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Synaptic Plasticity in the Hippocampal Area CA1-Subiculum Projection: Implications for Theories of Memory

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ABSTRACT: This paper reviews investigations of synaptic plasticity in the major, and underexplored, pathway from hippocampal area CA1 to the subiculum. This brain area is the major synaptic relay for the majority of hippocampal area CA1 neurons, making the subiculum the last relay of the hippocampal formation prior to the cortex. The subiculum thus has a very major role in mediating hippocampal-cortical interactions. We demonstrate that the projection from hippocampal area CA1 to the subiculum sustains plasticity on a number of levels. We show that this pathway is capable of undergoing both long-term potentiation (LTP) and paired-pulse facilitation (PPF, a short-term plastic effect). Although we failed to induce long-term depression (LTD) of this pathway with low-frequency stimulation (LFS) and two-pulse stimulation (TPS), both protocols can induce a "late-developing" potentiation of synaptic transmission. We further demonstrate that baseline synaptic transmission can be dissociated from paired-pulse stimulation of the same pathway; we also show that it is possible, using appropriate protocols, to change PPF to paired-pulse depression, thus revealing subtle and previously undescribed mechanisms which regulate short-term synaptic plasticity. Finally, we successfully recorded from individual subicular units in the freely-moving animal, and provide a description of the characteristics of such neurons in a pellet-chasing task. We discuss the implications of these findings in relation to theories of the biological consolidation of memory. *Hippocampus 2000; 10:447–456.* © 2000 Wiley-Liss, Inc.

KEY WORDS: subiculum; LTP; LTD; hippocampal-cortical interaction; synaptic plasticity; freely moving

INTRODUCTION

The hippocampal formation is composed of the hippocampus proper (dentate gyrus; areas CA1 and CA3), entorhinal cortex (EC), and subiculum.The subiculum constitutes the major synaptic relay for the majority of hippocampal area CA1 neurons (Amaral et al., 1991; Swanson and Cowan, 1977; Swanson et al., 1978; Witter, 1993), making it the last synaptic relay of the hippocampal formation prior to the cortex. The subiculum and EC process and transmit information between the neocortex and hippocampus proper. Electrophysiological and lesion studies demonstrated that the hippocampal formation is vital for normal memory function (Gaffan, 1993; Nadel and Moscovitch, 1997; Rolls and O'Mara, 1993; Squire, 1992). A central theme in current theories of hippocampal function in memory and amnesia (Cohen and Eichenbaum, 1993, Nadel and Moscovitch, 1997; Rolls, 1996; Graham and Hodges, 1997; Murre, 1996) is the existence of a hippocampal-cortical interface involved in translating temporary hippocampal information storage into a more permanent cortical store. These theories propose that connections between hippocampus and neocortex undergo use-dependent changes in synaptic strength, enabling the consolidation of memory (Nadel and Moscovitch, 1997; Rolls, 1996; Graham and Hodges, 1997; Murre, 1996). Thus, all of these theories make major claims about the nature of hippocampal-cortical interaction for both animal and human models of memory; to date, there have been few data which can be brought to bear on these theories.

Several lines of evidence support the contention that the subiculum is an important mediator of hippocampal-cortical interaction. The subiculum is the principal target of CA1 pyramidal cell axons (Amaral et al., 1991; Finch and Babb, 1980; Meibach and Seigal, 1977; Tamamaki et al., 1987) and thus represents the final relay in a synaptic loop between the EC and hippocampus. The subiculum is connected to the perirhinal, entorhinal, and prefrontal cortices as well as the presubiculum (Ferino et al., 1987; Gigg et al., 1994; Jay and Witter, 1991; Lopes da Silva et al., 1990; White et al., 1990). The subiculum, therefore, receives and integrates information from several sources and modalities (positional from the hippocampus; directional from the postsubiculum; sensory from entorhinal cortex and other sensory areas; mnemonic and contextual information from the hippocampus and prefrontal cortex) and can pass this information directly into downstream cortical circuits. These circuits are concerned with functions such as instrumental learning (Balleine and Dickinson, 1998), working memory (Funahashi et al., 1989, 1993), discriminative avoidance learning (Gabriel et al., 1991), visual and tactual memory

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(Suzuki et al., 1993; Zola-Morgan et al., 1989; Zola-Morgan and Squire, 1993), and spatial learning (Morris et al., 1990; Schenk and Morris, 1985; Taube et al., 1992).

In contrast to hippocampal areas, the subiculum has received little experimental attention. This is despite its importance in memory formation (Poucet, 1993; Squire, 1992) and pathophysiological states such as dementia (Hyman et al., 1984, 1986; Trillo and Gonzalo, 1992) and temporal lobe epilepsy (Jones and Lambert 1990; Pare et al., 1992). To date, very few studies have looked at the activity of subicular formation neurons in the behaving animal (Barnes et al., 1990; Ranck, 1973; Sharp, 1997, 1999a–c; Sharp and Green, 1994). Place cells can be found in the subiculum, although their firing specificity is less than that of, for example, CA1 neurons (Barnes et al., 1990; Sharp and Green, 1994). To investigate the hypothesis that the synaptic connections between the hippocampal formation and the neocortex are plastic in order that memories can be encoded and consolidated, we investigated the possibility that the major excitatory output of hippocampal area CA1 to the subiculum is capable of expressing either paired-pulse facilitation (PPF), long-term potentiation (LTP), or long-term depression (LTD) in vivo. LTP and LTD are commonly regarded as processes that engage some of the same mechanisms that are involved in the biological consolidation of memory. Studies of the interactions between LTP, LTD, and PPF may throw light on the regulation of synaptic plasticity and in particular on the role of presynaptic factors in the maintenance of long-term changes in synaptic strength. These experiments may provide further explanations of presynaptic mechanisms and provide insights into the relationships between the behavioral state of the animal and synaptic transmission.

Recordings of neuronal activity in the freely moving animal may throw light on the sensory and mnemonic mechanisms that control subicular neurons at the cellular level. We examine here whether subicular neuronal activity is plastic, i.e., can the subiculum reorganize its own spatial maps rapidly and efficiently? Furthermore, we attempt to understand the role of bursting cells (the majority of cells in the subiculum are the bursting cell type) compared to area CA1 (Stewart and Wong, 1993; Taube, 1993) in terms of its role in the transmission of information-rich spike trains which directly or indirectly synapse in the neocortex. We examine single-unit activity in the subiculum of freely moving rats during a pellet-chasing task. Sharp and Green (1994) showed that subicular place fields display plasticity in their spatial representations in a similar task; we extend their study to examine the effects of cue removal and subsequent cue replacement, as well as cue rotation, on the plasticity of subicular unit spatial representation.

PLASTICITY OF THE CA1-SUBICULAR PROJECTION

Long-Term Potentiation (LTP)

For the first time, we examined LTP as it occurs in the major projection from CA1 to the subiculum in vivo (Commins et al., 1998a, 1999). This projection sustains high-frequency stimulus (HFS)-induced LTP (HFS-LTP: 10 trains of 20 stimuli at 200 Hz; intertrain interval of 2 s). The plasticity of the CA1-subicular pathway was investigated by stimulating this input using standard protocols for the induction of long-term potentiation (LTP) and long-term depression (LTD) (Bliss and Collingridge, 1993; Bolshakov and Siegelbaum, 1994; Commins et al., 1998a; Doyle et al., 1996; Dudek and Bear, 1992; Mulkey et al., 1994; O'Mara et al., 1995a,b; Reymann, 1993). A rapidly stabilizing potentiation was induced in the CA1-subiculum pathway using the HFS protocol ($n = 15$). At 5 min post-HFS, the level of potentiation, measured by field excitatory postsynaptic potential (fEPSP) amplitude, was $156.61 \pm 11.5\%$. This potentiation remained stable, with little fluctuation over a 30-min period. This was demonstrated by examining the level of potentiation at 15 min post-HFS and at 30 min post-HFS; fEPSP amplitude was $159.9 \pm 12.5\%$ and $150.0 \pm 10.9\%$ at 15 and 30 min post-HFS, respectively (see Fig. 1a). In addition, input-output (I/O) curves showed a leftward and upward shift for all stimulation values. Additional experiments ($n = 5$) showed that potentiation, once induced, remains unchanged after 3 h, using the above HFS protocol (see Fig. 1c). Furthermore, once the CA1 to subiculum pathway is potentiated, it seems resistant to further episodes of HFS ($n = 6$; see Fig. 1b). Subsequent experiments examined the efficacy of theta-burst stimulation (TBS) for LTP induction; this is a more biologically realistic pattern of stimulation. After TBS, the level of potentiation, measured by fEPSP amplitude, stood at $118.39 \pm 4.5\%$ (relative to baseline), 5 min poststimulation. Potentiation remained stable over a 30-min period as demonstrated by the fEPSP amplitudes at both 15 min and 30 min poststimulation, which were $116.25 \pm 1.9\%$ and $116.88 \pm 4.2\%$, respectively (see Fig. 1d).

Paired-Pulse Facilitation (PPF) and LTP in the Subiculum

Studies of the interaction between LTP and paired-pulse facilitation (PPF) may throw light on the regulation of synaptic plasticity and, in particular, on the role of presynaptic factors in LTP. PPF is the well-known phenomenon whereby the fEPSP response to a second stimulus is enhanced relative to the first, if the second stimulus is delivered within a relatively brief period of time after the first (usually about 50 ms). We investigated (Commins et al., 1998b), for the first time, the nature of PPF in the pathway from hippocampal area CA1 to the subiculum. We found that this pathway has a reliable and robust PPF effect across a wide range of interstimulus intervals (ISI) from 10–500 ms; it reaches maximum at 50 ms. There is no PPF effect at a 1,000-ms ISI (see Fig. 2a). PPF decreases significantly in magnitude post-LTP induction across the middle range of ISI values tested (30, 50, and 100 ms; see Fig. 2b). Furthermore, we show that there is a positive linear relationship between initial PPF and the magnitude of LTP obtained in this pathway that varies as a function of ISI. The initial PPF value at a 100-ms ISI correlates more highly with subsequent LTP magnitudes com-

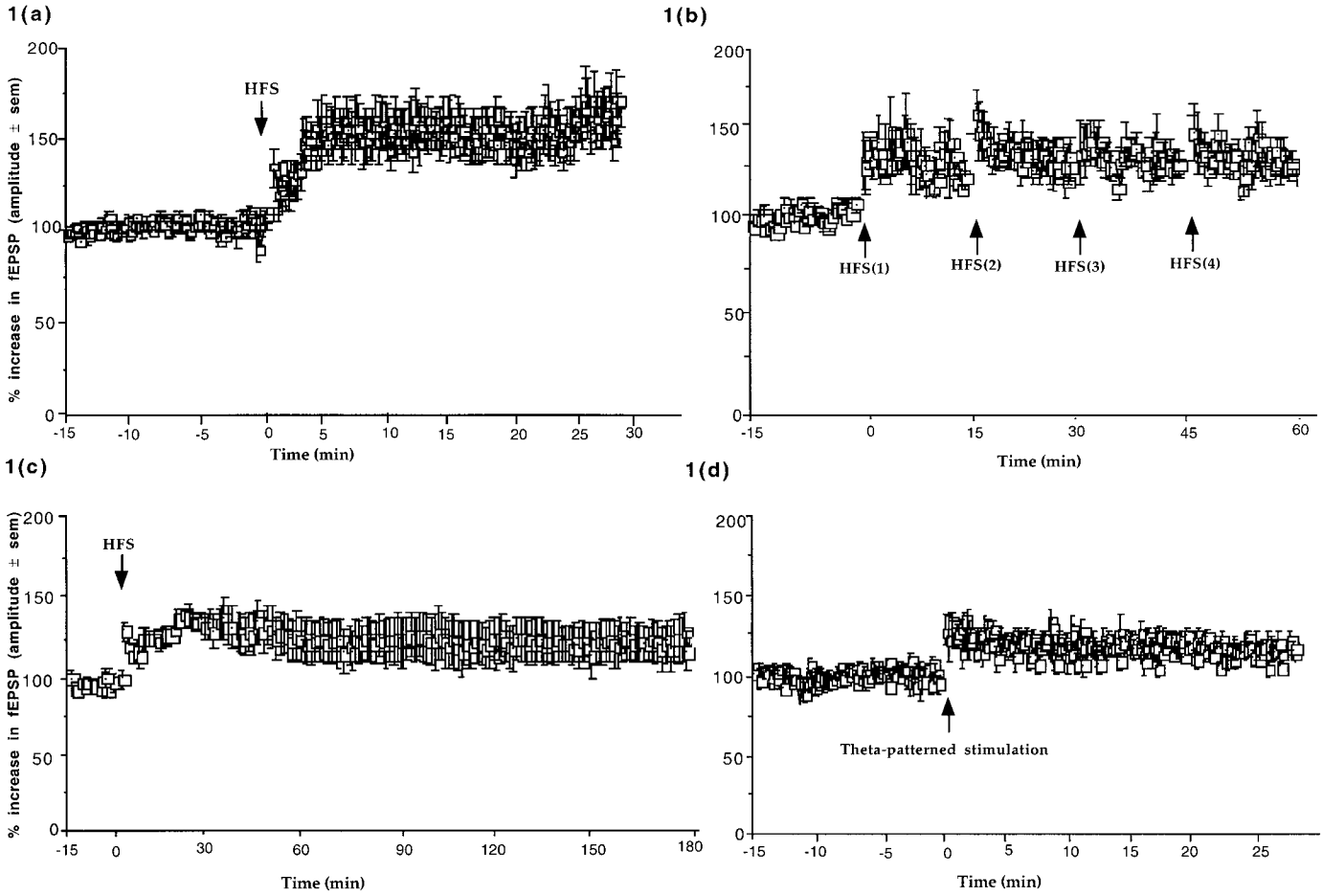


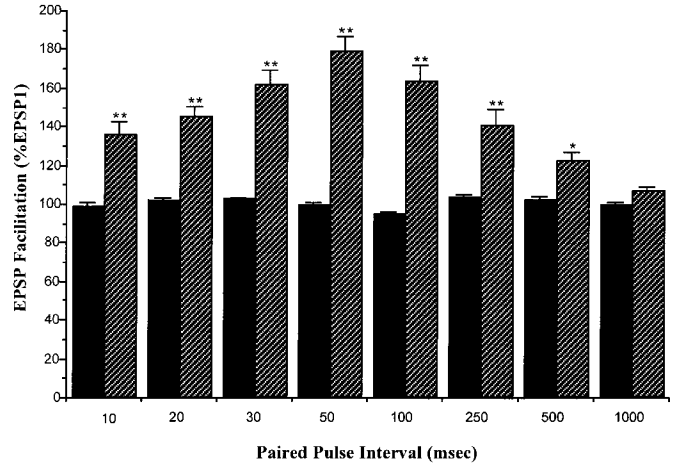
FIGURE 1. a: Effects of HFS on the amplitude of fEPSPs. Post-HFS values are expressed as percentage of prestimulation baseline ± SEM. b: Effects of multiple episodes of HFS. Post-HFS values are expressed as percentage of prestimulation baseline ± SEM. c: Effects of HFs on amplitudes of fEPSPs, recorded over a 3-h period (recorded every minute). Post-HFS values are expressed as percentage of prestimulation baseline ± SEM. d: Effects of theta-patterned stimulation on amplitudes of fEPSPs. Post-theta-patterned stimulation values are expressed as percentage of prestimulation baseline ± SEM.

pared to a 50-ms ISI. Finally, initial PPF value and the change in PPF post-LTP are negatively correlated. These results demonstrated for the first time that the CA1-subiculum pathway shows PPF. Furthermore, these data demonstrate the predictive validity of examining more than one time interval when investigating PPF-LTP interactions; longer intervals predict more precisely the probability of inducing LTP. PPF may act to increase the reliability of synaptic transmission by ensuring that signals which occur in rapid succession are amplified. Thus PPF may serve to increase the signal-to-noise ratio of an input, reducing the possibility that a signal is lost against a noisy background. Furthermore, the selectivity of response for particular stimulus intervals reduces the probability of random inputs firing their postsynaptic contacts. Hippocampal area CA1 units tend to have quite a low firing rate (<5–7 spikes /s) in both rats and monkeys (O'Keefe, 1979; O'Mara, 1995). Such brief bursts of spike firing may be sufficient to induce at least short-term changes in synaptic plasticity (Thomas et al., 1998) and at least transiently potentiate synaptic transmission between the hippocampus and cortex.

LONG-TERM DEPRESSION (LTD) IN THE SUBICULUM

We found no evidence of LTD induction in the CA1-subiculum pathway using two low-frequency stimulation (LFS) protocols (900 stimuli delivered at 1 Hz or 10 Hz; see Fig. 3a,b) and two two-pulse stimulation (TPS) protocols (450 pairs of stimuli; interpulse intervals (IPIs) of 5 ms or 40 ms; see Fig. 3c,d) (Anderson et al., 2000). Indeed, with LFS delivered at 1 Hz and using either TPS protocol, a "late-developing" potentiation of synaptic transmission is observed instead (at 25 min post-1-Hz LFS, fEPSP amplitude was 115.8 ± 4.7%; at 25 min post-TPS with 5-ms IPI, fEPSP amplitude was 115.0 ± 1.41%; at 25 min post-TPS with 40-ms IPI, fEPSP amplitude was 118.9 ± 4.1%. This potentiation begins to appear reliably some 10–15 min post-LFS and plateaus at about 25–30 min post-LFS. There was no change in fEPSPs after the administration of the 10-Hz protocol.

2(a)



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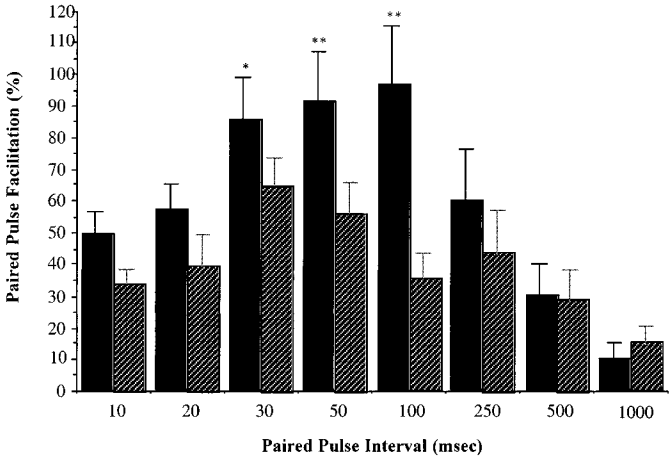


FIGURE 2. a: Bar chart showing paired-pulse facilitation in the CA1-subiculum pathway for intervals indicated. Bars represent mean peak amplitide for fEPSP1 (solid) and fEPSP2 (hatched) (*$P < 0.05$, **$P < 0.01$). Data are normalized to fEPSP1 (100%). b: Bar chart showing changes in PPF after LTP was induced. Mean PPF before (solid) and after (hatched) HFS that induced LTP (*$P < 0.05$, **$P < 0.01$).

Interaction Between LFS (10-Hz) and PPF

PPF was measured pre-LFS using 50-ms and 100-ms ISIs. For the 50-ms ISI, the increase of the second fEPSP compared to the first was 31.41 ± 2.8%; at the 100-ms ISI, facilitation was slightly less, at 23.36 ± 1.7%. The induction of LTD was then attempted by LFS (900 pulses) at 10 Hz. Initially there was a depression in synaptic response: fEPSP amplitude stood at 68.56 ± 10% of baseline 5 min post-LFS. The response gradually increased back to baseline levels; fEPSP amplitude stood at 102.42 ± 3.61% of baseline 30 min post-LFS (see Fig. 4a). PPF was measured at the end of the recording period for the two intervals. For the 50-ms ISI, the percentage increase of the second fEPSP compared to the first was found to be 44.99 ± 5.3%; at the 100-ms ISI, the percentage facilitation was again less, at 38.88 ± 4.8%. We also found (Commins and O'Mara, 2000) that there was a significant and unexpected increase in facilitation post-LFS at both the 50-ms and 100-ms ISIs (see Fig. 4b). These results indicate that it is possible to dissociate the regulation of baseline synaptic transmission from the paired-pulse stimulation of the same pathway.

INTERACTIONS BETWEEN PAIRED-PULSE FACILITATION, LOW-FREQUENCY STIMULATION, AND STRESS IN THE SUBICULUM

A method recently described to induce LTD effectively in vivo in area CA1 of the hippocampus is to stress the animal for 30 min prior to the commencement of the experiment (Xu et al., 1997). We examined whether LTD can be obtained using this protocol in the subiculum.

Interaction Between Stress and LFS (10 Hz)

Animals were stressed for 30 min prior to anesthetization by placing them in a novel, brightly lit, elevated environment; animals under these conditions frequently urinated and defecated, moved quickly around the environment, and showed piloerection. For the 50-ms ISI, the percentage increase of the second fEPSPcompared to the first was 49.74 ± 4.03%; at the 100-ms ISI, the percentage facilitation was less at 14.16 ± 2.2%. Stimulation was then resumed for approximately 5 min. The induction of LTD was then attempted by LFS (900 pulses) at 10 Hz. Baseline stimulation was again resumed at 0.1 Hz. Initially there was a depression in synaptic response (fEPSP amplitude stood at 43.01 ± 13.4% of baseline 5 min post-LFS). At the end of the 30-min recording period, fEPSP amplitude stood at 89.77 ± 13.1% of baseline, suggesting that some LTD was present (see Fig. 4c). PPF was measured at the end of the recording period: for the 50-ms ISI, the percentage increase of the second fEPSP compared to the first was found to be 3.89 ± 5.49%. There was evidence of paired-pulse depression (PPD) at the 100-ms ISI; the percentage depression was found to be −20.32 ± 6.65% (see Fig. 4d).

CHARACTERISTICS OF SUBICULAR UNIT FIRING IN THE FREELY MOVING RAT

We used a pellet-chasing task, similar to that developed by Muller et al. (1987, 1991), to analyze spatial representation in the subiculum. Rats are placed in a large, black plastic tub (height 78 cm; width 68 cm) into which food pellets are thrown at 10–15-s intervals. A large white cue card (21 × 29 cm) is placed on the inside wall of the tub to act as a polarizing cue. In a similar task, Sharp and Green (1994) showed that subicular units demonstrate reliable place-related firing, and that the firing fields of subicular

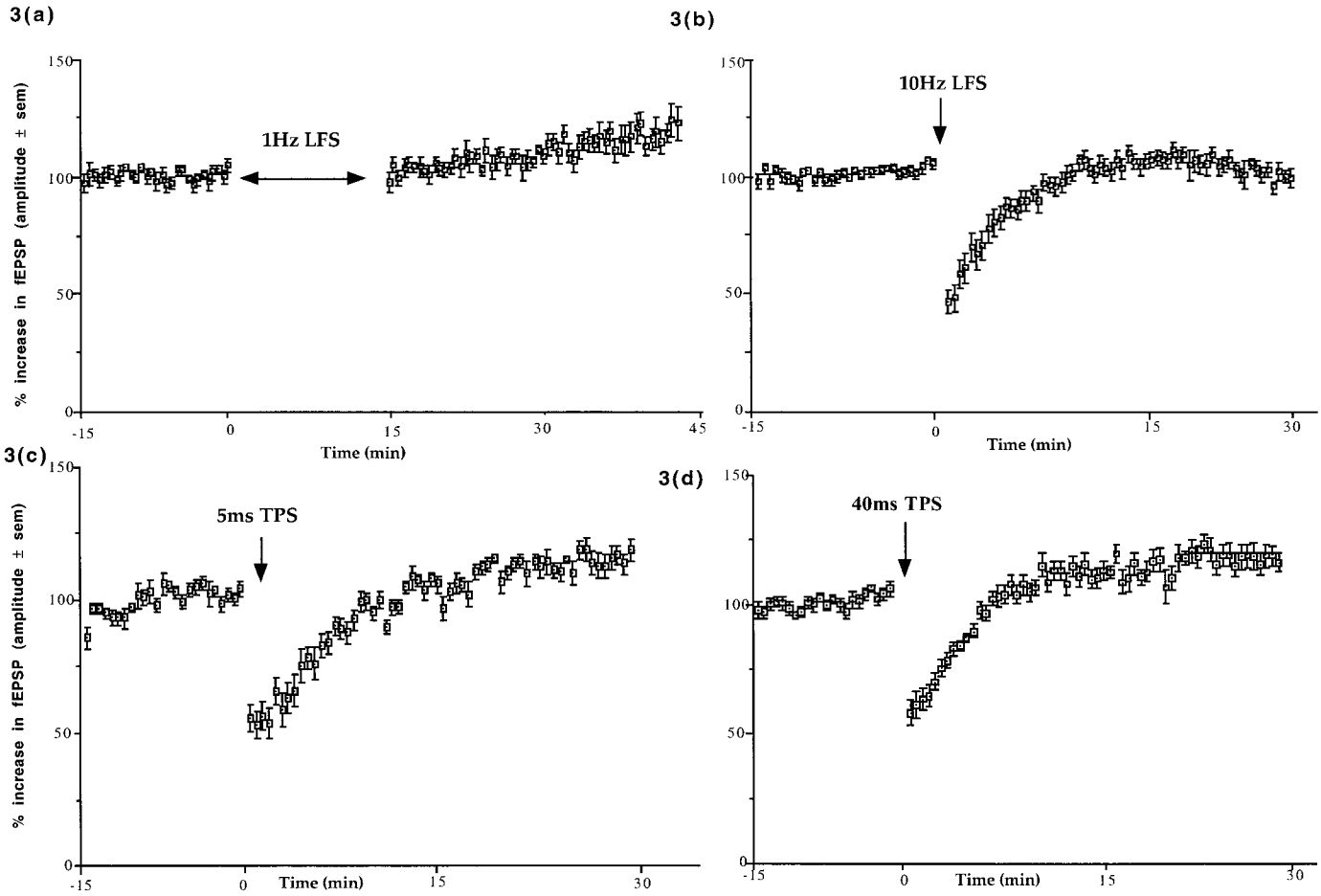


FIGURE 3. a: LFS delivered at 1 Hz induces a late-developing potentiation. b: LFS delivered at 10 Hz does not induce either LTD or a late-developing potentiation. c: TPS with an IPI of 5 ms induces a late-developing potentiation. d: TPS with an IPI of 40 ms induces a late-developing potentiation.

units can follow movements of the cue card. We extended these findings to examine the effects of cue removal and subsequent cue replacement, as well as cue movement, on the spatial firing correlates of subicular units. Specifically, our task consists of four conditions in which the position of the cue card is adjusted in each: 1) the cue card is attached to the side wall in the north position; 2) the cue card is moved to the south position; 3) the cue card is removed; and 4) the cue card is returned to the north position. Unit activity is recorded in each condition for 10 min; the animal is returned to its home cage for 5 min between each condition.

Figure 5 shows firing rate maps of two sample subicular units under the four conditions of the task. Figure 5a(i) shows a unit with a small, well-defined place field in the southwest portion of the environment. Following the movement of the card, the place field remains in the southwest, but with slight stretching in the direction of the card (Fig. 5a(ii)). Removal of the card has an interesting effect: two separate fields appear (Fig. 5a(iii)). While one of these fields is in the same position as in the first two conditions, the second field appears in a place opposite the first, as if removal of the cue has introduced uncertainty as to the animal's position in the environment. Replacing the cue card returns the place field to its original position, with a slight reduction in its spatial specificity (Fig. 5a(iv)). This unit appears to respond predominantly to fixed allothetic cues, or to idiothetic information: movement of the cue card has little effect on its place field. The cue card may modulate its response, however, in light of the impact of cue removal.

A second subicular unit is shown in Figure 5b. This unit is more typical of a subicular unit, in that its firing field covers a large proportion of the task environment. In the first condition its peak firing is in the southwest portion of the environment (Fig. 5b(i)). Movement of the cue card causes a rotation of the peak firing to the northeast; there is also an apparent reduction in the size of the overall firing field (Fig. 5b(ii)). Cue card removal causes the peak of firing to shift slightly, though the area covered by the firing field is largely unchanged (Fig. 5b(iii)). When the cue card is returned to its initial position, the firing field returns to the southwest (Fig. 5b(iv)). This unit appears to be predominantly under the control of the cue card.

Autocorrelation histograms (ACHs) were constructed for both units. Figure 5c shows the ACH for the unit analyzed in Figure 5a; both units, however, had very similar ACHs. Subicular units with

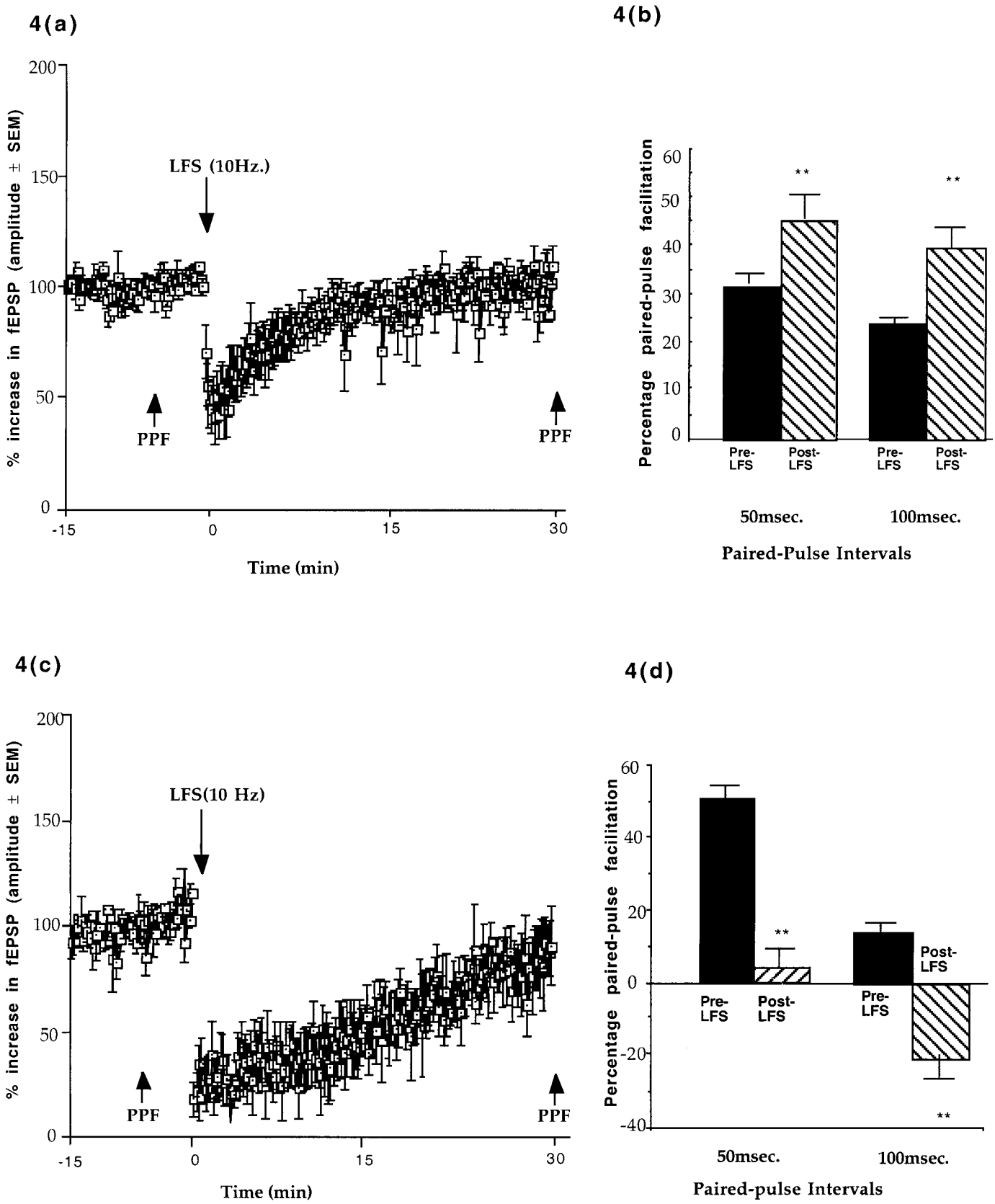
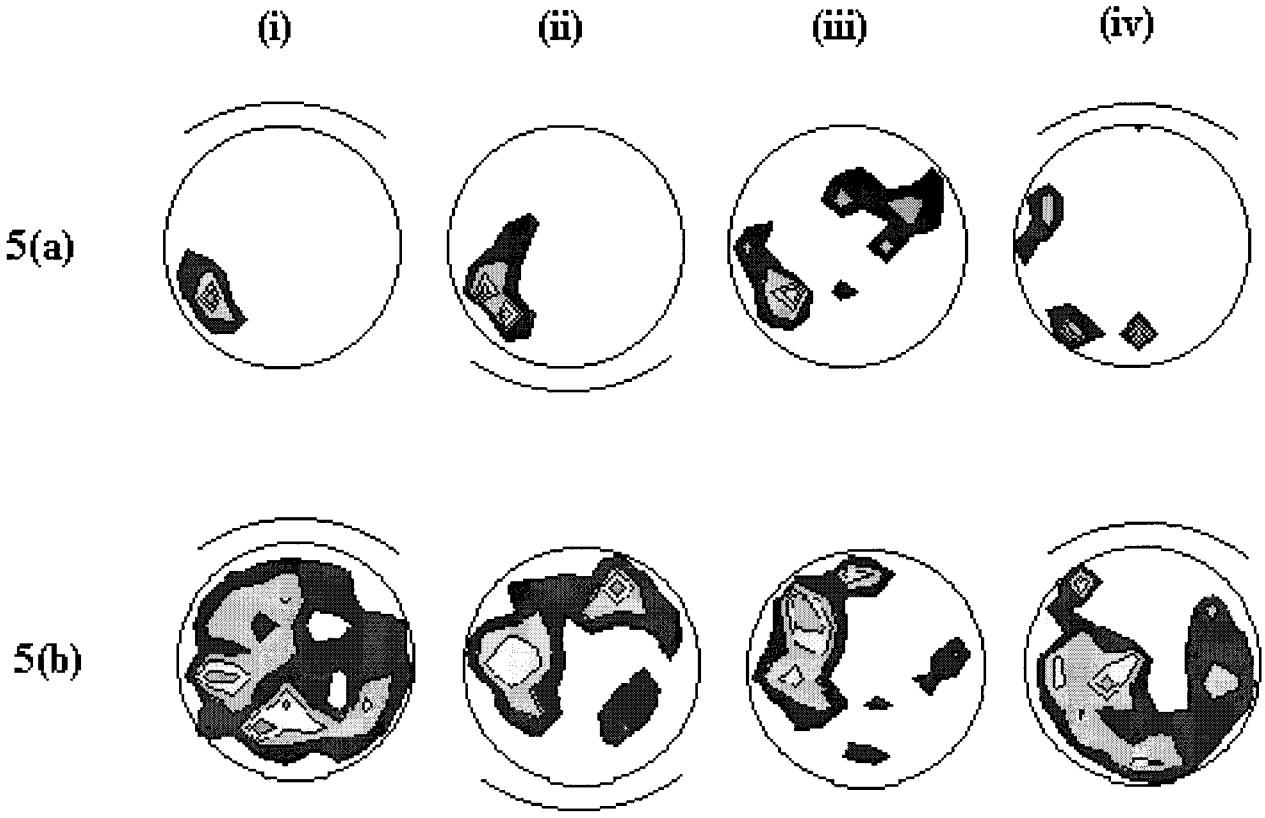


FIGURE 4. a: Effects of LFS (10 Hz) on amplitude of fEPSPs. Post-LFS values are expressed as percentage of prestimulation baseline ± SEM. b: Bar chart showing percentage PPF both pre- and post-LFS for the 50-ms and 100-ms ISIs. Note the increase in facilitation at both ISIs post-LFS. c: Effects of stress and LFS (10 Hz) on amplitude of fEPSPs. Post-LFS values are expressed as percentage of prestimulation baseline ± SEM. d: Bar chart showing percentage PPF both pre- and post-LFS for the 50-ms and 100-ms ISIs. Note the decrease in facilitation at 50 ms ISI post-LFS and PPD at the 100-ms ISI.



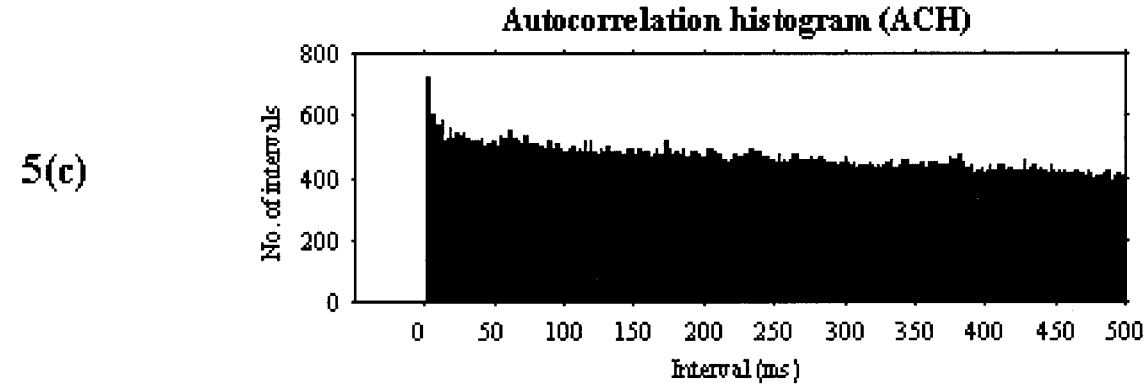


FIGURE 5. **a, b: Firing maps for two subicular units in the four conditions of the pellet-chasing task. Firing rate maps were constructed by dividing the environment into 6 × 6 cm pixels, and then mapping the resulting matrix in a contourplot. Each contour step represents 20% of the pixel peak firing rate. See text for details. c: Autocorrelation histogram (ACH) of the unit in a. Both units displayed here have similar ACHs.**

ACHs similar to this have been previously seen (Barnes et al., 1990). The ACH peaks in the 1–2 ms bin indicating a large number of small intervals between spikes, indicative of burst firing; however, there are also large numbers of longer intervals. There appears to be little rhythmicity in the firing of this type of unit. The average firing rate of these units is in the same range as units recorded in area CA1 (between 5–7 Hz), although units with much higher rates have also been encountered (so far up to 35 Hz, similar to Barnes et al., 1990).

HIPPOCAMPAL-CORTICAL INTERACTION: SYNAPTIC PLASTICITY AND THE ROLE OF THE SUBICULUM

Several authors (Rolls and O'Mara, 1993; Squire, 1992) have suggested that the hippocampus functions as an intermediate-term memory that allows memories to be stored in long-term memory (presumed to be situated in the neocortex). There are differing views on the nature of the processes of consolidation by the hippocampus. Nadel and Moscovitch (1997), for example, regard it as a largely instantaneous process, whereas Rolls and O'Mara (1993) suggest that it may take a much longer period of time. In addition, Rolls (1996) predicts that both the CA1-subiculum and subiculum-entorhinal projection should exhibit LTP. We have confirmed the first of these predictions. It was also hypothesized that the back-projection system from the hippocampus to the cortex should operate as rapidly as the modifiability within the hippocampus itself and should decay with a similar slow time course (Rolls, 1996). We also confirmed these predictions: LTP is rapidly induced and remains potentiated for at least 3 h in the CA1-subiculum pathway. Most importantly, the experiments here, demonstrating that the CA1-subiculum pathway is capable of undergoing changes in synaptic strength, are an important first step in determining the locus of plasticity for encoding memories. Further experiments should examine the plasticity of other loci en route to the cortex, for example, the subiculum to entorhinal/perirhinal cortices or even the subiculum to subcortical structures. Although we were unable to decrease synaptic efficacy in the CA1-subiculum pathway, i.e., to induce LTD using a number of protocols, we were able to show a small depression in synaptic response when we stressed the animal for 30 min prior to commencement of the experiment. This effect has been shown to be more dramatic in other regions of the hippocampal formation. In area CA1, for example, depression was induced immediately and responses remained consistently lowered for 30 min (Xu et al., 1997). As a consequence, different pathways may play functionally distinct roles in the consolidation of memories.

Theta rhythm occurs naturally during motor activity or novelty perception, and is believed to be important for memory formation because blocking theta rhythm impairs the ability of rats to learn spatial tasks (Winson, 1978). The subiculum possesses two principal cell types: regular firing cells (nonbursters), and bursting cells (Taube, 1993). These bursting cells may have a number of functional consequences. First, bursting cells coupled with complex spike activity, which is a natural firing pattern occurring in theta-frequency EEG rhythms, may play a role in the induction of LTP-like changes of synaptic strength in vivo. The experiments presented here confirmed that a change in synaptic efficacy can be produced in the subiculum with theta-patterned stimulation, which resembles these natural firing complex-spike patterns. Perhaps bursting cells alone could produce an LTP-like effect, providing that the phase of theta-EEG rhythm was synchronized with cell bursts. Emerging evidence that LTP can be produced with as few as 3 bursts of 5 pulses on the positive phase of theta rhythm in area CA1 (Hölscher et al., 1997) adds weight to this suggestion. We have also shown that the subiculum supports PPF. One of the consequences of PPF is an increased tendency of neurons to fire double or multiple spikes (Leung and Fu, 1994). This could increase the chance of LTP induction in the subiculum, not only in regular firing neurons, but especially if they were coupled to bursting cells, providing a tetanus-like effect.

We can draw some tentative conclusions from this freely moving study. Similar to Sharp and Green (1994), we found that the firing fields of subicular units are typically much larger and more diffuse than those found in area CA1, occupying a large proportion of the surface of the task environment; that subicular units typically display several peaks of firing within a more general firing field, again in contrast to area CA1; and that subicular place fields can rotate, following the movement of a cue card. We also found that subicular units can maintain their place fields in the absence of the cue card, even when it has been shown to control the spatial firing of the unit; and that the cue card, once replaced, can regain control over subicular unit firing.

Overall, the pattern of data presented here and from other sources (Sharp and Green, 1994) demonstrates clearly that the subiculum displays synaptic plasticity at differing levels of analysis. The input to the subiculum from hippocampal area CA1 is capable of showing both short- and long-term plastic effects. Furthermore, these effects are sensitive to the behavioral state of the organism: a short period of stress has marked effects on synaptic transmission. Equally, single subicular units in the freely moving animal also show dramatic changes in their representation of space, depending on the nature of the changes that are made in the environment. Thus, modifications to large polarizing cues are rapidly incorporated in the spatial map that appears to be represented in the activity of subicular neurons. Thus, the subiculum has many of the characteristics of a structure that might be important for memory: its synapses are readily modifiable, and it rapidly incorporates information from the external environment into its representation of the environment. The challenge for the future will be the fine-grained specification of hypotheses regarding the role of the subiculum as a possible mediator of hippocampal-cortical interaction, and their subsequent experimental testing.

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