Natural patterns of activity and long-term synaptic plasticity

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Long-term potentiation (LTP) of synaptic transmission is traditionally elicited by massively synchronous, high-frequency inputs, which rarely occur naturally. Recent *in vitro* experiments have revealed that both LTP and long-term depression (LTD) can arise by appropriately pairing weak synaptic inputs with action potentials in the postsynaptic cell. This discovery has generated new insights into the conditions under which synaptic modification may occur in pyramidal neurons *in vivo*. First, it has been shown that the temporal order of the synaptic input and the postsynaptic spike within a narrow temporal window determines whether LTP or LTD is elicited, according to a temporally asymmetric Hebbian learning rule. Second, backpropagating action potentials are able to serve as a global signal for synaptic plasticity in a neuron compared with local associative interactions between synaptic inputs on dendrites. Third, a specific temporal pattern of activity – postsynaptic bursting – accompanies synaptic potentiation in adults.

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Abbreviations

EPSP	excitatory postsynaptic potential
LTD	long-term depression
LTP	long-term potentiation
NMDA	*N*-methyl-D-aspartate
TD	temporal difference

Introduction

> Acts of recollection, as they occur in experience, are due to the fact that one movement has by nature another that succeeds it in regular order. If this order be necessary, whenever a subject experiences the former of two movements thus connected, it will (invariably) experience the latter.
>
> περὶ μνήμης καὶ ἀναμνησέως
>
> Aristotle, Fourth century B.C.
> *De memoria et reminiscentia*
> [Title translation: On memory and reminiscences]

This citation from Aristotle highlights two properties of long-term memories for facts and events: their associative nature and their temporal order. These properties were incorporated into an influential proposal for synaptic plasticity made by Donald Hebb in 1949. He suggested that reverberatory activity in transient assemblies of neurons carries a memory trace that becomes permanently laid down as changes in synaptic weights when a presynaptic neuron repeatedly or persistently takes part in firing the postsynaptic cell [1]. Major research efforts that are underway to explain long-term memory have uncovered mechanisms that are consistent with both the associative nature and the temporal order emphasized in Hebb's proposal.

The first biological mechanism discovered that could potentially support Hebb's learning rule was long-term potentiation (LTP) of synaptic transmission, as described by Bliss and Lømo [2,3]. The original protocol for inducing LTP was high-frequency stimulation of presynaptic neurons. However, the highly synchronous population activity required to induce this type of LTP has never been observed during learning *in vivo*. An important question is whether synaptic potentiation could be induced by more natural activity patterns based on the relative timing of presynaptic and postsynaptic activity as originally suggested by Hebb.

In 1994, Stuart and Sakmann [4] reported that action potentials can backpropagate in the dendrites of cortical pyramidal neurons. More recently, it has been shown that backpropagating spikes could directly serve as an associative signal for LTP induction under some experimental conditions [5,6]. These papers have raised interest in the induction criteria for LTP, using behaviorally relevant stimuli. This paper briefly reviews the type of neuronal activity that can be recorded during learning episodes *in vivo*, and, with this background, discusses three fundamental questions about synaptic learning rules based on recent experimental evidence obtained *in vitro*:

1. Are synaptic learning rules temporal coincidence rules, or is the temporal order of presynaptic and postsynaptic activity important?

2. Is the postsynaptic induction of long-term plasticity controlled by an associative signal localized in dendritic segments, or is there a signal that is global to the neuron?

3. Is all successful information transfer through a neuron associated with updating of synaptic weights, or is there a specific type of activity that occurs during synaptic modification?

In this review, we focus on the postsynaptic neuron in inducing and regulating synaptic plasticity and emphasize the predictive, in addition to the associative, nature of Hebbian learning.

Neuronal activity during behavioral learning

The conditions for synaptic plasticity in the behaving animal must be sought among the activity patterns that occur during learning. The hippocampus is a structure of critical importance in memory for facts and events [7]. In addition to its established role in the processing of spatial information in rodents [8], recent results indicate that hippocampal neurons can also encode non-spatial information [9•,10•] and take part in several memory processes [11•]. Recent experiments have shed light on the nature of the encoding system in the hippocampus. Although memory retrieval can be impaired by small localized lesions within the hippocampus, the induction of new memories is not [12••]. Also, repeated tetanization in a limited amount of hippocampal tissue can disrupt learning that would otherwise be supported [13•]. These findings raise the question of what the natural conditions are that lead to synaptic modifications that could support such a distributed encoding of memories.

Refinement of multielectrode recording techniques (multiple tetrodes and multisite silicon probes) has given us new insights into the neuronal activity that occurs during learning-related behavior in rats. Exploratory learning is associated with characteristic slow rhythmic activity in extracellularly recorded potentials [14]. Interestingly, similar oscillations in the electroencephalogram (EEG) are seen during memory tasks in humans [15•]. This so-called theta activity is coexistent with faster oscillations at gamma frequencies (30–100 Hz) [16•]. In hippocampal slice experiments, theta-like oscillations can be induced by carbachol, a cholinergic agonist, and 40 Hz activity can co-occur over a range of carbachol concentrations [17,18]. The occurrence of rhythmic oscillatory activity may engage learning mechanisms that depend on relative timing of activity in the presynaptic and postsynaptic neurons, since the rhythm will naturally organize the timing of the key elements of the neural circuit.

Hippocampal pyramidal neurons fire, on average, relatively infrequently (< 1 Hz) but their spikes are phase-related to the external theta field oscillation. They may be silent, fire single spikes or brief high-frequency trains of spikes ('bursts') during each cycle [19•]. Pyramidal neurons fire bursts primarily when the animal is in a specific location in space (the 'place field' of that particular neuron) [20,21]. Pyramidal layer interneurons have a higher firing rate, and fire often on every cycle during a theta rhythm [19•]. In behaving animals, interneurons fire at the same phase of theta as do pyramidal neurons [19•], in contrast to what has been reported in anaesthetized animals, where basket interneurons and pyramidal cells fire at opposite phases of the external theta oscillations [22]. As spikes in both the pyramidal neurons and the interneurons are phase-related to gamma oscillation [16•,23], and as interneurons fire on the same phase of theta as pyramidal cells, they might control the exact timing of pyramidal cell firing in 40 Hz subcycles of each theta cycle [24•]. There is now evidence that action potentials can backpropagate in pyramidal neuron dendrites *in vivo* [25], and backpropagating action potentials can, under some circumstances, trigger Ca^{2+}-spike-associated bursts [26•].

These observations raise the possibility that burst firing and phase-related firing patterns could support the induction of synaptic potentiation. Recent *in vitro* experiments have addressed this issue.

Temporal constraint on pre- and postsynaptic activity: an asymmetric Hebbian learning rule

The Hebbian learning rule has often been interpreted to mean that synaptic potentiation should occur as a consequence of coincident activity in presynaptic and postsynaptic neurons. However, Hebb's original suggestion incorporated a temporal constraint, namely that presynaptic activity must precede the activity in the postsynaptic element for potentiation to occur [1].

Experiments setting out to test the effects of relative timing of spikes directly using single backpropagating action potentials as the postsynaptic associative signal have uncovered that the precise temporal order of the pre- and postsynaptic signals of pairing is important [5,27•,28••,29•]. In developing neurons, the postsynaptic action potential needs to take place within a narrow time window (within ~20 ms) following the presynaptic action potential for robust potentiation to occur (as reported in studies in hippocampal slice cultures [27•], cultured hippocampal pyramidal neurons [28••] and developing frog tectal neurons *in vivo* [29•]). Moreover, when the pairing was reversed, so that the postsynaptic action potential occurred immediately before the presynaptic action potential, depression was induced [5,27•,28••,29•]. Thus, at least in developing systems, a correlational learning rule exists at the synaptic level where the sign of synaptic change depends on the relative timing of the presynaptic input and the postsynaptic action potential. These rules have been studied in networks of cultured neurons, where polysynaptic pathways are modified according to this temporally asymmetric Hebbian rule [30•].

In computer simulations of recurrent hippocampal networks, temporally asymmetric Hebbian synaptic plasticity supports sequence learning [31,32]. This occurs because the learning rule tends to wire together neurons that form causal chains; that is, if neuron A fires before neuron B and they represent two sequential sensory or motor states, the connection between them will strengthen so that in the future, neuron B is more likely to fire after neuron A. A sequence of patterns can be stored in an oscillating network model with recurrent excitatory synapses, as occurs in the CA3 region of the hippocampus where 5–8 Hz theta oscillations are observed *in vivo* [24•]. The sequence could then be rapidly retrieved from the network in 40 Hz subcycles of the slower theta oscillation [18,33].

The motion of visual stimuli provides the visual cortex with a sequence of highly correlated inputs. The development of direction selectivity in developing visual cortical neurons can be modeled with an asymmetric Hebbian rule implemented in a recurrent network [34••].

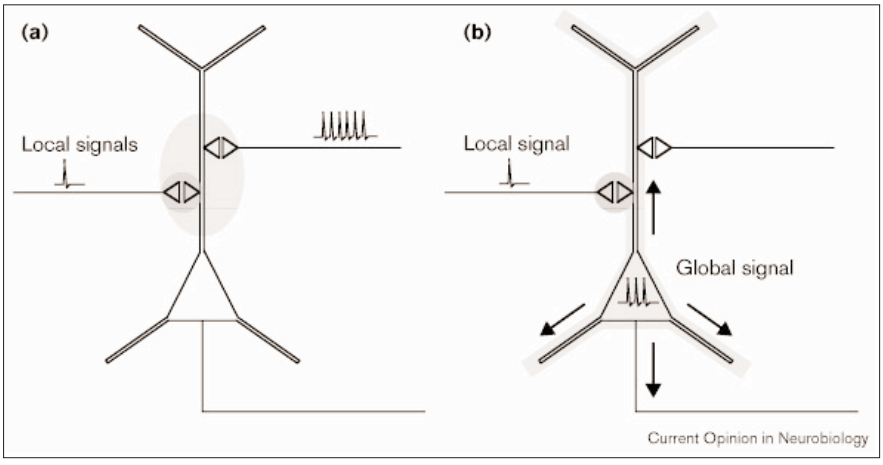
Backpropagating action potentials as a global neuronal associative signal

The induction of LTP at some excitatory synapses on pyramidal neurons depends on the activation of NMDA receptors [3]. NMDA receptors are thought to serve as molecular coincidence detectors, requiring the presynaptic release of glutamate immediately followed by postsynaptic depolarization. Where does the postsynaptic depolarization originate? The traditional view is that a 'strong' synaptic input can depolarize the local dendritic branch sufficiently to enable the activation of NMDA receptors at 'weak' inputs on neighboring synapses [3]. However, backpropagating action potentials could also provide the postsynaptic associative signal [35•]. A backpropagating action potential would serve as a global dendritic associative signal, reaching a large fraction — and potentially all — of the synapses on a single neuron. The extent of the influence of the backpropagating action potential could be subject to control by ion channels and synaptic inhibition. The physiological control of dendritic backpropagation of action potentials has recently been reviewed elsewhere [36•]. Figure 1 illustrates the difference between the concepts of local cooperativity in the dendrites and global backpropagating signals.

Induction of LTP depends on a postsynaptic Ca^{2+} increase [3]. It has been widely assumed that the permeation of Ca^{2+} through NMDA receptors provides the Ca^{2+} signal necessary for the induction of LTP [3]. However, voltage-gated Ca^{2+} channels and Ca^{2+}-induced Ca^{2+} release from intracellular stores may also contribute to the Ca^{2+} transient observed in dendritic spines following different types of activation [37•–40•]. Confocal imaging and two- and multiphoton microscopy have been used to measure Ca^{2+} transients in single dendritic spines during synaptic activation and following backpropagation of action potentials [37•–40•]. Single backpropagating action potentials produce a small Ca^{2+} influx [41], while the Ca^{2+} transient following pairing of synaptic activation and backpropagating action potentials depends critically on the relative timing of the backpropagating action potentials and the synaptic activation. The spinous Ca^{2+} transient evoked by pairing an excitatory postsynaptic potential (EPSP) and a backpropagating action potential was larger if the action potential followed the EPSP than if it preceded it [37•].

These observations can be modeled using MCell, a computer program which simulates the diffusion of neurotransmitter molecules and subcellular signaling [42•,43]. The rise and fall of the backpropagating action potential sets the time scale for the rapid depolarization pulse that occurs at distal synapses. This pulse, in turn, determines the conditions for massive entry of Ca^{2+} into the spine. The time course for glutamate binding to the NMDA receptor is much longer than the width of the backpropagating action potential, so the dynamics of Ca^{2+}, and the binding of Ca^{2+} to Ca^{2+}-binding proteins, depend in a highly nonlinear way on the relative timing of these two signals [43]. As a consequence of these biophysical mechanisms, the change in the synaptic strength depends not on the coincidence of presynaptic with postsynaptic activity, but, to a first approximation, with the time derivative of the postsynaptic activity [34••]. This temporally asymmetric form of the Hebbian learning rule has profound consequences for learning in highly recurrent networks of neurons, such as those found in the neocortex and area CA3 of the hippocampus.

Figure 1



Two models for induction of synaptic modifications in the hippocampus. **(a)** Conventional model for induction of LTP. A 'strong' input (large number of synchronously active afferent input fibers) produces a local dendritic depolarization that unblocks NMDA receptors. Synaptically released glutamate in neighboring excitatory synapses, concurrently active with the strong input, can activate the NMDA receptor providing the necessary Ca^{2+} signal for induction of LTP. **(b)** New model for induction of synaptic modifications based on backpropagating action potentials. In this scenario, postsynaptic action potentials provide a global signal in the neuron, allowing all synapses onto this neuron to be modified, according to their exact timing relative to the postsynaptic action potentials (temporally asymmetric Hebbian learning rule). Postsynaptic bursting signals potentiation in recently active synapses.

The nature of the postsynaptic associative signal in adult animals

In cultured hippocampal neurons, repeated pairings of single pre- and postsynaptic action potentials are sufficient to induce synaptic potentiation [27•,28••]. This would be expected to occur under normal developmental conditions during establishment of the network architecture, but does it also apply to hippocampal neurons in adult animals? Apparently not, according to two recent studies in hippocampal slices prepared acutely from adult mice and rats [44••,45••] where pairings of synaptic inputs with single postsynaptic action potentials was not sufficient to induce LTP; however, pairing with postsynaptic bursting activity did induce LTP.

A standard procedure for inducing synaptic plasticity in hippocampal slices from adult mice is a long train of relatively low-frequency afferent activity (1–10 Hz). Under these conditions, synaptic potentiation or depression could be induced depending on the frequency of activation, with depression occurring at the lowest frequencies and potentiation above a frequency threshold [46]. Certain genetic modifications can change the frequency threshold between LTP and LTD (long-term depression), and these usually lead to a deficit in performance in memory tasks [46,47,48•]. Consistent with theoretical models of developing cortex, which predicted a sliding modification threshold [49], the frequency threshold can be dynamically altered by priming with a high-frequency input [50•].

A recent discovery has raised another interesting possibility regarding the nature of the threshold separating LTP from LTD. By monitoring the postsynaptic cell with intracellular recording, it was shown that at 5 Hz afferent activity, induction of LTP depended on postsynaptic burst firing [44••]. A direct comparison of the efficiency of single spikes and bursts in inducing LTP using behaviorally plausible stimuli revealed that bursting was indeed more efficient than single spikes in inducing LTP, and might be necessary for potentiation to occur in slices from adult rats [45••]. In these experiments, postsynaptic bursting was both necessary and sufficient for synaptic potentiation when paired with presynaptic single spikes, whereas presynaptic bursting was neither necessary nor sufficient [45••]. It is conceivable that in the adult bursting satisfies the postsynaptic requirements for NMDA receptor activation, whereas single action potentials do not satisfy the requirements. Thus, a single burst of action potentials may replace the need in developing neurons for repeated pairing of single spikes (Figure 1).

What controls burst firing in neurons? A specific pattern of activity may provide the signal for bursting to occur. It was recently found in neocortical neurons that distal EPSPs that immediately follow backpropagating action potentials (3–7 ms later) can trigger Ca^{2+} spikes in the dendrites [51••]. Such dendritic Ca^{2+} spikes are accompanied by burst firing in the soma [51••,52,53]. Direct recording from dendrites of CA1 pyramidal cells in the hippocampus *in vivo* has confirmed that dendritic Ca^{2+} spikes are always preceded by fast action potentials [26•]. Interestingly, the magnitude of action-potential-induced dendritic Ca^{2+} transients correlate positively to LTP induction by theta burst stimuli in developing hippocampal neurons [54•].

Bursting in hippocampal neurons occurs naturally under two behavioral conditions. First, during active exploration of novel environments, hippocampal neurons that code for the current location in space of the animal typically show bursting activity repeated at an interburst frequency between 5 and 12 Hz [20,21]. These are the hippocampal neurons most likely to be involved in associative learning. Second, during slow-wave sleep, spike sequences detected during behavior are 'replayed' on a faster timescale during sharp-wave bursts, and it has been suggested that this activity is associated with the consolidation of memory [55•,56••]. It has been reported that LTP can be induced during sharp waves by pairing sharp-wave activity with strong postsynaptic depolarization of individual pyramidal cells [57•]. The occurrence of bursting under conditions presumed to be associated with memory induction *in vivo* along with the requirement of bursting for synaptic potentiation *in vitro* suggests that in the adult, bursting is a neuronal activity specifically signaling memory-related synaptic potentiation.

A specific postsynaptic activity signaling synaptic potentiation would be interesting for at least two reasons. First, it re-emphasizes the critical role of activity in the postsynaptic neuron for synaptic plasticity to occur. Second, it suggests that at least three logic levels of signaling exist in memory encoding: silence, single spikes transferring information, and bursts signifying changes in synaptic weights. Whereas in developing neurons single spikes provide the adequate signal for laying down the architecture of a network, in the adult a reinforcement signal — bursting triggered by a specific afferent input — might be required for synaptic plasticity to occur.

The existence of bursting as a global signal might have far-reaching implications. Burst firing in the cell body could play a role in synaptic plasticity also by action-potential-dependent regulation of gene expression [58]. But how could a signal from the nucleus reach and modify only the relevant synapses? Recently, Frey and Morris [59] showed that weak tetanization which would normally lead to short-lasting LTP ('early LTP') could induce longer-lasting LTP ('late LTP') if a separate pathway had been strongly tetanized earlier. Since late LTP requires both protein and mRNA synthesis, induction of LTP may be associated with the setting of a 'synaptic tag' at activated synapses, which is capable of sequestering a plasticity-maintenance chemical message from the nucleus [60••]. More recently it has been suggested that the late-LTP signal does not need to be synaptic, but can be replaced by postsynaptic bursting activity [61]. If this is indeed the case, it would be tempting to

speculate that the burst firing that is so prevalent during sleep might have a function related to the maintenance of synaptic weights in recently altered synapses ('consolidation') and for the structural reorganization of the neuropil, perhaps involving new spines and dendritic branches, which may require gene regulation [62–64].

Computational consequences

The demonstration that patterns of activity that occur *in vivo* during learning can elicit long-term changes of synaptic strengths *in vitro* makes it more likely that we are getting closer to understanding the mechanisms underlying learning and memory. If so, then some of the conditions accompanying these changes may be important clues to the cellular substrates of the behavioral changes that accompany learning. In particular, the time scale and the temporal asymmetry in the learning rule have important implications for the organization of cortical circuits. The importance of temporal order on a millisecond time scale for eliciting LTP and LTD suggests that precise cellular and molecular mechanisms may regulate spike timing in cortical circuits [65].

The timing of a spike in the postsynaptic neuron divides the excitatory input activities that occur during the +/–20 ms temporal window into two groups: those synapses that contributed to depolarization preceding the spike, and those that cannot have contributed because they were activated after the spike. This causal structure is directly translated into synaptic plasticity by the temporally asymmetric learning rule, which potentiates those synapses that are active immediately preceding the postsynaptic spike and depresses those synapses that are active directly after the spike [5]. This takes into account the temporal order of continuous events in the world, as noted by Aristotle.

The temporally asymmetric Hebbian learning rule implements the temporal difference (TD) learning algorithm in reinforcement learning [31]. TD learning allows predictions to be made about future events in the world as a consequence of experiencing sequences of inputs. For example, in a model system for honeybee foraging based on classical conditioning [66], the synaptic input learns to predict future reward: if the actual reward is greater than predicted, the postsynaptic neuron is depolarized and the synapse strengthens, but if the reward is less than predicted, the postsynaptic neuron is hyperpolarized and the synapse decreases in strength [66]. At the cellular level in the adult animal, 'reward' might be signaled by postsynaptic bursting activity, mediated by the ability of distal inputs to trigger dendritic Ca^{2+} spikes if timed immediately following a backpropagating fast action potential [51••]. Temporal order is also important for classical conditioning, though the time window is a few seconds — two orders of magnitude longer than that found in the cortex and hippocampus. Thus, TD learning can be used by the cortex to memorize long sequences of input states, which might be useful for storing a musical composition, in addition to the much slower learning of strategies for survival in an uncertain environment [67].

Perhaps the most exciting theoretical implication of the temporally asymmetric Hebbian learning rule is its ability to create and stabilize activity patterns in neural assemblies. First, the combination of LTP and LTD achieves a balance which overcomes the problem of synaptic saturation found to occur with learning rules that can only increase the strengths of synapses [68]. Second, rather than requiring a consensus of coupled neurons to fire together in order to wire together, the temporal asymmetry in the learning means that the first neuron to respond to a new pattern could help to recruit other neurons that are slower to respond through temporally asymmetric Hebbian plasticity [69•]. Finally, the temporally asymmetric Hebbian learning rule will tend to make persistent patterns of activity in a recurrent neural assembly more persistent, as Hebb first suggested, but ironically this model requires the anti-Hebbian version, in which a synapse decreases in strength when the EPSP precedes the postsynaptic spike, and increases in strength when the EPSP occurs after the spike [70•,71]. From discussions at a recent workshop where many of the experimental and theoretical researchers studying time-dependent synaptic plasticity gathered to compare notes on work in progress, it was clear that exciting new developments lie ahead [72].

Conclusions

All of the results reported here were from studies on pyramidal neurons. We do not have comparable knowledge of interneurons, which are highly diverse and may have a variety of different roles in regulating synaptic plasticity. Without an account of mechanisms for plasticity in interneurons it will not be possible to understand how a network of neurons learns new patterns of activity. Another important area that this review has not focused on is presynaptic mechanisms that might also be involved in the maintenance of synaptic plasticity.

The discovery of backpropagating action potentials has refocused attention on the role of the postsynaptic neuron in synaptic plasticity. Evidence is mounting that the relative timing of presynaptic activity and backpropagating action potentials in the postsynaptic cell can induce long-term synaptic changes in hippocampal pyramidal neurons by activity patterns known to occur during learning *in vivo*. The shift of emphasis to the temporal domain has opened up an exciting new chapter in the theoretical analysis of synaptic plasticity and neural networks, in which the predictive rather than the associative nature of Hebbian learning is being explored [73].

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