Neuron, Vol. 25, 707–715, March, 2000, Copyright ©2000 by Cell Press

# Experience-Dependent Asymmetric Shape of Hippocampal Receptive Fields

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## Summary

**We propose a novel parameter, namely, the skewness, or asymmetry, of the shape of a receptive field to characterize two properties of hippocampal place fields. First, a majority of hippocampal receptive fields on linear tracks are negatively skewed, such that during a single pass the firing rate is low as the rat enters the field but high as it exits. Second, while the place fields are symmetric at the beginning of a session, they become highly asymmetric with experience. Further experiments suggest that these results are likely to arise due to synaptic plasticity during behavior. Using a purely feed forward neural network model, we show that following repeated directional activation, NMDA-dependent long-term potentiation/long-term depotentiation (LTP/LTD) could result in an experience-dependent asymmetrization of receptive fields.**

## Introduction

When a rat moves through an environment, neurons in the hippocampus fire in a spatially and directionally selective fashion (O'Keefe and Dostrovsky, 1971) and provide an accurate estimate (Wilson and McNaughton, 1993) of the location of the rat. Changes in these fields as a result of experience in novel (Wilson and McNaughton, 1993) and familiar (Mehta et al., 1997) environments suggest that mechanisms of plasticity may be involved. While there have been studies of experience-dependent changes in the size and specificity of cortical maps (Wang et al., 1995) and hippocampal receptive fields (Mehta et al., 1997) and of the effect of change in the geometry of environment on place field dimensions (O'Keefe and Burgess, 1996), little has been done to investigate the shape of a receptive field and its dependence on experience. In this work, we show that the hippocampal receptive fields have an asymmetric shape and that this asymmetry is experience dependent. These results suggest that the amount of short-term familiarity with a sequence of events may be encoded in the skewness of the receptive fields. These results are compatible with and extend previous experimental (Mehta et al., 1997) and theoretical (Levy, 1989; Blum and Abbott, 1996; Tsodyks et al., 1996) works. Further, while these previous studies provided a novel connection between NMDA-dependent long-term potentiation (LTP) and changes in the average receptive field properties, such as size and specificity, the present work explores the relationship between LTP and the structure of a receptive field, which can be detected within a single trial. These results may provide insights into the role of plasticity in the structure of cortical receptive fields.

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†This author's contribution consisted of providing a significant part of the data.

## Results

We examined the activity of 173 place fields (Figure 1a) recorded from 142 putative pyramidal cells in the area CA1 in three rats in seven sessions while the animals performed a simple alternation task on a linear maze, such that they had to run back and forth between two goal locations (Figure 1a) without turning back midway. These place fields had an average width of 67 $\pm$ 30 cm and a mean in field firing rate of 14.3 $\pm$ 6.3 Hz.

Further examination of these place fields reveals that they are asymmetric (Figure 1b) with a negative skewness (see Experimental Procedures), such that the firing rate is low as the rat enters the place field but high at the trailing edge of the field. Of 173 place fields, a majority (73%; Figure 2a) had negative skewness (mean skewness = $-0.36 \pm 0.12$; see Experimental Procedures [Spiegel, 1994]). The population-averaged skewness was negative even when the analysis was restricted to very high (>40% of the peak) firing rate regions, demonstrating the robustness of the asymmetry.

Previous results (Mehta et al., 1997) have shown systematic changes in place field size and location with experience, which could interfere with the calculation of skewness of a trial-averaged place field, as is usually defined. Hence, place field firing rate distribution and its skewness were computed separately for each lap for each cell. The mean value of lap-specific skewness was negative for a majority (73%) of place fields (Figure 2b), and a large fraction (44%, t test, $p < 0.05$) of cells were significantly negatively skewed.

All of the results were quantified using an additional measure that is relatively insensitive to the instantaneous location or speed of the rat, viz., the firing rate asymmetry index (FRAI) (see Experimental Procedures). Figure 2c shows that a majority (78%) of place fields had a negative FRAI (population mean = $-0.15 \pm 0.016$), i.e., during a single pass, the mean firing rate for the second half of spikes within a place field was 35% $\pm$ 3% higher than that for the first 50% of spikes. These asymmetric place fields were distributed over the entire extent of both the rectangular and linear tracks (Figure 1); hence, the asymmetric shape is not a result of the track shape. Indeed, the distribution of occupancies in the place field had no significant skewness, and the behavioral asymmetry index (BAI) (similar to FRAI) was not significantly different from zero (see Experimental Procedures and Figure 2 legend for further details). This shows that the asymmetric place field shape cannot be

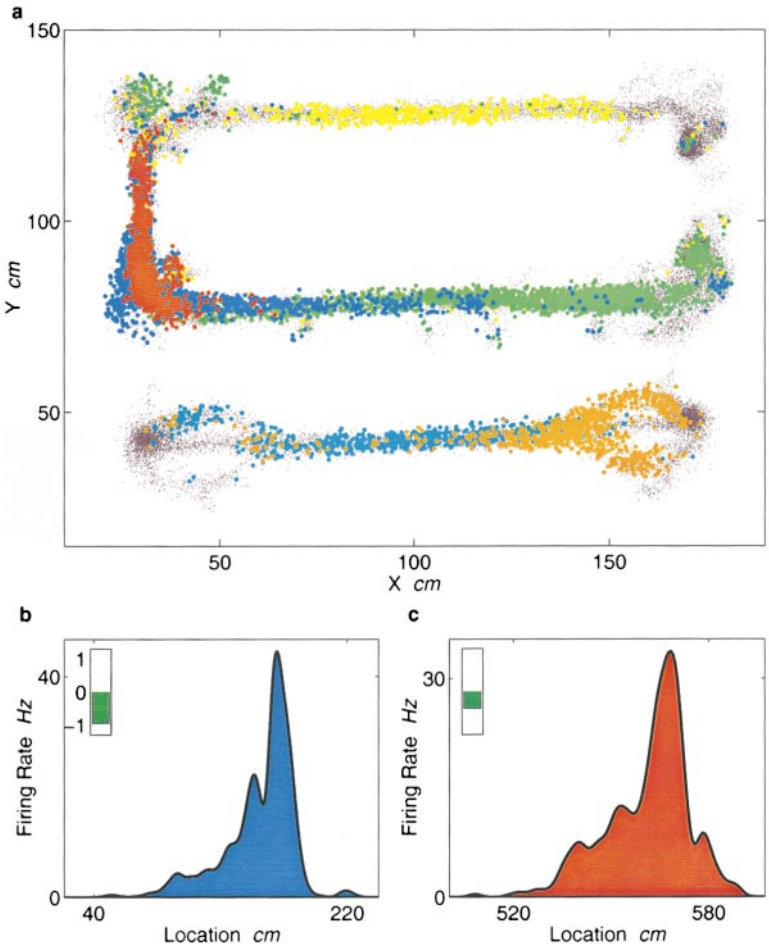


Figure 1. Examples of Single Units and Asymmetric Place Fields

(a) Black dots indicate the instantaneous location of the rat. The location of a rat at the time of occurrence of a spike is indicated by colored dots. Different cells are represented by different colors. The rat first ran on the (lower) linear track and then on the (upper) C-shaped track. Most of these cells fired in only one direction of the journey and had only one clear place field.

(b) Firing rate histograms as a function of location, i.e., place fields for two place cells, obtained from 5 (of 27) simultaneously active single units shown in (a). The rat ran in the direction of increasing distance in each panel. The color of the histogram corresponds to the color of the spikes in (a). The insets show the skewness (see Experimental Procedures [Spiegel, 1994]) of the place fields. These place fields are asymmetric, such that they are negatively skewed.

explained by parameters such as the track shape, the location of the place fields on the tracks, the behavior of the rat through the place fields, or a change in the rat's behavior with time.

One possible mechanism for such an asymmetry is the experience-dependent modification of inputs into CA1 cells. To characterize change in field shape with experience, the population-averaged skewness was computed as a function of the number of laps run by the animals during the session. The population of place fields had no significant mean asymmetry at the beginning of a session (Figures 3a–3c; Table 1), but they rapidly became highly negatively skewed with experience. Similar results were true for the FRAI (Figure 3d). Thus, there was a dramatic (>300%) change in the shape of the place fields with experience. This was not merely a result of an increase in the asymmetry of already skewed place fields, because even the ratio of the number of neurons with a negative skewness to those with a positive asymmetry almost doubled with experience.

In previous work (Mehta et al., 1997), which did not examine place field shape, experience-dependent changes in place field location and firing rate were reported. These results were confirmed in the present study, in which a 51% increase in the place field size (from 426 to 643 cm × Hz) and a predictive or backward (i.e., in a direction opposite to the direction of movement of the rat through the place field) shift in the location of the center of mass of the place fields by 8.2 cm were observed. Further, the location of the peak of the place field shifted backward by 5.5 cm, and the first spike in the place field occurred 9.2 cm earlier, whereas the last spike in the place field occurred 6.5 cm earlier. This resulted in an experience-dependent widening of place fields by 7.9 cm (Table 1; see Experimental Procedures). These changes in place field size and location were an order of magnitude less than the changes in place field shape (Table 1).

The amount of shift in the center of the place field reported here is much larger than that reported in previous work (Mehta et al., 1997). One reason for this difference could be that the length of the tracks traversed by the rats in the present experiments was more than twice as large as that of the tracks used in the previous work. The larger tracks may allow place fields to grow much more before they encounter a goal location or the end of the track.

It is important to note that skewness and FRAI are independent of the location of the center of mass and the size of place fields. A change in skewness (which is the third moment of the firing rate distribution) could result in an increase in the place field size (the zeroth moment of the firing rate distribution) and a backward shift in the place field center (the first moment of the

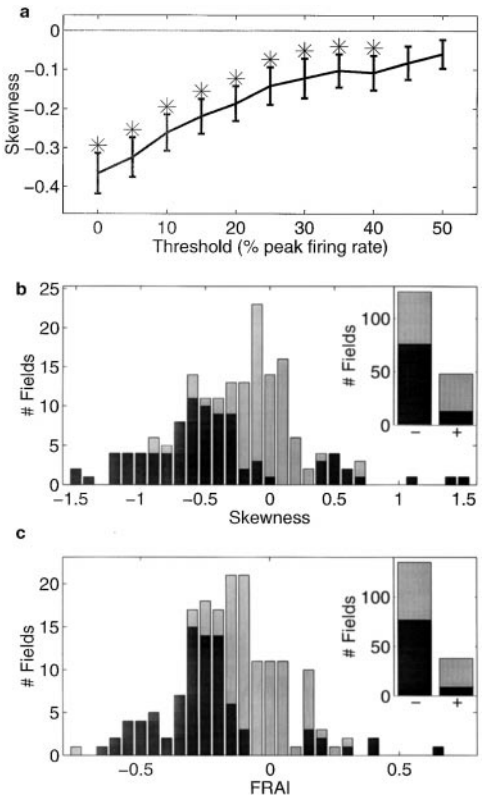


Figure 2. Distribution of Skewness and FRAI across a Population of 173 Place Fields

(a) Population average (mean ± standard error) skewness of place fields as a function of threshold. Only those regions of a place field where the firing rate exceeded a certain percentage of the peak firing rate were included in the analysis. The population mean value of skewness was negative for all of the values of the threshold tested. Threshold values for which the population had a significantly negative skewness (t test, $p < 0.01$) are indicated by stars. To control for the effect of behavior on skewness, the firing rate profile in each place field was replaced by a symmetric bell-shaped curve (a Gaussian), which was then divided by average occupancy at each location within the place field. The resulting "behavioral" field had no significant skewness (mean = −0.02, $p = 0.8$).

(b) Distribution of the mean spatial skewness (Spiegel, 1994) of all of the place cells (shaded bars) averaged across all, except the first five (see Figure 3), laps. A majority (inset, shaded bar, 125 of 173, 73%) of place fields had a negative skewness. The population of place cells had a highly significant mean skewness (−0.25 ± 0.04, $p < 0.001$), i.e., for an average cell, the skewness was 25% of the width of its place field; 52% (89 of 173) cells had a significant skewness ($p < 0.05$, closed bars). The mean skewness of this subpopulation was −0.45 ± 0.06, and 86% (76 of 89, inset, closed bars) had a negative skewness. A majority (72%) of place fields also had a negative Kurtosis (data not shown), and the population of place fields had a significantly negative Kurtosis (0.16 ± 0.07). Thus, place fields are negatively skewed and flat topped.

(c) Distribution of FRAI (see Experimental Procedures). A majority (78%) of place fields had a mean negative FRAI (mean = −0.15 ± 0.016). Further, 50% of place fields had a significantly negative FRAI. This subpopulation had a FRAI of −0.25 ± 0.02, and 90% of these had a negative FRAI. Thus, a majority of place fields had a higher mean firing rate in the second half of the spikes than in the first half. To estimate the effect of behavior on FRAI, we computed O1 and O2, the mean inverse occupancy (which is approximately equal to the velocity) for the first and second halves of spikes within a place field in a lap. The BAI was then computed in a manner similar to FRAI, i.e., BAI = (O1 − O2)/(O1 + O2). The lap-averaged BAI was not significant (mean = 0.02, $p = 0.1$), and 51% of place fields had a positive BAI. Thus, the asymmetric shape of place fields could not arise due to asymmetric behavior of the rat within the place field.

distribution) (Mehta et al., 1997), but the converse is not true. The previous work (Mehta et al., 1997) implicitly assumed that the place field shape did not change with experience and hence measured the change in population-averaged place field center, which could come about due to a change in shape. Indeed, the experience-dependent change in shape (skewness and FRAI) was an order of magnitude larger than the changes in all of the other parameters (Table 1). Thus, a change in shape with experience appears to be the dominant characteristic of experience-dependent changes in place field and may account for the previous finding of changes in place field center.

If these changes in shape were indeed experience dependent rather than time dependent, a change in the structure of the inputs or context should reset the skewness. To test this hypothesis, rats were allowed to run consecutively on two different tracks (Figure 1a), and a subset of cells (20 of 141) that were active in both environments was examined. While the place fields became asymptotically more negatively skewed with experience in the first familiar environment, the skewness was reset to more symmetric values when the rat entered the second familiar environment (Figure 3e), followed by a renewed asymmetrization of these place fields with experience in the second environment. Further, these changes occurred each day in a familiar environment. Therefore, the skewness is correlated with the amount of experience, or familiarity, on a given day with the environment and hence may serve as the neural correlate of familiarity with a sequence of events.

The shape of a place field could be affected by a wide range of phenomena that can be broadly divided into two categories: temporal, or activity-dependent, mechanisms, such as global excitability, spike frequency adaptation, and synaptic depression and facilitation; and spatial, or input-dependent, phenomena, such as asymmetric input. The spatial phenomena depend on the precise timing of the pre- and postsynaptic neuronal activities, whereas the temporal phenomena only depend on the overall duration or activity of these neurons. For example, if a rat traverses a region of space at a lower speed, the duration and the total amount of firing would increase. If the mechanism responsible for the asymmetric shape was dependent on these temporal phenomena, skewness would be more correlated with "temporal parameters," such as the duration of spiking or the total number of spikes, than with "spatial parameters," such as the spatial width of the place field or the location of the first spike in the field. The lap-by-lap fluctuations in skewness were most correlated with spatial parameters (Figure 3f), such as the location of the first and last spikes and the width of the place field, but poorly correlated with temporal, or activity-dependent, parameters, such as the number of spikes, the firing rate, and the duration of spiking. In particular, the skewness was significantly more correlated with the spatial width of the place fields than with the equivalent temporal width (i.e., duration of spiking). These results suggest

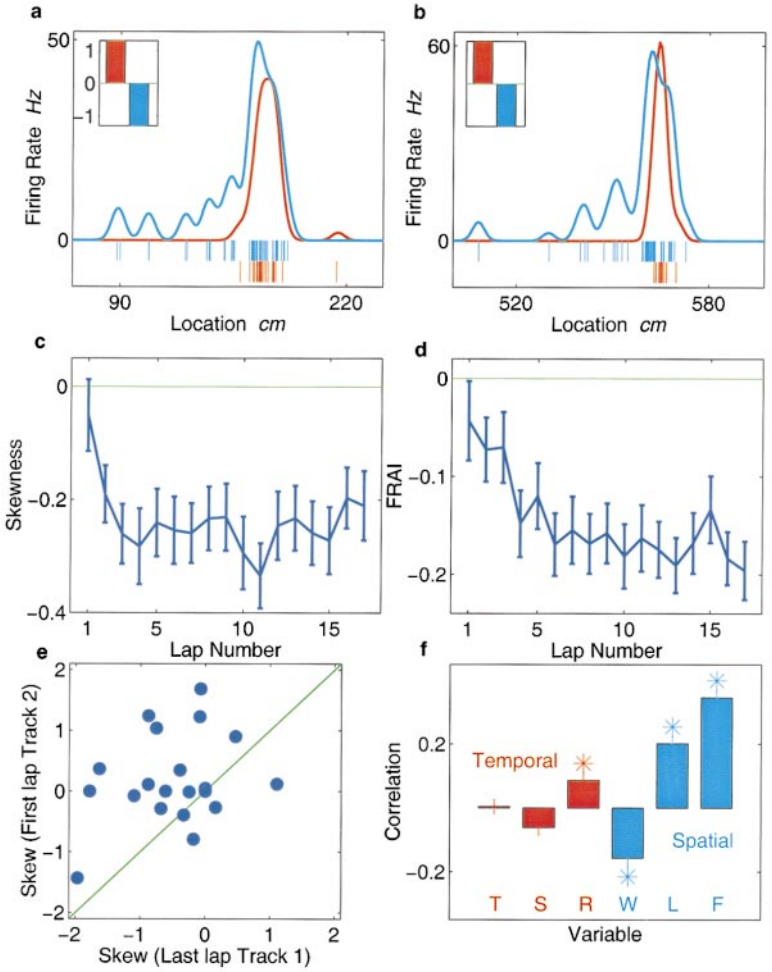


Figure 3. Change in Skewness and FRAI with Experience

(a and b) Experience-dependent change in skewness of the place fields shown in Figure 1b. Location of spikes during the first lap are shown by red tick marks. The corresponding place fields are shown in red. Similar data during the last lap are shown in blue. The insets show the skewness during the first (red) and last (blue) laps. The skewness was more negative in the last lap than in the first.

(c) Mean skewness was computed for each lap, averaged across the entire population of 173 cells, weighted by the firing rate (to allow for comparison across cells with different rates) of the cell during that lap. The mean skewness in the first lap was not significant (t test, $p = 0.2$). However, by the third lap the population mean skewness was significantly negative ($p < 0.01$). There was a >3-fold increase in skewness with experience. The mean skewness was highly correlated with the log of lap number ($r = -0.6$). There were an equal number of cells with positive and negative skewness at the beginning of a session. Within a few laps, there were twice as many cells with a negative skewness as with a positive skewness. Thus, place fields became more skewed with experience.

(d) Similarly, there was a highly significant 3.5-fold increase in FRAI and a 2.5-fold increase in the ratio of the number of neurons with a negative FRAI to those with a positive FRAI. There was no systematic change in the rat's behavior within the place field, i.e., there was no significant change in the mean running speed or BAI (see Figure 2c legend) with experience.

(e) Twenty place cells had place fields away from food reward locations (see Experimental Procedures) on both the first and second tracks. The skewness of these common place cells during the last lap on the first track (x axis) was significantly more negative than that measured on the subsequent first lap on the second track (y axis). Thus, skewness was reset when the rat entered a second familiar environment immediately after traversing the first. Similar results were true for FRAI. Thus, change in skewness and FRAI were experience rather than time dependent.

(f) Fluctuations in skewness are more correlated with spatial than temporal variables. These histograms show correlations between the lap-by-lap fluctuations in skewness with fluctuations in temporal or activity-dependent variables (red bars), such as duration of spiking (T), number of spikes (S), mean firing rate (R), and spatial parameters (cyan bars), such as width of the place field (W) and locations of the last (L) and first (F) spikes within the place field. Significant (t test, $p < 0.01$) population correlations are indicated by stars. Since most of the systematic changes in place field properties occurred within the first five laps, data from these laps were excluded from the analysis to avoid spurious correlations. There was no qualitative change in the results if these data were included in the analysis. Similar results were true for FRAI.

that the observed field shape may reflect the asymmetric nature of inputs to the CA1 cells. In particular, since the input is weaker at the beginning than at the end of the field, skewness would be more correlated with the location of the first spike than with that of the last spike (Figure 3f).

Such experience-dependent asymmetric input could result from the LTP and LTD (long-term depotentiation) (Hebb, 1949; Levy and Steward, 1983; Gustaffson and Wigstrom, 1986) of NMDA-dependent synapses (Figures 4a–4c). NMDA-dependent synapses are strengthened if postsynaptic activity lags behind presynaptic spiking (Markram et al., 1997; Bi and Poo, 1998; Zhang et al., 1998) and depotentiated if the converse is true—hence the amount of change in synaptic strength as a function of the time lag between the pre- and postsynaptic spike times is asymmetric, leading to a temporally asymmetric LTP curve. Further, the amount of LTP/LTD is inversely related to the absolute value of the time lag between the pre- and postsynaptic neuronal spike times. It is known that pyramidal neurons in CA1 receive excitatory inputs from pyramidal neurons in CA3, which also exhibit place-specific firing. LTP of these CA3→CA1 connections has been shown to be NMDA dependent.

To examine the effect of NMDA-dependent plasticity on field shape, a computational model of CA3→CA1 was constructed using biophysical $Ca^{2+}$ and synaptic dynamics. We assume for simplicity that CA1 neurons initially receive symmetric input (Figure 4a), which results in a symmetric, or even mildly positively skewed, receptive field (Figures 4b and 4d) due to spike frequency adaptation. Repeated traversals of a region of space would activate directionally selective place cells in both CA3 and CA1 and would strengthen synapses from those CA3 neurons that have a place field before that of a CA1 neuron (Figures 4a and 4c). Further, the afferent CA3 cells with place field centers far from the CA1 place field center would on an average fire much earlier than

Table 1. A comparison of changes in various parameters with experience

| Parameter | Mean | First Lap | Seventeenth Lap | Difference | Percent Change |
|---|---|---|---|---|---|
| Place field size (cm × Hz) | 605.8 ± 33.3 | 426.4 ± 34.6 | 643.5 ± 41.4 | 217.1 | 50.9% |
| Place field width (cm) | 47.4 ± 2.3 | 40.1 ± 3.0 | 48.0 ± 2.7 | 7.9 | 20.1% |
| Location of place field center (cm) | 0.0 | 7.3 ± 0.6 | −0.9 ± 0.7 | −8.2 | −17.3% |
| Location of first spike in place field (cm) | 0.0 | 9.2 ± 1.9 | −0.3 ± 1.1 | −9.3 | −19.6% |
| Location of last spike in place field (cm) | 0.0 | 5.7 ± 0.9 | −0.8 ± 0.6 | −6.5 | −13.7% |
| Location of place field peak (cm) | 0.0 | 5.5 ± 1.5 | −0.0 ± 1.0 | −5.5 | −11.6% |
| Field skewness | −0.27 ± 0.5 | −0.05 ± 0.06 | −0.21 ± 0.06 | −0.16 | 312.6% |
| Field FRAI | −0.15 ± 0.02 | −0.04 ± 0.04 | −0.20 ± 0.03 | −0.15 | 354.5% |
| Number of neurons with FRAI < 0 | 134 | 60 | 112 | 52 | 86% |
| Number of neurons with skewness < 0 | 124 | 67 | 107 | 40 | 60% |

All of the changes were highly significant ($p < 0.01$). Place field width was defined as the distance between the first and the last spikes in the field during a pass (see Experimental Procedures). The mean width was computed by averaging the width over each pass over all of the place fields. The location of the center of a place field in a given lap was measured with respect to the overall place field center. Hence, the mean value of the place field center is zero. The percentage change in the center of the field was computed by comparing the change in the place field center with the average place field width; likewise for the locations of the first and last spikes in the place field and for the location of place field peak. The largest experience-dependent changes thus occurred in the place field skewness and FRAI. These changes in shape were about an order of magnitude larger than all of the other experience-dependent changes, such as those in the place field width or the center.

the CA1 cell, resulting in a smaller amount of strengthening of the corresponding CA3→CA1 synapses than of the synapses from the CA3 cells with place field centers closer to the CA1 place field. Thus, on an average, the amount of strengthening is inversely related to the distance between the afferent CA3 and CA1 place fields. On the other hand, synapses from those CA3 neurons with place fields that follow a CA1 place field would be weakened due to LTD. Thus, after "experience," the place field begins earlier due to LTP of the synapses from cells that are activated before the CA1 cell (Figure 4e), and it terminates earlier due to LTD of the synapses from the cells that are activated after the CA1 cell. Therefore, the CA3→CA1 synaptic strengths as a function of location would come to reflect the temporal asymmetry of the underlying LTP curve (Figure 4a). As a result, when the rat enters a CA1 place field, the neuron would be driven by relatively weak synapses. As the rat moves further into the place field, the neuron would be driven by synapses with monotonically increasing strength until the very end of the place field, where the strength of the input would drop off relatively abruptly (Figures 4a and 4c), resulting in a negatively skewed place field (Figures 4b and 4d). Hence, the place fields would become more negatively skewed with experience (Figures 4b and 4d). The model also reproduces the observed (Figures 3a and 3b) large and small backward shifts in the locations of the first and last spikes (Figure 4e), respectively, and the observed (Figure 3f) distribution of correlations between the lap-by-lap fluctuations in skewness, the locations of first and last spikes, and the width of the place fields (Figure 4f).

To summarize, we have shown that following directional traversal on familiar tracks, the following significant changes occur in the hippocampal place fields: (1) a large increase in the skewness and FRAI, (2) a large increase in the place field size, (3) a backward or predictive shift in the place field center and place field peak location, (4) a predictive shift in the location of the first spike in the place field, and (5) the same for the location of the last spike in the place field. Further, we have shown that (6) the skewness is more correlated with spatial than with temporal parameters, (7) the skewness and the place field sizes are reset when the rat is moved to a second familiar track, and (8) the fluctuations in skewness are uncorrelated with the fluctuations in the activity-dependent parameters, such as the firing rate or the total number of spikes per lap.

These results cannot be explained by any simple "adaptation" phenomena. For example, synapse-specific but short-term mechanisms, such as synaptic depression or facilitation, cannot account for these results because under most conditions, synaptic depression should result in a reduced firing rate or place field size and a positive skewness. While synaptic facilitation could increase the place field size, it is not evident how facilitation can explain the backward shift of both the first and the last spikes in the place field.

All of these results summarized above, including the time course over which these changes occur, are accurately captured by a simple computational model based on one hypothesis: rapid, NMDA-dependent, temporally asymmetric LTP/LTD of the feed forward synapses from CA3 to CA1 during behavior.

## Discussion

The negative skewness of the hippocampal place fields is surprising for two reasons. First, it is commonly assumed that receptive fields, including place fields, are symmetric (e.g., O'Keefe and Burgess, 1996; Tsodyks et al., 1996). Second, pyramidal neurons exhibit spike

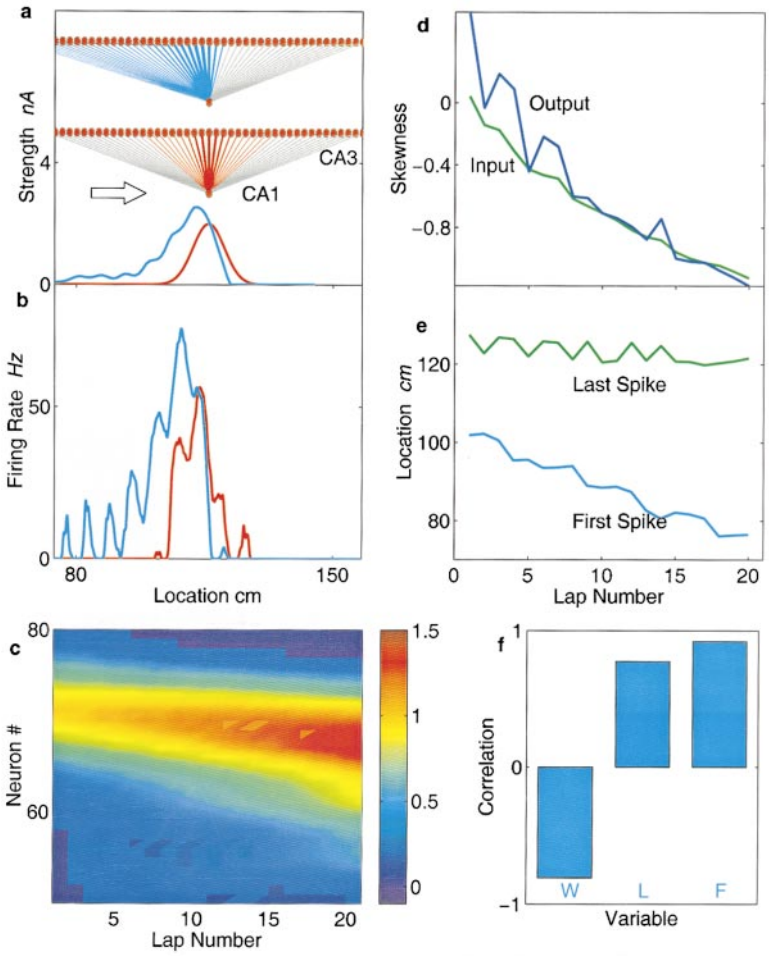


Figure 4. Results of Simulations of a Computational Model of CA3→CA1 with NMDA-Dependent Plasticity

(a) The rat travels from left to right (arrow), and CA3 place fields (dark blue dots) are ordered in the temporal order in which they are activated. The initial CA3→CA1 synaptic matrix is symmetric, and the strength of each synapse is proportional to the thickness of the red lines. Gray lines indicate connections with zero synaptic weight. The net input current, as a function of location, before learning is indicated by the red curve. In addition to these excitatory inputs, the CA1 neuron also receives an oscillatory inhibitory input. As a result of repeated directional activation (arrow) and NMDA-dependent modifications in the CA3→CA1 synaptic strengths (see Experimental Procedures), the synaptic matrix becomes asymmetric (blue lines and blue curve) after experience.

(b) During the first lap, the CA1 place field is positively skewed (red curve) because of spike frequency adaptation. Due to the asymmetric synaptic input (Figure 4a), the CA1 place field is negatively skewed after experience (blue curve).

(c) Strength of synapses (nA, color bar) between CA3 neurons and a CA1 neuron as a function of experience. The synaptic inputs to the simulated CA1 neuron are initially symmetric. As a result of repeated directional activation of the CA3 input cells and the temporally asymmetric nature of NMDA-dependent LTP, the symmetry of the inputs is broken and the synaptic matrix becomes progressively more negatively skewed.

(d) Thus, there is a large and rapid change in the skewness of the CA3→CA1 input synaptic matrix (green curve) within a few passes. The skewness of the resulting CA1 output (blue curve) is often more positive than that of the input matrix due to spike frequency adaptation.

(e) As found in the experimental results, such change in the shape of the input was reflected in an earlier appearance of the first and last spikes in the place field. While the first spike appeared earlier due to strengthening of connections with neurons that fired before the CA1 neuron, the last spike occurred at earlier locations due to weakening of synapses from the CA3 neurons that fired after the CA1 neuron. The change in the location of the last spike was less than that of the first spike.

(f) Thus, skewness of the simulated place field was more correlated with the location of the first spike (F) than with the location of the last spike (L) or the width (W) of the field. This is similar to the experimental data (Figure 3f).

frequency adaptation. Under most conditions, this would result in the typical large phasic response, followed by a small tonic response (Maunsell and Van Essen, 1983), i.e., a positive skew, which is the opposite of what is reported here.

An experience-dependent negative skewness might also be obtained by changes of the recurrent synapses within CA3. Indeed, previous theoretical work has suggested that place fields should shift in a predictive fashion with experience (Levy, 1989) and that the CA3 synaptic matrix should be asymmetric (Tsodyks et al., 1996). The effect of temporally asymmetric LTP on the recurrent network in CA3 was modeled by Blum and Abbott (1996) to show that the place fields should expand and shift with experience. Similar results about expansion and shift of CA3 place fields were later obtained by other models (Jensen and Lisman, 1996; Wallenstein and Hasselmo, 1997) using related mechanisms. However, these previous works did not discuss the effect of LTP on the shape of the place fields. Further, even if these experience-dependent changes arose in some network presynaptic to CA3→CA1, say within the recurrent connections in CA3, it is not evident how they can be propagated down to CA1. The model presented here explicitly demonstrates five points. First, the changes in place field size, location, and shape can be explained by a purely feed forward network, which relates most directly with the architecture of the area CA1, from which our data were obtained. Second, it shows that the amount of LTP/LTD is large enough to overcome the forces of adaptation and results in a net negative skewness that reflects the temporal asymmetry of the underlying LTP curve. Third, the time course over which the skewness changes (approximately five laps) is similar in both the data and the model. Also, the model accurately captures the correlations between the skewness and other parameters, such as the place field width and the locations of the first and the last spikes in the place field. Thus, the model provides quantitative support to the hypothesis that the place field dynamics reported here occur due to temporally asymmetric LTP. Fourth, while a CA1 place field initially represents the rat's "current" location,

with experience the cell also fires at a sequence of preceding locations, and the firing rate becomes correlated with the distance within the place field. The information about the sequence in which the locations were visited is thus stored in the asymmetric synaptic matrix with synaptic strength proportional to the position (Figure 4). Therefore, the model shows that information about a sequence of locations can be stored in a purely feed forward network. While the data presented here do not demonstrate an explicit dependence of CA1 firing on the sequence of past locations, the model does offer a potential mechanism for the establishment of such a dependency. Finally the model shows that due to LTP in a feed forward network, the receptive fields of downstream neurons would be wider than those of the afferent upstream neurons (Figures 3 and 4; Table 1). Indeed, the subicular place fields are wider than are the afferent CA1 place fields, which in turn are wider than are the upstream CA3 place fields (Barnes et al., 1990).

This suggests that the CA1 place cells initially receive a spatially symmetric input. The symmetry is broken by the pairing of the temporally asymmetric nature of NMDA-dependent LTP/LTD with repeated directional stimulation, resulting in place fields with experience-dependent, spatially asymmetric input and negative skewness.

Recurrence of these phenomena when a rat is reintroduced in a familiar environment after a day's absence could be explained as follows. Following the experience on the tracks, these place cells are probably reactivated when the rat returns to the sleep box or the home cage, etc. However, the order in which they fire is likely to be different from that which occurs during the track running, resulting in depotentiation of these synaptic strengths, and hence a resetting of skewness.

The model predicts that a blockade of NMDA receptors should abolish the negative skewness. Previous studies have investigated the effects of genetic (McHugh et al., 1996) and pharmacological (Kentros et al., 1998) blockade of NMDA receptors on the size and stability of place fields; however, skewness was not studied. Kentros et al. (1998) found that during random foraging in familiar environments, place fields were relatively insensitive to pharmacological NMDA receptor blockade. The model presented here predicts that changes in shape would not be observed in such a task but would be seen on directional trajectory traversal tasks, such as the linear track.

To navigate through, and form a cognitive map of, an environment, the information regarding the relationship between locations could be critical. This could be encoded in experience-dependent skewness. The recurrence of these phenomena in a familiar environment may be suggestive of the role of hippocampus in the storage of the short-term memory of such relationships.

These results could also provide a mechanism underlying the phenomenon of phase precession (O'Keefe and Recce, 1993), whereby the phase of the theta rhythm at which a CA1 neuron fires a spike steadily advances as a rat moves through its place field. If the latency to spiking is proportional to the net excitatory input, a monotonic increase in the latter would result in a phase advancement. Excitatory input to a place cell that increased monotonically and dropped off abruptly would lead to spike phase that advanced with the distance traveled within the place field, with little or no retardation toward the trailing edge of the place field. Several computational models (O'Keefe and Recce, 1993; Jensen and Lisman, 1996; Tsodyks et al., 1996; Wallenstein and Hasselmo 1997; Kamondi et al., 1998) have been proposed to explain phase precession. These models were based on, and assumed the existence of, asymmetric recurrent connections within CA3 (Jensen and Lisman, 1996; Tsodyks et al., 1996; Wallenstein and Hasselmo, 1997). They assume that the phase precession in CA1 occurs due to a passive propagation of these phenomena in CA3. Contrary to this, the mechanism proposed here is based on the asymmetric firing of CA1 cells, which could arise due to asymmetric feed forward connections from CA3 to CA1 (Figure 4). Thus, an increasing firing rate with distance is the key ingredient that could directly result in a reduction in phase, or equivalently, in "latency [from inhibition] to spiking."

It is believed that many adult cortical regions are not as plastic as is the hippocampus. Detection of an asymmetry similar to that presented here, in the shape of cortical receptive fields, might allow one to infer the influence of mechanisms of plasticity in their formation. For example, a majority of cells in the striate cortex are directionally tuned (Hubel and Wiesel, 1962) and have slanted or inseparable spatiotemporal receptive fields (Movshon et al., 1978; Reid et al., 1987; McLean and Palmer, 1989; Albrecht and Geisler, 1991), i.e., the response latencies (or the integration time to spiking) are shorter and the firing rates are larger as stimuli are flashed farther along the preferred direction. This is similar to the response properties of hippocampal place fields, in which the firing rate increases as the rat moves farther in the place field, accompanied by progressive phase advancement (reduced response latencies). Thus, the hippocampal and the striate receptive fields have similar spatiotemporal structures. This suggests that similar mechanisms of plasticity (Figure 4) may be involved in shaping receptive field characteristics in the visual cortex during development. Similar directional and inseparable spatiotemporal receptive fields are also found in the auditory cortex (deCharms et al., 1998). While the origin of such direction-selective and inseparable receptive fields is still being debated (see, e.g., Miura et al., 1995; Feidler et al., 1997; Chance et al., 1998; Livingstone, 1998; Anderson et al., 1999), none have proposed a model for the development of the inseparability based entirely on known physiological mechanisms. Analysis of receptive field shape may provide insights into the mechanisms involved. A delayed inhibition proportional to excitation would result in a larger response when the stimulus moves in the direction of increasing excitation than when it moves in the opposite direction, leading to direction selectivity. Such directional responses would become stronger and occur earlier as the receptive fields became more negatively skewed with experience, thereby allowing the animal to predict the future location of the stimulus earlier.

Thus, the experience-dependent asymmetric temporal dynamics shown here for hippocampal receptive fields may be a general principle underlying the formation of cortical receptive fields. Such dynamics could arise due to asymmetric patterns of neuronal activity

and the kinetics of NMDA-dependent LTP/LTD. Such receptive fields could encode associations between a sequence of past events and enable an animal to predict future events, such as the location of an object in visual, auditory, or somatosensory space, or an upcoming spatial location.

## Experimental Procedures

### Experiments

Three male Long Evans rats were trained to run back and forth, first on a linear track (150 cm length, 8 cm width) and then on a C-shaped track (150 cm long arm length, 55 cm short arm length, 6 cm width) for food rewards at the ends of the tracks (Figure 1a). After training, they were implanted with a 12 tetrode microdrive array (Wilson and McNaughton, 1993). All surgeries were done according to National Institutes of Health guidelines. The position and heading direction of the rats were recorded with a resolution of 0.66 cm/pixel and a sampling rate of 30 Hz. Spike data were sampled at 33 KHz/channel.

### Analysis

The tracks were linearized for the purpose of analysis. Since most place fields on linear tracks are directional, the outward and inward journeys from a goal location were treated separately. Thus, the rat's heading direction was always in the direction of increasing distance. Firing rate map of a cell as a function of location was obtained by dividing the total number of spikes fired by the cell in a given pixel by the total amount of time spent by the rat at that location. Since the rats exhibited periods of immobility at the food reward locations, which leads to state-dependent changes in hippocampal activity, place fields at these locations were not used for the purpose of analysis. Within each session, there were 9, 13, 14, 18, 27, 30, and 31 simultaneously recorded place cells away from the food reward locations. Some of these cells were either bidirectional ($<$10%) or had more than 1 place field. Since we are interested in the temporal dynamics of place fields within individual passes, these were treated as distinct place fields. There were a total of 173 distinct place fields, obtained from 141 place cells.

Integrated place field size was defined (Mehta et al., 1997) as the sum of instantaneous firing rate within each pixel and hence measured in the units of cm $\times$ Hz.

The location of the place field center was defined as the center of the mass of the firing rate distribution within the place field. Similarly, the location of the place field peak was defined as the location of the maxima of the firing rate distribution. The lap-specific place field center and peak were measured with respect to the lap-averaged place field center.

The width of a place field in a given lap was defined as the distance between the first and the last spikes within the place field in that lap. Hence, the place field width in a given lap is zero if the cell fired less than two spikes in that lap. However, in such cases the location of the first and the last spikes in the place field are not well defined. Hence, the analyses of the locations of the first and the last spikes in the place field were restricted to only those laps in which the cell fired more than one spike.

The skewness was defined, in dimensionless units, as the ratio of the third moment of the place field firing rate distribution divided by the cube of the standard deviation (Spiegel, 1994).

All of the spikes fired by a cell in a single passage through the place field were divided into two equal parts. If F1 and F2 are mean firing rates for the periods of time during which the first and second 50% of the total number of spikes were fired, the firing rate asymmetry index was defined as FRAI $= (F1 - F2)/(F1 + F2)$.

The skewness and rate asymmetry so defined are unaffected by the lap-by-lap variations in the location of place field center. Since the skewness and FRAI can be defined only when there are more than two spikes, all of the analyses were restricted to only such laps.

### Model

The firing rate, f(t)(Hz), as a function of time, t(ms), intracellular calcium concentration, Ca(t)($\mu$M), and the net input current, I(nA), of a CA1 pyramidal neuron with spike frequency adaption was modeled as (Wang, 1998)

$$f(t) = [f_0(t) - G_f(I)[Ca]]_+$$
$$d[Ca]/dt = -\alpha(I_{Ca}(I) + G_c c(I)[Ca]) - [Ca]/\tau_{Ca},$$

with $f_0(I) = -45I_1$, $G_f(I) = 295 - 75I_1$, $\alpha = 0.002$, $I_{Ca}(I) = 84I_1$, $G_c c(I) = 551 - 143I_1$, $\tau_{Ca} = 80$, $I_1 = [\ln(I/0.3)]_+$ for $I > 0.3$, and $I_1 = 0$ otherwise. The notation $[x]_+$ means $[x]_+ = x$ for $x > 0$, and $[x]_+ = 0$ otherwise.

The strength, s(nA), of an excitatory synapse from CA3 to CA1 was modified by an amount, ds(nA), after every lap according to the physiological learning rule (Markram et al., 1997; Bi and Poo, 1998; Zhang et al., 1998):

$$ds = \int_0^T dt \int_1^{50} d\tau [A_{ltp}\exp(-\tau/\tau_{ltp})\, f_{CA3}(t - \tau)\, f_{CA1}(t) -$$
$$A_{ltd}\exp(-\tau/\tau_{ltd})\, f_{CA3}(t + \tau)\, f_{CA1}(t)],$$

where $A_{ltp} = 0.0006$, $A_{ltd} = 0.9\, A_{ltp}$, $\tau_{ltp} = \tau_{ltd} = 10$ ms, and T is the total duration of a given lap. Finally, $f_{CA3}$ and $f_{CA1}$ are the firing rates of the presynaptic CA3 and postsynaptic CA1 neurons, respectively.

For the purpose of simulation, the rats were assumed to run with a uniform speed of 50 cm/s on a 200 cm long track. One hundred CA3 pyramidal neurons provided input to the CA1 neuron. The firing of each CA3 place cell was simulated by a symmetric Gaussian of 30 cm width and a maximum amplitude of 1 nA. These place cells were uniformly distributed on the track, and the distance between their place field centers was 1 cm. The theta-modulated inhibition on the CA1 neurons was modeled by an additional negative sinusoidal current with a frequency of 8 Hz. All simulations were carried out with the time difference between successive iterations dt $=$ 1 ms.

### Acknowledgments

We thank A. Osagawara for help with the experiments and W. Assad, J. Dani, A. Lee, G. Liu, K. Louie, E. Miller, G. Rainer, A. Siapas, S. Seung, and A. Tolias for careful readings of the manuscript. Some of this work has appeared in abstract form at Society for Neuroscience meeting 758.3 (1998).

Received August 11, 1999; revised January 19, 2000.

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