The Hippocampo-Neocortical Dialogue

In gross anatomical terms, the hippocampal archicortex can be conceived as an "appendage" of the large neocortex. In contrast to neocortical areas, the main output targets of the hippocampus are the same as its main inputs (i.e., the entorhinal cortex). Highly processed information about the external world (the context) reaches the hippocampus via the entorhinal cortex, whereas information about the "internal world" (the context) is conveyed by the subcortical inputs. Removal of the context makes the content illegible, as demonstrated by the observation that the behavioral impairment following surgical removal of hippocampopetal subcortical inputs is as devastating as removing the hippocampus itself. From its strategic anatomical position and input-output connections, it may be suggested that the main function of the hippocampal formation is to modify its inputs by feeding back a processed "reafferent copy" to the neocortex. I hypothesize that neocortico-hippocampal transfer of information and the modification process in neocortical circuits by the hippocampal output take place in a temporarily discontinuous manner and might be delayed by minutes, hours, or days. Acquisition of information may happen very fast during the activated state of the hippocampus associated with theta/gamma oscillations. Intrahippocampal consolidation and the hippocampal-neocortical transfer of the stored representations, on the other hand, is protracted and carried by discrete quanta of cooperative neuronal bursts during slow wave sleep.

The Anatomical Substrate

Traditionally, the organization of the hippocampus is thought of as a series of principal cell groups that form a unidirectional feedforward excitatory pathway from the entorhinal cortex to dentate granule cells to CA3 to CA1 pyramidal cells and subicular neurons and back to the deep layers of the entorhinal cortex (Fig. 1; Ramón y Cajal, 1899; Lorente de Nó, 1934; Steward, 1976; Lopes da Silva et al., 1990; Amaral and Witter, 1989). The entorhinal cortex is bidirectionally connected to nearly all areas of the neocortical mantle (Van Hoesen and Pandya, 1975; Swanson and Kohler, 1986), and is thus poised to route information into the hippocampus and return the consequence of hippocampal processing back to these neocortical targets. Ideally, the hippocampal output should address the same neocortical neuronal assemblies that gave rise to the hippocampal representations. Although the entorhinal cortex is remapped topographically onto the CA1 region (Tamamaki and Nojyo, 1995) and the granule cell projection onto CA3 pyramidal cells is rather focused (Claiborne et al., 1986), divergence of the entorhinal input to granule cells and CA3 cells and, in turn, divergence of CA3 pyramidal neurons in the CA3 and CA1 regions are extremely large (Fig. 2; Ishizuka et al., 1990; Li et al., 1994). Some anatomical (cf. Amaral and Witter, 1989), physiological studies argue for the lack of a clear topographical organization in the hippocampus (O'Keeffe and Nadel, 1978; Muller et al., 1987; Wilson and McNaughton, 1993), whereas others support an orderly arrangement (Eichenbaum et al. 1989; Tamamaki and Nojyo, 1991).

The major subcortical inputs are the medial septum and contiguous diagonal band that innervate all areas of the hippocampal formation. Other subcortical afferents, directly or largely via an influence on hippocampopetal septal neurons, can orchestrate activity in the hippocampus and entorhinal cortex and thus effectively and dramatically modify the physiological operations of the hippocampal system (Buzsáki, 1984; Freund and Antal, 1988).

In addition to the main principal cell types, several classes of inhibitory interneurons are known with different circuit, physiological and biochemical properties, and hypothesized functions. Interneuronal groups may receive different local and extrinsic inputs, possess various intrinsic molecular and functional properties, and target different somatodendritic segments of the principal cells (Freund et al., 1990; McBain and Dingledine, 1992; Miles and Ponce, 1993; Gulyás et al., 1993a,b; Buhl et al., 1994; Miles et al., 1994; Sik et al., 1994). Some interneuronal types exert a local control on the principal cell populations, whereas others form interstitium-like networks with axonal connectivity different from or opposite to the excitatory connectivity of the principal neurons (LaBelle and Schwartzkroin, 1988; Freund et al., 1990; Michelson and Wong, 1991; Sik et al., 1994; Whittington et al., 1995). Collectively, interneuronal networks maintain various slow and fast rhythms and through their widespread and strategically wired axon collateral systems they can regulate various aspects of the operational modes of principal cells, such as cooperative synchrony and plasticity (Chrobak and Buzsáki, 1995).

The Problem

The hippocampal formation has been long implicated in learning and memory in both humans and animals. It has also been recognized that memory traces of past events are eventually transferred or rerepresented in the neocortex (cf. Eichenbaum and Otto, 1992; Squire, 1992). A major task therefore is to reveal neuronal mechanisms responsible for the modification of neuronal connectivity within the hippocampus and in the neocortex by the hippocampal formation. If conjoint firing of neurons during explorative-learning behavior is a sufficient condition for synaptic modification (Larson and Lynch, 1986; Lynch 1986; Rose and Dunwiddie, 1986; Miller, 1989; Otto et al., 1991), then the issue one has to face is whether similar cooperative firing during other behavioral states produces similar alterations in synaptic weights. As will be discussed below, the most synchronous population bursts of principal cells occur during sleep. The problem therefore is why simultaneously bursting neurons during sleep and other consummatory behaviors do not induce "false" or random modifications of network connectivity and why these bursts do not erase or attenuate plastic changes brought about during explorative-learning behavior.

A possible solution to these problems is the suggestion that the information, gathered and stored in a temporally discontinuous manner during exploration, is played back together at a faster scale during synchronous population bursts associated with consummatory behaviors. Such organized pop-
Figure 1. Main excitatory connections in the hippocampal formation. Layer II of the entorhinal cortex forms a longitudinally widespread projection to granule cells and CA3 pyramidal cells via the perforant path. (The direct entorhinal to CA3 connection is not shown). The next stage is the lamellary organized mossy fiber projection from the granule cells to the CA3 pyramidal cells. CA3 pyramidal neurons are strongly interconnected by a longitudinally projecting recurrent, associational system. The CA3 to CA1 associational projection is, again, longitudinally widespread. The extent of CA3-CA3 and CA3-CA1 projections in the septotemporal direction is similar but more collaterals are present in CA1 than in CA3. In contrast to the divergent, multisynaptic system, layer III pyramidal cells of the entorhinal cortex provide a direct and spatially restricted innervation of CA1 pyramidal cells, which in turn, project back to the same columns in the entorhinal cortex (deep layers). In essence, the entorhinal cortex is mapped onto the CA1 region in a topographic fashion and the tri-synaptic, intrahippocampal "diffuse" system is superimposed on this organized topography. Another major output from CA1 is to the subicular complex (not shown). The main targets of the subiculum are subcortical (septal, hypothalamic, extrapyramidal) structures. Dark-shaded areas (layers II and III and dentate gyrus) are active predominantly during "open-loop" (awake) states, whereas the CA3-CA1—layer V entorhinal loop is involved in cooperative bursts during "closed-loop" (e.g., slow wave sleep) states. Superimposed on the excitatory projections are the locally projecting and widely projecting inhibitory interneurons that form an interneuronal network (not shown).

Table 1: Dichotomy of operations at different levels of neuronal organization

<table>
<thead>
<tr>
<th>Level</th>
<th>&quot;Open loop&quot;</th>
<th>&quot;Closed loop&quot;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Behavior</td>
<td>Aroused</td>
<td>Nonaroused</td>
</tr>
<tr>
<td>Field (EEG)</td>
<td>Gamma/theta</td>
<td>SPW, ripple, delta</td>
</tr>
<tr>
<td>Population</td>
<td>Phasic*</td>
<td>Intermittent</td>
</tr>
<tr>
<td>Cellular</td>
<td>Simple Na+ spikes</td>
<td>Bursts/Ca+ spikes</td>
</tr>
<tr>
<td>Control</td>
<td>Excitonic</td>
<td>Intronic</td>
</tr>
<tr>
<td>Function</td>
<td>Information processing</td>
<td>Memory consolidation</td>
</tr>
</tbody>
</table>

* REM sleep is regarded as an activated state at the hippocampal and thalamocortical levels, although clearly no behavioral arousal is present.

** Population activity of principal cells are entrained at both gamma and theta frequencies. However, individual cells typically fire intermittently. Burst discharge (cf. Ranck, 1973; McCormick 1992). Steady is or sustained sodium spike activity is viewed as the high-fidelity or throughput mode of neuronal transmission. The burst discharge mode, on the other hand, is an intrinsic feature of cortical and thalamic cells. The bursts of sodium spikes in the soma can backpropagate to the dendrites, where they often trigger calcium spikes, thereby facilitating calcium entry into the cell (Wong and Prince, 1978; Regen et al., 1989; Jaffe et al., 1992). The information transmitted by the cells to their respective targets during the burst is rather independent of their inputs in this mode of discharge because the burst is followed by a long-lasting afterhyperpolarization (AHP) and associated response refractoriness (Connors and Gutnick, 1990). In other words, the bursting mode of cell activity is the least optimal state for high-fidelity transfer detailed pre-synaptic temporal patterns. As will be discussed below, steady firing and burst discharges of hippocampal neurons are dominantly associated with "open loop" (preparatory, aroused) and "closed loop" (consummatory) operations of brain networks, respectively.

Network Level

In the "open loop" state the dominance of simple action potentials (sodium spikes) is due to the release of subcortical neurotransmitters (see below). In the "closed loop" state, the availability of subcortical neurotransmitters is reduced and neuronal synchrony is brought about by the combination of intrinsic connectivity (glutamate and GABA) and burst discharge at the single cell level. Burst firing of neurons have important consequences on the network pattern. First, burst firing in a pre-synaptic cell results in larger depolarization of its postsynaptic targets and a higher probability to discharge it (Miles and Wong, 1986). Second, prolonged hyperpolarization of the membrane in individual neurons facilitates the
emergence of network synchronization. Third, calcium entry into cells, a prerequisite for the induction of plasticity and gene expression in neurons (cf. Bliss and Collingridge, 1993; Badíe et al., 1993), may exert a long-term change on synaptic connectivity. During the burst mode of cell firing the electrical patterns can therefore most favorably be translated into molecular events. Thus, the two different states of neuronal operations at both cellular and network levels are possibly involved in different but equally important functions: information transmission and plasticity.

**System Level Changes Are Reflected by EEG**

The functional dichotomy of neuronal operations is reflected at the system level by the characteristically distinct EEG stages. In the thalamocortical system, these are traditionally referred to as "synchronization" and "desynchronization." The "closed loop" state (sleep) is defined by EEG synchronization in the neocortex; sleep spindles and delta waves (cf. Steriade and Buzsáki, 1989). In the hippocampus the "closed loop" state is dominated by intermittent population burst events, referred to as sharp waves (SPW). In contrast, the "open loop" state is characterized by low-amplitude fast rhythmic waves (gamma rhythms) in both neocortex and hippocampus (Bragin et al., 1995a; Gray, 1994). The gamma pattern is modulated by a slow "theta" rhythm (4-10 Hz) in the hippocampal formation (Green and Arduini, 1954; Bragin et al., 1995a).

**Critical Role of Subcortical Neurotransmitters**

Cortical networks are unstable without the homeostatic subcortical inputs. The isolated hippocampus operates extremely close to the transition point between a quiescent state and an abnormally active, epileptic state (Buzsáki et al., 1989; Traub et al., 1989). In the intact nervous system subcortically derived neuromodulators maintain cortical activity in a relatively narrow operating range. In the "open loop" state cortical neurons are under the constant influence of a dynamically changing array of neuroactive substances, which mostly affect the slow, potassium currents (cf. McCormick, 1992). Acetylcholine, histamine, serotonin, and noradrenaline attenuate the AHP of pyramidal cells (Haas and Konnerth, 1983; Cole and Nicoll, 1984; Madison and Nicoll, 1986; McCormick, 1992), making synaptic responsiveness of the neurons more efficient, providing a high-fidelity transfer by fast sodium spikes. When the amount of these homeostatic neuromodulators are reduced at the onset of the "closed loop" state, burst firing with calcium spikes at the neuron level and populations bursts at the network level began to dominate.

**Rhythms and Intermittent Population Bursts in the Hippocampal Formation**

Various population patterns, as reflected by spontaneous field potentials and rhythms, are present in the hippocampal formation (Table 2), including theta activity and associated gamma pattern (40-100 Hz oscillation), hippocampal sharp waves (SPW) and associated high-frequency (200 Hz) oscillation ("ripple"), dentate spikes, sleep spindles, and delta waves of sleep (cf. O'Keefe and Nadel, 1978; Buzsáki et al., 1983, 1994; Bland 1990).

**"Open Loop" Patterns: Theta and Gamma Oscillations**

Hippocampal rhythmic slow activity (RSA or theta) is present in rodents, carnivores, and primates (Green and Arduini, 1954; O'Keefe and Nadel, 1978; Buzsáki et al., 1983; Stewart and Fox, 1991) during exploratory behaviors and the paradoxical phase of sleep. Theta activity has been implicated in various theories of hippocampal function from sensory processing to the voluntary control of movement (Fig. 3; Grastyán et al., 1959; Vanderwolf, 1969). Several afferent and intrahippocampal systems are involved in the generation of extracellular currents recorded as field theta. The most important of these are the entorhinal afferents to the granule cells and CA1-CA3 pyramidal cells (Buzsáki et al., 1983; Leung, 1984; Lopes da Silva et al., 1990). Removal of the entorhinal input abolishes the large theta dipole observed at the level of hippocampal fissure in the intact rat (Bragin et al., 1995a; Ylinen et al., 1995b). Another important theta dipole is set up by inhibitory currents on the somata of pyramidal cells (Buzsáki et al., 1983, 1986; Leung and Yim, 1986; Fox, 1989; Brankack et al., 1993; Soltész and Deschénes, 1993; Ylinen et al., 1995b). These currents result from rhythmic phasing of hippocampal inhibitory interneurons by the medial septum (Stewart and Fox, 1990; Lee et al., 1994). In addition to the theta dipoles set up by the entorhinal afferents and interneuron-mediated somatic inhibition, efferents of all intrahippocampal and extrahippocampal cell groups, phase-locked to theta waves, contribute to the rhythmic field pattern. The systematic phase-shifts of these various dipoles produce the unique and behavior-dependent voltage-versus-depth profiles of theta activity in the intact animal (Buzsáki et al., 1986; Brankack et al., 1993). During theta activity the vast majority of pyramidal neurons and granule cells are virtually silent (Rácz, 1973; Fox and Rácz, 1981; Buzsáki et al., 1993; Traystman et al., 1993). In contrast, only a limited number of pyramidal and granule cells, representing, for example, the spatial position of the animal show a transient increase in firing as the animal moves into unique spatial locations (O'Keefe and Nadel, 1978; Jung and McNaughton, 1993; O'Keefe and Recce, 1993).

Hippocampal theta activity may serve several interdependent functions. First, its large-scale oscillation in the entorhinal-hippocampal network makes it possible for hippocampal neurons to be activated with the least amount of energy because the intrinsic "resonant" properties of hippocampal neurons are "tuned" to theta frequency (Alonso and Linás 1989; Leung and Yim, 1991; Ylinen et al., 1995b). Second, theta activity increases the "signal-to-noise" ratio by silencing most principal cells and keeping their membrane voltage close but below the firing threshold. As a result, a relatively few active entorhinal cortex afferents or mossy fibers of the granule cells are sufficient to discharge the principal cells. Because theta activity induces a fluctuation in cellular excitability, the probability that spatially distant and otherwise noninteractive neurons discharge nearly simultaneously is substantially increased. A third important function of theta may be inferred from a recent observation that the discharge of hippocampal pyramidal cells...
advances to progressively earlier phases of the theta cycle as the rat passes through the cells' spatial field (O'Keefe and Recce, 1993). An implication of this observation is that successive spatial fields are locked to different phases of theta waves. The temporal discharge sequence of the anatomically interconnected CA3 pyramidal neurons, in turn, may potentiate their connectivity (Muller et al., 1991; Burgess et al., 1994; Skaggs et al., 1996). In essence, the map of the environment will be "encoded" as a temporally ordered pattern in the recurrent collateral matrix of the CA3 region. It is fair to point out that a similar hypothesis in connection with gamma waves in the striate cortex has been put forward earlier by Gray and Singer (1989).
Concurrent with theta waves, a fast oscillatory pattern in the gamma band (40-100 Hz), is present in the hilus and to some extent in the vicinity of the pyramidal cell layer of CA1 and CA3 (Buzsáki et al., 1983; Leung, 1992; Bragin et al., 1995a). Interneurons are tightly coupled to the gamma rhythm and may discharge on each gamma wave. The gamma oscillation in interneurons may be intrinsic due to a voltage-dependent persistent sodium current (Llinás, 1988) and coupling of interneurons via GABA_A receptors in the background of diffuse activation may be sufficient to maintain a network oscillation (Whittington et al., 1995; X.-J. Wang and G. Buzsáki, unpublished observations). Such network rhythms may independently emerge in the entorhinal cortex (Chrobak and Buzsáki, 1995; Charpak et al., 1995) and hilus, the CA3 and CA1 regions (cf. Leung, 1992). In the behaving rat, the entorhinal and hilar rhythms are tightly coupled and tonically suppress gamma oscillation in the CA3-CA1 networks (Bragin et al., 1995a). The hilar and CA1 gamma rhythms are only rarely coherent, but these phase-locked couplings may be critical for memory trace retrieval (see below). Although, the slow theta and the fast gamma oscillations can be dissociated (Buzsáki et al., 1983, 1987b), in the intact animal they are intimately interrelated. First, changes in theta frequency (6-10 Hz) are coupled to changes in gamma frequency (40-100 Hz). Second, the frequency and power of gamma activity is modulated by the phase of the theta rhythm (Bragin et al., 1995a). Third, most interneurons oscillate at both theta and gamma field frequencies.

The functional significance of the hippocampal gamma pattern is not known. However, given the hypothesized rela-
relationship between features of the input signal (the "binding" problem) and gamma oscillations in the sensory areas of the neocortex (Gray, 1994), one may speculate that a transiently emerging high coherence of gamma oscillations in the neocortex and hippocampus may signal the binding of the perceived and recalled attributes of objects and events (Buzsáki et al., 1994; Bragin et al., 1995a). Another implication of the theta-modulated gamma pattern is that the dentate gyrus provides a net oscillatory output to the CA3 network, whereby the converging and concurrently active granule cells provide a high-frequency (40–100 Hz) stimulation to their CA3 pyramidal cell targets. Since some of the information-bearing pyramidal cells discharge at the same time, the Hebbian conjunction between the presynaptic tetanus and postsynaptic discharge may lead to a transient heterosynaptic modification of the active cells and create distinct subsets of hyperexcitable population in the CA3 recurrent network (Buzsáki and Czéh, 1992).

"Closed-Loop" Patterns: Sharp Waves, Ripples, and Dentate Spikes

At the end of exploration, decreased activity of subcortical inputs will result in an increased tendency for population burst firing in hippocampal principal cells. At the network level, this change is expressed as sharp waves (SPW) of 40–120 msec duration. SPWs occur irregularly (0.02–3/sec) during slow wave sleep, awake immobility, drinking, eating, face washing, and grooming (Buzsáki et al., 1983; Buzsáki 1986; Suzuki and Smith, 1987). Groups of pyramidal cells in CA1-3, subiculum, and deep layers of the entorhinal cortex now fire in synchronous population bursts associated with the field SPW (see Figs. 4, 6). The large amplitude SPWs in CA1 region reflect synchronous excitation (EPSP) of pyramidal cells by the Schaffer collaterals of CA3 neurons (Fig. 3c). The population bursts in CA3 pyramidal cells also propagate to the hilar mossy cells and can discharge granule cells, as well (Ylinen et al., 1995b). Overall, the probability of cooperative discharge of principal cells significantly increases during the SPW event (Fig. 5).

Besides CA1 pyramidal cells, the concurrently discharging CA3 pyramidal cells during the SPW also depolarize their target CA1 interneurons. This transient depolarization results in a fast (200 Hz) discharge in some interneuron types (Ylinen et al., 1995a). Phase-locked discharge of the interneurons, either through gap junctions or by pyramidal cell drive, in turn, induces a coherent intracelluar oscillation in CA1 pyramidal neurons. Phase-locked intracelluar events are reflected as fast field oscillations ("ripples") in the CA1 pyramidal layer (O'Keefe and Nadel, 1978; Buzsáki, 1986; Buzsáki et al., 1992; Ylinen et al., 1995a). Ripples consist of packets of 5 to 15 sinusoid waves with approximately 200 Hz intraburst frequency, and are highly coherent along the septotemporal axis of the CA1 region.

The oscillatory inhibition in the soma has two important consequences on the population behavior of pyramidal cells. First, the somatic and/axon initial segment inhibition, coupled to the dendritic drive of CA1 pyramidal cells (Fig. 3c), provokes the recruitment of CA1 pyramidal cell discharge. Second, the subtle but concerted inhibitory oscillation can efficiently time the occurrence of sodium spikes during the "regenerative" burst. As a result, spatially distant pyramidal cell groups can emit action potentials within less than 3 msec (Buzsáki et al., 1992).

In essence, the SPW bursts provides a short (40–100 msec), high-frequency (200 Hz) network burst to the target neurons within the hippocampus and in retrohippocampal structures. As a result, deep layer retrohippocampal (entorhinal and presubicular) and subicular neurons are depolarized and exhibit a concurrent population discharge (Fig. 6; Chrobak and Buzsáki, 1994). Importantly, the CA1 output during SPWs sets into motion a fast (200 Hz) population oscillation in the deep layers of the entorhinal cortex, as well (Chrobak and Buzsáki, 1994). Thus, during the SPW population burst principal cells of the hippocampal formation, from dentate granule cells to layer V pyramidal neurons, discharge coherently, and output from the entorhinal cortex exerts a net tetanic stimulation on its neocortical targets. The CA1 region may also directly affect prefrontal cortical areas, since neurons in this region can also be driven by the hippocampal SPW burst (Chrobak and Buzsáki, unpublished observations). Quasi-synchronous discharge of several thousand neurons within a 50–100 msec time window with action potentials overlapping with better than 3 msec precision is likely to be a significant event for the brain. Temporal coordination of presynaptic neuronal activity is among the most important conditions for the induction of synaptic modification. The question therefore is, what kind of information is encoded in these population bursts events?

Although neurons in layers II and III of the entorhinal cortex are active during theta (Mitchell and Ranck, 1980; Quirk et al., 1992), they are not recruited to the SPW bursts. Their
population discharge during "closed loop" states may, however, contribute to population bursts of the hilar region (Paré et al., 1995), termed dentate spikes (DS; Bragin et al., 1995b). DSs are large amplitude (2–4 mV), short duration (< 30 msec) field potentials that occur during the same behavioral conditions as SPW bursts. However, DS and SPW never occur simultaneously. Current source density analysis revealed sinks in the dentate molecular layer coupled with large sources in the granule cell layer. DSs are invariably coupled to synchronous population bursts of putative hilar interneurons. On the hand, CA3 pyramidal cells are suppressed during dentate spikes, and SPWs never follow dentate spikes within 200 msec. A further illustration of the antagonism between DS and SPW is that following bilateral removal of the entorhinal cortex DS disappear, whereas the incidence of SPWs increase several-fold (Bragin et al., 1995b). These findings indicate that DS-associated synchronized bursts of hilar region interneurons provide a suppressive effect on the excitability of the CA3–CA1 network in the intact brain.

To summarize, activity in the superficial layers of the entorhinal cortex can activate the dentate area during both "open-loop" and "closed-loop" states, leading to a suppression of gamma oscillation and SPW bursts in the CA3–CA1 subiculum–deep entorhinal cortex circuitry, respectively. The dentate gyrus thus provides stability to the recurrent circuitry of the CA3 region, upon which activation of a few selected CA3 pyramidal cells are superimposed during theta. In the "closed loop" state, population discharge of the CA3 region recruits neuronal activity in both feedforward (CA1 subiculum–entorhinal cortex) and feedback (dentate gyrus) directions.

Sharp Wave-Associated Population Bursts: A Physiological Candidate for Memory Consolidation

Linking learning-associated changes to neuronal networks and demonstration of ensuing synaptic/molecular modifications is a major challenge of modern neuroscience. The strongest argument for the involvement of the hippocampal formation in memory derives from lesion studies (cf. Squire, 1992). On the other end, numerous laboratories are working on the molecular mechanisms of long-term potentiation (LTP), as a proposed model of synaptic plasticity (Bliss and Lomo, 1973). The extensive research on LTP has established the major rules expected to be operating in the brain during memory trace formation. These are (1) conjunctive pre- and postsynaptic activity; (2) requirement of channel-mediated calcium influx; (3) specificity to those inputs that were coactivated with the postsynaptic depolarization of the cell; (4) neither postsynaptic depolarization alone nor weak afferent excitation in the absence of postsynaptic depolarization results in synaptic modification; and that (5) LTP is not an all or none phenomenon but consists of several stages with different biochemical
machineries, including protein synthesis (cf. Kelso et al., 1983; Bliss and Collingridge, 1993). However, the significance of LTP ultimately rests on its physiological role in the intact nervous system (McNaughton and Morris, 1987; Eichenbaum and Otto, 1992; Treves and Rolls, 1994). Demonstration of endogenous, network-induced neuronal plasticity is the first essential step towards that goal. Physiological patterns in the intact animal provide a logical starting point to examine whether the requirements of LTP are present in the behaving animal.

Cooperative activation of a group of pyramidal cells during theta activity-associated exploration might produce sufficient depolarization and consequent synaptic modification in their common targets (Larson and Lynch, 1986; Rose and Dunwiddie, 1986; Skaggs et al., 1995). It remains to be revealed, however, whether neuronal cooperativity during theta is powerful enough to bring about a nondecrementing LTP-like change and whether these changes can affect retrohippocampal circuitries. In this context, it is significant to emphasize that SPWs are associated with significantly more powerful population bursts of pyramidal neurons than during theta-related synchrony. The issue therefore is whether and how SPW bursts can consolidate representations acquired during theta-concurrent exploration. The argument is straightforward: if SPWs will not serve such a function, then additional mechanism(s) must be postulated that prevent plastic changes during "closed loop" operations of the brain.

The position taken in this article is that the behavior-dependent electrical changes in the hippocampus (theta and SPW-associated states) might subserve a two-stage process of information storage. In essence, the central idea is this: (1) activation vectors from the entorhinal cortex code mnemonic representations in subsets of CA3 pyramidal cells during theta-associated exploratory activity where information is temporarily held. (2) At the end of exploration, SPW bursts are initiated by those cells whose recurrent connectivity has been transiently potentiated during the explorative stage.
(burst initiators). Excitation therefore spreads from the most to the least excitable pyramidal cells by the extensive recurrent CA3 collateral system. The spatiotemporally structured and powerful SPWs bursts are hypothesized (1) to consolidate the connectivity change brought about by the exploratory ("open loop") behavior, and (2) to transfer the stored representations to neocortical networks by way of the CA1 region and the entorhinal cortex. In essence, the information gathered during the exploratory stage is "replayed" during the SPW bursts in a reversed order (Buzsáki, 1989). Although the two-stage model has yet to withstand future experimental challenges, some of its predictions have been tested and confirmed.

A critical assumption of the two-stage model, for instance, that neuronal participation in the SPW bursts is modified by experience, is backed up by empirical data. First, participation of pyramidal cells in consecutive SPW events is not random. Some neurons may discharge in 40% of the SPW bursts, whereas others fire very rarely (Ylinen et al., 1995a). Second, when pyramidal cells were activated by confining the animal in the spatial field of those cells, they fired significantly more frequently during the subsequent sleep episode than nonactivated neurons (Pavlides and Winson, 1989). Although their association with SPW events were not examined, pyramidal neurons likely discharged during the SPW bursts since there is little activity between these events during slow wave sleep. Third, when SPWs of two slow wave sleep episodes, separated by exploratory waking activity, were compared, the most consistent partners of SPW bursts in the second sleep episode were those cells that were most active during the preceding explorative activity (Fig. 7). Finally, Wilson and McNaughton (1994) have recently demonstrated that neurons that represented similar parts of the environment, and therefore fired in a temporally overlapping manner during exploration, exhibited an increased tendency to fire together during the subsequent slow wave sleep episode in comparison to sleep episodes preceding the behavioral task. Cells that had nonoverlapping spatial firing or were inactive during behavior did not show increased correlations. Overall, these findings indicated that information acquired during waking experience is reexpressed during SPWs.

A further prediction of the model is that the sequential recruitment of individual cells into SPW population bursts (i.e., its spatiotemporal structure) is based on the representations acquired during exploration. The assumption is that excitability of the CA3 pyramidal neurons is a function of the synaptic weights among them, which in turn, results from use-dependent activity during exploration. Thus, everything being equal, CA3 pyramidal cells, coactivated last before the shift from the "open loop" to the "closed loop" state, will initiate the SPW burst, followed by cell groups that fired together in progressively earlier phases of explorative behavior. Since neuronal ensembles active during sequential parts of the explorative activity are reactivated in a reversed order and at a faster time scale, many more neurons are coactivated during SPW than during any phase of exploration (Fig. 5). In essence, the SPW burst events "compress" time and allow temporarily distinct neuronal representations, acquired during explorative behavior, to be combined into a coherent whole. The sequential and orderly discharge of CA3 neurons during successive SPW bursts (at the statistical level) is hypothesized to be the mechanism for transferring such combined representations to the CA1 region, entorhinal cortex, and eventually the neocortex (Buzsáki, 1989; Chrobak and Buzsáki, 1994). Cells discharging early in the population event (initiator cells) will be depolarized most and for the longest duration and therefore are likely to fire bursts of sodium spikes and enter calcium through their dendrites. No direct evidence is available to support the above scenario. However, by repeated tetanic stimulation the shape and amplitude of SPW's recorded along the longitudinal axis of the CA1 region could be modified in such a way that the CA3 neurons that were most activated by the trains initiated the subsequently occurring spontaneous population events (Buzsáki, 1989). In addition, in a model of the CA3 network, neurons with stronger synaptic weights were more likely to initiate population events and emitted more action potentials during the population burst than other neurons (Traub and Buzsáki, unpublished observations).
theless, a main thesis of the hypothesized two-stage scenario, namely, that the spatiotemporal structure of SPW bursts contains a compressed information about representations acquired during theta-related exploration, needs to be buttressed by more direct empirical data.

The dentate gyrus may play a critical role in modifying synaptic "tetanic" stimulation by the entorhinal and mossy fiber inputs. Since in vitro experiments have shown that such cooperative coupling results in heterosynaptic potentiation of the recurrent collateral system (Chattarji et al., 1989), it is conceivable that the theta-associated potentiation process may increase the synaptic weights among the anatomically interconnected and activated CA3 pyramidal cells. These new functional connections, I hypothesize, are further consolidated by the SPW-induced reactivation.

To date, no direct evidence is available to support the view that SPW bursts in the intact brain play a role in LTP-like synaptic modification. However, when SPW-like bursts were mimicked in the slice preparation by local (CA3) application of the GABA blocker, bicuculline, single pulse activation of CA1 pyramidal cells in conjunction with the induced CA3 population bursts resulted in LTP of the Schaffer collateral-CA1 pyramidal cell synapse (Buzsáki et al., 1987a). Similar results were obtained with kainic acid-induced population bursts in the CA3 region (Ben-Ari and Gho, 1988). A subsequent experiment using the same bicuculline paradigm demonstrated that the CA3 burst-induced LTP is NMDA receptor dependent (Azouz et al., 1992).

Conclusions

Studies of physiological, cooperative neuronal patterns of the hippocampus in the behaving animal provide clues to the possibilities and constraints of its network performance. The intrinsic features of hippocampal neurons and their network patterns display two major cooperative states, as expressed by theta/gamma oscillation during explorative activity and SPW/200 Hz ripple bursts during consummatory behaviors. The shift between these two, antagonistic population patterns is regulated by the activity of hippocampopetal subcortical modulatory systems. It is postulated that theta and SPW states subserve a two-stage process of memory consolidation: the information gathered sequentially during theta is replayed in a compressed form during SPW-concurrent population bursts. This hypothesis provides a mechanism to associate events experienced in a temporally discontiguous manner. In addition, the SPW burst is an ideal candidate to transfer information from the hippocampus to the neocortex. Since the key emphasis is on network cooperation, experimental tests of the hypothesis will require large-scale, parallel recording of neuronal activity in both hippocampus and neocortex in order to reveal the precise spatiotemporal structure of population events during both theta and SPW bursts. In addition, it is becoming increasingly clear, that revelation of the intrinsic rules of such large complex networks would profit from computer modeling based on known anatomical connectivity and functional principles of the hippocampal formation.

Notes

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