The Computing Neuron
R. Durbin, C. Miall, G. Mitchison (Eds.)
Addison-Wesley 1989

Induction of Synaptic Plasticity by Hebbian Covariance in the Hippocampus

Terrence Sejnowski, Sumantra Chattarji & Patric Stanton

7.1 Introduction

Most models of information storage in neural networks rely on changing the synaptic strengths, or weights, between model neurons (Hinton & Anderson, 1989). The weights in these simplifying models are altered by learning rules or algorithms so that the network can later retrieve the stored information, or perform the desired task. A great variety of such learning rules have been postulated, analysed, and simulated (Sejnowski & Tesauro, 1989). Most of these algorithms are based on mechanisms for which there is little or no experimental evidence (Crick, 1989). Indeed, experimental evidence for the long-term alteration of synaptic strengths is very difficult to obtain, and until recently there was no direct evidence for changes of the required duration at any synapse in adult neurons. This situation is rapidly changing as new experimental preparations and techniques are being developed (Alkon, 1987; Kandel *et al.*, 1987; Brown *et al.*, 1989). In this chapter we will explore what is currently known about synaptic plasticity in the mammalian hippocampus and will present experimental data that supports a particular class of learning algorithms.

One of the most popular learning rules is the 'Hebb' rule, which requires the strength of a synapse to increase upon the simultaneous coactivation of pre-synaptic and post-synaptic activity (Hebb, 1949). The defining characteristics of a Hebbian synapse are, first, that it depends only on pre-synaptic and post-synaptic variables, and secondly, that the alteration of the weight depends interactively on these two variables, and not separately (Brown *et al.*, 1989). Thus, a mechanism that depended only on the state of the pre-synaptic neuron, such as post-tetanic potentiation (Katz & Miledi, 1968), would not qualify as Hebbian. This interactive requirement makes the mechanism fundamentally associative. This said, it should be noted that the Hebb rule can nonetheless be implemented by non-associative mechanisms with circuitry of sufficient complexity (Sejnowski & Tesauro, 1989).

Many variations on the Hebb rule have been proposed. For example, some aspects of classical conditioning can be mimicked by a single Hebbian synapse if the temporal sensitivities of the pre-synaptic and post-synaptic elements are suitably

arranged (Sutton & Barto, 1981; Tesauro, 1986; Klopf, 1987). There are also good reasons for allowing the sign of the alteration to change, so that selective decreases as well as increases in strength can be made (Sejnowski, 1977b). Thus, it has been proposed that long-term decreases of synaptic strength should occur during conditions when the pre-synaptic and post-synaptic activities are negatively correlated (Sejnowski, 1977a). Similar suggestions have been made for changes in synaptic strengths during development (Bienenstock *et al.*, 1982).

In translating an algorithm like the Hebb rule into testable physiological hypotheses, general terms such as 'activity' must be made explicit. Thus, activity could mean the average level of membrane potential, the stimulation of action potentials, or perhaps the raised level of particular ionic concentrations. Many of these physiological variables are, of course, linked, but one or another of them might be particularly critical to the plasticity. Specific experiments must be designed to determine which variables are the critical ones. In the next section, we will summarize what is currently known about the important variables for the long-term potentiation of synaptic transmission in the hippocampus. Later in the chapter we will present experimental evidence for associative long-term depression as well as associative long-term potentiation of synaptic strength. The conditions under which this plasticity is observed are consistent with a Hebbian covariance model of synaptic plasticity (Sejnowski, 1977a).

7.2 Existing evidence for Hebbian and non-Hebbian synaptic plasticity in the hippocampus

A brief, high frequency activation of excitatory synapses in the hippocampus produces a long-lasting increase in synaptic strength, called long-term potentiation (LTP) (Bliss & Lomo, 1973). Typically, many fibers are synchronously activated for several seconds at frequencies greater than 50 Hz, and the synaptic potentials typically increase by 50-100%. Most of the experiments on LTP have been performed on thin, transverse slices of hippocampal tissue that are maintained *in vitro* in a perfusion chamber. The various regions and layers of cells in the hippocampus can be easily visualized and direct access is possible with recording and stimulating microelectrodes. In addition, pharmacological agents that alter neuronal properties can be easily applied. LTP can be reliably maintained within stimulated slices for the lifetime of the slice, which is around 10 hours. When stimulated *in vitro*, induction of LTP elevates synaptic strengths for weeks or months (Bliss & Gardner-Medwin, 1973).

If LTP depended only on pre-synaptic activation, then it would not be Hebbian, as defined above. The critical test to determine whether LTP also depends on the post-synaptic cell was performed on pyramidal cells in area CA1 by several groups, all of which came to essentially the same conclusion: LTP requires the simultaneous release of neurotransmitter from pre-synaptic terminals coupled with post-synaptic depolarization (Kelso *et al.*, 1986; Malinow & Miller, 1986; Gustafsson & Wigstrom, 1987). However, the plasticity is not critically dependent

on action potentials *per se*, since LTP can be induced even when action potentials are selectively blocked in the post-synaptic cell (Kelso *et al.*, 1986; McNaughton *et al.*, 1978). LTP should thus be called pseudo-Hebbian, since the original hypothesis required the post-synaptic cell to be excited or to persistently fire coincidentally with pre-synaptic activity (Hebb, 1949). The consequences of this difference will be taken up in the discussion.

There is a form of long-term plasticity, called associative LTP, that can be produced in some hippocampal neurons when two separate pathways, a test input and a conditioning input that impinge on the same cells, are simultaneously activated (Levy & Steward, 1979, 1983; Barrionuevo & Brown, 1983). In these experiments, a weak test input when stimulated alone does not have a long-lasting effect on synaptic strength; however, when this input is paired with stimulation of a conditioning input sufficient to produce homosynaptic LTP of that pathway, the test pathway is *associatively* potentiated. How is information about the conditioning input transmitted through the dendrites to the synapses from the test inputs? The spread of current from the conditioning input can depolarize the post-synaptic membrane near the synapses of the test input. A voltage-dependent mechanism in the post-synaptic cell could then account for the associative induction of LTP.

The neurotransmitter that mediates the excitatory post-synaptic potentials (EPSPs) in area CA1, and in most long-distance projections in the brain, is likely to be glutamate or a closely related amino acid. There are at least two distinct types of glutamate receptors on the post-synaptic membrane. One of these is responsible for the fast transmission of excitation, the Kainate/Quisqualate, or the K/Q receptor. The other receptor, called the NMDA receptor after the agonist N-methyl-D-aspartate which selectively activates it, has a voltage dependence that permits it to open only when the post-synaptic membrane is strongly depolarized at the same time that glutamate binds to the receptor. The specific NMDA receptor antagonist 2-amino-5-phosphonovaleric acid (AP5) blocks the induction of associative LTP in CA1 pyramidal neurons (Collingridge *et al.*, 1983; Harris *et al.*, 1984; Wigstrom & Gustafsson, 1984). Thus, the NMDA receptor is likely to be an essential component in the Hebbian mechanism underlying LTP in area CA1. Interestingly, AP5 does not block the induction of LTP in another pathway within the hippocampus, that between the mossy fibers and pyramidal cells in area CA3. This observation serves as the starting point for the new experiments that are presented in a later section.

In addition to Hebbian plasticity, non-Hebbian forms of synaptic plasticity have also been found in the hippocampus. Post-tetanic potentiation (PTP) is an elevation of synaptic strengths for many minutes following a high frequency tetanus of the synapse. PTP is a consequence of pre-synaptic mechanisms and does not depend on the post-synaptic cell (Katz & Miledi, 1968; Scharfman & Sarvey, 1985). Another non-Hebbian form of plasticity in the hippocampus is the heterosynaptic depression produced in an unstimulated or weakly-stimulated pathway when another pathway converging on the same neurons is stimulated at a high rate for a prolonged duration (Levy & Steward, 1979, 1983; Lynch *et al.*,

1977). In this case, the depression does not depend on activity of the test input and does not seem to be as long lasting as LTP.

7.3 The covariance model of associative information storage

Probably the most important and most thoroughly explored use of the Hebb rule in neural network models is in the formation of associations between one stimulus or pattern of activity in one neural population and another (Kohonen, 1984). The Hebb rule is appealing for this use, because it provides a way of forming global associations between large-scale patterns of activity in assemblies of neurons using only the local information available at individual synapses. The earliest models of associative memory were based on network models in which the output of a model neuron was assumed to be proportional to a linear sum of its inputs, each weighted by a synaptic strength. Thus,

$$V_B = \sum_{A=1}^{N} W_{BA} V_A \tag{7.1}$$

where V_B are the firing rates of a group of M output cells, and V_A are the firing rates of a group of N input cells, and W_{BA} is the synaptic strength between input cell A and output cell B.

The transformation between patterns of activity on the input vectors to patterns of activity on the output vectors is determined by the synaptic weight matrix, W_{BA}. This matrix can be constructed from pairs of associated input and output vectors using the simplest version of the Hebb rule (Steinbuch, 1961; Anderson, 1970; Kohonen, 1970; Longuet-Higgins, 1968):

$$\Delta W_{BA} = \varepsilon V_B V_A \tag{7.2}$$

where the strength of the learning ε can be adjusted to scale the outputs to the desired values.

More than one association can be stored in the same matrix, so long as the input vectors are not too similar to each other. This is accomplished by using Equation 7.2 for each input-output pair. This model of associative storage is simple and has several attractive features: first, the learning occurs in only one trial; second, the information is distributed over many synapses, so that recall is relatively immune to noise or damage; and third, input patterns similar to stored inputs will give output similar to the stored outputs, a form of generalization. This linear model has been generalized to non-linear models of associative memory, which has led to a new class of learning algorithms based on the principle of error-correction (Sejnowski & Tesauro, 1989). In these algorithms, more than one

presentation is needed for each input since the storage must be optimized for the entire set of stored patterns.

Numerous variations have been proposed on the conditions for Hebbian plasticity (Sejnowski, 1977a,b; Kohonen, 1984; Levy *et al.*, 1984). One problem with any synaptic modification rule that can only increase the strength of a synapse is that the synaptic strength will eventually saturate at its maximum value. Non-specific decay can reduce the sizes of the weights, but the stored information will also decay and be lost at the same rate. Another approach is to renormalize the total synaptic weight of the entire terminal field from a single neuron to a constant value (von der Malsburg, 1973). One learning algorithm that accomplishes this uses the selective decrease of synaptic strength to accomplish optimal error-correction learning based on storing the covariances between the pre-synaptic and post-synaptic neurons (Sejnowski, 1977a,b). According to this rule, the change in strength of a plastic synapse should be proportional to the covariance between the pre-synaptic firing and post-synaptic firing:

$$\Delta W_{BA} = \varepsilon (V_B - \langle V_B \rangle)(V_A - \langle V_A \rangle) \tag{7.3}$$

where $\langle V_B \rangle$ are the average firing rates of the output neurons and $\langle V_A \rangle$ are the average firing rates of the input neurons (see also Chauvet, 1986). Thus, the strength of the synapse should increase if the firing of the pre-synaptic and post-synaptic elements are positively correlated, decrease if they are negatively correlated, and remain unchanged if they are uncorrelated. The covariance rule is an extension of the Hebb rule and it is easy to show that traditional Hebbian synapses can be used to implement it. Taking a time average of the change in synaptic weight in Equation 7.3:

$$\langle \Delta W_{BA} \rangle = \varepsilon (\langle V_B V_A \rangle - \langle V_B \rangle \langle V_A \rangle) \tag{7.4}$$

The first term on the right hand side has the same form as the simple Hebbian synapse in Equation 7.2. The second term is a learning 'threshold' that varies with the product of the time-averaged pre-synaptic and post-synaptic activity levels. The learning threshold ensures that no change in synaptic strength should occur if the average correlation between the pre-synaptic and post-synaptic activities is at chance level; that is, when there is no net covariance. The time averages in Equations 7.3 & 7.4 should be taken over a time interval that is long compared to the moment-by-moment fluctuations occurring within synapses. In the hippocampus, which has an intrinsic 5-6 Hz theta rhythm, the averaging time should be greater than 200 ms.

The covariance model is based both on information contained in the membrane potentials within populations of neurons and on information transmitted between neurons in the spatio-temporal patterns of spike trains. Recent recordings from pairs of neurons in visual cortex and from local field potentials reflecting pooled activity in hundreds of neurons indicate that oscillatory stimulus-selective correlations are present in cortical networks (Gray & Singer, 1989). Furthermore, experiments with visual stimuli that extend over a wide area of the visual field

indicate that these correlations could carry important global information about visual stimuli (Gray *et al.*, 1989). Thus, significant correlations exist between neurons in cerebral cortex that could provide a signal to a covariance storage mechanism.

7.4 Experimental evidence for the Hebbian covariance rule in the hippocampus

7.4.1 Hebbian synapses in area CA1

Recently, a new type of synaptic plasticity has been reported in field CA1 of the hippocampus that results in a long-term depression (LTD) of synaptic strengths (Stanton & Sejnowski, 1989). LTD is associative and can be induced in a test input when interacting with a stronger conditioning input on the same dendritic tree, but only if the two inputs are negatively correlated in time. The stimulus paradigm that was used, illustrated in Figure 7.1B, was based on the finding that high-frequency bursts of stimuli spaced 200 ms apart are optimal in eliciting LTP (Larson & Lynch, 1986). The conditioning, or strong stimulus pattern, which was almost always effective in eliciting maximal LTP, consisted of trains of 10 bursts of 5 pulses each at a frequency of 100 Hz, with a 200 ms interburst interval. Each train lasted 2 seconds and had a total of 50 stimuli. The test, or weak stimuli, a train of single shocks at 5 Hz frequency, were given either superimposed on the middle of each burst (positively correlated, or 'in phase'), or symmetrically between the bursts (negatively correlated, or 'out of phase').

The strong stimulus was applied to the Schaffer collaterals and the test stimulus was applied to the subicular input on the opposite side of the recording site, as shown in Figure 7.1A. The weak stimulus train was first applied alone and did not itself induce long-lasting changes. The conditioning site was then stimulated alone, which elicited *homosynaptic* LTP of this pathway but did not significantly alter the amplitude of responses to the test input. When the test and conditioning inputs were activated in phase, the test input synapses were associatively potentiated, as predicted (Figure 7.2A). In contrast, when test and conditioning inputs were applied out of phase, an associative depression of the test input synapses was induced that lasted for hours (Figure 7.2B). The duration of associative LTD was at least 30 minutes (Figure 7.2C) and up to 3 hours following stimulation. The amplitude and duration of associative LTD or LTP could be increased by stimulating input pathways with more trains of shocks. When weak input shocks were applied both superimposed *and* between the bursts, so that the average covariance was zero between test and conditioning inputs, there was no net change in synaptic strength. Thus, the associative LTP and LTD mechanisms appear to be balanced.

A weak stimulus that is out of phase with a strong conditioning stimulus arrives when the post-synaptic neuron is hyperpolarized as a consequence of

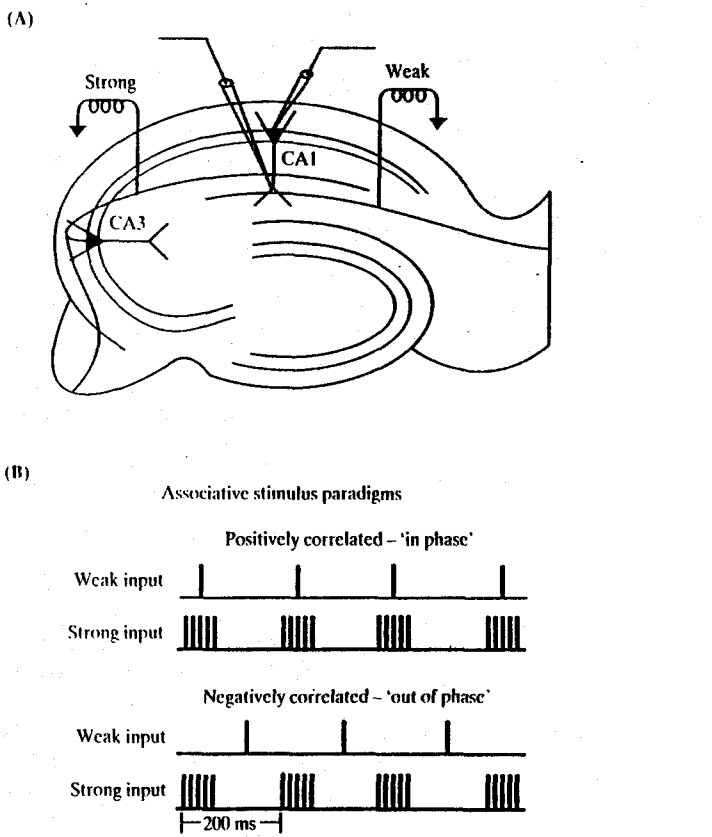

Figure 7.1 Hippocampal slice preparation for area CA1. **A.** Schematic diagram of the *in vitro* hippocampal slice showing recording sites in the CA1 pyramidal cell somatic (stratum pyramidale) and dendritic (stratum radiatum) layers, and conditioning stimulus sites activating Schaffer collateral (Strong) and commissural test afferents (Weak). Hippocampal slices (400 μm thick) were prepared by standard methods and incubated in an interface slice chamber at 34-35°C. Extracellular (1-5 MΩ resistance, 2M NaCl filled) and intracellular (70-120 MΩ, 2M K-acetate filled) recording electrodes, and bipolar glass-insulated platinum wire stimulating electrodes (50 μm tip diameter), were prepared by standard methods. **B.** Schematic diagram of stimulus paradigms used. Conditioning input stimuli (Strong input) were four trains of 100 Hz bursts. Each burst had 5 stimuli and the interburst interval was 200 ms. Each train lasted 2 seconds and had a total of 50 stimuli. Test input stimuli (Weak input) were four trains of shocks at 5 Hz frequency, each train lasting for 2 seconds. When these inputs were *in phase*, the test single shocks were superimposed on the middle of each burst of the conditioning input, as shown. When the test input was *out of phase*, the single shocks were placed symmetrically between the bursts.

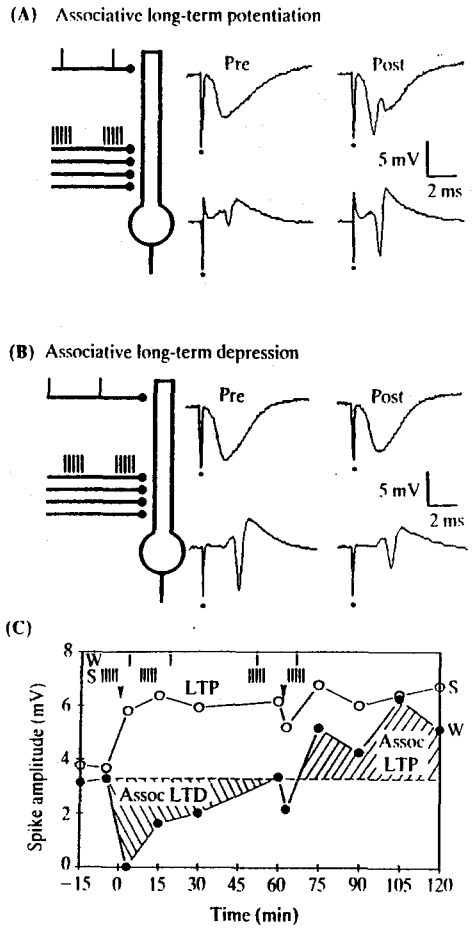

Figure 7.2 Associative LTP and associative long-term depression (LTD) of evoked extracellular potentials. **A.** Associative LTP of evoked EPSPs and population action potential responses in the test input. Test responses are shown before and 30 min after application of test stimuli in phase with the coactive conditioning input. **B.** Associative LTD of evoked EPSPs and population spike responses in the test input. Test responses are shown before and 30 min after application of test stimuli out of phase with the coactive conditioning input. **C.** Time course of the changes in population spike amplitudes for a typical experiment. Inset at the top shows the stimulus patterns for the test (T) and conditioning (C) inputs and arrows show the time of stimulation. Single responses from the conditioning input (open circles), show that the high- frequency bursts (5 pulses/100 Hz, 200 ms interburst interval as in Figure 7.1) elicited synapse-specific LTP independent of other input activity. Single responses from the test input (filled circles) show that stimulation of the test pathway out of phase with the conditioning one produced associative LTD (Assoc LTD) of this input. In-phase stimulation of the same pathway elicited (cont. opposite)

inhibitory post-synaptic potentials and after-hyperpolarization from mechanisms intrinsic to pyramidal neurons. This suggests that post-synaptic hyperpolarization coupled with pre-synaptic activation may trigger LTD. To test this hypothesis, we injected current through intracellular microelectrodes to hyperpolarize or depolarize the cell while stimulating a synaptic input. Pairing the injection of depolarizing current with the low-frequency stimulation led to LTP of the stimulated synapses (Figure 7.3A), while a response to a control input inactive during the stimulation did not change, as reported previously (Kelso *et al.*, 1986; Malinow & Miller, 1986; Gustafsson *et al.*, 1987). Conversely, prolonged hyperpolarizing current injection paired with the same low frequency stimuli led to induction of LTD in the stimulated pathway, but not in the unstimulated pathway (Figure 7.3B). The application of either depolarizing current, hyperpolarizing current, or the 5 Hz synaptic stimulation alone did not induce long-term alterations in synaptic strengths. Thus, the pairing of post-synaptic hyperpolarization and pre-synaptic activity is sufficient to induce LTD of the intracellular EPSPs in CA1 pyramidal neurons.

Associative LTP is believed to depend on the spread of current from conditioning synapses to test synapses in the dendritic tree, where the simultaneous depolarization of the post-synaptic membrane and activation of glutamate receptors of the N-methyl-D-aspartate (NMDA) subtype leads to LTP induction (Collingridge *et al.*, 1983; Harris *et al.*, 1984; Wigstrom & Gustafsson, 1984). Consistent with this hypothesis, we find that the NMDA receptor antagonist 2-amino-5-phosphonovaleric acid (AP5, 10μM) blocked the induction of associative LTP by the in-phase stimuli in CA1 pyramidal neurons. In contrast, the application of AP5 to the bathing solution at this same concentration did not affect associative LTD. Thus, the induction of associative LTD does not appear to involve the activation of the NMDA receptor.

These experiments confirm predictions made from the covariance model of information storage in neural networks (Sejnowski, 1977a,b). The plasticity is associative, long-lasting, and is produced when pre-synaptic activity occurs while the post-synaptic membrane is hyperpolarized. The other condition that should produce synaptic depression according to the predictions of the covariance model - the absence of pre-synaptic activity while the post-synaptic neuron is strongly depolarized - has also been found in the hippocampus (Levy & Steward, 1983; Lynch *et al.*, 1977). However, this heterosynaptic depression is not as long lasting as LTP and requires stronger stimulation. For example, the control stimulation of the strong pathway in our experiments did not produce measurable depression of the inactive test pathway. This may indicate that the algorithm for synaptic plasticity in the hippocampus only approximates the covariance.

(Fig. 7.2 cont.) associative LTP (Assoc LTP). The duration of associative LTD was at least 30 minutes and up to 3 hours following stimulation. The amplitude and duration of associative LTD or LTP could be increased by stimulating input pathways with more trains of shocks.

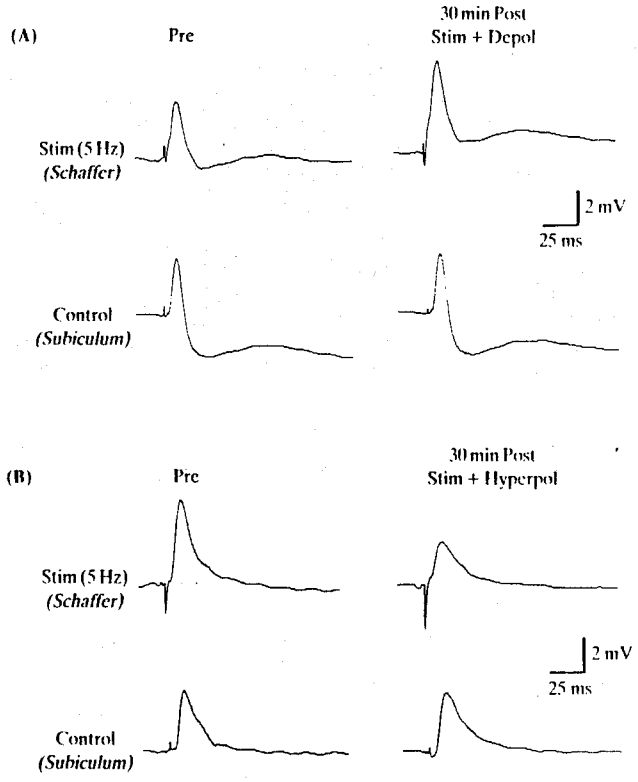

Figure 7.3 Pairing of post-synaptic hyperpolarization with stimulation of synapses on CA1 hippocampal pyramidal neurons produces LTD specific to the activated pathway, while pairing of post-synaptic depolarization with synaptic stimulation produces synapse-specific LTP. **A.** Intracellular evoked EPSPs are shown at stimulated (Stim 5 Hz) and unstimulated (Control) pathway synapses before and 30 min after pairing depolarizing current injection with 5 Hz synaptic stimulation (the constant +2.0 nA current produced a 20 mV depolarization of the soma without synaptic stimulation). The stimulated pathway exhibited associative LTP of the EPSP, while the control, unstimulated input showed no change in synaptic strength. **B.** Intracellular EPSPs are shown evoked at stimulated and control pathway synapses before and 30 min after pairing a 20 mV hyperpolarization at the cell soma with 5 Hz synaptic stimulation (the constant −1.0 nA current produced a 20 mV hyperpolarization of the soma in the absence of synaptic stimulation). The input (Stim 5 Hz) activated during the hyperpolarization showed associative LTD of synaptic evoked EPSPs, while synaptic strength of the silent input (Control) was unaltered. The cell fired action potentials during the depolarizing current injection, but not during injection of the hyperpolarizing current. In a previous study, hyperpolarizing current applied during high-frequency synaptic stimulation blocked LTP, but LTD of the synaptic input was not reported (Malinow & Miller, 1986). However, the input stimulus was typically 30 Hz or higher compared to the 5 Hz used in our experiment, so that the dendritic membrane potential during synaptic stimulation was probably significantly more positive at the 30 Hz rate.

7.4.2 Non-Hebbian and Hebbian synapses in area CA3

Area CA3 of the hippocampus exhibits two forms of LTP, one of which is dependent on NMDA receptors - the commissural pathway - and another that is not - the mossy fiber pathway (Harris *et al.*, 1984). We will summarize here our recent finding that both associative LTP and associative LTD can be induced in the commissural pathway, but neither can be elicited in the mossy fiber pathway of area CA3 (Chattarji *et al.*, 1989). The differences in the rules for plasticity in these pathways are likely to be related to the different functions that these pathways have in guiding the storage of information in the hippocampus: in particular, the mossy fiber pathway is non-Hebbian, but the commissural inputs are Hebbian.

In our experiments, extracellular field potential recordings were made in the CA3 pyramidal cell body and apical dendritic layers of rat hippocampal slices (Figure 7.4). Stimulating electrodes were placed on opposite sides of the hippocampal fissure and stimuli applied to separate Commissural/Schaffer collateral (COM) and mossy fiber (MF) afferents converging on CA3 pyramidal cells (Figure 7.4). The degree of potentiation or depression was evaluated by change in amplitude of the population spike and the peak initial slope of the compound excitatory post-synaptic potential (EPSP). In some control experiments, specific activation of mossy fibers was verified by inducing LTP of this pathway in the presence of AP5 (Harris *et al.*, 1984), which shows that this pathway is indeed the one that is independent of the activation of NMDA receptors. The same stimulus paradigm that was effective at eliciting associative LTP and associative LTD in area CA1 was used in area CA3.

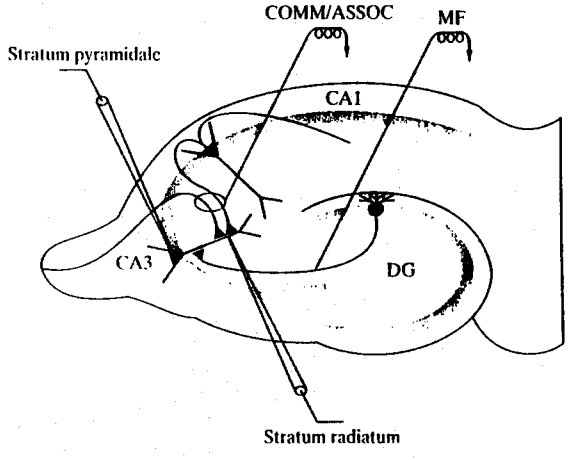

Figure 7.4 Hippocampal slice preparation and stimulus paradigms for area CA3. Schematic diagram of the *in vitro* hippocampal slice preparation showing recording sites in the CA3 pyramidal cell somatic (stratum pyramidale) and dendritic (stratum radiatum) layers, and stimulus sites activating Commissural/ Schaffer (COM) or mossy fiber (MF) afferents.

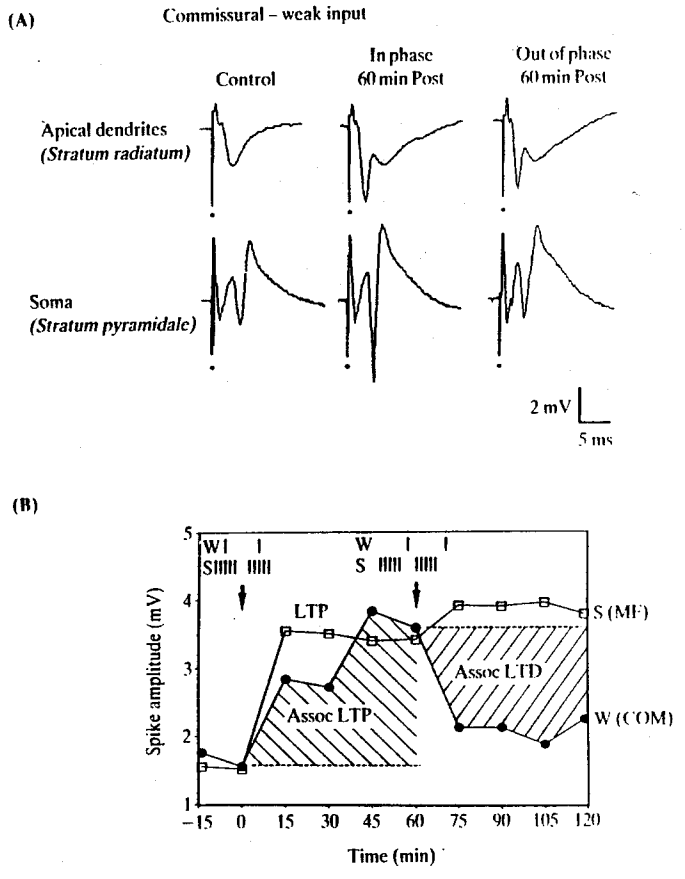

Figure 7.5 CA3 commissural synapses exhibit both associative LTP and associative LTD. A. When the COM side received a weak (W) input *in phase* with a strong (S) MF tetanus, the W site exhibited associative long-term potentiation (LTP) of both the synaptic EPSP in the apical dendritic layer (upper traces) and the population action potential in the cell soma layer (lower traces). This was followed by application of W stimuli to the COM site *out of phase* with the S stimuli to MF, which caused an associative long-term depression (LTD) seen as a marked reduction in the population spike amplitude with a lesser decrease in EPSP slope. Test responses are shown before (Control) and 60 min after application of weak stimuli in phase and out of phase with the strong MF input, respectively. B. Time course of the changes in population spike amplitude observed at each input for a typical experiment where synaptic strengths could be alternately enhanced and depressed in the same slice. Test responses from the strong input (S, open squares), show that the high-frequency bursts elicited LTP specific to MF synapses. Test responses from the weak input (W, filled circles) show that stimulation of the weak pathway in phase with the strong one produced associative LTP (Assoc LTP) of this input. Associative LTD of the same pathway was then elicited following out of phase stimulation.

In initial experiments, the commissural pathway was used as the test, or weak input site (W) and the mossy fiber pathway received the conditioning, or strong stimuli (S) (Figure 7.5). The weak stimulus train was first applied alone and did not itself induce long-lasting changes, following which strong site stimulation alone elicited homosynaptic LTP of the strong pathway without significantly altering weak input synaptic strength. However, when the commissural (COM) side received a weak input in phase with a strong mossy fiber (MF) tetanus, it elicited an associative long-term potentiation (LTP) of the weak input synapses, as shown in Figure 7.5A. Both the EPSP and population action potential (Figure 7.5A) were significantly enhanced for at least 60 min and up to 180 min following stimulation (Figure 7.5B).

In contrast, application of weak stimuli to the commissural site out of phase with the strong mossy fiber tetanus caused an associative long-term depression (LTD) of the weak input synapses (Figure 7.5A). There was a marked reduction in the population spike with smaller decreases in the EPSP. As in the experiments in area CA1 reported above, the stimulus patterns applied to each input were identical in these two experiments, and only the relative phase of the weak and strong stimuli was varied. Synaptic strengths could be alternately enhanced and depressed in the same slice, as is shown in Figure 7.5B.

In the second series of experiments, the stimulus paradigms were reversed so that the mossy fibers received the weak input and the strong tetanus was applied to commissural afferents. In contrast to commissural synapses, when the mossy fiber pathway received weak stimuli in phase with strong stimuli via the commissural input, mossy fiber synapses did not exhibit any associative potentiation of either synaptic EPSP or population spike (Figure 7.6A). Similarly, application of weak stimuli out of phase with strong stimuli also failed to elicit associative LTD of the EPSP or population spike (Figure 7.6). Finally, although a weak input to mossy fiber synapses failed to elicit either associative LTP or LTD, homosynaptic LTP was shown in response to a strong tetanus to mossy fiber afferents alone, verifying the intact LTP-generating mechanisms in these synapses.

Our studies of interactions between strong and weak inputs onto the same dendritic tree of hippocampal pyramidal cells of field CA3 suggest that these pyramidal cells receive two separate synaptic inputs that differ fundamentally in their processing capabilities. The CA3 commissural synapses, which depend on NMDA receptor activation for the induction of LTP, exhibit associative LTP when they receive weak stimuli positively correlated in time with a strong mossy fiber tetanus. This result supports evidence that these synapses show depolarization-dependent associativity, a property thought to derive from the voltage dependence of the NMDA receptor (Bliss & Lomo, 1973; Mayer *et al.*, 1984; Kelso *et al.*, 1986). When the same weak input stimulation of the CA3 commissural synapses is negatively correlated in time with the conditioning mossy fiber input, a long-term depression (LTD) of the test commissural input is induced, similar to our findings in CA1 (Stanton & Sejnowski, 1989).

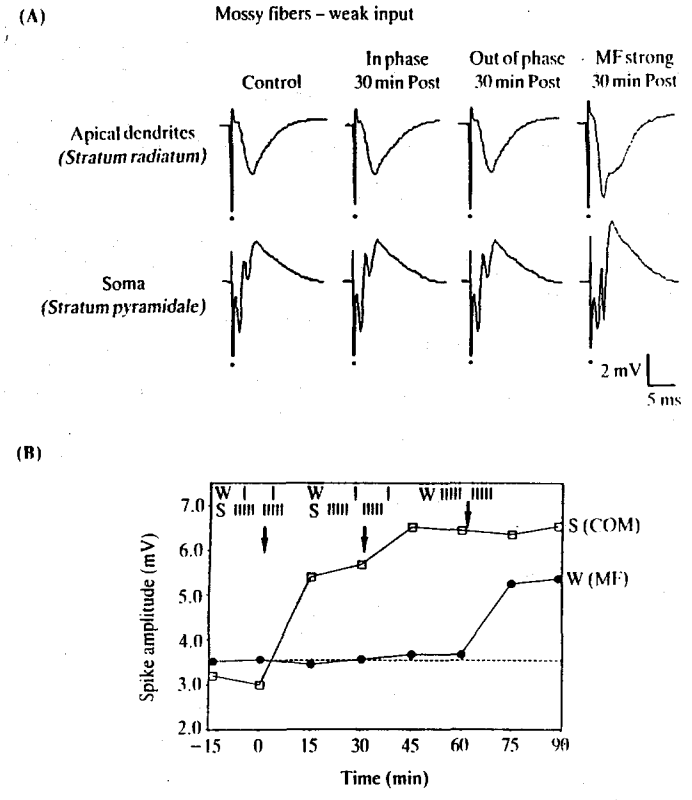

Figure 7.6 CA3 mossy fiber synapses do not exhibit either associative LTP or LTD. A. When the MF pathway received a weak stimuli (W) in phase with a strong stimulus (S) via the commissural input (COM), weak input MF synapses did not exhibit potentiation of either the synaptic EPSP in the apical dendritic layer or population spike in the cell body layer. Following this, application of W stimuli to the MF site out of phase with S stimuli to COM, also failed to elicit depression in population spike or EPSP. Finally, MF synapses did show homosynaptic LTP when presented with an S tetanus (MF Strong) to the MF pathway alone. Test responses are shown before (Control) and 30 min after application of in phase, out of phase and MF strong stimuli, respectively. B. Time course of the changes in population spike amplitude observed at each input for a representative experiment. Test responses from the strong input (S, open squares), show that the high-frequency bursts elicited homosynaptic LTP specific to COM synapses. Test responses from the weak input (W, filled circles) show that neither in phase nor out of phase stimulation elicited any potentiation or depression of this input. However, MF synapses did show homosynaptic LTP following the application of the strong bursts (S) to the MF pathway alone.

The rules for induction of long-term synaptic plasticity in mossy fiber inputs onto CA3 pyramidal neurons appear to be fundamentally different from those of commissural inputs. We have shown that a weak mossy fiber input failed to exhibit associative LTP when it was positively correlated in time with a strong commissural tetanus. This finding is in agreement with other studies (Kauer & Nicoll, 1989) and can be explained by the lack of NMDA receptors at this synapse (Monaghan & Cotman, 1985). The failure of these synapses to elicit associative LTD, however, is rather surprising, since results from similar experiments in area CA1 suggest that post-synaptic hyperpolarization coupled with pre-synaptic activation triggers associative LTD without requiring NMDA receptor activation (Stanton & Sejnowski, 1989). Our findings do not, however, rule out long-lasting potentiation or depression at these synapses that may require different stimulus patterns or important modulatory factors supplied by subcortical inputs to area CA3 (Hopkins & Johnston, 1984; Stanton & Sarvey, 1985).

7.5 Discussion

Most of the simplifying models of learning in neural networks leave out much of the biological detail, such as current spread in dendrites, active membrane conductances, and realistic patterns of connectivity. This does not mean that they cannot make contact with biological experiments, only that the predictions that come out of these models are necessarily broad, dealing with general relationships and not with specific details. These models can nonetheless suggest stimulus variables that should be explored and can help in interpreting the results.

For example, in our experiments on synaptic plasticity in the hippocampus, the covariance model suggested that negatively correlated inputs might be associated with synaptic depression, but did not provide the details of the stimulus paradigm (Sejnowski, 1977a,b). Thus, the choice of 100 Hz for the burst rate and 5 Hz for the burst repetition rate were determined by properties of the hippocampus and not the model. What the model did provide was the idea that synaptic depression comparable in magnitude and duration to LTP might be found in the hippocampus, and the general stimulus conditions that would be likely to characterize its induction. The covariance model pointed to negative temporal correlation between pre-synaptic and post-synaptic activity as a key variable and helped us design suitable patterns of stimuli.

Pyramidal cells in area CA3 have recurrent collaterals, which make it a good candidate area for a content-addressable associative memory (Kohonen, 1984; Hopfield, 1982; Rolls, 1987). The striking differences between synapses onto CA3 pyramidal neurons are likely to reflect their different roles in processing the flow of information from dentate granule cells to CA1 pyramidal neurons. Mossy fibers have a type of LTP that is non-associative and non-Hebbian. In contrast, the LTP and LTD exhibited by the commissural fibers to area CA3 are associative. Thus, the mossy fibers can 'instruct' the commissural inputs through associative interactions, but cannot themselves be influenced by information arriving from other pathways.

The recurrent collaterals of pyramidal cells within area CA3 have not been separately tested and it will be interesting to determine if they are of the associative or non-associative variety. It is also not known if there are associative interactions between mossy fiber synapses, though this would be unlikely given our present findings.

One of the consequences of having an associative mechanism that is pseudo-Hebbian rather than Hebbian (Kelso *et al.*, 1986), is that synapses on localized regions of a dendrite can interact with each other independently of processing occurring on other dendrites. The voltage-sensitive NMDA receptors which trigger LTP, effectively make each patch of dendrite a non-linear processing unit. This would greatly increase the amount of information that could be stored by a single neuron. The processing power of such a 'product' unit has been explored recently in the context of simplifying models by Durbin & Rumelhart (1989). More needs to be known about the timing relationships for LTP and LTD in the hippocampus, and also about the spatial integration possible within dendritic trees. Realistic models can help with sorting out these relationships, but only if enough data can be obtained to fully constrain the models.

The principles of neural representation and neural computation are likely to be different from the way that representation and computation are accomplished in digital computers (Churchland & Sejnowski, 1988). Discovering these principles, however, is a difficult undertaking that will require combined experimental and modeling techniques (Sejnowski *et al.*, 1989).

Acknowledgements

This research was supported by grants from the National Science Foundation and the Office of Naval Research to TJS. We have benefitted from discussion with Drs Thomas Brown, Charles Stevens, and Francis Crick.

References

Alkon D.L. (1987) **Memory Traces in the Brain**. Oxford University Press, Oxford.

Anderson J.A. (1970) Two models for memory organization using interacting traces. **Math. Biosci. 8**, pp. 137-160

Barrionuevo G. & Brown T.H. (1983) Associative long-term potentiation in hippocampal slices. **Proc. Nat. Acad. Sci. USA 80**, pp. 7347-7351

Bienenstock E.L., Cooper L.N. & Munro P.W. (1982) Theory for the development of neuron selectivity: orientation specificity and binocular interaction in visual cortex. **J. Neurosci. 2**, pp. 32-48

Bliss T.V.P. & Gardner-Medwin A. R. (1973) Long-lasting potentiation of synaptic transmission in the dentate area of the unanaesthetized rabbit following stimulation of the perforant path. **J. Physiol. (Lond.) 232**, pp. 357-374

Bliss T.V.P. & Lomo T. (1973) Long-lasting potentiation of synaptic transmission in the dentate area of the anaesthetized rabbit following stimulation of the perforant path. **J. Physiol. (Lond.) 232**, pp. 331-356

Brown T.H., Ganong A.H., Kariss E.W., Keenan C.L. & Kelso S.R. (1989) Long-term potentiation in two synaptic systems of the hippocampal brain slice. In: **Neural Models of Plasticity**. J.H. Byrne & W.O Berry (eds.) Academic Press, New York, in press.

Chattarji S., Stanton P.K. & Sejnowski T.J. (1989) Commissural synapses, but not mossy fiber synapses, in hippocampal field CA3 exhibit associative long-term potentiation and associative long-term depression. **Brain Res.** submitted.

Chauvet G. (1986) Habituation rules for a theory of the cerebellar cortex. **Biol. Cybern. 55**, pp. 201-209

Churchland P.S. & Sejnowski T.J. (1988) Neural representations and neural computations. In: **Neural Connections and Mental Computation**. L. Nadel (ed.) MIT Press, Cambridge, MA.

Collingridge G.L., Kehl S.L. & McLennan H. (1983) Excitatory amino acids in synaptic transmission in the Schaffer collateral-commissural pathway of the rat hippocampus. **J. Physiol. (Lond.) 334**, pp. 33-46

Crick F. (1989) The recent excitement about neural networks. **Nature 337**, pp. 129-132

Durbin R.M. & Rumelhart D.E. (1989) Product units for backpropagation networks. **Neural Computation 1**, pp. 133-142

Gray C.M. & Singer W. (1989) Neuronal oscillation in orientation columns of cat visual cortex. **Proc. Nat. Acad. Sci. USA 86**, pp. 1698-1702

Gray C.M., Konig P., Engel A.K. & Singer W. (1989) Oscillatory responses in cat visual cortex exhibit inter-columnar synchronization which reflects global stimulus properties. **Nature 338**, pp. 334-337

Gustafsson B., Wigstrom H., Abraham W.C. & Huang Y.Y. (1987) Long-term potentiation in the hippocampus using depolarizing current pulses as the conditioning stimulus to single volley synaptic potentials. **J. Neurosci. 7**, pp. 774-780

Harris E.W., Ganong A.H. & Cotman C.W. (1984) Long-term potentiation in the hippocampus involves activation of N-methyl-D-aspartate receptors. **Brain Res. 323**, pp. 132-137

Hebb D.O. (1949) **Organization of Behavior**. John Wiley & Sons, NY.

Hinton G.E. & Anderson J.A. (1989) **Parallel models of distributed memory**. Lawrence Erlbaum Press, Hillsdale, New Jersey.

Hopfield J.J. (1982) Neural networks and physical systems with emergent collective computational abilities. **Proc. Nat. Acad. Sci. USA. 79**, pp. 2554-2558

Hopkins W.F. & Johnston D. (1984) Frequency-dependent noradrenergic modulation of long-term potentiation in the hippocampus. **Science 226**, pp. 350-352

Kandel E.R., Klein M., Hochner B., Shuster M., Siegelbaum S.A., Hawkins R.D., Glanzman D.L. & Castellucci V.F. (1987) Synaptic modulation and learning: new insights into synaptic transmission from the study of behavior. In: **Synaptic Function**. pp. 471-518, G.M. Edelman, W.E. Gall & W.M. Cowan, (eds.) John Wiley & Sons, NY.

Katz B. & Miledi R. (1968) The role of calcium in neuromuscular facilitation. **J. Physiol. (Lond.) 195**, pp. 481-492

Kauer J.A. & Nicoll R.A. (1989) An APV-resistant non-associative form of long-term potentiation in the rat hippocampus. In: **Synaptic Plasticity in the Hippocampus**. Springer-Verlag, NY.

Kelso S.R., Ganong A.H. & Brown T.H. (1986) Hebbian synapses in hippocampus. **Proc. Nat. Acad. Sci. USA 83**, pp. 5326-5330

Klopf A.H. (1987) A neuronal model of classical conditioning. Air Force Wright Aeronautical Laboratories Technical Report **AFWAL-TR-87-1139**.

Kohonen T. (1970) Correlation matrix memories. **IEEE Trans. Comp. C-21**, pp. 353-359

Kohonen T. (1984) **Self-Organization and Associative Memory**. Springer Verlag, NY.

Larson J. & Lynch G. (1986) Induction of synaptic potentiation in hippocampus by patterned stimulation involves two events. **Science 232**, pp. 985-987

Levy W.B., Anderson J.A. & Lehmkuhle W. (1984) **Synaptic Change in the Nervous System**. Erlbaum, Hillsdale, New Jersey.

Levy W.B. & Steward O. (1979) Synapses as associative memory elements in the hippocampal formation. **Brain Res. 175**, pp. 233-245

Levy W.B. & Steward O. (1983) Temporal contiguity requirements for long-term associative potentiation/depression in the hippocampus. **Neurosci. 8**, pp. 791-797

Longuet-Higgins H.C. (1968) Holographic model of temporal recall. **Nature 217**, pp. 104-107

Lynch G.S., Dunwiddie T.V. & Gribkoff V.K. (1977) Heterosynaptic depression: a post synaptic correlate of long-term potentiation. **Nature 266**, pp. 737-739

Malinow R. & Miller J.P. (1986) Postsynaptic hyperpolarization during conditioning reversibly blocks induction of long-term potentiation. **Nature 320**, pp. 529-531

von der Malsburg C. (1973b) Self-organization of orientation sensitive cells in striate cortex. **Kybernetik 14**, p. 85.

Mayer M.L., Westbrook G.L. & Guthrie P.B. (1984) Voltage-dependent block by Mg^{2+} of NMDA responses in spinal cord neurons. **Nature 309**, pp. 261-263

McNaughton B.L., Douglas R.M. & Goddard G.V. (1978) Synaptic enhancement in fascia dentata: cooperativity among coactive afferents. **Brain Res. 157**, pp. 277-293

Monaghan D.T. & Cotman C.W. (1985) Distribution of N-methyl-D-aspartate-sensitive L-[^{3}H] glutamate-binding sites in rat brain. **J. Neurosci. 5**, pp. 2909-2919

Rolls E.T. (1987) Information representation, processing and storage in the brain: analysis at the single neuron level. In: **Neural and Molecular Mechanisms of Learning**. Springer-Verlag, Berlin.

Scharfman H. E. & Sarvey J. M. (1985) Postsynaptic firing during repetitive stimulation is required for long-term potentiation in hippocampus. **Brain Res. 331**, pp. 267-274

Sejnowski T.J. (1977a) Storing covariance with nonlinearly interacting neurons. **J. Math. Biol. 4**, pp. 303-321

Sejnowski T.J. (1977b) Statistical constraints on synaptic plasticity. **J. Theor. Biol. 69**, pp. 385-389

Sejnowski T.J., Koch C. & Churchland P.S. (1989) Computational neuroscience. **Science 241**, pp.1299-1306

Sejnowski T.J. & Tesauro G.J. (1989) The Hebb rule for synaptic plasticity: implementations and applications. In: **Neural Models of Plasticity**. pp. 94-103, J.H. Byrne & W.O. Berry (eds.), Academic Press, San Diego.

Stanton P.K. & Sarvey J.M. (1985) Depletion of norepinephrine, but not serotonin, reduces long-term potentiation in the dentate of rat hippocampal slices. **J. Neurosci. 5**, pp. 2169-2176

Stanton P.K. & Sejnowski T.J. (1989) Associative long-term depression in the hippocampus: induction of synaptic plasticity by Hebbian covariance. **Nature**, in press.

Steinbuch K. (1961) Die Lernmatrix. **Kybernetik 1**, pp. 36-45

Sutton R.S. & Barto A.G. (1981) Toward a modern theory of adaptive networks: expectation and prediction. **Psych. Rev. 88**, pp. 135-170

Tesauro G. (1986) Simple neural models of classical conditioning. **Biol. Cybern. 55**, pp. 187-200

Wigstrom H. & Gustafsson B. (1984) A possible correlate of the post-synaptic condition for long-lasting potentiation in the guinea pig hippocampus *in vitro*. **Neurosci. Lett. 44**, pp. 327-332.

8
The Representation and Storage of Information in Neuronal Networks in the Primate Cerebral Cortex and Hippocampus

Edmund Rolls

Summary

The ways in which information is represented, processed, and stored in neuronal networks in primates as shown by recordings from single neurons are considered.

1) Through the connected stages of the taste system of primates, neurons become more finely tuned to individual tastes, yet neurons which respond to only one taste are rare.

2) In the temporal lobe visual areas, which receive visual information after several prior stages of cortical processing, some neurons are found which are quite selective in that they respond to faces. However, even these neurons do not respond to the face of only one individual, but instead information about the individual is present across an ensemble of such cells.

3) It is suggested that ensemble encoding is used because this allows the emergent properties of completion, generalization, and graceful degradation to be generated in pattern association and auto-association matrix memory neuronal networks. It is suggested that nevertheless the representation is sparse, that is each pattern is represented by the firing of relatively small numbers of relatively finely tuned neurons, so that the patterns can be relatively orthogonal to each other, in order to minimize interference in the memory between the patterns and in order to increase the number of patterns which can be stored or associated. Given that the majority of neurons recorded in the cerebral cortex and hippocampal cortex of primates have positive responses, that is the response consists of an increase of firing rate from a low or zero spontaneous firing rate, the activity patterns for different inputs can only be relatively orthogonal to each other if the representation is sparse.

4) The hippocampal CA3 stage has recurrent collaterals which have Hebbian modifiability and a 4.3% contact probability. This network functional architecture suggests that it acts as an auto-association memory. It is suggested that this is the basis of episodic memories, which are formed in the