Spike Timing–Dependent Plasticity: A Hebbian Learning Rule

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Key Words

long-term potentiation, long-term depression, synapse, memory, backpropagating action potential

Abstract

Spike timing–dependent plasticity (STDP) as a Hebbian synaptic learning rule has been demonstrated in various neural circuits over a wide spectrum of species, from insects to humans. The dependence of synaptic modification on the order of pre- and postsynaptic spiking within a critical window of tens of milliseconds has profound functional implications. Over the past decade, significant progress has been made in understanding the cellular mechanisms of STDP at both excitatory and inhibitory synapses and of the associated changes in neuronal excitability and synaptic integration. Beyond the basic asymmetric window, recent studies have also revealed several layers of complexity in STDP, including its dependence on dendritic location, the nonlinear integration of synaptic modification induced by complex spike trains, and the modulation of STDP by inhibitory and neuromodulatory inputs. Finally, the functional consequences of STDP have been examined directly in an increasing number of neural circuits in vivo.

Contents

INTRODUCTION

Electrical activity plays crucial roles in the structural and functional refinement of neural circuits throughout an organism's lifetime (Buonomano & Merzenich 1998, Gilbert 1998, Karmarkar & Dan 2006, Katz & Shatz 1996). Manipulations of sensory experience that disrupt normal activity patterns can lead to large-scale network remodeling and marked changes in neural response properties. Learning and memory are also likely to be mediated by activity-dependent circuit modifications. Understanding the cellular mechanisms underlying such functional plasticity has been a long-standing challenge in neuroscience (Martin et al. 2000).

In his influential postulate on the cellular basis for learning, Hebb stated that "when an axon of cell A is near enough to excite a cell B and repeatedly or persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells such that A's efficiency, as one of the cells firing B, is increased" (Hebb 1949). This postulate gained strong experimental support with the finding of long-term potentiation (LTP) of synaptic transmission, initially discovered in the hippocampus (Bliss & Gardner-Medwin 1973, Bliss & Lomo 1973) and subsequently reported in a large number of neural circuits, including various neocortical areas (Artola & Singer 1987, Iriki et al. 1989, Hirsch et al. 1992), the amygdala (Chapman et al. 1990, Clugnet & LeDoux 1990), and the midbrain reward circuit (Liu et al. 2005, Pu et al. 2006). Traditionally, LTP is induced by high-frequency stimulation (HFS) of the presynaptic afferents or by pairing low-frequency stimulation (LFS) with large postsynaptic depolarization (>30 mV). In contrast, long-term depression (LTD) is induced by LFS, either alone or paired with a small postsynaptic depolarization (Artola et al. 1990, Dudek & Bear 1993, Kirkwood & Bear 1994, Linden & Connor 1995, Mulkey & Malenka 1992, Stanton & Sejnowski 1989). Together, LTP and LTD allow activity-dependent bidirectional modification of synaptic strength, thus serving as promising candidates for the synaptic basis of learning and memory (Bliss & Collingridge 1993; Ito 2005; Siegelbaum & Kandel 1991).

To characterize the temporal requirements for the induction of LTP and LTD, Levi & Steward (1983) varied the relative timing of a strong and a weak input from the entorhinal cortex to the dental gyrus and found that synaptic modification depended on the temporal order of the two inputs. Potentiation was produced when the weak input preceded the strong input by less than 20 ms, and reversing the order led to depression. Subsequent studies further demonstrated the importance of the temporal order of pre- and postsynaptic spiking in synaptic modification and delineated the critical window on the order of tens of milliseconds (Bi & Poo 1998, Debanne et al. 1998, Magee & Johnston 1997, Markram et al. 1997,

LTP: long-term potentiation

HFS: high-frequency stimulation

LFS: low-frequency stimulation

LTD: long-term depression

Zhang et al. 1998) (**Figure 1*a***, I). Such spike-timing-dependent plasticity (STDP) (Abbott & Nelson 2000) has now been observed at excitatory synapses in a wide variety of neural circuits (Boettiger & Doupe 2001, Cassenaer & Laurent 2007, Egger et al. 1999, Feldman 2000, Froemke & Dan 2002, Sjostrom et al. 2001, Tzounopoulos et al. 2004). Compared with the correlational forms of synaptic plasticity, STDP captures the importance of causality in determining the direction of synaptic modification, which is implied in Hebb's original postulate.

Recent studies have further characterized the mechanism and function of STDP in both in vitro and in vivo preparations, addressing the following questions: Which cellular mechanisms determine the STDP window, and how similar are they to the mechanisms underlying LTP and LTD induced by HFS and LFS, respectively? Does the window depend on the dendritic location of the input, and can it be regulated by neuromodulatory inputs? Does a similar learning rule apply to the inhibitory circuits? Can we observe the consequences of the asymmetric window in vivo, and can it account for the synaptic modifications induced by complex, naturalistic spike trains? In this review we summarize recent progress in these areas.

CELLULAR MECHANISMS

For many glutamatergic synapses, the inductions of LTP by HFS and LTD by LFS both require the activation of NMDA (N-methyl-d-aspartate) receptors and a rise in postsynaptic Ca^{2+} level (Malenka & Bear 2004). The NMDA receptor is thought to serve as the coincidence detector: The presynaptic activation provides glutamate and the postsynaptic depolarization causes removal of the Mg^{2+} block (Mayer et al. 1984, Nowak et al. 1984), which together allow Ca^{2+} influx though the NMDA receptors. The level and time course of postsynaptic Ca^{2+} rise depend on the induction protocol: HFS leads to fast, large Ca^{2+} influx, whereas LFS leads to prolonged, modest Ca^{2+} rise (Malenka & Bear 2004, Yang et al. 1999). In the Ca^{2+} hypothesis (Artola & Singer 1993, Lisman 1989, Yang et al. 1999), these two types of Ca^{2+} signals cause the activation of separate molecular pathways. Activation of Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) by large Ca^{2+} rise is required for LTP, whereas recruitment of phosphatases such as protein phosphatase 1 (PP1) and calcineurin by modest Ca^{2+} increase is necessary for LTD (Malenka & Bear 2004). Spike timing–dependent LTP (tLTP) and LTD (tLTD) also depend on NMDA

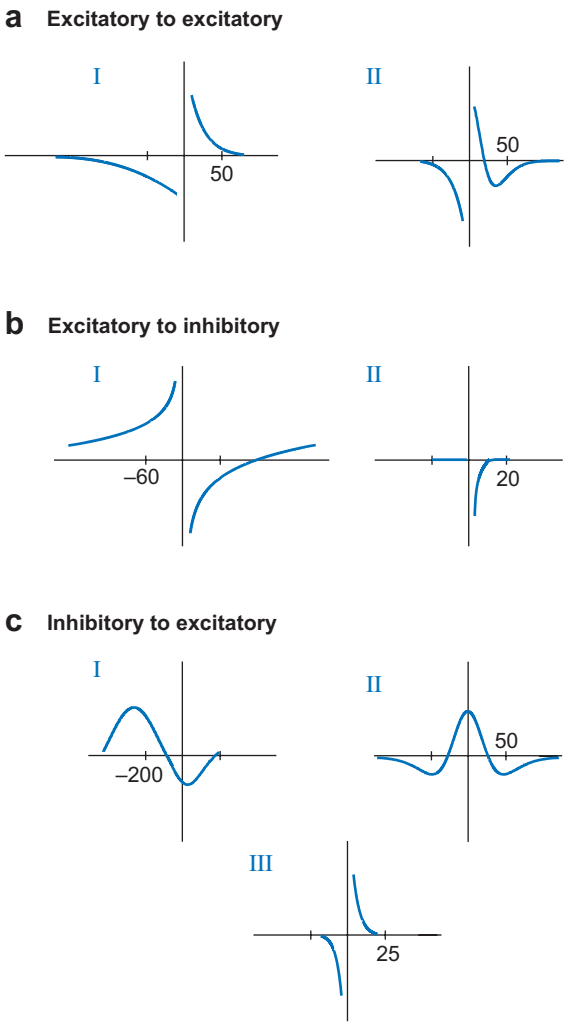

Figure 1

Diversity of temporal windows for STDP induction. *a:* Windows for excitatory to excitatory connections. *b:* Windows for excitatory to inhibitory connections. *c:* Windows for inhibitory to excitatory connections. Temporal axis is in milliseconds.

STDP: spike timing–dependent plasticity

N-methyl-d-aspartate (NMDA) receptor: subtype of glutamate receptors

BAP: back-propagating action potential

AP: action potential

VDCC: voltage-dependent Ca^{2+} channel

receptor activation and the rise in postsynaptic Ca^{2+} level (Bi & Poo 1998, Debanne et al. 1998, Feldman 2000, Magee & Johnston 1997, Markram et al. 1997, Sjostrom et al. 2001, Zhang et al. 1998). Can this simple model for conventional LTP and LTD account for STDP, in particular for its temporal window on the time scale of tens of milliseconds?

tLTP Window

Induction of tLTP requires activation of the presynaptic input milliseconds before the backpropagating action potential (BAP) in the postsynaptic dendrite (pre → post, positive intervals). The BAP can facilitate Mg^{2+} unblocking of NMDA receptors and thus allow Ca^{2+} influx, leading to tLTP induction. However, the width of the tLTP window cannot be explained solely by the time course of NMDA receptor activation. The dissociation of glutamate from the NMDA receptors occurs on the order of hundreds of milliseconds (Lester et al. 1990), much longer than the observed tLTP windows (**Figure 1*a***). The short duration of the window may be due to the kinetics of Mg^{2+} unblocking NMDA receptors (Kampa et al. 2004), such that the BAPs arriving soon after the onset of the excitatory postsynaptic potential (EPSP) are better able to open the NMDA receptors.

In addition to the Mg^{2+} unblock of NMDA receptors, the tLTP window could also be shaped by other types of interactions between the EPSP and the BAP. For example, the EPSP can cause changes in the dendritic conductances that affect the action potential (AP) backpropagation into the dendrites. In the hippocampus, the distal dendrites of CA1 pyramidal neurons express a high density of A-type K^+ channels, which regulate the BAP amplitude (Hoffman et al. 1997). An EPSP that depolarizes the dendrite and inactivates these channels can boost the BAPs arriving within tens of milliseconds (Magee & Johnston 1997, Watanabe et al. 2002). This boosting of the BAPs can in turn increase the Ca^{2+} influx through voltage-dependent Ca^{2+} channels (VDCCs), which can modulate the magnitude of tLTP (Bi & Poo 1998, Froemke et al. 2006, Magee & Johnston 1997). In the neocortex, a similar boosting of the BAP by the preceding EPSP is achieved by voltage-gated Na^{2+} channel activation in the distal dendrites (Stuart & Hausser 2001). Such nonlinear interactions between the EPSP and BAP at short positive intervals could explain the supralinear summation of Ca^{2+} influx to the active synapse in both hippocampal (Magee & Johnston 1997) and neocortical (Koester & Sakmann 1998) (Nevian & Sakmann 2004) neurons.

tLTD Window

Models based on the Ca^{2+} hypothesis have also been used to explain the tLTD window (post → pre, negative intervals) (Karmarkar & Buonomano 2002, Shouval et al. 2002). Assuming that the BAP contains an afterdepolarization lasting for tens of milliseconds and that all relevant Ca^{2+} enters the postsynaptic cell through NMDA receptors, the tLTD window can be explained by the interaction between the EPSP and the BAP. Unlike pairing of the BAP and the EPSP at positive intervals, which causes large Ca^{2+} influx through the NMDA receptors, the EPSP coinciding with the afterdepolarization leads to a moderate Ca^{2+} influx, resulting in tLTD. It should be noted that this model predicts an additional tLTD window at positive intervals outside the tLTP window (**Figure 1*a***, II), where the rise in postsynaptic Ca^{2+} falls within the range for LTD induction. This additional tLTD window has indeed been observed in hippocampal CA1 neurons (Nishiyama et al. 2000, Wittenberg & Wang 2006) but not at other synapses. This suggests a distinct form of STDP at hippocampal synapses, or it could reflect insufficient sampling of long positive intervals in the experimental studies of STDP in other circuits.

In another model for tLTD based on the Ca^{2+} hypothesis (Froemke et al. 2005), a BAP preceding an EPSP induces Ca^{2+} influx through VDCCs, which inactivates the NMDA receptors (Rosenmund et al. 1995, Tong et al. 1995). The reduced Ca^{2+} influx

through NMDA receptors in turn leads to tLTD. This model is supported by the observations that tLTD induction requires activation of VDCCs (Bender et al. 2006, Bi & Poo 1998, Froemke et al. 2005, Nevian & Sakmann 2006) and that pairing EPSPs and BAPs at negative intervals leads to sublinear summation of Ca^{2+} influx (Koester & Sakmann 1998, Nevian & Sakmann 2004). Furthermore, in L2/3 pyramidal neurons in visual cortical slices, BAP-induced Ca^{2+}-dependent NMDA receptor inactivation varied with dendritic location, mirroring the location dependence of the tLTD window at these synapses (Froemke et al. 2005).

In some other synapses, tLTD induction does not depend on activation of postsynaptic NMDA receptors (Bender et al. 2006, Egger et al. 1999, Nevian & Sakmann 2006, Sjostrom et al. 2003). These studies suggest a model involving two coincidence detectors, with the NMDA receptor for tLTP and an additional coincidence detector for tLTD. In a two-detector model proposed by Karmarkar & Buonomano (2002), tLTD induction requires activation of postsynaptic mGluRs (metabotropic glutamate receptors) and Ca^{2+} influx through VDCCs, a premise supported by experimental findings in the barrel cortex (Bender et al. 2006, Egger et al. 1999, Nevian & Sakmann 2006). Signaling through mGluRs can lead to phospholipase C (PLC) activation, and Ca^{2+} influx through VDCCs can facilitate mGluR-dependent-PLC activation (Hashimotodani et al. 2005, Maejima et al. 2005). Thus, PLC can serve as a potential coincidence detector for tLTD.

Downstream of coincidence detection, PLC may generate inositol 1,4,5-triphosphate (IP_3), which in turn triggers release of Ca^{2+} from internal stores through IP_3 receptors (IP_3Rs) (Bender et al. 2006). Both PLC activation and Ca^{2+} level elevation (due to influx through VDCCs and/or NMDA receptors, or release from internal stores) can promote endocannabinoid synthesis and release (Hashimotodani et al. 2007). Endocannabinoids play important roles in both short- and long-term depression of many synapses (Chevaleyre et al. 2006). Signaling through presynaptic CB1 endocannabinoid receptors is also required for tLTD for several excitatory–excitatory (Bender et al. 2006; Nevian & Sakmann 2006; Sjostrom et al. 2003) and excitatory–inhibitory connections (Tzounopoulos et al. 2007), presumably by inhibiting presynaptic transmitter release. In **Figure 2**, we have outlined the major signaling pathways implicated in STDP.

mGluR: metabotropic glutamate receptor

STDP OF INHIBITION

Balanced excitation and inhibition are crucial for normal brain functions (Shu et al. 2003) and

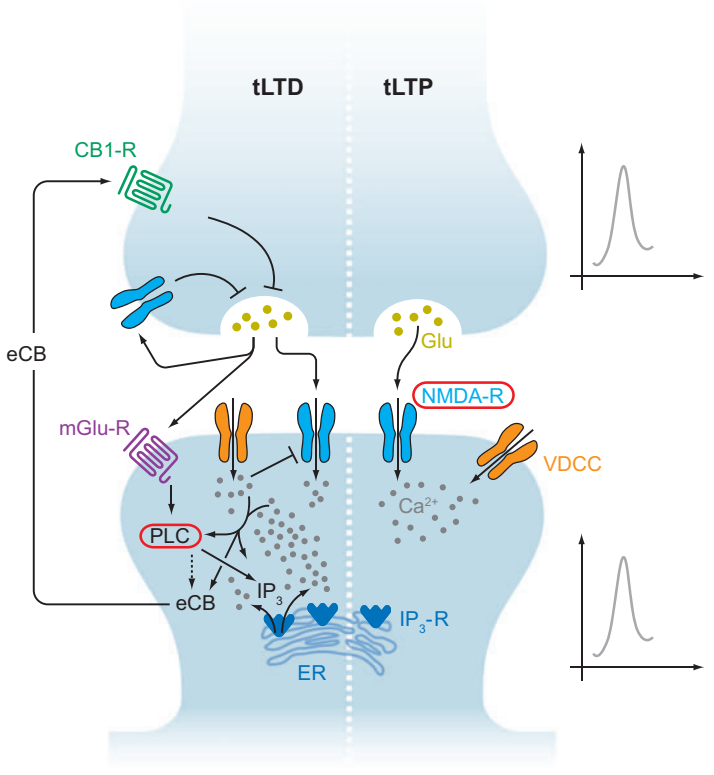

Figure 2

Schematic representation of signaling pathways involved in STDP induction. In tLTP induction (*right*), the NMDA receptors act as coincidence detectors for pre- and postsynaptic spiking. In tLTD induction (*left*) the coincidence detector may vary across synapses. The diagram includes several pathways that have been suggested to play a role in tLTD. Red oval indicates possible coincidence detectors. Arrow indicates activation/potentiation. Blunt-ended line indicates inhibition/suppression. Abbreviations: eCB, endocannabinoids; ER, endoplasmic reticulum; Glu, glutamate; IP_3, inositol 1,4,5-triphosphate; PLC, phospholipase C; VDCCs, voltage-dependent Ca^{2+} channels.

for regulating experience-dependent developmental plasticity (Hensch 2005). Although the strength of excitatory synapses can be modified through STDP, an important question is whether and how correlated pre- and postsynaptic activity affects inhibitory circuits. Inhibition in a network depends on both the excitatory synapses onto inhibitory neurons and the inhibitory synapses themselves. Spike timing–dependent plasticity has been studied at both of these synapses.

STDP of Excitatory Synapses onto Inhibitory Neurons

In a cerebellum-like structure in the electric fish, Bell and colleagues (1997) measured the excitatory inputs to Purkinje-like GABAergic neurons to study the dependence of synaptic modification on the temporal order of pre- and postsynaptic spiking. Pre → post pairing within a 60-ms window induces LTD, whereas post → pre pairing leads to LTP (**Figure 1*b***, I). This asymmetrical window is thus opposite in polarity to the STDP window for the synapses between excitatory neurons (**Figure 1*a***, I). However, given the difference in the postsynaptic neurons, the functional consequences of the two learning rules may be similar, and they could act cooperatively in activity-dependent network modifications. Mechanistically, LTD induced by pre → post pairings required NMDA receptor activation and postsynaptic Ca^{2+} elevation (Han et al. 2000), similarly to tLTD for excitatory-excitatory connections. However, LTP of these synapses can be induced by EPSPs alone without postsynaptic spiking, indicating a nonassociative component of the synaptic plasticity.

Another study of excitatory inputs to inhibitory neurons was conducted in mouse brain stem slices by pairing parallel fiber stimulation with cartwheel neuron spiking (Tzounopoulos et al. 2004, 2007). Pre → post pairing within a narrow window (<10 ms) induces LTD, whereas post → pre pairing causes no change in synaptic strength (**Figure 1*b***, II). For these synapses, LTD depends on postsynaptic NMDA receptor activation, Ca^{2+} influx, and endocannabinoid signaling, similar to the findings at excitatory synapses onto pyramidal neurons (see previous section). Interestingly, synapses from the same presynaptic fibers onto excitatory postsynaptic neurons (fusiform principal neurons) exhibit a STDP window similar to that of other excitatory-excitatory connections (**Figure 1*a***, I) (Tzounopoulos et al. 2004, 2007). This target specificity of the learning rule can be attributed to the selective distribution of presynaptic endocannabinoid CB1 receptors in different axonal terminals.

STDP of GABAergic Synapses

Compared with the glutamatergic synapses, the learning rules for GABAergic synapses appear more variable. In a study of inhibitory inputs to neocortical L2/3 pyramidal neurons, synaptic modification was induced by pairing single presynaptic spikes with high-frequency postsynaptic bursts. Overlapping pre- and postsynaptic spiking induced LTD, and nonoverlapping post → pre spiking within hundreds of milliseconds induced LTP (Holmgren & Zilberter 2001) (**Figure 1*c***, I). In the hippocampus, GABAergic synapses onto CA1 pyramidal neurons exhibit a symmetrical window, with pairing of single pre- and postsynaptic spikes at short intervals (within ±20 ms) leading to LTP, and pairing at long intervals leading to LTD (Woodin et al. 2003) (**Figure 1*c***, II). In contrast, in the entorhinal cortex GABAergic inputs to layer II excitatory stellate cells exhibit an asymmetric window similar to the STDP window for excitatory-excitatory connections: LTP was found at positive intervals and LTD at negative intervals (Haas et al. 2006) (**Figure 1*c***, III). Despite the differences between these temporal windows for GABAergic synapses, both the induction mechanism and the loci of expression have similarities. In both hippocampal CA1 (Woodin et al. 2003) and the entorhinal cortex (Haas et al. 2006), the induction of synaptic modification

depends on postsynaptic Ca^{2+} influx through the L-type Ca^{2+} channels, and presynaptic expression was excluded because no change was observed in the paired pulse ratio. In the hippocampus (Woodin et al. 2003), the changes in inhibitory postsynaptic current (IPSC) amplitude are due to changes in the Cl^- reversal potential mediated by modification of the KCC2 K^+-Cl^- cotransporter, further indicating that the expression is postsynaptic.

STDP WITH COMPLEX SPIKE PATTERNS

To study synaptic plasticity, the induction paradigms are often selected for their effectiveness rather than for their physiological relevance, thus providing limited information on how circuits are modified by natural patterns of activity. Although most induction protocols for STDP consisted of repetitive pairing of pre- and postsynaptic spikes at regular intervals, neuronal activity in vivo is far from regular (Softky & Koch 1993), with periods of almost no activity intermingled with short bouts of high-frequency spike bursts. During each presynaptic burst, transmitter release is likely to be affected by short-term plasticity (Zucker & Regehr 2002), and in each postsynaptic burst the efficacy of individual spike propagation may depend on the spike pattern (Spruston et al. 1995; Williams & Stuart 2000). How well does the STDP learning rule measured with simple spike patterns account for the synaptic changes induced by naturalistic spike trains? When multiple spike pairs fall within the STDP window, how are the contributions of individual spikes integrated?

One simple strategy to study the interaction among multiple spikes is to add one spike at a time to the existing pairing protocol. In L2/3 of visual cortical slices (Froemke & Dan 2002) and in hippocampal cultures (Wang et al. 2005), spike "triplets" (pre → post → pre or post → pre → post) and "quadruplets" (pre → post → post → pre or post → pre → pre → post) were used to induce synaptic modifications. In both studies, the interaction between multiple spikes was nonlinear, but the specific forms of nonlinearity were different. In cortical L2/3, the nonlinear interactions could be accounted for by a suppression model, in which the efficacy of later spikes in each train for synaptic modification is reduced by the preceding spikes (Froemke & Dan 2002). This model accurately predicted the synaptic changes induced by natural spike trains recorded in vivo in response to visual stimulation. In cultured hippocampal neurons, the "pre → post → pre" triplets induce no synaptic change, which suggests that LTP and LTD cancel each other, but the "post → pre → post" triplets induce LTP, which suggests that LTP "wins over" LTD under this condition. A third study using spike triplets showed that in hippocampal slices, different learning rules are revealed with different numbers of spike pairings (Wittenberg & Wang 2006). With 20–30 pairings at 5 Hz, LTP was induced regardless of the temporal order of the spikes. With 70–100 repeats, however, LTP was observed at short positive intervals (<30 ms), and LTD was found at both negative intervals and at long positive intervals (>30 ms) (**Figure 1*a***, II). These results suggest that the integration across multiple spike pairs depends on the activity patterns over several minutes.

The effects of pre- and/or postsynaptic spike bursts on synaptic modification have also been examined. Paired recordings from L5 pyramidal neurons in visual cortical slices showed that the synaptic change depends on both the spike frequency within each burst and the interval between the pre- and postsynaptic spikes (Sjostrom et al. 2001). At high frequencies (≥50 Hz), LTP is induced regardless of the pre/post interval, whereas at intermediate frequencies (10–40 Hz), the pre/post interval determines the sign and magnitude of synaptic modification as described by the STDP window (**Figure 1*a***, I). Pairing at low frequencies (<1 Hz) notably fails to induce LTP. This is likely caused by the small EPSPs evoked by activating a single presynaptic neuron in paired recordings because LTP can be rescued by adding extracellular stimulation that provides additional

depolarization. The combined dependence of synaptic modification on burst timing and frequency can be accounted for by a model in which LTP wins over LTD, and only the interactions between neighboring spikes contribute to synaptic modification (Sjostrom et al. 2001). In another study in L2/3 neurons in rat visual cortical slices (Froemke et al. 2006), pairing of pre- and postsynaptic bursts at high frequencies also favored LTP regardless of the pre/post spike timing. However, systematic examination of the dependence of synaptic modification on both the number and the timing of pre- and postsynaptic spikes led to a modified suppression model (Froemke et al. 2006), which incorporates short-term depression of the presynaptic input (Zucker & Regehr 2002) and frequency-dependent attenuation of postsynaptic spikes (Spruston et al. 1995). Note that in both models described above, burst-induced synaptic modification is accounted for by integrating the contributions of individual spike pairs. However, in some synapses the learning rule for bursts seems to be completely different from that for individual spikes (Birtoli & Ulrich 2004, Kampa et al. 2006, Pike et al. 1999).

Although the above studies focused on synaptic modifications induced by short bursts lasting for tens of milliseconds, in some circuits bursts can last for hundreds of milliseconds to several seconds. In the developing retinogeniculate synapse, bursts of retinal ganglion cells lasting seconds are believed to be critical for circuit refinement (Butts & Rokhsar 2001). Temporally overlapping pre- and postsynaptic bursts (interval within a window of ~1 s) result in synaptic potentiation, whereas nonoverlapping bursts cause a slight depression (Butts et al. 2007). The degree of potentiation can be predicted by a model in which LTP depends on the interval but not the order between the pre- and postsynaptic bursts, and it increases linearly with the number of spikes in the burst. This is reminiscent of the classic correlation-based learning rule for synaptic plasticity (Stent 1973). A strikingly similar window for burst timing was found in the hippocampal CA3 region for correlated activation of the associational/commissural (A/C) fibers and the mossy fibers (Kobayashi & Poo 2004), although no depression was observed. In both studies, the width of the temporal window seems to scale with the duration of the spike bursts used in the induction protocol, and the changes in synaptic strength depend on the interburst interval rather than the precise timing of individual spikes. Such burst timing–dependent plasticity rules may be functionally advantageous for the circuits in which the information relevant for synaptic refinement is contained in the timing of the bursts rather than that of individual spikes (Butts & Rokhsar 2001).

Together, the studies described above indicate that the integration across multiple spike pairs for the induction of synaptic modification is highly nonlinear. The nature of the nonlinear interaction is likely to depend on short-term plasticity of the presynaptic neurons, on the biophysical properties of the postsynaptic dendrites, and on the downstream signaling pathways present in different cell types. Further characterization of the diversity of integration mechanisms for STDP will allow better understanding of circuit remodeling induced by natural patterns of neuronal activity.

DEPENDENCE ON DENDRITIC LOCATION

In the central nervous system, each neuron may receive thousands of synaptic inputs distributed throughout its dendritic tree. The processing of each input depends on the dendritic location (Hausser & Mel 2003) owing to both the passive cable properties (Rall 1967) and the nonuniform distribution of active conductances (Migliore & Shepherd 2002). Such location-dependent processing and integration of synaptic inputs are believed to be essential aspects of neuronal computation. Since a hallmark of STDP is its dependence on the BAPs, which are strongly attenuated along the dendrite (Stuart & Sakmann 1994, Stuart et al. 1997b, Waters et al. 2005), synaptic modification is likely to vary with

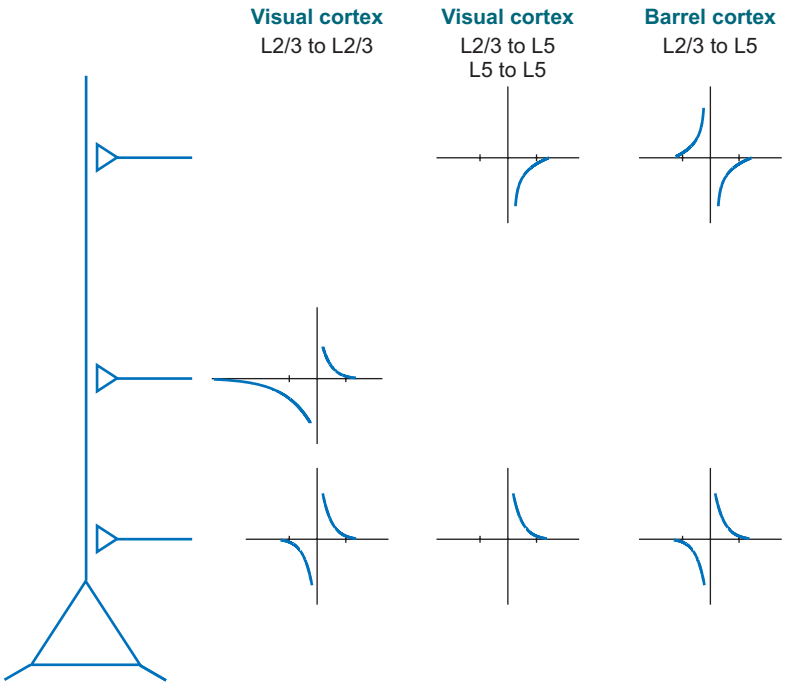

Figure 3

Dependence of STDP on dendritic location.

dendritic location (Rao & Sejnowski 2001b). Recent studies have examined the location dependence of both tLTP and tLTD. In L2/3 of rat visual cortex, the magnitude of tLTP induced by pre → post pairing of single spikes was smaller at intermediate-distal (100–150 μm) than at proximal (<50 μm) segments of the apical dendrite (Froemke et al. 2005) (**Figure 3**, left column). This reduction of tLTP amplitude is likely due to distance-dependent attenuation of the BAP. In experiments with paired recordings from a L5 and a L2/3 pyramidal neuron or from two L5 neurons (Sjostrom & Hausser 2006), burst pairing at positive intervals led to LTP at the proximal synapses but LTD at the distal synapses (**Figure 3**, middle column). Similar location dependence was also found among L2/3 to L5 connections by pairing a single EPSP with a postsynaptic burst at positive intervals (Letzkus et al. 2006) (**Figure 3**, right column). BAP boosting by subthreshold local dendritic depolarization or extracellular stimulation recovered tLTP at distal synapses (Letzkus et al. 2006, Sjostrom & Hausser 2006), which suggests that distal tLTP requires cooperativity among inputs.

Two distinct effects have been reported for post → pre pairing. In L2/3 pyramidal neurons, the width of the tLTD window measured with single spike pairing is broader for intermediate-distal than for proximal inputs (Froemke et al. 2005) (**Figure 3**, left column). This difference in width is correlated with the window for AP-induced suppression of NMDA receptor activation, which suggests that the suppression plays an important role in setting the tLTD window. In L2/3–L5 synapses in rat barrel cortex, pairing single presynaptic spikes with postsynaptic bursts at negative intervals leads to LTD at proximal locations but LTP of distal inputs (Letzkus et al. 2006) (**Figure 3**, right column). This distal LTP could be explained by the induction of dendritic Ca^{2+} spikes by the later BAPs in the burst (Larkum et al. 1999a, Stuart et al. 1997a), such that the EPSP coincides with the peak postsynaptic depolarization. Local dendritic spikes can also play a prominent role in coincidence detection in the neocortex

(Larkum et al. 1999b) and in LTP induction in hippocampal CA1 (Golding et al. 2002) and the amygdala (Humeau & Luthi 2007).

Comparison across these studies suggests that the degree of spatial variation of the learning rule depends on the dendritic morphology, with quantitative changes over short distances (e.g., dendrite of L2/3 neurons) and qualitative differences along long dendrites (e.g., apical dendrites of L5 pyramids). Although the dendritic variations of STDP summarized above can be explained largely by differences in the local active conductances, the backpropagation of APs, or the local generation of Ca^{2+} spikes, differential distribution of other pre- and postsynaptic molecular machineries could also contribute to the observed heterogeneity. Functionally, the spatial variation of the STDP rule may lead to differential input selection at distal and proximal dendrites. For example, the relative paucity of LTP at distal dendrites after pre → post pairing predicts that proximal inputs should be stronger than distal inputs (Sjostrom & Hausser 2006). The involvement of locally generated Ca^{2+} spikes in LTP induction (Golding et al. 2002, Kampa et al. 2006) likely rewards cooperativity among distal inputs because their synchronous activation is known to evoke dendritic spikes. Furthermore, the broader LTD window for intermediate distal inputs to L2/3 neurons suggests that the distal dendrites strongly favor transient over prolonged inputs (Froemke et al. 2005).

MODULATION OF STDP BY OTHER INPUTS

In addition to the spiking of the pre- and postsynaptic neurons, STDP is also regulated by other inputs. In particular, neuromodulators and inhibitory activity in the network can affect both the magnitude and the temporal window of STDP.

Neuromodulators such as norepinephrine and acetylcholine (ACh) play important roles in experience-dependent neural plasticity (Bear & Singer 1986, Kilgard & Merzenich 1998). At the cellular level, neuromodulators can influence AP backpropagation by modulating the activation and inactivation of various active conductances (Johnston et al. 1999). For example, agonists to muscarinic ACh receptors can reduce spike attenuation during high-frequency bursts, probably through reduction of Na^+ channel inactivation (Johnston et al. 1999, Tsubokawa & Ross 1997). Both β-adrenergic and muscarinic ACh receptor agonists can boost AP backpropagation by downregulating transient K^+ channels through protein kinase A (PKA) and protein kinase C (PKC) activation, respectively (Hoffman & Johnston 1998, 1999). Dopamine also has a similar effect on the BAP (Hoffman & Johnston 1999).

Such modulations of the BAPs are likely to have profound effects on STDP, particularly at distal dendritic locations. In the Schaffer collateral pathway to hippocampal CA1, pairing a weak and a strong input (which evokes postsynaptic spiking) at positive intervals can induce NMDA receptor–dependent tLTP within a narrow window of 3–10 ms. Bath application of isoproterenol, a β-adrenergic receptor agonist, broadens the window to 15 ms without changing the magnitude of tLTP (Lin et al. 2003), an effect that depends on PKA and mitogen-activated protein kinase (MAPK) signaling. In the amygdala, dopamine can gate the induction of tLTP by suppressing feedforward inhibitory inputs to the postsynaptic cell (Bissiere et al. 2003). In L5 pyramidal neurons of the prefrontal cortex, nicotine application converted tLTP to tLTD by reducing dendritic Ca^{2+} signals during spike pairing (Couey et al. 2007), and this reduction is mediated by an enhancement of GABAergic synaptic transmission. In L2/3 pyramidal neurons, activation of M1 muscarinic receptors promotes tLTD induction through a PLC-dependent pathway, whereas β-adrenergic receptor activation promotes tLTP through the adenylate cyclase cascade (Seol et al. 2007). Thus, neuromodulators can regulate both the magnitude and the polarity of synaptic modifications.

The timing and location of inhibitory inputs can also affect STDP. Somatic inhibition can prevent AP propagation through hyperpolarization and shunting (Miles et al. 1996, Tsubokawa & Ross 1996), which may preclude STDP induction. In contrast, inhibitory inputs to the dendrites have a variety of effects, from reducing dendritic depolarization through shunting to facilitating depolarization and even spike generation (Gulledge & Stuart 2003). An additional layer of complexity is added by the fact that the strength and distribution of inhibition are developmentally regulated (Hensch 2005), predicting that the learning rule can vary considerably across developmental stages. In hippocampal CA1 pyramidal neurons, pairing single pre- and postsynaptic spikes at positive intervals leads to tLTP in juvenile (p9–p14) but not in young (p22–p28) rats (Meredith et al. 2003). However, in young rats tLTP can be rescued by replacing the single postsynaptic spike with a burst or by adding $GABA_A$ antagonists, suggesting that the change in tLTP threshold might be due to a developmental enhancement of inhibition in this circuit.

PLASTICITY OF NEURONAL EXCITABILITY AND SYNAPTIC INTEGRATION

Information processing by neuronal networks depends not only on the connectivity between neurons, but also on the intrinsic conductances in each neuron that determine its excitability and synaptic integration. Changes in neuronal excitability have been reported in a variety of invertebrate and vertebrate neural circuits during associative learning (Daoudal & Debanne 2003, Zhang & Linden 2003). At the cellular level, LTP induction by tetanic stimulation also leads to increases in intrinsic excitability in both the hippocampus and the cerebellum (Aizenman & Linden 2000, Armano et al. 2000, Bliss & Gardner-Medwin 1973, Bliss & Lomo 1973). These activity-dependent changes in intrinsic neuronal properties may interact synergistically with synaptic plasticity to mediate learning and memory.

Changes in neuronal excitability have also been examined in the context of STDP. In hippocampal cell cultures (Ganguly et al. 2000) and neocortical slices (Li et al. 2004), repeated pre → post pairing of single spikes leads to LTP and to an enhancement of excitability and spike time reliability of the presynaptic neurons. Pairings at negative intervals result in LTD and a reduction in presynaptic excitability (Li et al. 2004). Mechanistically, these presynaptic changes require NMDA receptor activation and Ca^{2+} influx to the postsynaptic neuron, suggesting the involvement of retrograde signaling. On the presynaptic side, PKC is necessary for the increase in excitability (Ganguly et al. 2000), and both PKC and PKA are required for the decrease (Li et al. 2004). Interestingly, the changes in excitability can be dissociated from the changes in synaptic strength because presynaptic blockage of PKC and/or PKA abolished the excitability changes with little effect on the synaptic modifications.

Activity-dependent changes in intrinsic membrane properties can also affect synaptic integration (Magee & Johnston 2005). A recent study examined the changes in spatial summation between two input pathways in hippocampal CA1 neurons following STDP induction (Wang et al. 2003). Induction of tLTP in one pathway resulted in an increase in the linearity of spatial summation of the two pathways, whereas induction of tLTD produced the opposite effect. The observed changes depend on NMDA receptor activation and may be mediated by modifications of the I_h channels. In another study in hippocampal CA1, LTP induction by paired theta bursts causes an increase in the linearity of temporal summation between the potentiated input and a neighboring input (Xu et al. 2006); the temporal specificity of this effect varied with dendritic location. For distal inputs, the increase in linearity is limited to EPSPs arriving within 5 ms of each other, favoring summation of coincident inputs. In contrast, for proximal inputs the increase can be observed for EPSPs arriving within

a broader window of 20 ms. Such location-dependent modulation of synaptic integration may interact with the location dependence of the STDP learning rule (see above) to further enrich dendritic processing.

STDP IN VIVO

Whereas most of the early experiments on STDP were conducted in slices and cell cultures, an increasing number of studies have begun to address the functional consequences of STDP in intact nervous systems. Neural circuits in vivo exhibit both spontaneous activity and sensory-evoked responses, modulated by the behavioral states of the animal. Backpropagation of the APs may also be more variable in vivo, as the neurons receive barrages of excitatory and inhibitory inputs (Destexhe et al. 2003). These factors could significantly complicate the rules for synaptic plasticity. How well does the STDP learning rule described in vitro apply to activity-dependent synaptic modification in vivo?

Electrical Stimulation

The first demonstration of STDP in vivo came from a study at the retinotectal projection in the developing *Xenopus* (Zhang et al. 1998). Repetitive electrical stimulation of the retinal ganglion cells within 20 ms before tectal neuron spiking leads to LTP, whereas pairings at negative intervals lead to LTD. Both LTP and LTD are NMDA receptor dependent, and the temporal window is similar to the STDP windows measured in vitro (e.g., Bi & Poo 1998, Froemke & Dan 2002, Tzounopoulos et al. 2004). In addition to the strength of the retinotectal connection, the amplitude of the tectal visual response can also be modified by pairing visual stimulation with postsynaptic spiking (Mu & Poo 2006, Vislay-Meltzer et al. 2006).

Plasticity with similar asymmetric windows has also been demonstrated in the mammalian visual cortex. Optical imaging in the kitten visual cortex showed that pairing visual stimulation at a given orientation with cortical electrical stimulation leads to changes in the orientation map (Schuett et al. 2001). Electrical activation after the arrival of the visual input causes expansion of the cortical representation of the paired orientation, whereas the reverse order causes a reduction. Whole-cell recordings in juvenile rat visual cortex showed that pairing visual stimulation with single neuron spiking leads to potentiation or depression of the visual response, depending on the order between the visual inputs and the postsynaptic spiking (Meliza & Dan 2006).

STDP has also been described in other sensory modalities in vivo. In the somatosensory cortex of anesthetized rats, pairing subthreshold whisker deflections with postsynaptic spiking at negative intervals leads to LTD of the paired whisker (Jacob et al. 2007). In an olfactory circuit of the locusts (β-lobe in the mushroom body), pairing odor-induced synaptic activity with postsynaptic spiking results in robust synaptic modifications, with a temporal window similar to those for vertebrate excitatory synapses (**Figure 1*a***, I) (Cassenaer & Laurent 2007).

In the motor system, STDP has been demonstrated in human subjects. Pairing electrical stimulation of a somatosensory afferent nerve with transcranial magnetic stimulation (TMS) of the motor cortex leads to long-lasting changes in the motor-evoked potentials (MEPs) elicited by TMS (Wolters et al. 2003). The direction and magnitude of the change depend on the relative timing between the afferent stimulation and the TMS within a window of tens of milliseconds, comparable to the STDP windows measured in vitro. The potentiation induced by pairing at positive intervals can be blocked by NMDA receptor antagonists (Stefan et al. 2002), and the depression at negative intervals is blocked by both NMDA receptor and VDCC antagonists (Wolters et al. 2003), consistent with the pharmacological properties of STDP found in several studies (Bi & Poo 2001). Wolters et al. (2005) also used a similar experimental protocol to demonstrate STDP in human somatosensory cortex.

Paired Sensory Stimulation

Although electrical stimulation affords excellent control of spike timing in the study of STDP, an important question is whether the temporal requirements of this learning rule can be satisfied under natural conditions, as spiking responses to sensory stimuli are known to be highly variable (Shadlen & Newsome 1994). Several studies on the functional role of STDP in vivo have been performed with pure sensory stimulation. In anesthetized adult cats, repetitive presentation of gratings at a pair of orientations induced shifts in orientation tuning of individual V1 neurons; the direction of the shift depended on the temporal order of the two orientations (Yao et al. 2004, Yao & Dan 2001). In a parallel set of experiments in the space domain, repeated visual stimulation in two adjacent retinal regions induced shifts in V1 receptive fields (Fu et al. 2002), with a similar dependence on the stimulus order. In both the orientation and space domain, significant changes in cortical response properties were observed at intervals within ± 40 ms, similar to the STDP windows observed in vitro. For the shift in orientation tuning, the effect showed complete interocular transfer, indicating that the underlying neuronal modifications occur largely in the cortex, after the inputs from the two eyes converge (Yao et al. 2004). Psychophysical experiments in human subjects using analogous induction protocols showed perceptual changes consistent with the electrophysiological effects (Fu et al. 2002, Yao et al. 2004, Yao & Dan 2001), which suggests that the neuronal changes have direct consequences in visual perception.

Motion Stimuli

Compared with the repetitively flashed stimuli used in the above studies, moving stimuli are much more common in nature. Motion stimuli are intrinsically sequential (e.g., an object moving across the visual field should sequentially enter the neuronal receptive fields distributed along its trajectory) and are thus ideally suited for interacting with the STDP learning rule. In the *Xenopus* tadpole, repeated presentation of a moving bar in a given direction selectively potentiated the response to the conditioned direction, resulting in the emergence of direction sensitivity in the tectal neurons (Engert et al. 2002). Induction of direction selectivity through STDP has indeed been predicted in a theoretical study (Rao & Sejnowski 2001a). A follow-up experiment using both sequentially flashed bars and moving bars provided further support for the role of STDP in the induction of direction selectivity (Mu & Poo 2006). The selective enhancement at the conditioned direction manifests as a potentiation of the early phase and a reduction of the late phase of the visual response, consistent with the prediction from STDP. Blocking the cellular signaling pathways underlying STDP abolished the effect of unidirectional motion stimuli in inducing direction selectivity.

In the visual cortex, the interaction between motion stimuli and STDP has been used to predict two receptive field properties and to explain two motion-position illusions. Model simulations predicted that the prevalence of motion stimuli in various directions during visual cortical development would lead to a spatial asymmetry in the direction-selective inputs to each cortical neuron (e.g., inputs preferring rightward motion are biased toward the left side of the receptive field) (Fu et al. 2004). This asymmetry in the mature cortex in turn predicts that (*a*) receptive field position depends on the local motion signals within the test stimuli, and (*b*) motion adaptation causes the receptive field position to shift. Both effects were confirmed experimentally in anesthetized cat V1. Psychophysical measurement using matching stimulus parameters showed that these physiological effects could each explain a known visual illusion involving the interaction between motion and perceived object position (De Valois & De Valois 1991, Nishida & Johnston 1999, Ramachandran & Anstis 1990, Snowden 1998, Whitaker et al. 1999).

In addition to the motion signals in sensory inputs, locomotion of the animal may also induce circuit modification through STDP. The

place fields of hippocampal neurons are known to be dynamically modified as the animal navigates in a novel environment. During repeated running of a linear track, the place fields of both CA1 and CA3 cells are initially symmetrical, but they experience a gradual asymmetric expansion against the direction of locomotion (Lee et al. 2004; Mehta et al. 1997, 2000). Simulation with a simple feedforward network model showed that this effect can be explained by STDP (Blum & Abbott 1996, Mehta et al. 2000). In the orientation domain, Yu et al. (2006) recently reported a similar shift in head-direction tuning curves in thalamic head-direction cells as the animal runs in a circular track.

Sensory Deprivation

STDP may also play a role in other forms of experience-dependent plasticity, even if the sensory inputs do not explicitly involve timing on the order of tens of milliseconds. In an experiment measuring the neural activity during sensory deprivation, rats were chronically implanted with electrode arrays to monitor the spiking activity in L4 and L2/3 of the barrel cortex during free-moving behaviors (Celikel et al. 2004). Stimulus deprivation induced by trimming a single whisker, a manipulation known to induce whisker map reorganization, caused an immediate reversal of the firing order and decreased correlation between L4 and L2/3 neurons. Both of these changes are known to drive tLTD in barrel cortical slices (Feldman 2000), thus providing a plausible explanation for deprivation-induced LTD of L4 to L2/3 connections (Allen et al. 2003). In addition to the somatosensory system, sensory deprivation induces circuit reorganization in the visual and auditory systems (Buonomano & Merzenich 1998, Gilbert 1998). It would be interesting to test whether deprivation in these modalities (e.g., monocular deprivation of visual input) also induces changes in the relative spike timing among neurons that could cause the observed circuit modifications through STDP.

FINAL REMARKS

Over the past decade, the STDP learning rule has been demonstrated in a range of species from insects to humans, and our understanding of its cellular mechanisms and functional implications has progressed significantly. However, many questions remain unresolved.

Regarding the mechanism, it remains unclear whether a single model can explain STDP at different synapses or whether different neurons employ distinct molecular machineries to achieve similar outcomes. Studies are only beginning to examine whether and how STDP depends on several signaling events that have been strongly implicated in conventional LTP and LTD, including secretion of brain-derived neurotrophic factor (BDNF) and nitric oxide (Mu & Poo 2006), activation of CaMKII (Tzounopoulos et al. 2007) and phosphatases (Froemke et al. 2005), and modification and insertion/removal of AMPA receptors. It would also be interesting to investigate whether the type of NMDA receptor subunits (NR2A/NR2B) and their synaptic location play a role in STDP (Sjostrom et al. 2003), as has been suggested for LTP/LTD induced by HFS/LFS (Cull-Candy & Leszkiewicz 2004, Liu et al. 2004). In addition, whereas several molecules have been proposed as coincidence detectors at excitatory synapses (**Figure 2**), there is so far no candidate for inhibitory synapses. Furthermore, although postsynaptic Ca^{2+} signals are required for STDP in most cell types, recent imaging experiments showed that volume-averaged Ca^{2+} transients in the dendritic spines are poorly correlated with the direction of synaptic modification (Nevian & Sakmann 2006). Perhaps new techniques that allow measurement of Ca^{2+} signals at a more microscopic scale (e.g., microdomains) will shed new light on the cellular mechanisms of STDP.

To understand the functional consequences of STDP, an important factor to consider is the high level of ongoing activity in vivo. Spontaneous activity can significantly affect membrane potential, conductance, and intracellular

Ca^{2+} levels, and in some cases it can boost AP backpropagation in vivo (Waters & Helmchen 2004). These effects will likely modulate the rules for synaptic modification. Furthermore, spontaneous postsynaptic spiking reduces the persistence of synaptic potentiation and depression (Zhou et al. 2003). An important question is how experience-dependent synaptic modifications can persist in vivo in the face of the ongoing network activity. Recent studies have suggested that sensory-evoked activity patterns can reverberate in subsequent spontaneous activity in early sensory circuits (Galan et al. 2006, Yao et al. 2007) or be replayed in the hippocampus during sleep (Ji & Wilson 2007, Louie & Wilson 2001, Nadasdy et al. 1999, Ribeiro et al. 2004, Wilson & McNaughton 1994). These reactivated patterns may serve to consolidate the transient effects of sensory stimulation into long-lasting circuit modifications. Characterization of neuronal plasticity at the network level during natural behaviors is a crucial step in understanding the neural basis for learning and memory.

DISCLOSURE STATEMENT

The authors are not aware of any biases that might be perceived as affecting the objectivity of this review.

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