the basal ganglia. *Annu Rev Neurosci* 25:563–593
- Ragozzino KE, Leutgeb S, Mizumori SJ (2001) Dorsal striatal head direction and hippocampal place representations during spatial navigation. *Exp Brain Res* 139:372–376
- Rasmussen M, Barnes CA, McNaughton BL (1989) A systematic experiment of cognitive mapping, working memory and temporal discontinuity theories of hippocampal function. *Psychobiology* 17:335–348
- Rawlins JNP (1985) Association across time: the hippocampus as a temporary memory store. *Behav Brain Sci* 8:479–496
- Redish AD, Battaglia FP, Chawla MK, Ekstrom AD, Gerrard JL, Lipa P, Rosenzweig ES, Worley PF, Guzowski JF, McNaughton BL, Barnes CA (2001) Independence of firing correlates of anatomically proximate hippocampal pyramidal cells. *J Neurosci* 21:RC134
- Shapiro LM, Caramanos Z (1990) NMDA antagonist MK-801 impairs acquisition but not performance of spatial working and reference memory. *Psychobiology* 2:231–243
- Shapiro M, Eichenbaum H (1999) Hippocampus as a memory map: synaptic plasticity and memory encoding by hippocampal neurons. *Hippocampus* 9:365–384
- Tulving E, Kapur S, Craik F, Moskovitch M, Houle S (1994) Hemispheric encoding/retrieval asymmetry in episodic memory: positron emission tomography findings. *Proc Natl Acad USA Sci* 91:2016–2020
- Vnek N, Rothblat LA (1996) The hippocampus and long-term object memory in the rat. *J Neurosci* 16:2780–2787
- Wise SP, Murray EA, Gerfen CR (1996) The frontal cortex-basal ganglia system in primates. *Crit Rev Neurobiol* 10:317–56
- Wood ER, Dudchenko PA, Robitsek RJ, Eichenbaum H (2000) Hippocampal neurons encode information about different types of memory episodes occurring in the same location. *Neuron* 27:623–33
- Zola-Morgan S, Squire LR, Amaral DG (1986) Human amnesia and the medial temporal region: enduring memory impairment following a bilateral lesion limited to CA1. *J Neurosci* 6:2950–2967