1 Dynamical information processing in the CA1 microcircuit of the hippocampus

Bruce P. Graham and Vassilis Cutsuridis

A major challenge to understanding cortical function is the complexity found at both the single-cell and microcircuit levels. Here we outline what is known about the microcircuitry of the CA1 region of the mammalian hippocampus. We then explore the possible functional roles of the variety of neuronal types within this microcircuit during dynamic information processing. This is considered within the framework of CA1 acting as an associative storage device during encoding and retrieval of episodic memories.

1 Introduction

The local circuitry to be found in many parts of mammalian nervous systems consists of a complex architecture involving many different neuronal types connected in feedforward and feedback loops. Synaptic connections may be excitatory or inhibitory and target specific spatial locations on a neuron. In addition to synaptic input, a neuron and the microcircuit it is a part of are subject to diffuse neuromodulatory signals. Neural synaptic transmission and neuromodulation combine to provide a complex dynamics of neural activity and presumed information processing in a neuronal microcircuit.

Computational models of cognitive behaviour generally seek to provide a simple but cogent explanation of the functionality required to produce a particular behaviour. A model may be more or less interpretable in terms of the workings of a particular brain area, or set of connected areas. Often an artificial neural network (ANN) approach is used in which the simple computing units may correspond to populations of neurons rather than to individual biological neurons. The next level of biological detail is to use spiking neuron models where the identification with real neurons may be one-to-one. Such spiking models are of the integrate-and-fire type, or they may include explicit biophysical properties of a neuron in a compartmental model. Typically the neuronal types in such models are restricted to the principal excitatory cells, plus one or two sources of inhibition.

As we learn more about the details of real neural microcircuitry, it is clear that our current models lack the richness in spatial and temporal

information processing that brain circuits possess. The challenge is to build models that include more of the known biological details – such as further cell types and more complex models of individual neurons – but remain simple enough that they are understandable and provide explanatory power for cognitive function. To explore the ways forward, here we outline what is known about a particular neuronal microcircuit: the CA1 region of the mammalian hippocampus. We then try to relate aspects of this microcircuit directly to the general cognitive function of the storage and recall of information in an associative memory.

2 The hippocampal CA1 microcircuit

For both historical and experimental reasons, the hippocampus is among the most widely studied of mammalian brain regions, yielding a wealth of data on network architecture, cell types, the anatomy and membrane properties of pyramidal cells and some interneurons, and synaptic plasticity (Andersen, Morris, Amaral, Bliss, & O'Keefe, 2007). Its basic functional role is hypothesized to be the formation of declarative, or episodic, memories (Andersen et al., 2007; Eichenbaum, Dudchenko, Wood, Shapiro, & Tanila, 1999; Wood, Dudchenko, & Eichenbaum, 1999). Various subsystems, such as dentate gyrus, CA3 and CA1, may be involved in the storage of information in context, such as location in a particular spatial environment (Andersen et al., 2007), with appropriate recoding of afferent information depending on familiarity or novelty (Treves & Rolls, 1994).

The mammalian hippocampus contains principal excitatory neurons (pyramidal cells in CA3 and CA1) and a large variety of inhibitory interneurons (Freund & Buzsaki, 1996; Somogyi & Klausberger, 2005). The circuitry they form exhibits different rhythmic states in different behavioural conditions. Multiple rhythms, such as theta (4–7 Hz) and gamma (30–100 Hz) oscillations, can coexist (Whittington & Traub, 2003). This dynamic complexity presumably corresponds to specific functional processing of information (Axmacher, Mormann, Fernandez, Elger, & Fell, 2006). Much work has been devoted to trying to understand the cellular and network properties that generate these rhythms (Buzsaki, 2002; Traub, Jefferys, & Whittington, 1999), but much is still to be been done to decipher the function of the detailed microcircuits. In particular, how is plasticity controlled so that it does not interfere with previously stored memories while appropriately assimilating familiar and new information? This is the fundamental question that we will address, concentrating on the operation of the CA1 area.

2.1 External inputs to CA1

The CA1 region is one of several stages of information processing in the hippocampus. Its major sources of input are from the CA3 region of the hippocampus and the entorhinal cortex. It sends excitatory output back to

the entorhinal cortex, both directly and via the subiculum, and sends diverse outputs to a variety of other brain regions, such as the olfactory bulb. In addition, there are inhibitory projections from CA1 to the medial septum (MS) and back to CA3 (Sik, Ylinen, Penttonen, & Buzsaki, 1994). In turn, CA1 receives GABAergic inhibition and cholinergic neuromodulation from the MS (Freund & Antal, 1988; Frotscher & Lenrath, 1985).

CA1 also receives a variety of other neuromodulatory inputs, including dopaminergic and noradrenergic pathways. Much of this neuromodulation is directed to the distal apical dendrites of CA1 pyramidal cells, where it coincides with the entorhinal glutamatergic input (Otmakhova & Lisman, 2000).

2.2 Neuronal types and their connectivity

The basic hippocampal CA1 microcircuit is shown in Figure 1.1. The single excitatory cell type is the pyramidal cell (PC), which is the putative major

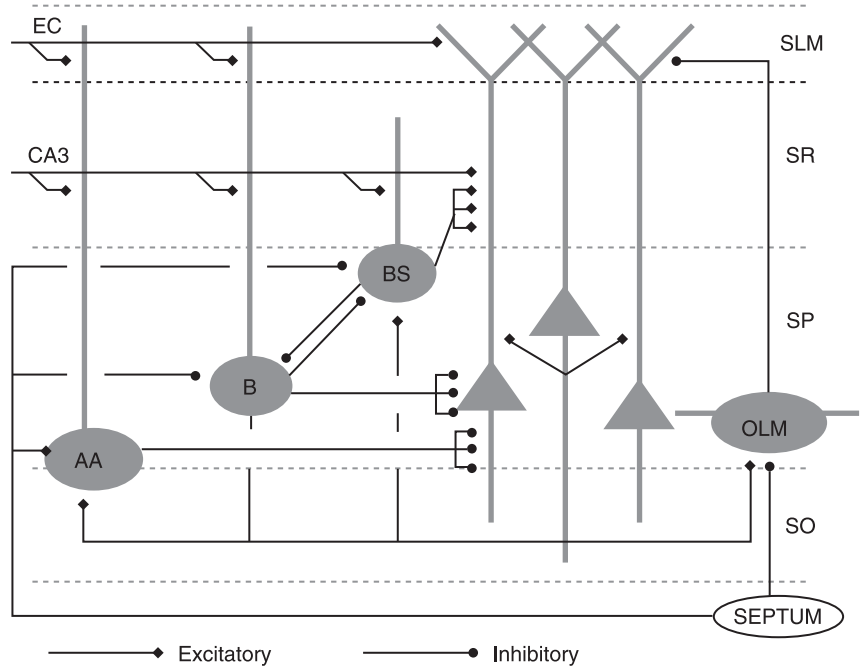

Figure 1.1 Hippocampal CA1 microcircuit showing major cell types and their connectivity. Large filled triangles: pyramidal cells. Large filled circles: CA1 inhibitory interneurons. EC: entorhinal cortex input; CA3: CA3 Schaffer collateral input; AA: axo-axonic cell; B: basket cell; BS: bistratified cell; OLM: oriens lacunosum-moleculare cell; SLM: stratum lacunosum moleculare; SR: stratum radiatum; SP: stratum pyramidale; SO: stratum oriens.

information processor for signals entering this brain region and is the major source of output from CA1. Pyramidal cells, here and elsewhere in the hippocampus and neocortex, have a large dendritic tree that is divided into apical and basal dendrites. These dendrites are the target for synaptic inputs that have distinct spatial segregation depending on the neuronal source.

Excitatory inputs from outside CA1 make connections on specific portions of the apical and basal dendrites of PCs (Ishizuka, Cowan, & Amaral, 1995). The Schaffer collateral input from pyramidal cells in the CA3 region of the hippocampus is exclusively to the proximal region of the apical dendrites constituting stratum radiatum (SR) and to the basal dendrites in stratum oriens (SO). Perforant path input from layer III of entorhinal cortex (EC) reaches the distal part of the apical dendritic tree in stratum lacunosum-moleculare (SL-M). Recurrent collaterals from other CA1 PCs synapse on the basal dendrites. Such collaterals are rather sparse in CA1, with only about 1% recurrent connectivity between pyramidal cells (Deuchars & Thomson, 1996). There are additional excitatory inputs from the thalamus to SL-M and from the amygdala to SO (Somogyi & Klausberger, 2005).

The pyramidal cells are surrounded by a variety of inhibitory interneurons (INs). These INs differ in morphology, pharmacology and connectivity (Freund & Buzsaki, 1996; Maccaferri & Lacaille, 2003; McBain & Fisahn, 2001; Somogyi & Klausberger, 2005). Though a complete catalogue of interneuronal types remains to be determined, at least 16 classes can be distinguished on anatomical, electrophysiological and pharmacological grounds (Somogyi & Klausberger, 2005). The most clear-cut types are basket cells, bistratified cells, axo-axonic (chandelier) cells and oriens lacunosum-moleculare (horizontal) cells. However, basket cells in particular consist of at least two subtypes: one that expresses parvalbumin and one that expresses cholecystokinin. Others include horizontal and radial trilaminar cells and INs that only synapse onto other INs (Freund & Buzsaki, 1996). A subclass of horizontal trilaminar cells (HTCs) sends axon collaterals out of the hippocampus to the medial septum (MS). There is also an inhibitory projection from CA1 to CA3. All these INs are inhibitory GABAergic cells.

Like excitatory afferents, different IN types target specific spatial regions on PCs (Megias, Emri, Freund, & Gulyas, 2001). They also receive excitatory input from particular pathways and may form synaptic (inhibitory) and gap junction (excitatory) connections with other INs (Gulyas, Megias, Emri, & Freund, 1999). In what follows we concentrate on four major classes of IN:

- **Basket cells (BCs)** receive feedforward excitation from CA3 and entorhinal PCs and feedback excitation from CA1 PCs. They form inhibitory connections on the perisomatic region of CA1 PCs, as well as with each other and with other IN classes. They also appear to form at least a partial syncitium through dendritic gap junctions with each other, ensuring high-frequency synchronization of their firing (Bartos, Vida, & Jonas, 2007).

- **Bistratified cells (BSCs)** are also driven by feedforward input, largely from CA3. They inhibit PCs in the same dendritic regions in SR and SO that are the site of CA3 input. They also inhibit other INs, including BCs.
- **Axo-axonic cells (AACs)** are driven in the same fashion as BCs, but they form synapses exclusively on the initial segment of PC axons.
- **Oriens lacunosum-moleculare (OLM) cells** are predominantly driven by CA1 PCs and provide feedback inhibition to the distal dendrites of PCs, corresponding to the site of entorhinal cortex input to these cells.

Recent data indicate that these cell types may be distinguished by their firing patterns in different brain states (Klausberger et al., 2003, 2004). The firing rate and timing of action potentials (APs) relative to the theta rhythm are distinct for the different cell types, arising from differences in network connectivity and intracellular properties. One factor here is differences in the short-term dynamics of the excitatory drive to these INs. Excitatory synapses onto BCs, BSCs and AACs are powerful and quickly depress in response to repeated stimulation (Ali, Deuchars, Pawelzik, & Thomson, 1998; Sun, Lyons, & Dobrunz, 2005). This results in these INs responding rapidly to the onset of excitatory drive and then adapting as the stimulus continues. In contrast, excitatory synapses onto OLM cells have low release probability and facilitate with repeated stimulation, resulting in OLM cells responding most strongly later in a stimulus rather than at the onset (Ali & Thomson, 1998; Losonczy, Zhang, Shigemoto, Somogyi, & Nusser, 2002). Thus inhibition onto CA1 PCs from OLM cells is delayed relative to these other inhibitory pathways. The difference in firing properties between IN types is a key indicator of their potential functional roles in different behavioural states.

2.3 Rhythm generation

Cellular activity shows distinct characteristics depending on the behavioural mode of an animal. This has been most extensively studied in rats. During exploration of the environment, the EEG recorded from CA1 exhibits a modulation in a frequency range of around 4–7 Hz, the so-called theta rhythm. At the same time, gamma-frequency (30–100 Hz) modulation of the EEG is also present. A typical pyramidal cell fires only one or two spikes per theta cycle and is not active in every cycle. Fast-spiking INs (BC, AAC, BSC) will fire multiple spikes at gamma frequency.

Microcircuit interneurons and external inputs are responsible for theta and gamma rhythm generation and modulation of PC synaptic plasticity. The network of BCs provides the robust gamma rhythm due to their fast-firing properties and mutual interconnections (Bartos et al., 2007). Inhibition from BCs onto PCs can synchronize PC firing (Cobb, Buhl, Halasy, Paulsen, & Somogyi, 1995).

Theta rhythm generation is highly complex and may take different forms

in different *in vivo* and *in vitro* experimental preparations (Buzsaki, 2002). Recent modelling studies have demonstrated that slow inhibition provided by OLM cells coupled with fast inhibition from fast-spiking INs, such as BCs, can generate an intrinsic theta rhythm in CA1 (Orban, Kiss, & Erdi, 2006; Rotstein et al., 2005). The medial septum also oscillates at theta rhythm and provides rhythmic GABA-A inhibition, principally to interneurons in the hippocampus (Freund & Antal, 1988; Hasselmo & Fehlau, 2001). It also provides slower cholinergic modulation to multiple cellular targets (Frotscher & Lenrath, 1985; Hasselmo & Fehlau, 2001).

2.4 Synaptic plasticity

Experiments have revealed wide-ranging synaptic plasticity in the CA1 microcircuit. All excitatory inputs that have been studied, either onto PCs or onto INs, appear to be modifiable in response to patterns of pre- and post-synaptic activity (Bliss, Collingridge, & Morris, 2007). There is also some evidence for plasticity of inhibitory synapses onto pyramidal cells (Bliss et al., 2007).

The rules underpinning plasticity are largely Hebbian, in which correlated pre- and post-synaptic activity leads to a strengthening of the synaptic connection (long-term potentiation, LTP). Uncorrelated firing leads to a weakening of the synapse (long-term depression, LTD). The precise nature of the required correlations is still to be determined. There is evidence for spike-timing-dependent plasticity (STDP) at Schaffer collateral synapses onto PCs (Bi & Poo, 1998, 2001; Magee & Johnston, 1997). Plasticity may also depend purely on local dendritic activity rather than rely on spiking in the soma and axon (Golding, Staff, & Spruston, 2002; Holthoff, Kovalchuk, & Konnerth, 2006; Lisman & Spruston, 2005). This situation leads to the possibility of spatial specificity in learning, rather than just synapse specificity, in which activation of colocated synapses may increase the chances of all these synapses being modified (Mehta, 2004).

Not all plastic connections may be modified in a Hebbian fashion. Excitatory connections onto OLM INs appear to be subject to an anti-Hebbian learning rule in which presynaptic activity alone leads to LTP, whereas correlated pre- and post-synaptic activity results in LTD (Lamsa, Heeroma, Somogyi, Rusakov, & Kullmann, 2007).

3 Associative memory

The hippocampal regions CA3 and CA1 have been proposed to be auto- and heteroassociative memories, respectively (Treves & Rolls, 1994), for the storage of declarative information. Associative memory is one of the oldest ANN paradigms. It has been widely studied due to being plausibly a model of how certain brain regions, such as the hippocampus, may operate, but also due to the discovery of simple implementations that are analytically

tractable (Amit, 1989; Hopfield, 1982; Willshaw, Buneman, & Longuet-Higgins, 1969).

The requirements for building a workable associative memory are rather simple. Memory patterns are encoded as the activity patterns across a network of computing units, or neurons. Patterns are stored in the memory by Hebbian modification of the connections between the computing units. A memory is recalled when an activity pattern that is a partial or noisy version of a stored pattern is instantiated in the network. Network activity then evolves to the complete stored pattern as appropriate units are recruited to the activity pattern, and noisy units are removed, by threshold-setting of unit activity. Memory capacity for accurate recall is strongly dependent on the form of patterns to be stored and the Hebbian learning rule employed.

Simple ANN models are amenable to mathematical analysis, leading to estimates of memory capacity (Amit, 1989) and the definition of optimal Hebbian learning rules (Dayan & Willshaw, 1991). Biologically plausible modifications to these simple models allow efficient memory storage in partially connected networks (Buckingham & Willshaw, 1993; Graham & Willshaw, 1995, 1997) with unreliable connections (Graham & Willshaw, 1999). Noise due to inputs to a neuron arriving over spatially extensive dendrites may not seriously reduce memory capacity and can be ameliorated by certain intracellular properties found in hippocampal pyramidal cell apical dendrites (Graham, 2001).

All of this work addresses the mechanics of pattern recall in networks containing a single (principal) neuron type. The mechanics of pattern storage and how it may be dynamically interleaved with recall are not considered. The cellular and network mechanisms underlying pattern specification, learning (storage) rules and threshold-setting during recall are not explicitly included. These mechanisms must be manifest in biological neural nets through the microcircuitry formed by the large variety of neuronal types.

3.1 Associative memory and the hippocampus

These considerations have led to the formulation of neural models of associative memory based on the architecture and operation of hippocampal areas CA3 and CA1 (Kunec, Hasselmo, & Kopell, 2005; Menschik & Finkel, 1998; Wallenstein & Hasselmo, 1997). These models include multiple cell types and their connectivity, with cells represented by biophysically based compartmental models of spiking neurons. The models seek to mimic the hippocampal activity seen in rats exploring a novel environment, absorbing and storing new spatial information (O'Keefe & Recce, 1993).

Theta and gamma rhythms are a feature of this activity. These models instantiate a working hypothesis that the theta rhythm, which is prominent during exploration, modulates episodes of storage of new information and recall of old information in its half-cycles (Hasselmo, Bodelon, & Wybl, 2002a; Hasselmo, Hay, Ilyn, & Gorchetchnikov, 2002b). During exploration

an animal is likely to encounter both familiar and novel situations. Storage of new episodes with minimal interference from already encoded episodes takes place most efficiently if storage and recall are temporally separated in the encoding neural networks. Waxing and waning of GABA-mediated inhibition from the medial septum leads alternately to disinhibition and inhibition of PCs during a theta cycle, corresponding to ideal conditions for pattern recall and pattern storage, respectively. The higher-frequency gamma rhythms (30–100 Hz) constitute a basic clock cycle such that patterns of activity for storage and recall correspond to PCs that are active in a particular gamma cycle (Axmacher et al., 2006; Buzsaki & Chrobak, 1995; Lisman & Idiart, 1995).

Patterns of PC activity for storage are determined by the spatiotemporal correspondence of direct afferent input from the entorhinal cortex and indirect input via dentate gyrus onto CA3 PCs and via CA3 PC input onto CA1 PCs. Such patterns are stored autoassociatively in CA3 by Hebbian modification of recurrent connections between CA3 PCs, and heteroassociatively in CA1 by modification of CA3 input onto CA1 PCs (Hasselmo et al., 2002a).

Storage and recall dynamics are influenced by synaptic and intrinsic cellular properties and by alteration of these properties by neuromodulation with acetylcholine. Acetylcholine and GABA-B-mediated inhibition may serve to set appropriate conditions for pattern storage by reducing synaptic transmission while promoting plasticity on the modifiable pathways (Hasselmo, 1993; Hasselmo, Anderson, & Bower, 1992). Neuromodulation is slower than the theta rhythm and serves to generally bias the network towards storage (if, say, the animal is exploring a novel environment) or recall (if the environment is largely familiar). This bias may be controlled by inhibitory input to the medial septum from CA1, which is likely largest when CA1 PC cells are most active during recall, leading to a reduction in MS modulatory output back to CA1 (Hasselmo & Schnell, 1994; Hasselmo, Schnell, & Barkai, 1995).

4 Functionality of the microcircuit

Though these models are much closer to biological neural nets than ANN models, they still very much simplify the neuronal circuitry of the mammalian hippocampus. The role of inhibition has largely been confined to BCs acting to threshold PC activity during pattern recall (Sommer & Wennekers, 2001). Other ideas include the possibility that AACs provide the negative weights due to pattern storage required in some ANN models of associative memory (Menschik & Finkel, 1998).

The challenge remains to provide functional explanations that include more details of the known circuitry. Ideas concerning interneuronal network involvement in rhythm generation and control of PC networks are explored in Buzsaki and Chrobak (1995). Paulsen and Moser (1998) consider how GABAergic interneurons might provide the control structures necessary for

phasing storage and recall in the hippocampus. Building on their ideas, we propose the following hypotheses concerning the functioning of the CA1 microcircuit, including a number of different neuronal types and their specific roles in storage and recall. We then present a model that instantiates these ideas (Figure 1.2).

4.1 Functional hypothesis

As described above, it has been suggested that the hippocampal theta rhythm (4–7 Hz) can contribute to memory formation by separating encoding (storage) and retrieval of memories into different functional half-cycles (Hasselmo et al., 2002a). Recent experimental data show that the activity of different neuronal types is modulated at specific phases relative to the theta rhythm (Klausberger et al., 2003). Given that PC firing is biased towards the recall phase (e.g., place cells firing when a rat is in a familiar location), then it follows from the experimental data that BCs and AACs fire in phase with the encoding (storage) cycle of the theta rhythm, whereas the PCs, BSCs, OLMs and GABAergic MS input to CA1 fire on the recall cycle (180° out of phase) (see also Kunec et al., 2005).

We propose (see also Paulsen & Moser, 1998) that during encoding (Figure 1.2A), when the MS input is minimal, the role of the BCs and AACs is to provide enough hyperpolarization for the prevention of PCs from firing, as their output is not relevant. During this phase a PC may receive input from EC in its distal dendrites and CA3 in its proximal dendrites. Those PCs that receive combined EC and CA3 inputs can show sufficient local activity (manifest as membrane depolarization and a rise in calcium level) in their proximal dendrites to lead to a strengthening of the active CA3-input synapses. This is aided by strong BC inhibition, which leads to activation of the hyperpolarization-activated, but depolarizing H-current, resulting in rebound excitation of PCs on each gamma cycle.

Experimental evidence (Leung, Roth, & Canning, 1995) has suggested that conduction latency of the EC-layer III input to CA1 lacunosum-moleculare (LM) dendrites is less than 9 ms (ranging between 5 and 8 ms), whereas the conduction latency of EC-layer II input to CA1 radiatum dendrites via the trisynaptic (via dentate gyrus and CA3) path is greater than 9 ms (ranging between 12 and 18 ms). Given that it is synchronous activity in EC layers II and III that carries the information to be stored in CA1, these different delays mean that forward pairing in time of the EC and CA3 inputs, as required by the encoding strategy, is impossible. A different mechanism is required to associate the two inputs. We suggest that the paired signal for learning is provided by a back-propagating action potential (BPAP) mediated by activation of the H channels due to strong hyperpolarization by the BCs and AACs on the PCs soma and axon. This BPAP is generated without full-blown action potential generation in the soma or axon (which is blocked by the BC and AAC input) and meets the incoming CA3 input at the PC

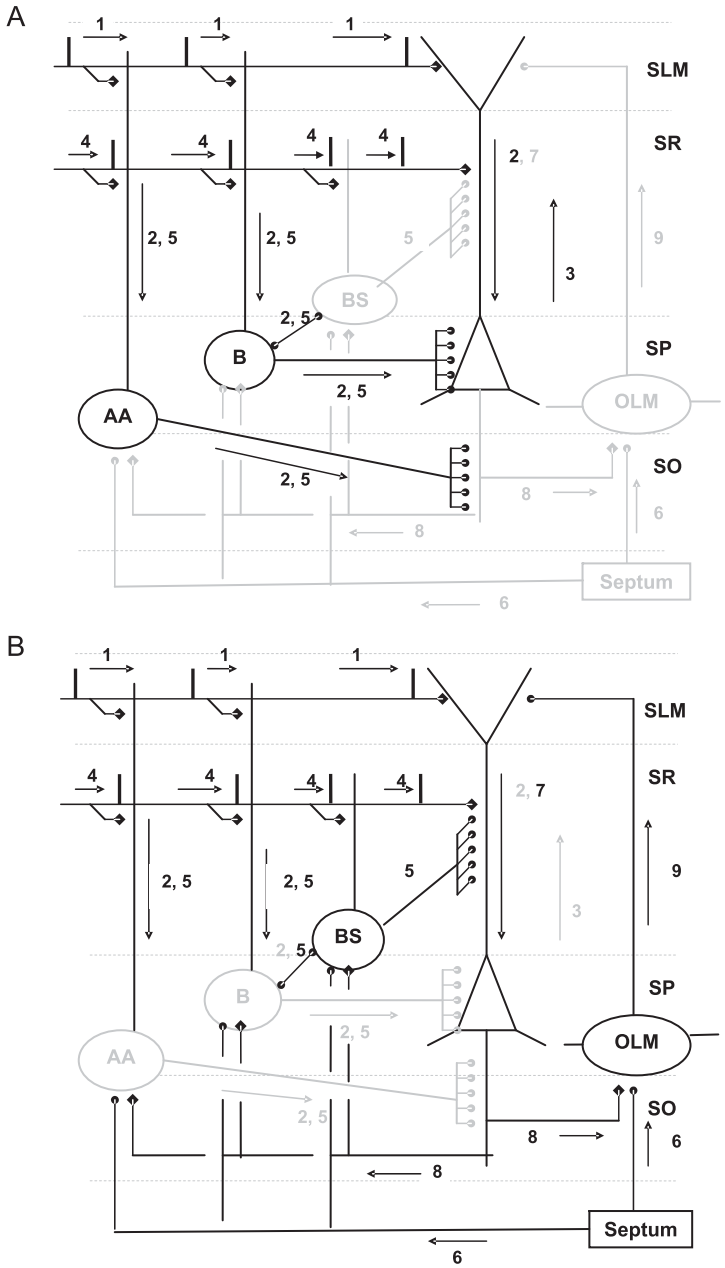

Figure 1.2 Active network pathways during (A) encoding cycle and (B) retrieval cycle. Only black solid-lined cells and pathways are active in each cycle. Numbers above and next to pathways indicate the temporal order of information processing during each cycle.

stratum radiatum medial dendrites to provide the underlying mechanism for associating the EC- and CA3-input patterns.

On the other hand, during retrieval (Figure 1.2B), when the BCs and AACs are silent due to a strong inhibitory input from the medial septum, the BSCs and OLM cells are active. The role of the BSCs is to provide a non-specific inhibitory signal to all PCs in the network that will raise the threshold enough to allow only the PCs that have learnt the EC–CA3-input association to fire (recall), whereas the role of the OLM cells is to inhibit the EC input to distal PC dendrites in order to prevent errors during retrieval. PC activity is due solely to strong CA3 input.

4.2 A computer model

To begin to explore these hypotheses, we are building a computer model of the CA1 microcircuit containing these major cell types. The initial small model consists of 100 PCs, 4 BCs, 2 BSCs, 2 AACs and 18 OLM cells.

- **Cellular morphology.** Moderately detailed compartmental models are used for the individual cells. The morphology and dimensions of the somatic, axonic and dendritic compartments of the model cells were adapted from Gulyas et al. (1999) and Megias et al. (2001). Compartments: PC, 15; B and AA, 17; BS, 13; OLM, 4. Cell structures and their firing properties are illustrated in Figure 1.3.
- **Cellular properties.** Each PC membrane contains a calcium pump and buffering mechanism, a calcium-activated mAHP potassium current, an LVA L-type Ca^{2+} current, an HVA L-type Ca^{2+} current, an MVA R-type Ca^{2+} current, an HVA T-type Ca^{2+} current, an H current, Hodgkin–Huxley-style sodium and delayed rectifier currents, a slow Ca^{2+}-dependent potassium current, a slow non-inactivating K^+ channel

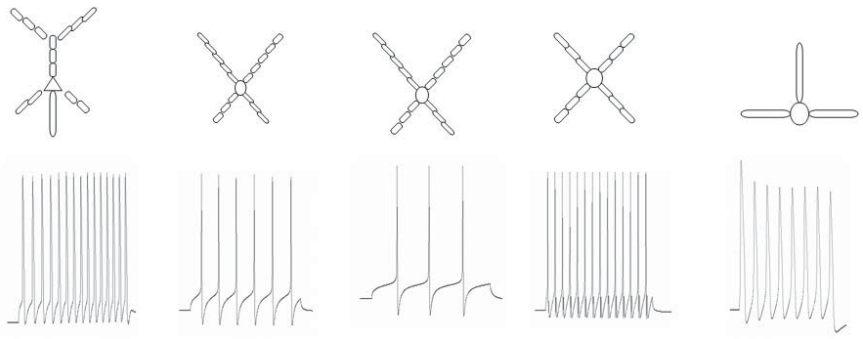

Figure 1.3 Compartmental structure models for the different cell types, plus their firing properties in response to depolarizing current injection (amplitude: 0.2 nA; duration: 200 ms). *From left to right:* pyramidal cell (PC), axo-axonic cell (AAC), basket cell (BC), bistratified cell (BSC), olm cell (OLM).

with HH-style kinetics and a K^+ A current (Poirazi, Brannon, & Mel, 2003a). Each BC, BSC and AAC contains a leak conductance, a sodium current, a fast delayed rectifier K^+ current, an A-type K^+ current, L- and N-type Ca^{2+} currents, a Ca^{2+}-dependent K^+ current and a Ca^{2+}- and voltage-dependent K^+ current (Santhakumar, Aradi, & Soltetz, 2005). Each OLM cell has a sodium (Na^+) current, a delayed rectifier K^+ current, an A-type K^+ current and an H current (Saraga, Wu, Zhang, & Skinner, 2003).

- **Synaptic properties.** AMPA, NMDA, GABA-A and GABA-B synapses are included. GABA-A are present in all strata, whereas GABA-B synapses are present in medium and distal SR and SLM dendrites. AMPA synapses are present in strata LM (EC connections) and radiatum (CA3 connections), whereas NMDA receptors are present only in stratum radiatum (CA3 connections).
- **Synaptic contacts.** AMPA only: all EC and CA1 PC recurrent connections; AMPA with NMDA: CA3 onto PCs. GABA-A synaptic contacts (Buhl, Halasy, & Somogyi, 1994): 8 by each AAC onto each PC axon; 9 by each BC onto each PC soma; 6 by each BSC onto each PC; 2 by each OLM cell with each PC cell.
- **Network connectivity.** Less than 1% recurrent connections between PCs. All-to-all connectivity for BCs and BSCs and between BCs and BSCs. No recurrent connections between AACs. All-to-all connectivity in PC–IN–PC loops for all types of IN.
- **Plasticity.** STDP learning rule at CA3–AMPA synapses on PCs (Song, Miller, & Abbott, 2000). Presynaptic spike times compared with timing of peak post-synaptic voltage amplitude due to a BPAP at the synapse. Synaptic strengthening (LTP due to an increase in AMPA conductance) occurs for a BPAP arriving just after the presynaptic spike (10-ms time window), whereas weakening (LTD) occurs if the BPAP arrives prior to the spike (similar 10-ms window.)
- **Inputs.** Excitatory inputs come from EC and CA3 Schaffer collaterals. PCs, BCs, AACs and BSCs receive CA3 input; PCs, BCs and AACs receive EC input. Initially, EC input arrives at PC apical LM dendrites between 0 and 9 ms (relative to the start of a theta cycle), whereas the CA3-input pattern arrives 9 ms later (Leung et al., 1995). Both EC and CA3 inputs are repeated to PC apical LM and medial radiatum dendrites, respectively, every 7 ms.

  Input for the medial septum provides GABA-A inhibition to all INs (strongest to BC and AAC). MS input is phasic at theta rhythm and is on for 70 ms during the retrieval phase, and off otherwise.
- **Storage and recall.** An experiment is conducted with the model in which a pattern of activity in CA1 is associated with a CA3 activity pattern. Initial CA3–CA1 synaptic conductances are set to random values, and so the pattern association takes place on top of this background synaptic noise. During the encoding (storage) phase, 20 randomly selected PCs exclusively receive EC input in the LM dendrites, creating

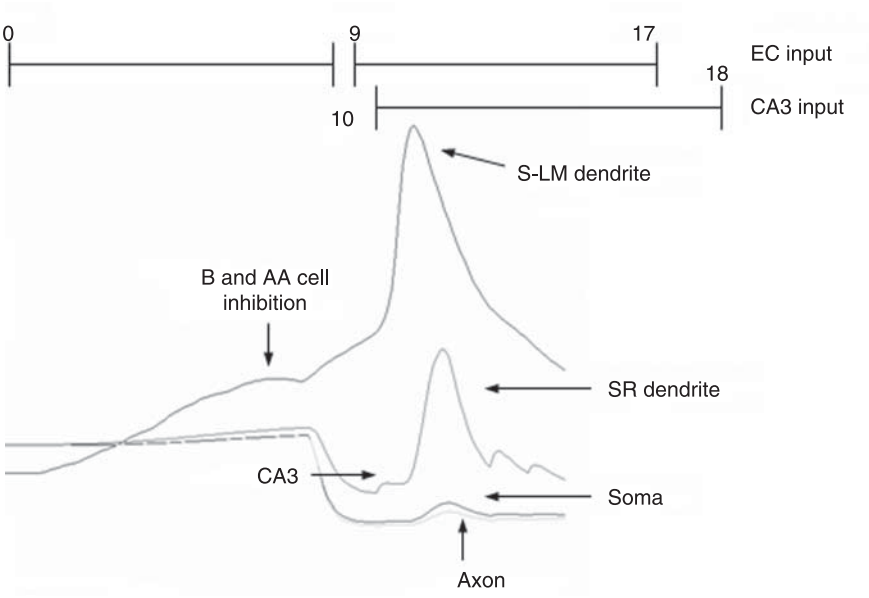

Figure 1.4 Post-synaptic signal of a CA1 pyramidal cell in response to EC and CA3 inputs. EC input is presented twice in two separate time intervals (0–8 ms and 9–17 ms). CA3 input is presented only once (10–18 ms). The inhibitory effects of the basket (B) cells and the axo-axonic (AA) cells on the pyramidal (P) cells are "seen" at about 6 ms. Due to the strong B and AA inhibition on the P soma and axon, an H-current-induced back-propagating action potential (BPAP) propagates back towards the SR dendrites of the P cell, where it coincides with the incoming CA3 and EC inputs. The SR dendrite of each P cell is the location where learning (storage) is taking place. Note that no action potential is generated in the soma or axon due to BC and AAC inhibition.

the CA1 activity pattern for storage. All PCs in the network are activated by the CA3 input in their medial radiatum dendrites. The STDP learning rule "teaches" the CA1 PCs to hetero-associate the H-current-activated BPAP with the incoming EC and CA3 inputs (Figure 1.4).

Cellular activity during a storage-and-recall cycle is shown in Figure 1.5. The pyramidal cell receives both EC and CA3 input during storage and thus becomes associated with the CA3 input. The PC is then active in response to CA3 input alone during the recall cycle.

5 Conclusions and further work

The hypotheses and model presented above are still very simple compared with what we know of the CA1 microcircuit and its putative role in different animal behaviours. More cell types and their connectivity could be included in the model. However, we still require further data on type-specific cell

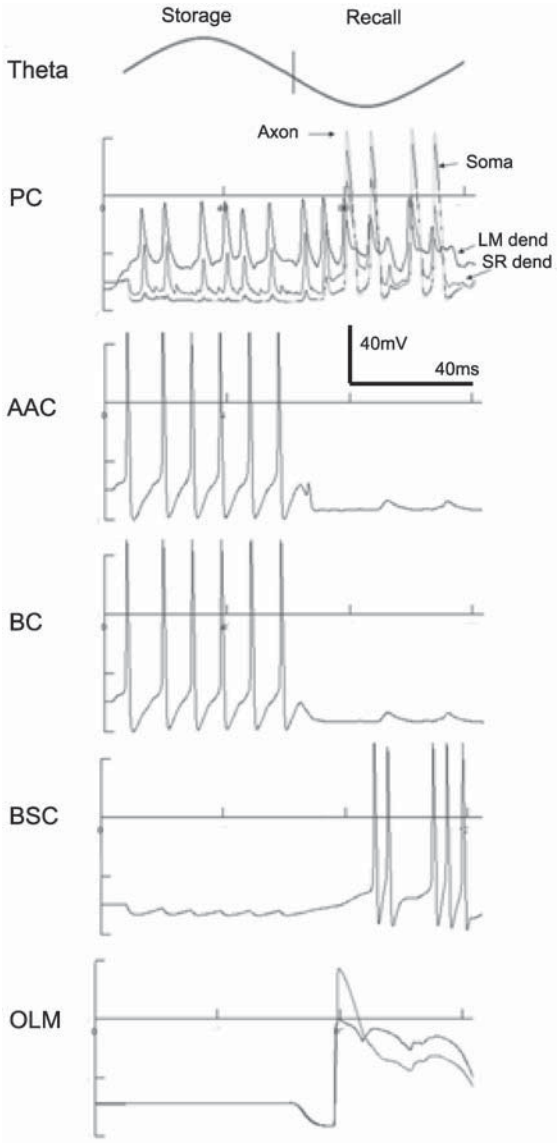

Figure 1.5 Firing responses of model cells during storage and recall of a theta cycle. From top to bottom: theta cycle oscillation, pyramical cell, axo-axonic cell, basket cell, bistratified cell and OLM cell.

properties and their *in vivo* firing patterns in particular behavioural states. We have chosen to concentrate on data related to environmental exploration in awake, behaving animals. Theories of hippocampal function also postulate how it interacts with neocortex in the formation of long-term memories (Morris, 2006; O'Reilly & Norman, 2002). In particular, there is evidence that information encoded during exploration is replayed in the hippocampus during sleep, possibly to drive memory consolidation in the neocortex (Ji & Wilson, 2007). A more complete model will propose the roles and activity dynamics of the different cell types in this behaviour too.

One aspect that we have not dealt with here is the complex membrane properties of neurons, particularly PCs that allow nonlinear integration of synaptic input. Detailed models of CA1 PCs have investigated the interaction of synaptic input with active membrane dynamics (Kali & Freund, 2005; Poirazi, Brannon, & Mel, 2003a, 2003b). Aspects of spatiotemporal cellular dynamics are lost in the reduced PC models used in large-scale network models. This can be redressed through new formulations of reduced models or through increased computing power that allows more complex cellular models to be used in networks.

Current models of specific brain circuits that include an aspect of learning usually only allow synaptic modification in one principal pathway. This is true here in that only the CA3 input to CA1 PCs is to modifiable synapses. In reality most, if not all, synaptic pathways are modifiable in the face of particular patterns of activity. For example, the entorhinal input to the distal dendrites of CA1 PCs is Hebbian-modifiable, and the post-synaptic signals in these dendrites are under specific inhibitory and neuromodulatory control (Remondes & Schuman, 2002). EC input can, in fact, appear largely inhibitory due to activation of feedforward interneurons and can result in a reduction of plasticity at CA3 synapses onto CA1 PCs (Remondes & Schuman, 2002). New models of CA1 function clearly need to take into account further aspects of this pathway (Pissadaki & Poirazi, 2007) – in particular, what learning may take place.

Also, the excitatory synapses on the inhibitory interneurons may be plastic, and hence the INs can be a part of smaller circuits within the global CA1 microcircuit capable of carrying out specific functionalities – for example, encoding Item A as opposed to Item B of a sequence of items A–B–A–B. Notably, OLM cells are active during slow-wave sleep but are silenced during sharp-wave ripples (SWRs), which are hypothesized to be recall episodes for consolidation of long-term memories in neocortex (Axmacher et al., 2006; Somogyi & Klausberger, 2005). In addition, the apparent learning rule at PC to OLM synapses leads to strengthening of these connections when PCs are active but OLM cells are silent (Lamsa et al., 2007). Thus it is likely that these synapses are being strengthened during SWRs, perhaps to reinforce their role during theta/gamma activity.

With any model, the great challenge is for the model to provide a consistent account of neural activity seen in different behavioural states and recorded

in different experimental paradigms. Experimental data is often contradictory and difficult to combine due to reliance on very specific experimental protocols. *In vivo* data from animals in different behavioural states is clearly the most important to match but is usually insufficient in itself for the formulation of the model. For example, details of intracellular properties must be derived from wide-ranging *in vitro* experiments. Nonetheless, even given these limitations, models that (a) include more biological detail, (b) can match certain brain dynamics and (c) provide an instantiation of particular cognitive functions will definitely aid us in the quest of understanding how brains work.

6 References

Ali, A., Deuchars, J., Pawelzik, H., & Thomson, A. (1998). CA1 pyramidal to basket and bistratified cell EPSPs: Dual intracellular recordings in rat hippocampal slices. *Journal of Physiology*, *507*, 201–217.

Ali, A., & Thomson, A. (1998). Facilitating pyramid to horizontal oriens-alveus interneurone inputs: Dual intracellular recordings in slices of rat hippocampus. *Journal of Physiology*, *507*, 185–199.

Amit, D. J. (1989). *Modeling brain function: The world of attractor neural networks*. Cambridge: Cambridge University Press.

Andersen, P., Morris, R., Amaral, D., Bliss, T., & O'Keefe, J. (Eds.) (2007). *The hippocampus book*. Oxford: Oxford University Press.

Axmacher, N., Mormann, F., Fernandez, G., Elger, C., & Fell, J. (2006). Memory formation by neuronal synchronization. *Brain Research Reviews*, *52*, 170–182.

Bartos, M., Vida, I., & Jonas, P. (2007). Synaptic mechanisms of synchronized gamma oscillations in inhibitory interneuron networks. *Nature Reviews Neuroscience*, *8*, 45–56.

Bi, G.-q., & Poo, M.-m. (1998). Synaptic modifications in cultured hippocampal neurons: Dependence on spike timing, synaptic strength, and postsynaptic cell type. *Journal of Neuroscience*, *18*, 10464–10472.

Bi, G.-q., & Poo, M.-m. (2001). Synaptic modification by correlated activity: Hebb's postulate revisited. *Annual Review of Neuroscience*, *24*, 139–166.

Bliss, T., Collingridge, G., & Morris, R. (2007). Synaptic plasticity in the hippocampus. In P. Andersen, R. Morris, D. Amaral, T. Bliss, & J. O'Keefe (Eds.), *The hippocampus book* (pp. 343–474). Oxford: Oxford University Press.

Buckingham, J., & Willshaw, D. (1993). On setting unit thresholds in an incompletely connected associative net. *Network*, *4*, 441–459.

Buhl, E., Halasy, K., & Somogyi, P. (1994). Diverse sources of hippocampal unitary inhibitory postsynaptic potentials and the number of synaptic release sites. *Nature*, *368*, 823–828.

Buzsaki, G. (2002). Theta oscillations in the hippocampus. *Neuron*, *33*, 325–340.

Buzsaki, G., & Chrobak, J. (1995). Temporal structure in spatially organized neuronal ensembles: A role for interneuronal networks. *Current Opinion in Neurobiology*, *5*, 504–510.

Cobb, S., Buhl, E., Halasy, K., Paulsen, O., & Somogyi, P. (1995). Synchronization of neuronal activity in hippocampus by individual GABAergic interneurons. *Nature*, *378*, 75–78.

Dayan, P., & Willshaw, D. (1991). Optimising synaptic learning rules in linear associative memories. *Biological Cybernetics*, *65*, 253–265.

Deuchars, J., & Thomson, A. (1996). CA1 pyramid–pyramid connections in the rat hippocampus in vitro: Dual intracellular recordings with biocytin filling. *Neuroscience*, *74*, 1009–1018.

Eichenbaum, H., Dudchenko, P., Wood, E., Shapiro, M., & Tanila, H. (1999). The hippocampus, memory, and place cells: Is it spatial memory or a memory space? *Neuron*, *23*, 209–226.

Freund, T., & Antal, M. (1988). GABA-containing neurons in the septum control inhibitory interneurons in the hippocampus. *Hippocampus*, *336*, 170–173.

Freund, T., & Buzsaki, G. (1996). Interneurons of the hippocampus. *Hippocampus*, *6*, 347–470.

Frotscher, M., & Lenrath, C. (1985). Cholinergic innervation of the rat hippocampus as revealed by choline acetyltransferase immunocytochemistry: A combined light and electron microscopic study. *Journal of Comparative Neurology*, *239*, 237–246.

Golding, N., Staff, N., & Spruston, N. (2002). Dendritic spikes as a mechanism for cooperative long-term potentiation. *Nature*, *418*, 326–331.

Graham, B. (2001). Pattern recognition in a compartmental model of a CA1 pyramidal neuron. *Network*, *12*, 473–492.

Graham, B., & Willshaw, D. (1995). Improving recall from an associative memory. *Biological Cybernetics*, *72*, 337–346.

Graham, B., & Willshaw, D. (1997). Capacity and information efficiency of the associative net. *Network*, *8*, 35–54.

Graham, B., & Willshaw, D. (1999). Probabilistic synaptic transmission in the associative net. *Neural Computation*, *11*, 117–137.

Gulyas, A., Megias, M., Emri, Z., & Freund, T. (1999). Total number and ratio of excitatory and inhibitory synapses converging onto single interneurons of different types in the CA1 area of the rat hippocampus. *Journal of Neuroscience*, *19*, 10082–10097.

Hasselmo, M. (1993). Acetylcholine and learning in a cortical associative memory. *Neural Computation*, *5*, 32–44.

Hasselmo, M., Anderson, B., & Bower, J. (1992). Cholinergic modulation of cortical associative memory function. *Journal of Neurophysiology*, *67*, 1230–1246.

Hasselmo, M., Bodelon, C., & Wyble, B. (2002a). A proposed function for hippocampal theta rhythm: separate phases of encoding and retrieval enhance reversal of prior learning. *Neural Computation*, *14*, 793–817.

Hasselmo, M., & Fehlau, B. (2001). Differences in time course of ACh and GABA modulation of excitatory synaptic potentials in slices of rat hippocampus. *Journal of Neurophysiology*, *86*, 1792–1802.

Hasselmo, M., Hay, J., Ilyn, M., & Gorchetchnikov, A. (2002b). Neuromodulation, theta rhythm and rat spatial navigation. *Neural Networks*, *15*, 689–707.

Hasselmo, M., & Schnell, E. (1994). Laminar selectivity of the cholinergic suppression of synaptic transmission in rat hippocampal region CA1: Computational modeling and brain slice physiology. *Journal of Neuroscience*, *14*, 3898–3914.

Hasselmo, M., Schnell, E., & Barkai, E. (1995). Dynamics of learning and recall at excitatory recurrent synapses and cholinergic modulation in rat hippocampal region CA3. *Journal of Neuroscience*, *15*, 5249–5262.

Holthoff, K., Kovalchuk, Y., & Konnerth, A. (2006). Dendritic spikes and activity-dependent synaptic plasticity. *Cell and Tissue Research*, *326*, 369–377.

Hopfield, J. (1982). Neural networks and physical systems with emergent collective computational abilities. *Proceedings of the National Academy of Science*, *79*, 2554–2558.

Ishizuka, N., Cowan, W., & Amaral, D. (1995). A quantitative analysis of the dendritic organization of pyramidal cells in the rat hippocampus. *Journal of Comparative Neurology*, *362*, 17–45.

Ji, D., & Wilson, M. (2007). Coordinated memory replay in the visual cortex and hippocampus during sleep. *Nature Neuroscience*, *10*, 100–107.

Kali, S., & Freund, T. (2005). Distinct properties of two major excitatory inputs to hippocampal pyramidal cells: A computational study. *European Journal of Neuroscience*, *22*, 2027–2048.

Klausberger, T., Magill, P., Maki, G., Marton, L., Roberts, J., Cobden, P., et al. (2003). Brain-state and cell-type-specific firing of hippocampal interneurons in vivo. *Nature*, *421*, 844–848.

Klausberger, T., Marton, L., Baude, A., Roberts, J., Magill, P., & Somogyi, P. (2004). Spike timing of dendrite-targeting bistratified cells during hippocampal network oscillations in vivo. *Nature Neuroscience*, *7*, 41–47.

Kunec, S., Hasselmo, M., & Kopell, N. (2005). Encoding and retrieval in the CA3 region of the hippocampus: A model of theta-phase separation. *Journal of Neurophysiology*, *94*, 70–82.

Lamsa, K., Heeroma, J., Somogyi, P., Rusakov, D., & Kullmann, D. (2007). Anti-Hebbian long-term potentiation in the hippocampal feedback circuit. *Science*, *315*, 1262–1266.

Leung, L., Roth, L., & Canning, K. (1995). Entorhinal inputs to hippocampal CA1 and dentate gyrus in the rat: A current-source-density study. *Journal of Neurophysiology*, *73*, 2392–2403.

Lisman, J., & Idiart, M. (1995). Storage of 7±2 short-term memories in oscillatory subcycles. *Science*, *267*, 1512–1514.

Lisman, J., & Spruston, N. (2005). Postsynaptic depolarization requirements for LTP and LTD: A critique of spike timing-dependent plasticity. *Nature Neuroscience*, 8, 839–841.

Losonczy, A., Zhang, I., Shigemoto, R., Somogyi, P., & Nusser, Z. (2002). Cell type dependence and variability in the short-term plasticity of EPSCs in identified mouse hippocampal interneurones. *Journal of Physiology*, *542*, 193–210.

Maccaferri, G., & Lacaille, J.-C. (2003). Hippocampal interneuron classifications – making things as simple as possible, not simpler. *Trends in Neuroscience*, *26*, 564–571.

Magee, J., & Johnston, D. (1997). A synaptically controlled, associative signal for Hebbian plasticity in hippocampal neurons. *Science*, *275*, 209–213.

McBain, C., & Fisahn, A. (2001). Interneurons unbound. *Nature Reviews Neuroscience*, *2*, 11–23.

Megias, M., Emri, Z., Freund, T., & Gulyas, A. (2001). Total number and distribution of inhibitory and excitatory synapses on hippocampal CA1 pyramidal cells. *Neuroscience*, *102*, 527–540.

Mehta, M. (2004). Cooperative LTP can map memory sequences on dendritic branches. *Trends in Neuroscience*, *27*, 69–72.

Menschik, E., & Finkel, L. (1998). Neuromodulatory control of hippocampal function: Towards a model of Alzheimer's disease. *Artificial Intelligence in Medicine*, *13*, 99–121.

Morris, R. (2006). Elements of a neurobiological theory of hippocampal function:

The role of synaptic plasticity, synaptic tagging and schemas. *European Journal of Neuroscience*, *23*, 2829–2846.

O'Keefe, J., & Recce, M. (1993). Phase relationship between hippocampal place units and the EEG theta rhythm. *Hippocampus*, *3*, 317–330.

Orban, G., Kiss, T., & Erdi, P. (2006). Intrinsic and synaptic mechanisms determining the timing of neuron population activity during hippocampal theta oscillation. *Journal of Neurophysiology*, *96*, 2889–2904.

O'Reilly, R., & Norman, K. (2002). Hippocampal and neocortical contributions to memory: Advances in the complementary learning systems framework. *Trends in Cognitive Sciences*, *6*, 505–510.

Otmakhova, N., & Lisman, J. (2000). Dopamine, serotonin, and noradrenaline strongly inhibit the direct perforant path-CA1 synaptic input, but have little effect on the Schaffer collateral input. *Annals of the New York Academy of Sciences*, *911*, 462–464.

Paulsen, O., & Moser, E. (1998). A model of hippocampal memory encoding and retrieval: GABAergic control of synaptic plasticity. *Trends in Neuroscience*, *21*, 273–279.

Pissadaki, E., & Poirazi, P. (2007). Modulation of excitability in CA1 pyramidal neurons via the interplay of entorhinal cortex and CA3 inputs. *Neurocomputing*, *70*, 1735–1740.

Poirazi, P., Brannon, T., & Mel, B. (2003a). Arithmetic of subthreshold synaptic summation in a model CA1 pyramidal cell. *Neuron*, *37*, 977–987.

Poirazi, P., Brannon, T., & Mel, B. (2003b). Pyramidal neuron as a two-layer neural network. *Neuron*, *37*, 989–999.

Remondes, M., & Schuman, E. (2002). Direct cortical input modulates plasticity and spiking in CA1 pyramidal neurons. *Nature*, *416*, 736–740.

Rotstein, H., Pervouchine, D., Acker, C., Gillies, M., White, J., Buhl, E., et al. (2005). Slow and fast inhibition and an H-current interact to create a theta rhythm in a model of CA1 interneuron network. *Journal of Neurophysiology*, *94*, 1509–1518.

Santhakumar, V., Aradi, I., & Soltetz, I. (2005). Role of mossy fiber sprouting and mossy cell loss in hyperexcitability: A network model of the dentate gyrus incorporating cell types axonal typography. *Journal of Neurophysiology*, *93*, 437–453.

Saraga, F., Wu, C., Zhang, L., & Skinner, F. (2003). Active dendrites and spike propagation in multicompartmental models of oriens-lacunosum/moleculare hippocampal interneurons. *Journal of Physiology*, *552*, 673–689.

Sik, A., Ylinen, A., Penttonen, M., & Buzsaki, G. (1994). Inhibitory CA1–CA3–Hilar region feedback in the hippocampus. *Science*, *265*, 1722–1724.

Sommer, F., & Wennekers, T. (2001). Associative memory in networks of spiking neurons. *Neural Networks*, *14*, 825–834.

Somogyi, P., & Klausberger, T. (2005). Defined types of cortical interneurone structure space and spike timing in the hippocampus. *Journal of Physiology*, *562*(1), 9–26.

Song, S., Miller, K., & Abbott, L. (2000). Competitive "Hebbian" learning through spike-timing-dependent synaptic plasticity. *Nature Neuroscience*, *3*, 919–926.

Sun, H., Lyons, S., & Dobrunz, L. (2005). Mechanisms of target-cell specific short-term plasticity at Schaffer collateral synapses onto interneurones versus pyramidal cells in juvenile rats. *Journal of Physiology*, *568*, 815–840.

Traub, R., Jefferys, J., & Whittington, M. (1999). *Fast oscillations in cortical circuits*. Cambridge, MA: MIT Press.

Treves, A., & Rolls, E. (1994). Computational analysis of the role of the hippocampus in memory. *Hippocampus*, *4*, 374–391.

Wallenstein, G., & Hasselmo, M. (1997). GABAergic modulation of hippocampal population activity: Sequence learning, place field development, and the phase precession effect. *Journal of Neurophysiology*, *78*, 393–408.

Whittington, M., & Traub, R. (2003). Inhibitory interneurons and network oscillations in vitro. *Trends in Neuroscience*, *26*, 676–682.

Willshaw, D., Buneman, O., & Longuet-Higgins, H. (1969). Non-holographic associative memory. *Nature*, *222*, 960–962.

Wood, E., Dudchenko, P., & Eichenbaum, H. (1999). The global record of memory in hippocampal neuronal activity. *Nature*, *397*, 613–616.