Novel spatial information is encoded in the hippocampus by plastic changes of synaptic properties. Novel space consists of several types of information that may evoke differential synaptic responses in individual hippocampal subregions. To examine this possibility, we recorded field potentials from the dentate gyrus (DG) and CA1 region in freely moving adult rats. Stimulation protocols that were marginally subthreshold for the induction of persistent long-term potentiation (LTP) or long-term depression (LTD) were implemented concurrently with exposure to novel spatial information. We found that in both hippocampal subregions, exploration of a novel empty hole board facilitated LTP. However, LTD facilitation was subregion specific and dependent on the nature of the cues. In the CA1 region, partially concealed cues had a facilitatory effect on LTD. LTD in the DG was facilitated by large directional cues. Thus, although LTP was facilitated uniformly in both areas by the same novel environment, LTD was facilitated in a region-specific manner, although LTP was facilitated uniformly in both areas by the same cues. Furthermore, LTD facilitation was found that in both hippocampal subregions, exploration of a novel empty hole board facilitated LTD. However, LTD facilitation was subregion specific and dependent on the nature of the cues. In the CA1 region, partially concealed cues had a facilitatory effect on LTD. LTD in the DG was facilitated by large directional cues. Thus, although LTP was facilitated uniformly in both areas by the same novel environment, LTD was facilitated in a region-specific manner, based on the nature of the cue. This implies that spatial changes within an environment elicit local changes of synaptic weights dependent on the type of information and, hence, generate a complete cognitive map as a consequence of cooperation of synaptic plasticity in all participating subregions.

Keywords: CA1, dentate gyrus, long-term depression, long-term potentiation, novelty acquisition, spatial learning

Introduction

In contrast to the vivid discussion of the contribution of hippocampus as a whole to memory function, the individual contributions of the hippocampal subregions are much less explored. The hippocampus is generally considered to be an intermediate encoding device, participating in consolidation of episodic memories (Squire and Zola 1996). There is evidence that not only spatial memories but also associative memories (i.e., memories with a temporal aspect) may be processed by the hippocampus (Wood et al. 1999; Fortin et al. 2002). Anatomical investigations have shown, furthermore, that in addition to the main trisynaptic hippocampal network, direct cortical connections to the CA1 region occur, as well as autoassociative connections within CA3, which may play a decisive role in the computational integration of spatial information (Amaral and Witter 1989; Remondes and Schuman 2002; Rolls and Kesner 2006). Although subregional analyses regarding distinct memory processes have largely not been implemented, there are some indications of region specificity for certain types of information encoding. The study of place fields has suggested that different hippocampal subregions differ in their reaction to changes of environment: conducting either pattern separation or completion (Guzowski et al. 2004). Furthermore, behavioral analysis has demonstrated that spatial versus temporal associations may be assigned to subregional functions (Gilbert et al. 2001; for review, see Kesner et al. 2004) The hippocampus is also intrinsically involved in novelty detection, although some controversies exist regarding the subregional locus for the mismatch detection (Lisman and Otmakhova 2001; Vinogradova 2001). Novelty-elicited changes have been observed in both CA1 and CA3 regions (Vianna et al. 2000; Lee et al. 2004), whereas in the dentate gyrus (DG), plasticity is affected by “novel” empty space (Staub, Korz, and Frey 2003). Thus, whether novelty detection actually occurs in the CA3 or CA1 region (or both) is an issue that further studies need to clarify. The nature of the novel “item” could be a factor that contributes to processing in different subregions.

One way of obtaining functional differences in subregional processing could comprise opposed polarity of synaptic plasticity. Synaptic plasticity, in the form of long-term potentiation (LTP) and long-term depression (LTD), is thought to be a continuum that includes not only these forms of plasticity but also many others such as depotentiation and de-depression as well as forms of short-term plasticity. The direction of change in magnitude of synaptic strength are determined by the history of the synapse as much as the present activity (Bienenstock et al. 1982; Abraham and Bear 1996; Bear 1996). There is growing evidence that not only LTP but also LTD participate in encoding of spatial information (Manahan-Vaughan and Braunewell 1999; Nakao et al. 2002; Kemp and Manahan-Vaughan 2004, 2005). All studies characterizing LTD in learning, to date, have focused on the CA1 region. It is not known if learning-facilitated LTD is exclusive to this subregion or indeed if synaptic plasticity in other hippocampal subregions is influenced by learning events. We examined whether synaptic plasticity in the DG undergoes learning-induced facilitation. Intriguingly, we found distinct differences between the CA1 region and DG in the correlation of novelty acquisition with long-term plasticity. Whereas LTD was facilitated by exploration of empty space in both structures, and LTD in the CA1 region was facilitated by small novel features, exposure to large novel orientational cues facilitated LTD in the DG and impaired synaptic depression in the CA1 region. This suggests a precise division of labor with regard to the processing of distinct aspects of spatial information, whereas space per se is computed uniformly throughout the hippocampus.

Materials and Methods

Surgery

Seven- to eight-week-old male Wistar rats were prepared as described previously (Manahan-Vaughan and Reymann 1997). Briefly, under sodium pentobarbitone (Synopharm, Germany) anesthesia (“Nembutal”,...
Measurement of Evoked Potentials

The field excitatory postsynaptic potential (fEPSP) slope was employed as a measure of excitatory synaptic transmission in the CA1 region. To obtain these measurements, an evoked response was generated in the stratum radiatum by stimulating at low frequency (0.025 Hz) with single biphasic square wave pulses of 0.2 ms duration per half wave, generated by a constant current isolation unit. For each time point measured during the experiments, 5 records of evoked responses were averaged. The first 6 time points recorded at 5-min intervals were used as baseline, and all points are shown in relation to the average of these 6 points. fEPSP was measured as the maximal slope through the 5 steepest points obtained on the first negative deflection of the potential. By means of input-output curve determination (evaluation of 9 different stimulation intensities in 100 µA steps) the maximal fEPSP was found, and during experiments, all potentials employed as baseline criteria were evoked at a stimulus intensity that produced 40% of this maximum.

To measure synaptic activity in the DG, analysis of both the population spike (PS) amplitude and fEPSP slope was conducted. The maximal PS amplitude was determined by input-output curve analysis, as described above. PS was measured as the maximal slope through the 5 steepest points obtained on the first negative deflection of the PS. fEPSP was measured as the maximal slope through the 5 steepest points obtained on the first positive deflection of the potential. The stimulus intensity used during experiments was set to evoke a potential that was 40% of the maximum obtained in the input-output analysis. Because the changes in fEPSP followed the changes in PS amplitude, data for fEPSP slope are shown in Figure 2 only. Cortical electroencephalography was continuously monitored throughout the experiments. Here, no disturbances were identified as being provoked by the experimental protocols.

All plasticity-inducing stimulation protocols used in this study were selected on the basis of being subthreshold. Thus, we used protocols that we previously have found to induce short-lasting (< 4 h) changes in synaptic efficacy. In area CA1, 600 pulses at 1 Hz reliably induce short-term depression (STD; Kemp and Manahan-Vaughan 2004, 2005). This protocol was thus used to induce STD in the DG. Short-term potentiation (STP) was successfully induced in DG by application of 3 bursts of 15 pulses at 200 Hz with an interburst interval of 10 s (Manahan-Vaughan et al. 1996).

Novel Spatial Exploration

Each animal was assigned one recording chamber where all experiments were conducted. To enable proper acclimatization, the home cages were transferred to the experiment room on the day before commencement of experimentation. The recording chamber measured 40 × 40 × 40 cm. It was constructed of opaque gray Perspex except for a removable translucent Perspex sliding door at the front of the recording chamber. The boxes were open at the top. The implanted electrodes were connected via a flexible cable and swivel connector to the stimulation and recording equipment, and thus the animal could move around freely in the recording chamber. Before any novel stimuli were applied, all animals underwent a baseline experiment without any plasticity-inducing stimuli and an experiment where synaptic plasticity was induced by electrical stimulation in the absence of behavioral manipulation. This served 2 purposes: first, habituation to the familiar recording chamber was enabled; second, the effectiveness of the electrical stimulation protocols could be assessed in each individual animal. Hole board, landmark, and cue card experiments were done in a randomized order. Each animal was never subjected to more than 2 different cue conditions. To ensure that no odor cues were available, boxes, cues, hole boards, etc. were cleaned between animals.

Novel spatial stimuli consisted of objects that were essential for handling alone under our experimental conditions is not sufficient to generate changes in synaptic strength. This is probably because the animals are quite familiar with the recording chamber and the experimenter when the experiments are commenced. However, it has been shown by others that handling of naive animals (rats that are not used to handling) reverses hippocampal LTP (Korz and Frey 2003). We have previously reported (Manahan-Vaughan and Braunewell 1999) that exposure to the hole board does not cause elevations of serum corticosterone that would be sufficient to influence synaptic plasticity, as was reported under conditions of marked stress by others (Xu et al. 1997).

A hole board (39.8 × 39.8 cm, washable blue plastic) was inserted into the floor of the recording chamber by moving the sliding door upward so that the hole board could be gently slotted into the recording chamber. This was done just before application of low-frequency stimulation (LFS) or high-frequency tetanization (HFT) and after baseline recordings. The hole board was removed immediately after LFS/HFT (or after 10 min in experiments where weak HFT was applied). Each corner of the hole board contained a hole, 5.5 cm in diameter and 5 cm deep. In cases where subthreshold low-frequency stimulation (LFS) or subthreshold high-frequency tetanization (HFT) was applied, an object was placed in each hole before the hole board was introduced to the animal. The objects (small toy figures) differed from each other in appearance, color, texture, and size and easily fitted within the holes. They could not be seen without examining the interior of the hole. Each animal was always presented with the same 4 objects. In one series of experiments, the objects were hidden under bedding to examine how relevant the visibility of the object in the environment was to LTD facilitation. Fresh bedding was used that was identical to that used in the home cage and therefore did not serve as a novel stimulus in its own right.

In some experiments, no objects were placed in the hole board (empty hole board). In these cases, a subthreshold high-frequency tetanization (subHFT; 15 pulses at 200 Hz repeated 3 times with 10-s interval) was given immediately after insertion of the hole board. To equalize the exploration time between experiments, the novel hole board was left in the recording chamber for 10 min before removal. Each animal was subjected to only one of the 3 different hole board experiments.

The large environmental cues were of varying height (7–16 cm) and with a diameter of between 5 and 7 cm. They were made out of different materials, that is, plastic, metal, and glass, and were so heavy that the rats could not knock them over or displace them. When the animals were presented with 1 single object (large environmental cue), it was placed in a clearly visible location in the center of the recording chamber. In the case of multiple large environmental cues, 3 were used in order to polarize the environment and these were placed in corners of the recording chamber, with a distance of 5 cm to each of the nearest walls. Each animal was always presented with the same 3 environmental cues, and in the last experiment where the cues were
rearranged, it was ensured that the positions matched the previous locations.

The cue card was a black-and-white striped laminated paper (size: A5, line width: 2 cm, distance between the lines: 2.5 cm). During LFS, it was placed on the back wall of the recording chamber opposite to the Perspex wall (in the middle, vertically, and 11 cm below the upper rim). This elicited an initial reexploration of the area near the card followed by exploration of the rest of the recording chamber.

Data Analysis
For each time point, 5 consecutive evoked responses at 40-s intervals were averaged and the results were expressed as the mean percentage ± standard error of the mean (SEM) of the average of the first 6 recordings. Recordings were made every 5 min until 30 min after LFS/HFT and then every 15 min until 4 h had elapsed. The following day an additional 1 h of recordings was obtained. For analysis of differences between groups (between factor), a 2-way analysis of variance (ANOVA) was applied. Statistical differences between individual time points were assessed using the Student’s t-test. The level of significance was set at $P < 0.05$.

Results

Exploration of a Novel Empty Hole board Facilitates LTP in DG
Novel spatial exploration in the absence of salient objects promotes the induction of LTP in the CA1 region (Kemp and Manahan-Vaughan 2004). To investigate if the same phenomenon is evident in the DG, we paired empty hole board exploration (Fig. 1a) with a mild subHFT. SubHFT, given alone, induced a decremental STP (Fig. 1b, $n = 10$). When the hole board was inserted into the recording chamber for 10 min and subHFT was given immediately after insertion ($n = 10$), exploration prolonged the potentiation. LTP was still evident on the following day.

Exploration of a Novel Object-Containing Hole board Does Not Facilitate LTD in the DG
Our foremost aim with this study was to investigate learning-induced facilitation of plasticity in the DG and compare it with effects that we have observed in the CA1 region (Manahan-Vaughan and Braunewell 1999; Kemp and Manahan-Vaughan 2004, 2005). Field potentials were obtained from the DG granule cell layer by stimulation of the medial perforant path. As observed in the CA1 region, application of 600 pulses at 1 Hz resulted in a STD with an initial PS amplitude of 50.2 ± 7.3% (Fig. 2a) and fEPSP slope value of 80.5 ± 4.2% (Fig. 2c, $n = 8$). When the rats were exposed to a novel object-containing hole board during LFS (Fig. 2a), no significant changes in the profile of STD occurred. ANOVA of PS amplitude revealed $F_{1,24} = 3.75$, $P = 0.0537$ and $F_{1,24} = 0.01$, $P = 0.9140$ for fEPSP slope.

The Exploration of a Hole board with Partially Concealed Objects Induces LTD in the CA1 Region
In part of this study, we wanted to differentiate between objects that are large and highly visible (and thus can serve as immediate orientational cues in an environment) and those that are less immediately evident but serve as environmental features. Thus, to prevent animals from immediately seeing the small objects within the hole board holes, we covered the objects with bedding so that they first would have to be found. In that way, the animals cannot use the objects as visible orientational cues but rather must encode the position of the concealed objects using other proximal landmarks. Typical behavior comprised exploration of the novel environment with rearing and dipping and rapid commencement of exploration of the holes. Within the allocated exploring time, all the rats explored all holes and uncovered all the objects.

Under these conditions, we did not observe any LTD facilitation in the DG (Fig. 3c). Thus, no differentiation between the hidden and the not hidden objects was observed in terms of altered synaptic plasticity. ANOVA revealed $F_{1,24} = 2.19$ ($n = 11$ in both groups).

In the CA1 region, STD was facilitated into LTD under these conditions (Fig. 3a). At 30 min after stimulation, the depression was significantly larger after hole board exploration ($t$-test: $P = 0.0227$), where a depression to 64.6 ± 3.7% ($n = 6$) of baseline values was evident in animals that were exposed to the hole board. In animals which received subLFS only, the depression had returned to 81.56 ± 4.50% 30 min later ($n = 10$). The following day a synaptic depression to 67.4 ± 6.1% of basal synaptic transmission remained after hole board exploration. When the animals only received subLFS, the average fEPSP was 106.6 ± 6.5% of the basal value. The overall difference, as assessed by ANOVA, revealed a significantly higher depression in the exploration group ($F_{1,24} = 245.3$, $P < 0.0001$). When the animals were reexposed to the familiar hole board with the hidden familiar objects, no facilitation of synaptic depression
suggested that LTD may be involved in the encoding of spatial details within an environment. The question arises as to whether LTD is also involved in the processing of environmental cues in the context of large orientational features. Thus, animals were introduced to a single large novel cue, in a familiar environment, during LFS (Fig. 4a). The cue was placed in the center of the box and was removed after 10 min as soon as the subLFS was complete. No facilitation of synaptic depression occurred in the CA1 region under these conditions (Fig. 4b). The initial level of depression in the CA1 region was 78.9 ± 3.9% of pre-LFS values, which was not significantly different from the corresponding recording done after LFS was applied alone (69.4 ± 5.4%, n = 14 in both groups). In the period from 15 to 30 min post-LFS, the synaptic depression was less after cue exploration than that seen following subLFS given alone, suggesting that LTD was slightly attenuated by this form of exploration (ANOVA: F_{1,24} = 11.44, P = 0.0008). Thus, in contrast to exploration of novel partially concealed objects in the hole board, cue exploration had a mild attenuating effect on synaptic depression in the CA1 region.

The effect of exploration of one novel cue on the field potentials recorded from DG was also investigated. The cue was identical to the one used in the experiment where recordings were obtained from the CA1 region. Intriguingly, exploration of the novel large cue led to a facilitation of LTD in this hippocampal subregion (Fig. 4c; ANOVA: F_{1,24} = 160.12, P < 0.0001). LFS alone induced an initial depression of PS amplitude to 64.9 ± 12.4% (n = 7) 5 min later compared with 42.2 ± 5.3% (n = 7) where the cue had been explored. The prolongation of the synaptic depression became prominent 105 min after subLFS was applied (P = 0.0011; t-test). Twenty-four hours after exploration, LTD was still present (59.3 ± 10.5). Thus, the introduction of a single novel environmental cue during subLFS results in robust LTD in DG.

### Exploration of a Constellation of Multiple Large Novel Environmental Cues Is a Strong Reinforcer of LTD in DG and Attenuates Synaptic Depression in CA1

We next increased the spatial load by putting 3 different cues into the chamber instead of one (Fig. 5f). Although the increased number of objects did not facilitate LTD in CA1, we again observed a slight impairment of STD (Fig. 5a,b, n = 9 in both groups). The cues were arranged in the corners of the recording chamber with equal distances between the objects and a fixed distance to the walls. Consistent with the previous experiment (Fig. 4b), the exploration of 3 large cues attenuated the duration of STD (ANOVA: F_{1,24} = 4.94, P = 0.007). Statistical analysis of the recording made at individual time points showed a significantly weaker depression in the period of 60–90 min after cue exploration. The profile of STD after exploration of 3 large cues was not significantly different to STD induced after exploration of one novel cue (ANOVA: F_{1,24} = 1.20, P = 0.2729).

The next question was whether increasing the spatial load by increasing the number of large cues, and thereby also enhancing the spatial component of novelty exploration, influences the facilitatory effect on LTD by cue exploration in the DG (Fig. 5c). The difference between application of subLFS alone and subLFS with the introduction of 3 cues was highly significant (ANOVA: F_{1,24} = 707.3 and P < 0.0001, n = 19 in both groups). As early as 5 min after LFS, a higher degree of depression was evident. This strong LTD was also present the following day. In conclusion, exploration of 3 large novel
environmental cues during LFS not only prolonged the synaptic depression but also enhanced the initial phase of STD.

The experiment was repeated 8 days later (Fig. 5f). The rationale behind this experiment was the same as in a previous study where reexposure to the object-containing hole board was conducted during recordings from the CA1 region (Kemp and Manahan-Vaughan 2004). The objective was thus to assess if novelty acquisition, that is, the formation of a memory of the spatial cues, is the factor driving the induction of LTD.

Exposure to the, now familiar, cues did not facilitate LTD (Fig. 5d, n = 17) in contrast to conditions where the cues are novel (ANOVA: F1,24 = 0.06). Given the correlation between novel object location and the induction of LTD in the CA1 region, we investigated if the location of the environmental cues was the determining factor in facilitating LTD in DG. Thus, we randomly changed the constellation of the individual cues to differ from the familiar constellation. The location in the recording chamber and the reciprocal distance between the objects were maintained, however. Under these conditions, the exploration of the familiar environmental cues in a novel spatial location in conjunction with LFS led to an enhanced depression (ANOVA: F1,24 = 492.53, P < 0.0001). Not only was the novelty of the spatial change of the cues sufficient to facilitate induction of LTD anew but also the profile of LTD did not differ from the first exposure to the cues (ANOVA: F1,24 = 2.38, P = 0.1231). Thus, acquisition of novel cue location is associated with induction of LTD.

**Introduction of a Novel Cue Card Facilitates LTD in DG but not CA1**

By placing a cue card on the wall, we wanted to obtain a novel “nonobject” spatial polarization of the familiar environment. This was to investigate the difference between the small objects that were partially hidden in the holes of the hole board and the larger objects which should serve as highly visible landmark cues. A single striped cue card put was then placed on the wall during subLFS. We discovered that this type of spatial manipulation leads to facilitation of LTD in the DG but not in the CA1 region (Fig. 6).

In the CA1 region, there was significantly less depression after concurrent exploration of the cue card (Fig. 6a,b, n = 7) than with the electrical protocol given alone (ANOVA: F1,24 = 27.24, P < 0.0001). A comparison with the baseline experiment revealed that STD was completely blocked by insertion of the cue card during subLFS (ANOVA: F1,24 = 0.8098, P = 0.3689; cue card exploration compared with baseline experiment, n = 7 in both groups). This is in contrast to the DG, which responded...
with robust facilitation of LTD, which was highly significant from \( t = 20 \) min onward (Fig. 6b,c; \( t \)-test: \( P = 0.0016 \), \( n = 9 \) and \( n = 7 \)). Twenty-four hours after subLFS in the presence of the cue card, LTD of \( 42.6 \pm 9.4\% \) of baseline values was evident. When subLFS was given in the absence of exploration, the recording was \( 83.17 \pm 7.15\% \) of baseline values \( 24 \) h later (\( t \)-test: \( P = 0.0066 \); ANOVA: \( F_{1,24} = 240.1 \)).

Similar to all other plasticity-augmenting effects described above, the facilitatory effect of the cue card was correlated to the novelty of the cue card position. The second time the cue card was placed in the box, no induction of LTD was apparent (Fig. 6d; \( n = 7 \)). An ANOVA confirmed no change in the profile of STD by reexposure to the cue card (\( F_{1,24} = 1.085 \), \( P = 0.298 \)). This was due to the familiarity of the cue card in this location, as verified by placing the cue card on another side of the recording chamber. The same cue card presented in a new location facilitated STD into LTD in the DG (ANOVA: \( F_{1,24} = 154.5 \), \( P < 0.0001 \) for reexposure to cue card in familiar position compared with cue card in a new position). The prolongation of the synaptic depression was evident as a significantly higher depression as early as \( 30 \) min after stimulation (\( t \)-test: \( P = 0.0013 \), \( n = 7 \) and \( n = 6 \)). In summary, the orientational cue in the form of a cue card triggered LTD expression in the DG, in the same manner as the large environmental cues.

**Discussion**

In this study, we found a distinctive and highly differentiated correlation between novel stimuli and facilitation of synaptic plasticity in the 2 areas of hippocampus studied: the exploration of orientational visual cues is associated with induction of LTD in DG, whereas no such facilitation is observed in the CA1 region. On the other hand, exploration of small features located "within" a spatial reference frame facilitates LTD in the CA1 region but not in the DG. Interestingly, facilitation of LTP was found in both areas following exploration of an empty and perceptually uniform hole board.

**No Facilitation of LTD in the DG by Spatial Constellations of Small Objects**

In this study, no change in synaptic strength occurred in the DG as a consequence of exploration of a novel object-containing hole board. This finding is in contrast to the CA1 region where exposure to a novel object-containing hole board results in LTD. Here, a coincidence of events appears to be necessary: no afferent stimulation during hole board exploration fails to elicit CA1 LTD (Manahan-Vaughan and Braunewell 1999). But LFS is also not essential: intermittent test pulse during novel object exploration enables a depression of basal LTD.
synaptic transmission lasting several hours (Manahan-Vaughan and Braunewell 1999). Not only does this suggest that exploration of novel spatial constellations induces changes in synaptic efficacy but also it suggests that afferent stimulation during spatial object exploration enables LTD rather than depotentiation. Furthermore, these findings imply that a coincidence of events (afferent activity, with novel spatial exploration) is required in order for the LTD to occur.

The finding that novel exposure to an object-containing hole board does not affect synaptic strength in the DG could suggest that the DG does not participate in the encoding of spatial detail, apart from the encoding of an orientational reference frame (Gothard et al. 2001). In this experiment, we stimulated the medial perforant pathway, which is the locus of grid cells that encode the spatial topographic map of space (Hafting et al. 2005). Thus, information in this pathway contains a highly spatial component that presumably conveys topographical information to the DG and directly to the CA1 region (Witter and Moser 2006). Taken together, these data support that hippocampal subregions may encode different aspects of spatial information.

**LTD Occurs in the DG in Response to Novel Large Environmental Cues**

Exposure of our animals to novel large environmental cues enabled the induction of robust and persistent LTD in the DG. This is an intriguing finding as it suggests that both the CA1

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**Figure 5.** A spatial constellation of environmental cues facilitates LTD in the DG. (a) In the CA1 region, exposure to 3 large novel environmental cues in fixed locations during application of subLFS (1 Hz, 600 pulses) elicited a significantly faster recovery to baseline values as compared with application of subLFS alone. Line breaks indicate change in timescale. (b) CA1 analog traces showing a characteristic evoked field potential recorded in CA1. Top row is from an experiment where only LFS was applied, and bottom row is from the same animal in the novelty exploration experiment. The analogs were recorded at (i) 5 min pre-LFS, (ii) 5-min post-LFS, and (iii) 24-h post-LFS. Horizontal scale bar: 2 mV, vertical scale bar: 5 ms. (c) Concurrent exploration of 3 novel large cues in a fixed constellation facilitated STD into LTD in the DG. (d) No facilitatory effect was elicited on LTD in the DG by environmental cue exploration when the cues were familiar (reexposure). However, rearrangement of familiar cues in a new configuration facilitates LTD. (e) Top row: DG analog traces from the reexposure experiment as compared with traces in the new configuration experiment (bottom row). (i) 5 min before subLFS, (ii) 5 min after subLFS, and (iii) 24 h after subLFS. Horizontal scale bars: 4 mV, vertical scale bars: 5 ms. (f) Schematic drawing of the experimental protocol.
region and the DG express LTD in response to exposure to novel objects. However, a subregional differentiation occurs, whereupon the CA1 responds preferentially to exposure to novel small (and/or spatially concealed) objects, whereas the DG responds to large orientational/environmental cues. One interpretation is that these hippocampal subregions are object size specific. In fact, it has been shown that the hippocampus does in fact discriminate object size (Cassaday and Rawlins 1995, 1997). But an additional interpretation is that the specificity is for the function. Evidence already exists for a division of labor with regard to spatial processing within the hippocampus. Orthogonalization, also referred to as pattern separation, is believed to occur in the DG (Kesner et al. 2004). The CA3 region engages in pattern completion when small changes occur in a familiar environment but switches to pattern separation when the differences between 2 environments become more substantial (Rolls and Kesner 2006). On the other hand, in the CA1 region, a linear relationship exists between the changes in input and the changes in output (Guzowski et al. 2004).

**Synaptic Changes in CA1 after Environmental Cue Changes**

Although we found that LTD occurs in the CA1 region following exposure to a novel object-containing hole board, in accordance with previous reports (Manahan-Vaughan and Braunewell 1999; Kemp and Manahan-Vaughan 2004, 2005), LTD did not occur when the animals were exposed to large environmental cues. Rather, an impairment of synaptic depression was seen that was most pronounced when cue cards were used. It has been reported that exploration of a novel environment containing visible objects facilitates LTP in CA1 (Li et al. 2003). Although the novel environment in itself is a facilitator of LTP, environmental cues as visible objects may also enhance synaptic weights in the CA1 region, which could lead to the impaired synaptic depression elicited by low-frequency stimulation that we observed in our study under these conditions.

The DG is notable for its strong $\gamma$-aminobutyric acid (GABA)ergic influence. Mossy fibers from DG granule cells project connect not only to CA3 pyramidal cells but also to interneurons of the CA3 region (Acsady et al. 1998). An inverse correlation between granule cell activity and excitability of CA3 pyramidal neurons has been demonstrated (Bragin et al. 1995). Reduced mossy fiber synaptic transmission may thus lead to disinhibition of CA3 pyramidal cells, thereby enhancing excitability that is relayed to the CA1 region. Thus, LTD occurring in the DG may alter synaptic plasticity thresholds in the CA1 region such that LTD induction is impeded. This possibility is corroborated by findings that brief stimulation of the basolateral amygdala, shortly before induction of LTP, in either the CA1 region or the DG, impairs the expression of LTP in the CA1 region but enhances DG LTP (Vouimba and Richter-Levin 2005). Thus, modulatory inputs...
Coherent Facilitation of LTP in DG and CA1

Previously, it was reported that exploration of a novel environment (empty space) facilitates LTP in the DG when the empty environment is introduced within 30 min before tetanus (Straube, Korz, Balschun, and Frey 2003). This is in agreement with our observations with regard to the DG in this study and the CA1 region in a former study (Kemp and Manahan-Vaughan 2004). Others have additionally found that rats that are placed into a novel chamber that contains large visible objects undergo a facilitated induction and longevity of LTP in the DG (Davis et al. 2004). The apparent discrepancy with our data can be explained by the fact that 2 novel situations were implemented in this study: the simultaneous exposure to novel space and novel large visible objects (environmental cues). The encoding of novel space may have a stronger impetus in DG than the encoding of cues. Another possibility, which has yet to be investigated, is the possibility that the encoding of the cues by a LTD mechanism only happens when opposing changes occur in a mapped environment. This implies that LTD serves to update and fine-tune the representation of known space.

Implications

The dissociation of LTP and LTD in terms of their response to spatial information is intriguing. It suggests that LTP is facilitated as a consequence of the exploration of new empty space, whereas LTD is facilitated in the acquisition of spatial novelty related to objects, regardless of whether this concerns a constellation of new objects or old objects in a new location. Here, the object in the form of a directional cue (large object) or a positional cue (small object) serves to direct which subregion will be facilitated. The finding that LTP typically occurs in all studied hippocampal subregions, following the first exploration of novel simple space, suggests on the one hand that LTP may create the template upon which the details of space are written by LTD. On the other hand, LTP may enable contrast enhancement for LTD. It is also possible and not mutually exclusive that LTP is intrinsically involved in encoding episodes of changing space.

Although subregional analyses regarding distinct memory processes are not so widely studied, some indications of region specificity for certain types of information encoding exist. The study of place field formation has revealed that the different hippocampal subregions do not respond in the same manner to changes in the environment (Guzowski et al. 2004). Another hypothesis that has been put forward is that the encoding of cues and landmarks is “connected” to the place fields by an LTP-like process (Barnes 2003). However, the place fields themselves may change after introducing or rearranging the constellation of cues (Lenck-Santini et al. 2005). Repositioning of the fields may also be mediated via synaptic plasticity (Dragoi et al. 2003). In fact, both the creation and the termination of place fields have been shown to depend on the activation of N-methyl-D-aspartic acid receptors (Shapiro and Eichenbaum 1999). This provides a link between place field size, appearance and disappearance of place fields, and synaptic plasticity. This would suggest that both LTP and LTD subserve a means whereby features are integrated into the cognitive map.

In our study, we distinguished between spatial features (or detail) and environmental cues. Spatial features are items, in this case objects hidden in a hole board, which although are bound to a specific location and are encoded by using landmarks, cannot themselves be used for navigation in an environment. This is in contrast to environmental cues, in this case represented by the large objects and the cue card, which strongly polarize the environment and serve as landmarks that may be used to guide spatial navigation. This reflects the “parallel map” theory (Jacobs 2003; Jacobs and Schenk 2003), which postulates that a cognitive map is formed from 2 different types of spatial maps that are generated within the hippocampus. The bearing map is formed in the DG. It is based on self-motion and directional cues, such as the large environmental cues used in our study, and incorporates relatively primitive orientational information such as light and sound gradients. A more sophisticated map is generated in the CA1 region. This map, known as the sketch map, is derived from the processing of spatial features. The sketch map concept dictates that every individual spatial feature, and the relationship between them, must be learned. It is the integration of the bearing with the sketch map that leads to a complete cognitive spatial map. It is intriguing that LTD was facilitated in both subregions by precisely that type of spatial information that is postulated to be processed there (Jacobs 2003).

In the first phase of processing new spatial information, orientation in space would be expected to take precedence over the features of the same space. In keeping with this hypothesis, we found that LTD was facilitated in the DG by exploration of highly visible environmental cues, whereas LTD in the CA1 region was facilitated by small spatial features. This suggests a division of labor within the hippocampus with regard to the encoding of novel features (CA1) and novel orientation (DG).

Concluding Comments

With this study, we have revealed a distinct subregional delineation with regard to the processing of spatial information via hippocampal LTD. Whereas the CA1 region appears to process features of space, the DG processes orientation in space. Both phenomena are strongly associated with the expression of LTD in these hippocampal subregions. Taken together with our findings that persistent expression of LTP occurs in the DG and CA1 regions following exposure to novel empty space, one could speculate that LTP is generated as an instantaneous response to exposure to empty space. Superimposed on this phenomenon comes the processing of novel spatial orientation through LTD in the DG and the processing of novel spatial features through LTD in the CA1 region. The integration of these individual aspects of space results in the basis for a complete spatial map of a novel environment. This implies that feature-rich spatial memory is acquired by bidirectional synaptic plasticity and that in the subregions different types of functional spatial information trigger LTD.
Notes
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