CHAPTER

9

Spike Timing-Dependent Plasticity

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OUTLINE

9.1 INTRODUCTION

Since its discovery 15 years ago, spike timing-dependent plasticity (STDP) has emerged as a leading candidate mechanism for activity-dependent synaptic plasticity during neural circuit development and for driving neural plasticity and learning in adults. This is due to its physiologically realistic induction requirements, powerful Hebbian properties, and prevalence across many cell types and synapses from insects to mammals. However, STDP is a more complex and less understood phenomenon than apparent from initial studies in *in vitro* brain slices. Though STDP is widely observed *in vitro*, whether STDP is a plausible learning mechanism under natural conditions *in vivo* has been questioned. A substantial number of studies have now characterized STDP from the molecular to the circuit and systems levels. The purpose of this review is to critically analyze the data on diversity of STDP, predicted functional properties, cellular mechanisms, and its role in circuit development and adult plasticity *in vivo*. Several excellent reviews of specific aspects of STDP

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have been published (Abbott and Nelson, 2000; Caporale and Dan, 2008; Dan and Poo, 2006; Fino and Venance, 2011; Letzkus et al., 2007; Lisman and Spruston, 2005; Paulsen and Sejnowski, 2000). We conclude that STDP occurs broadly and with diverse cellular mechanisms; that it is powerfully modulated by dendritic excitability, network activity, and neuromodulation, which both enriches its computational role and will constrain its relevance *in vivo*; that STDP does occur *in vivo* at least under controlled experimental conditions; and that STDP may contribute to several basic features of neural circuit development and to several forms of adult learning.

9.2 DISCOVERY OF STDP

Activity-dependent long-term modification of synapse strength is critical for the development of neural circuits and underlies learning and memory in young and adult brains. The seminal theoretical description of activity-dependent plasticity was by Donald Hebb, who proposed that when cell A reliably contributes to spiking of postsynaptic cell B, synapse strength from A to B is functionally enhanced (Hebb, 1949). This rule was later amended to include weakening of ineffective synapses (Bienenstock et al., 1982; Sejnowski, 1977; Stent, 1973; von der Malsburg, 1973). In the period between the 1970s and 1990s, long-term synaptic potentiation and depression (LTP and LTD) were discovered and shown to implement Hebbian synaptic plasticity. These forms of synaptic plasticity have since been observed in almost every area of the brain. In classical LTP and LTD, the change in synaptic weight depends on temporally correlated pre- and postsynaptic activity (reviewed in Fregnac and Shulz, 1999). This is termed correlation-dependent plasticity (CDP). The temporal requirement for pre- and postsynaptic coactivation in CDP was not considered to be very stringent ($\pm$50 ms or more), and plasticity was thought to be largely independent of the precise timing and order of action potentials.

Some studies, however, noted that the order of activation of the presynaptic and postsynaptic neurons was crucial in determining the sign of plasticity (LTP or LTD) (Levy and Steward, 1983). Gustafsson et al. (1987) showed that LTP was induced if an excitatory postsynaptic potential (EPSP) preceded a postsynaptic spike burst by $<$100 ms and was not induced if the EPSP immediately followed the burst. This order of pre- and postsynaptic activity was later shown to induce LTD (Debanne et al., 1994, 1996). In 1997, several groups discovered that induction of LTP and LTD by pairing pre- and postsynaptic action potentials was critically dependent on the order and relative timing of single spikes, down to the millisecond scale (Bell et al., 1997; Bi and Poo, 1998; Debanne et al., 1994, 1997; Markram et al., 1997; Figure 9.1). Confirmation at many other synapses followed. This form of temporally precise bidirectional Hebbian plasticity was termed STDP (Abbott and Nelson, 2000). STDP has been proposed on theoretical grounds to be a major mechanism for the induction of *in vivo* synaptic plasticity (Abbott and Nelson, 2000; Gerstner et al., 1996; Song et al., 2000; van Rossum et al., 2000). In the canonical form of STDP, as occurs in cortical pyramidal cells, when a presynaptic spike (and the resulting EPSP) leads a postsynaptic spike by up to 10–20 ms, an increase in synapse strength (LTP) is induced. Conversely, LTD is observed when a postsynaptic spike precedes a presynaptic spike and EPSP by short (0–20 ms) or long (0–100 ms) intervals, depending on the synapse being studied (Feldman, 2000; Froemke and Dan, 2002; Markram et al., 1997; Nishiyama et al., 2000; Sjostrom and Nelson, 2002; Sjostrom et al., 2001). Functionally, this rule causes synaptic inputs that contribute to postsynaptic firing being potentiated, while uncorrelated inputs onto otherwise active postsynaptic cells are depressed. This implements Hebb's learning rule (Abbott and Nelson, 2000; Paulsen and Sejnowski, 2000).

STDP has been extensively studied both experimentally and computationally. The mechanisms and functional consequences of STDP have been characterized in many different systems both *in vivo* and *in vitro*. Here, recent progress in the relevance of STDP in the intact brain is reviewed, with a particular emphasis on its functional properties, its multiple cellular mechanisms, and its implication in development, adult plasticity, and learning.

9.3 PREVALENCE AND DIVERSITY OF STDP

STDP is highly prevalent in the nervous system, from insects to mammals. It has been observed at a wide variety of excitatory and inhibitory synapses in many brain areas and in multiple cell types and preparations, including neuronal cell cultures, *in vitro* brain slices, and *in vivo*. While all STDP depends on precise timing and order of pre- and postsynaptic spikes, the precise temporal windows, magnitude, and sign of plasticity are remarkably diverse across synapses (Figure 9.2) (reviewed in Caporale and Dan, 2008; Shulz and Jacob, 2010). This diversity of STDP rules reflects both the existence of distinct cell type-specific forms of STDP, and the fact that nonassociative factors (i.e., factors besides pre–post spike timing) strongly modulate STDP induction. These factors include the number and frequency of postsynaptic spikes during induction (Froemke and Dan, 2002; Froemke et al., 2005; Sjostrom et al., 2001), the level

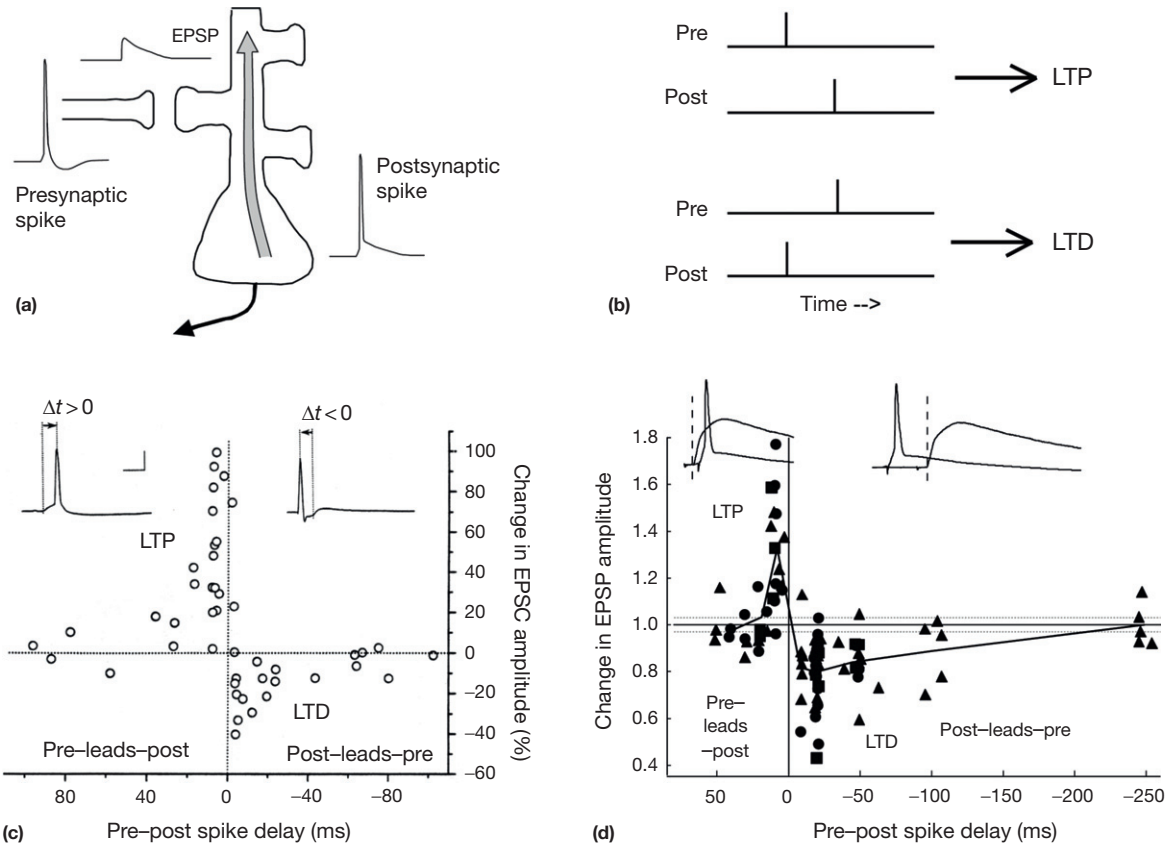

FIGURE 9.1 Spike timing-dependent plasticity. (a) Induction of STDP by pairing presynaptic spikes, which evoke EPSPs in dendrites, with postsynaptic spikes that backpropagate from the soma through the dendritic tree. (b) Temporal order dependence of STDP. (c) STDP learning rule reported by Bi and Poo (1998) for synapses in hippocampal cell culture. Each symbol is one neuron, which was presented with pre–post spike pairing at one delay. (d) STDP learning rule reported by Feldman (2000) for putative L4 synapses onto L2/3 pyramidal cells in acute slices of somatosensory cortex.

of postsynaptic depolarization evoked by presynaptic spikes (Sjostrom and Hausser, 2006; Sjostrom et al., 2001, 2004, 2008), synapse location in the dendritic tree (Froemke et al., 2005; Letzkus et al., 2006; Sjostrom and Hausser, 2006), and regulation by neuromodulators (Pawlak and Kerr, 2008; Reynolds and Wickens, 2002; Seol et al., 2007).

Three major classes of STDP can be distinguished within the substantial diversity of STDP forms. These are (a) canonical Hebbian STDP in which pre-leading-post and post-leading-pre spike pairings lead to LTP and LTD, respectively; (b) anti-Hebbian STDP in which both LTP and LTD occur but with an inverse relationship to spike timing compared to Hebbian STDP; and (c) all-LTD STDP in which LTD of synaptic transmission occurs irrespective of pre–post temporal order but only for pre–post intervals within a defined time window. This latter case is correlation-dependent, but with the opposite sign to that predicted by Hebb, and is often termed anti-Hebbian LTD. Variation within these classes is substantial and may reflect the existence of cell type-specific subforms of STDP or the effects of nonassociative factors that vary across experiments.

In canonical Hebbian STDP (e.g., Bi and Poo, 1998; Feldman, 2000; Markram et al., 1997), induction of LTP occurs when presynaptic spikes occur up to ~10–20 ms before postsynaptic spikes. LTD is induced by the reverse order, when postsynaptic spikes lead presynaptic spikes by up to 20–100 ms, depending on the synapse. This form of STDP is prevalent at excitatory synapses onto cortical pyramidal neurons (Figure 9.2(j); Bi and Poo, 1998; Feldman, 2000; Markram et al., 1997; Nevian and Sakmann, 2006; Nishiyama et al., 2000; Sjostrom et al., 2001; Wittenberg and Wang, 2006) and nonpyramidal excitatory neurons in the auditory brainstem (Figure 9.2(g)) (Tzounopoulos et al., 2004). It also occurs at excitatory synapses onto some striatal interneurons (Figure 9.2(a) and 9.2(d); Fino et al., 2008, 2009). In anti-Hebbian STDP, spike order and timing trigger LTP versus LTD induction but with a time dependence opposite to canonical Hebbian STDP: post-leading-pre spiking drives LTP, while pre-leading-post spike order drives LTD. This

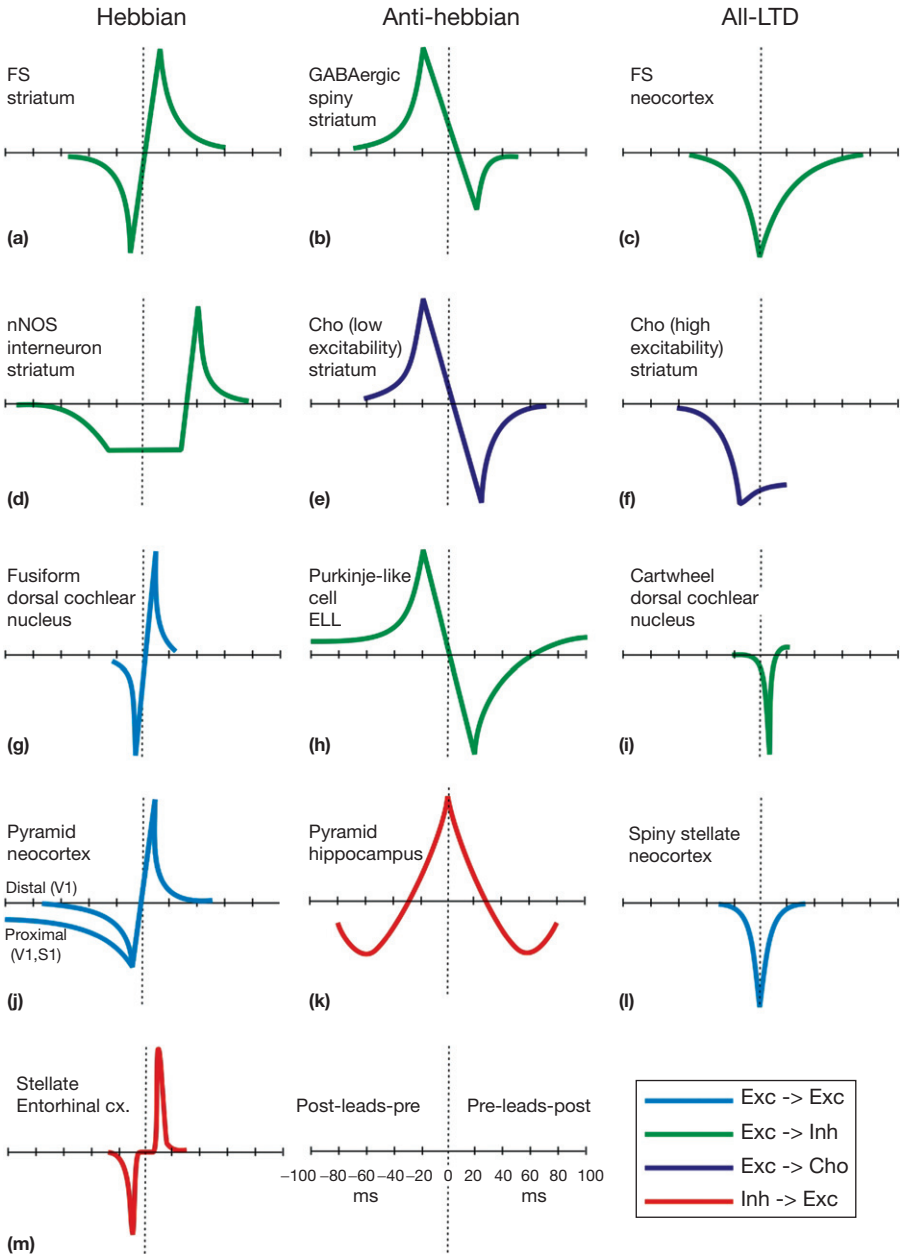

FIGURE 9.2 Three classes of STDP rules. Schematic STDP learning curves for selected examples of STDP. Light blue, excitatory synapses onto excitatory postsynaptic neurons. Green, excitatory synapses onto inhibitory interneurons. Blue, cholinergic (Cho) interneurons. Red, inhibitory synapses onto excitatory neurons. All curves are normalized to the maximal effect. For truncated curves, no data are available for longer intervals. (a, e, f) Adapted from Fino E, Deniau JM, Venance L (2008) Cell-specific spike-timing-dependent plasticity in GABAergic and cholinergic interneurons in corticostriatal rat brain slices. *The Journal of Physiology* 586: 265–282. (b) Adapted from Fino E, Glowinski J, Venance L (2005) Bidirectional activity-dependent plasticity at corticostriatal synapses. *Journal of Neuroscience* 25: 11279–11287. (c) Adapted from Lu JT, Li CY, Zhao JP, Poo MM, Zhang XH (2007) Spike-timing-dependent plasticity of neocortical excitatory synapses on inhibitory interneurons depends on target cell type. *Journal of Neuroscience* 27: 9711–9720. (d) Adapted from Fino E, Paille V, Deniau JM, Venance L (2009) Asymmetric spike-timing dependent plasticity of striatal nitric oxide-synthase interneurons. *Neuroscience* 160: 744–754. (g, i) Adapted from Tzounopoulos T, Kim Y, Oertel D, Trussell LO (2004) Cell-specific, spike timing-dependent plasticities in the dorsal cochlear nucleus. *Nature Neuroscience* 7: 719–725. (h) Adapted from Bell CC, Han VZ, Sugawara Y, Grant K (1997) Synaptic plasticity in a cerebellum-like structure depends on temporal order. *Nature* 387: 278–281. (j) Adapted from Feldman DE (2000) Timing-based LTP and LTD at vertical inputs to layer II/III pyramidal cells in rat barrel cortex. *Neuron* 27: 45–56; Froemke RC, Dan Y (2002) Spike-timing-dependent synaptic modification induced by natural spike trains. *Nature* 416: 433–438. (k) Adapted from Woodin MA, Ganguly K, Poo MM (2003) Coincident pre- and postsynaptic activity modifies GABAergic synapses by postsynaptic changes in Cl^- transporter activity. *Neuron* 39: 807–820. (l) Adapted from Egger V, Feldmeyer D, Sakmann B (1999) Coincidence detection and changes of synaptic efficacy in spiny stellate neurons in rat barrel cortex. *Nature Neuroscience* 2: 1098–1105. (m) Adapted from Haas JS, Nowotny T, Abarbanel HD (2006) Spike-timing-dependent plasticity of inhibitory synapses in the entorhinal cortex. *Journal of Neurophysiology* 96: 3305–3313. ELL, electrosensory lobe; FS, fast-spiking; S1, primary somatosensory cortex; V1, primary visual cortex.

has been observed at parallel fiber synapses onto GABAergic Purkinje-like neurons in the electrosensory lobe of the electric fish (a structure analogous to the mammalian cerebellum) (Bell et al., 1997; Figure 9.2(h)) and at excitatory synapses onto medium-sized spiny neurons of the striatum, which are GABAergic output neurons (Fino et al., 2005; Figure 9.2(b)), as well as excitatory inputs onto cholinergic striatal interneurons (Fino et al., 2008; Figure 9.2(e)). In all-LTD STDP, synapses undergo LTD irrespective of the temporal order, as long as the pre–post interval is less than ~20–50 ms, depending on cell type. All-LTD STDP occurs at excitatory inputs onto several excitatory and inhibitory neurons (Figure 9.2(c), 9.2(i), and 9.2(l); Birtoli and Ulrich, 2004; Egger et al., 1999; Tzounopoulos et al., 2004), including fast-spiking inhibitory neurons in neocortex (Birtoli and Ulrich, 2004; Egger et al., 1999; Lu et al., 2007; Tzounopoulos et al., 2004). Classical cerebellar LTD at parallel fiber inputs onto Purkinje neurons is also a form of all-LTD STDP (Wang et al., 2000).

These distinct STDP forms occur in the same brain structure and even at synapses made by single axons on two distinct target cell types. For example, parallel fiber excitatory input onto fusiform principal neurons of the dorsal cochlear nucleus shows classical Hebbian STDP, while parallel fiber input onto glycinergic cartwheel neurons shows an all-LTD form of STDP triggered by pre–post spike intervals (Tzounopoulos et al., 2004; Figure 9.2(g) and 9.2(i)). This difference is likely to result from the interaction of different transmitter systems. An even stronger example is the excitatory cortical input to the striatum (Fino and Venance, 2011). Excitatory synapses from cortical pyramidal cells onto striatal parvalbumin-positive fast-spiking neurons show Hebbian STDP (Fino et al., 2008; Figure 9.2(a)). Cortical inputs onto neuronal nitric oxide synthase (nNOS)-expressing interneurons also show Hebbian STDP but with a peculiar time course in which the LTD window extends to pre-leading-post intervals up to +20 ms (Fino et al., 2009; Figure 9.2(d)). Excitatory inputs onto cholinergic interneurons show either anti-Hebbian STDP (Figure 9.2(e)) or LTD-only STDP (Figure 9.2(f)), depending on the excitability state of the postsynaptic neuron. Thus, multiple postsynaptic cell type-specific forms of STDP coexist in the striatum. This diversity of STDP forms may affect striatal output in ways that are not yet fully explored (Fino and Venance, 2011).

STDP of inhibitory synapses onto excitatory neurons has been much less studied but seems distinct from excitatory synapses. In the entorhinal cortex, inhibitory inputs from layer two onto stellate cells exhibit a modified Hebbian STDP with a temporal range between −5 and +5 ms in which no plasticity is induced (Haas et al., 2006; Figure 9.2(m)). In the hippocampus, inhibitory inputs to CA1 pyramids exhibit a symmetrical curve, with potentiation induced by both pre–post and post–pre pairings within ±20 ms and depression induced by longer negative or positive intervals (Woodin et al., 2003; Figure 9.2(k)).

In conclusion, STDP has diverse forms, though three main classes can be distinguished. The wide variety of cell type-specific STDP rules may extend the computational power of neuronal circuits and enable differential control of processing and storage of information by subpopulations of neurons. Despite this diversity, most of our understanding of STDP in neural development and learning focuses on canonical Hebbian STDP. Additional regional variation in STDP may result from neuromodulatory gradients (see Reynolds and Wickens, 2002 for dopamine).

9.4 FUNCTIONAL PROPERTIES OF STDP

STDP differs from classical CDP in its requirement for postsynaptic somatic action potentials, its dependence on pre- versus postsynaptic spike order, and its 10-ms-scale spike timing dependence. Historically, correlation-dependent LTP and LTD were first discovered in response to sustained high-frequency or low-frequency presynaptic spiking, which drive strong postsynaptic depolarization and LTP or weak postsynaptic depolarization and LTD, respectively (Bliss and Lomo, 1973; Dudek and Bear, 1992; Mulkey and Malenka, 1992). The critical induction requirement at most synapses is temporally correlated presynaptic spiking and postsynaptic depolarization, as shown by pairing presynaptic activation with direct intracellular depolarization of the postsynaptic neuron (Wigstrom et al., 1986). The molecular coincidence detector is the postsynaptic *N*-methyl-D-aspartate (NMDA) receptor, which fluxes calcium in response to simultaneous glutamate and postsynaptic depolarization (Wigstrom and Gustafsson, 1986). Correlation-dependent, NMDA receptor (NMDAR)-dependent LTP and LTD became regarded as the canonical form of LTP and LTD at excitatory synapses onto excitatory neurons, though other, distinct forms of LTP and LTD are plentiful (e.g., Chevaleyre et al., 2006; Nicoll and Malenka, 1995).

In CDP, postsynaptic depolarization can arise from any source including subthreshold dendritic depolarization, local dendritic spiking, or somatic action potentials, and the sign of plasticity is determined by the magnitude of postsynaptic depolarization, not the precise order or timing of pre- and postsynaptic spikes (Lisman and Spruston, 2005; Paulsen and Sejnowski, 2000). In contrast, STDP explicitly depends on postsynaptic somatic action potentials, which backpropagate through the dendrites to synapses, and the sign and magnitude of plasticity depend on the sequential order and precise

(10-ms scale) timing of pre- versus postsynaptic spikes (Bi and Poo, 1998; Magee and Johnston, 1997; Markram et al., 1997). The existence of STDP therefore reveals the critical importance of precise spike timing for LTP and LTD.

A common function of Hebbian STDP and CDP is that they both implement bidirectional Hebbian synaptic plasticity at excitatory synapses, which is the basis for most modern theories of activity-dependent synapse development and associative learning (Miller, 1994). In bidirectional Hebbian plasticity, when neuron A consistently participates in driving spikes in neuron B, the A → B synapse is strengthened (Hebb, 1949), while ineffective inputs that do not drive postsynaptic spikes are weakened (Bienenstock et al., 1982; Sejnowski, 1977; Stent, 1973; von der Malsburg, 1973). CDP approximates this rule by assuming that when pre- and postsynaptic activities are strongly correlated, effective synapses exist that causally drive postsynaptic spikes and therefore should be potentiated. In contrast, synapses with weak firing correlations are assumed to be ineffective and should be depressed. Hebbian STDP implements this rule by virtue of precise spike timing: synapses at which presynaptic spikes lead postsynaptic spikes by a brief 10–20 ms interval must help drive postsynaptic spikes and are potentiated, while synapses at which postsynaptic spikes lead presynaptic spikes are ineffective synapses onto otherwise active neurons and are depressed (Song and Abbott, 2001; Song et al., 2000; van Rossum et al., 2000). Moreover, Hebbian STDP at many synapses is biased toward LTD (Figures 9.1(d) and 9.2(j)) (e.g., Debanne et al., 1998; Feldman, 2000; Froemke et al., 2005; Sjostrom et al., 2001). This LTD-biased STDP drives depression of presynaptic inputs that are uncorrelated with postsynaptic spiking, thus providing an additional means of weakening ineffective inputs (Feldman, 2000). Thus, Hebbian STDP implements bidirectional Hebbian plasticity (Abbott and Nelson, 2000; Paulsen and Sejnowski, 2000). Because STDP drives Hebbian potentiation at low, physiologically realistic firing rates, STDP may be the natural means of LTP induction in low firing rate brain regions, neuron classes, or brain states (Paulsen and Sejnowski, 2000).

Hebbian STDP has other functional properties that are distinct from CDP, and arise from the spike order dependence and overall shape of the STDP learning rule. (1) LTD-biased STDP promotes stable firing rates in neuronal networks because LTP at effective synapses (which promotes higher firing rates) is counterbalanced by synapse weakening by spontaneous uncorrelated spiking (which reduces firing rates). This results in a stable state in which postsynaptic spikes occur relatively rarely and spike trains are irregular and physiologically realistic (Song et al., 2000; van Rossum et al., 2000). In contrast, CDP is unstable due to positive feedback between firing rate, firing correlation, and synapse strengthening (unless negative correlation is taken into account or a homeostatic form of metaplasticity is added). (2) STDP prevents formation of strong bidirectional recurrent excitation, which forms with correlation-based learning rules and helps drive runaway network activity (Abbott and Nelson, 2000; Clopath et al., 2010). (3) STDP implements competition between convergent inputs to a postsynaptic cell, which is a key feature of developmental plasticity (Katz and Shatz, 1996). Competition arises because synapses that fire first tend to generate pre-leading-post spike order and are strengthened, while later inputs exhibit post-leading-pre spike order and are weakened. As a result, strong early inputs competitively weaken other synapses with later or less effective input (Abbott and Nelson, 2000; Kempter et al., 1999; Song et al., 2000; Zhang et al., 1998). Correlation-based learning rules do not generate competition between inputs without constraints on total synapse strength or other normalization rules like history-dependent metaplasticity (Bienenstock et al., 1982). (4) STDP helps maintain synchronous spiking during signal propagation in feedforward networks, which is critical for network function (Bruno and Sakmann, 2006; Swadlow and Gusev, 2000; Usrey and Reid, 1999). Consider a feedforward network in which neurons exhibit a wide range of spike latency to a synchronous network input. With STDP, feedforward synapses onto postsynaptic cells that spike earliest will be weakened, thereby increasing spike latency, while synapses onto those cells that spike later will be strengthened, reducing their spike latency (Cassenaer and Laurent, 2007; Suri and Sejnowski, 2002; Zhigulin et al., 2003). (5) STDP is a powerful mechanism for learning temporal sequence information because sequential activation of connected neurons drives LTP at synapses from the first to the second neuron, but drives LTD at synapses in the reverse direction. The result is emergence of directional connectivity, tuning for learned sequences, and the ability to predict future events from past stimuli (Blum and Abbott, 1996; Engert et al., 2002; Fiete et al., 2010; Rao and Sejnowski, 2001). In contrast, CDP cannot, on its own, learn rapid sequence information.

Because of these theoretical properties, Hebbian STDP is widely proposed to store learned associations and temporal sequence information in excitatory networks and to contribute to use-dependent developmental maturation of excitatory synapses. In contrast, anti-Hebbian STDP is appropriate to reduce the representation of inputs that are temporally associated with a strong, spike-eliciting input (e.g., as occurs in cerebellum during storage of negative images of predicted sensory input) (Abbott and Nelson, 2000; Bell, 2001).

A major, unresolved debate is the relationship between Hebbian STDP and CDP. Section 9.5 discusses

whether these are mechanistically distinct forms of plasticity versus different operating regimes of the same fundamental plasticity mechanism. Here, functional evidence that STDP and CDP are strongly interrelated is reviewed. Despite the widespread notion that STDP depends only on spike timing, and not on firing rate, substantial evidence shows that STDP depends on pre- and postsynaptic firing rate and burst structure (Froemke and Dan, 2002; Markram et al., 1997; Nevian and Sakmann, 2006; Pfister and Gerstner, 2006; Sjostrom et al., 2001; Tzounopoulos et al., 2004; Wang et al., 2005; Wittenberg and Wang, 2006; Zilberter et al., 2009). For example, neocortical L5 and CA1 pyramidal cell synapses exhibit Hebbian STDP at moderate firing rates, but high pre- and postsynaptic firing rates (>10–50 Hz) induce LTP independent of spike timing, and low firing rates generate LTD with post-leading-pre firing order and no plasticity with pre-leading-post order (Markram et al., 1997; Sjostrom et al., 2001; Wittenberg and Wang, 2006). Unitary L2/3–L2/3 synapses similarly exhibit only LTD at low postsynaptic firing rates but exhibit Hebbian STDP during high-frequency postsynaptic bursts (Zilberter et al., 2009). These observations suggest that STDP operates primarily in a permissive middle range of firing frequency, while high firing rates drive correlation-dependent LTP and low firing rates produce a strong bias toward LTD (Figure 9.3(a)). STDP also requires a critical level of subthreshold dendritic depolarization prior to spiking, which is generated by summation of EPSPs across multiple synaptic inputs and is necessary to allow effective backpropagation of spikes (Delgado et al., 2010; Sjostrom and Hausser, 2006; Sjostrom et al., 2001; Stuart and Hausser, 2001). Thus, STDP is interdependent on spike timing, firing rate, and subthreshold dendritic depolarization.

These experimental data suggest that STDP and CDP represent two functional modes of a single, more general plasticity mechanism. Some groups have argued that STDP is the fundamental 'kernel' of long-term plasticity – that STDP is driven by individual pairs of pre- and postsynaptic spikes and that nonlinear summation of STDP across spike pairs explains firing rate-dependent plasticity driven by sustained or complex spike trains (Froemke and Dan, 2002; Froemke et al., 2006; Pfister and Gerstner, 2006; Wang et al., 2005; Wittenberg and Wang, 2006). Other groups have argued that STDP and CDP represent distinct fundamental modes of a single, unified plasticity process that is sensitive to spike timing, firing rate, and postsynaptic voltage. Indeed, a unified biochemical model based solely on calcium and NMDA receptor dynamics successfully explains major properties of both STDP and firing rate-dependent LTP and LTD (Badoual et al., 2006; Shouval et al., 2002, 2010). Similarly, a phenomenological plasticity model based on interaction of presynaptic spikes with time-filtered postsynaptic membrane potential predicts all

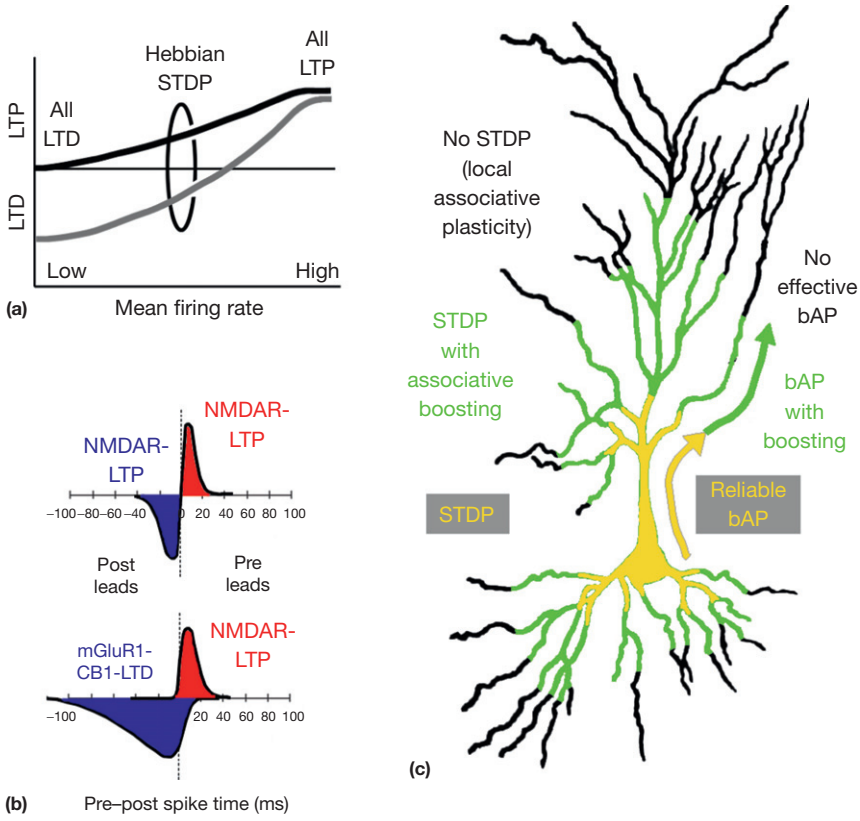

FIGURE 9.3 Cellular mechanisms for STDP. (a) Firing rate dependence of STDP. Curves show magnitude of LTP or LTD that results from pre-leading-post (black) or post-leading-pre (gray) spike pairings, as a function of mean pre- or postsynaptic firing rate. Bidirectional Hebbian STDP occurs with moderate firing rates. (b) Hebbian STDP can be composed of NMDAR-LTP and NMDAR-LTD (top) or NMDAR-LTP and mGluR1–CB1-LTD (bottom). (c) Proposed dendritic zones for STDP, based on efficiency of action potential backpropagation through the dendrites.

major features of Hebbian STDP (Clopath et al., 2010; Pfister and Gerstner, 2006). If this unified view is correct, the term 'STDP' should be taken to describe the spike time dependence of the general hybrid time- and rate-dependent plasticity process, rather than a biochemically distinct form of plasticity.

The hybrid time- and rate-dependent model of plasticity powerfully predicts major features of circuit development in a cortical column-like network containing feedforward and recurrent synapses (Clopath et al., 2010). When input to the model consists of long-duration spike trains mimicking rate coding of sensory stimuli, feedforward synapses modify to generate small receptive fields, and recurrent synapses develop strong bidirectional connections between neurons with similar receptive fields (due to timing-independent LTP driven by high firing rates of coactive neurons). This behavior is classically expected from correlation-dependent Hebbian plasticity. In contrast, when model input consists of spatiotemporal sequences of brief spiking responses, feedforward synapses still undergo Hebbian plasticity to generate receptive fields, but recurrent synapses develop strong unidirectional connections that reflect the temporal sequence in the learned pattern, as predicted by STDP. Thus, the hybrid time- and rate-dependent model can explain activity-dependent development of key circuit features according to input statistics to different brain regions (Clopath et al., 2010).

In summary, Hebbian STDP has robust Hebbian properties and appears well suited to drive realistic circuit development for neurons, brain regions, and activity states with low firing rates. Despite its name, STDP depends not only on spike timing but also on firing rate and postsynaptic voltage, suggesting a close relationship to CDP. One view, supported by recent modeling studies, suggests that STDP and CDP are different operating regimes of a hybrid spike timing-, rate-, and depolarization-dependent plasticity mechanism. Because neuromodulation can also powerfully regulate STDP (see Section 9.5), three-factor plasticity rules that include presynaptic spiking, postsynaptic activity, and neuromodulatory signals are capturing increasing interest computationally (e.g., Fremaux et al., 2010) and experimentally.

9.5 CELLULAR MECHANISMS OF STDP

The distinct forms of STDP (Section 9.3) are mediated by distinct biochemical and molecular plasticity mechanisms. In addition, even nominally identical forms of STDP (e.g., Hebbian STDP at excitatory synapses) can be mediated by different biochemical pathways in different neurons or synapses. Thus, STDP is mechanistically heterogeneous across synapses. Here, a discussion is presented on STDP mechanisms in comparison with mechanisms for classical correlation-dependent LTP and LTD, which are triggered by joint activation of glutamate receptors (NMDA receptors or metabotropic glutamate receptor – mGluRs) and postsynaptic depolarization. STDP appears to involve identical biochemical pathways, but the primary source of postsynaptic depolarization is somatic action potentials that backpropagate through the dendrites to active synapses (backpropagating APs, bAPs).

Three major, biochemically distinct forms of LTP and LTD have been shown to underlie both CDP and STDP: (1) NMDAR-dependent LTP, in which NMDARs detect correlated presynaptic glutamate release and postsynaptic depolarization by their dual requirement for glutamate binding and voltage-dependent relief of Mg^{2+} blockade. NMDARs flux calcium, which is the postsynaptic second messenger for plasticity. Strong correlated activity generates strong NMDA currents and high postsynaptic calcium, which activates protein kinases including CaMKII. CaMKII phosphorylates AMPA receptors (AMPARs), increasing single-channel conductance and triggering AMPAR delivery to the postsynaptic membrane, which is the primary expression mechanism for LTP (Malinow and Malenka, 2002). Presynaptic components of expression can also occur but are less understood (Enoki et al., 2009). (2) NMDAR-dependent LTD, in which weaker pre- and postsynaptic activity correlations evoke less NMDAR current than for LTP, leading to lower dendritic calcium. This activates protein phosphatases including PP1 and calcineurin, which trigger LTD by trafficking of AMPARs away from the postsynaptic membrane (Malinow and Malenka, 2002). In NMDAR-dependent LTP and LTD, the NMDAR is the sole coincidence detector for plasticity, and the sign of plasticity is determined by the magnitude and time course of NMDAR-mediated calcium flux, with high calcium generating LTP, moderate calcium LTD, and low calcium no plasticity (Artola and Singer, 1993; Lisman, 1989; Yang et al., 1999). (3) mGluR-dependent and/or cannabinoid type 1 (CB1) receptor-dependent LTD, which usually leads to LTD via a decrease in presynaptic transmitter release probability. Postsynaptic NMDARs are not required for this LTD. In CB1-dependent LTD, the retrograde signal is an endocannabinoid (eCB), a phospholipid transmitter synthesized by postsynaptic dendrites in response to calcium and/or mGluR activation, which diffuses retrogradely to activate CB1 receptors on the presynaptic terminal. CB1 receptors are G protein-coupled receptors that drive a long-lasting decrease in release probability via mechanisms that are still not completely understood (Chevaleyre et al., 2006; Wilson and Nicoll, 2002). While mGluR-dependent LTD typically involves CB1 signaling, some mGluR-dependent, CB1-independent forms of LTD also exist; however, they are not discussed separately here.

The large majority of STDP is composed of combinations of these three forms of LTP and LTD. Other forms of LTP and LTD exist but are less studied or not yet linked to STDP and are generally not considered here (Malenka and Bear, 2004).

9.5.1 Biochemical Signaling Pathways for Hebbian STDP

At least two mechanistically distinct forms of Hebbian STDP exist. The first form is composed of NMDA-dependent LTP and NMDA-dependent LTD and occurs at CA3–CA1 hippocampal synapses and some synapses on neocortical L2/3 pyramidal cells (Figure 9.3(b)). In this form of STDP, the NMDAR is the sole coincidence detector for appropriate pre- and postsynaptic spike timing. Thus, both LTP and LTD components of STDP require NMDARs (Froemke et al., 2005; Nishiyama et al., 2000). When a presynaptic spike occurs just before a postsynaptic spike (pre-leads-post), a strong supralinear calcium signal is produced via dendritic NMDARs, while post-leading-pre spike order triggers a weaker, sublinear calcium signal (Koester and Sakmann, 1998; Magee and Johnston, 1997). The magnitude of calcium signal is thought to be the sole trigger for plasticity, with high calcium driving LTP and low calcium driving LTD (Lisman, 1989). Spike timing is thought to control NMDAR-mediated calcium signals by several mechanisms. Brief pre-leading-post spike intervals drive maximal calcium signals because (i) the noninstantaneous kinetics of Mg^{2+} unblock of NMDA receptors causes maximal NMDA current to occur when glutamate release leads postsynaptic depolarization by a short interval (Kampa et al., 2004) and (ii) presynaptically evoked EPSPs inactivate A-type K^+ channels and activate voltage-gated sodium channels, generating a brief temporal window in which bAPs are boosted. This boosting of the bAP promotes greater NMDA current (Hoffman et al., 1997; Holbro et al., 2010; Stuart and Hausser, 2001). Post-leading-pre spike order generates weaker calcium signals because (i) glutamate release coincides with the modest depolarization following the bAP, generating NMDA currents only modestly greater than would occur at V_{rest} (Karmarkar and Buonomano, 2002; Shouval et al., 2002), and (ii) at some synapses, calcium influx during the bAP causes calcium-dependent inactivation of NMDA receptors so that presynaptic release evokes even less NMDA current (Froemke et al., 2005; Rosenmund et al., 1995; Tong et al., 1995).

This single coincidence detector model for STDP predicts that as pre-leading-post spike interval increases beyond the brief window for LTP, a second temporal window for LTD will occur because calcium will be reduced compared to its high value at short pre-leading-post intervals (Abarbanel et al., 2003; Karmarkar and Buonomano, 2002; Shouval et al., 2002). This second LTD window has been observed at CA3–CA1 synapses (Wittenberg and Wang, 2006) but, surprisingly, not at L2/3 synapses that are proposed to also use the single coincidence detector mechanism (Froemke and Dan, 2002).

The second major form of Hebbian STDP involves a combination of NMDA-dependent LTP and mGluR- and/or CB1-dependent LTD (Figure 9.3(b)). This form occurs at several synapses in L2/3 and L5 of the somatosensory and visual cortex and at cortical synapses onto striatal medium spiny neurons under conditions of GABAergic blockade. Here, postsynaptic NMDA receptors are required for spike timing-dependent LTP, but not LTD (Bender et al., 2006b; Corlew et al., 2007; Fino et al., 2010; Nevian and Sakmann, 2006; Rodriguez-Moreno and Paulsen, 2008; Sjostrom et al., 2003). LTD instead requires postsynaptic group I mGluRs; its effector phospholipase C; low-threshold T-, R-, or L-type voltage-sensitive calcium channels (VSCCs); and calcium release from inositol trisphosphate (IP3) receptor-gated internal stores (Bender et al., 2006b; Bi and Poo, 1998; Fino et al., 2010; Nevian and Sakmann, 2006; Nishiyama et al., 2000; Seol et al., 2007). These are components of a major NMDAR-independent pathway for synaptically evoked postsynaptic calcium release (Berridge, 1993). In addition, mGluRs and postsynaptic calcium synergistically drive eCB synthesis and release (Nakamura et al., 1999), leading to activation of presynaptic CB1 receptors and a reduction in release probability (Chevaleyre et al., 2006; Wilson and Nicoll, 2002). Thus, this form of LTD requires retrograde eCB signaling to CB1 receptors, and expression occurs by a decrease in presynaptic transmitter release probability (Bender et al., 2006b; Fino et al., 2010; Nevian and Sakmann, 2006; Rodriguez-Moreno and Paulsen, 2008; Sjostrom et al., 2003). This STDP involves two separate coincidence detectors: NMDA receptors detect pre-leading-post spike intervals and exclusively trigger LTP, whereas a separate mechanism within the mGluR–VSCC–PLC–IP3R–CB1 pathway detects post-leading-pre spike intervals and exclusively triggers LTD (Bender et al., 2006b; Fino et al., 2010; Nevian and Sakmann, 2006). As a result, dendritic calcium concentration is not strictly correlated with the sign of plasticity (Nevian and Sakmann, 2006), and unlike for the single coincidence detector form of STDP, no second LTD window exists (Bender et al., 2006b; Feldman, 2000; Froemke and Dan, 2002; Sjostrom et al., 2001). Remarkably similar mechanisms have been observed during non-Hebbian STDP LTD at the parallel fiber–cartwheel cell synapse in the dorsal cochlear nucleus (Tzounopoulos et al., 2007).

Though independent of postsynaptic NMDARs, the mGluR–CB1-dependent form of LTD often depends on

presynaptic NMDARs (preNMDARs) (Bender et al., 2006b; Casado et al., 2002; Corlew et al., 2007; Rodriguez-Moreno and Paulsen, 2008; Sjostrom et al., 2003). Extensive anatomical and physiological evidence supports the existence of preNMDARs at some synapses, which act as autoreceptors to boost release probability during baseline synaptic transmission (Berretta and Jones, 1996; Brasier and Feldman, 2008; Corlew et al., 2008; McGuinness et al., 2010). At synapses with this form of STDP, intracellularly loading the NMDAR blocker MK-801 into the presynaptic neuron blocks only LTD, while loading MK-801 into the postsynaptic neuron blocks only LTP (Rodriguez-Moreno and Paulsen, 2008). PreNMDARs contain NR2B, NR2C/D, and/or NR3A subunits, and STDP LTD is selectively blocked by NR2B and NR2C/D antagonists and in NR3 knockouts (Banerjee et al., 2009; Bender et al., 2006b; Corlew et al., 2008; Larsen et al., 2011; McGuinness et al., 2010; Sjostrom et al., 2003; Woodhall et al., 2001). PreNMDAR function is most prominent in early postnatal development, and spike timing-dependent LTD that is presynaptic and requires preNMDARs in juvenile cortex can become postsynaptic and independent of preNMDARs in older animals (Corlew et al., 2007) or can disappear altogether (Banerjee et al., 2009).

How the mGluR–VSCC–CB1–preNMDA signaling pathway detects appropriate post-leading-pre spike intervals for LTD is not known. In one model, each postsynaptic spike releases eCB to activate presynaptic CB1Rs, each presynaptic spike provides depolarization (and likely glutamate) to activate preNMDARs, and coincident CB1 and preNMDAR activation is required to drive LTD (Duguid and Sjostrom, 2006; Sjostrom et al., 2003). In this model, the post-leading-pre window for LTD reflects the delay and duration of CB1 activation following each postsynaptic spike, and preNMDAR activation restricts LTD to temporally coactive synapses. Consistent with this model, increasing eCB signal duration by inhibiting eCB catalysis broadens the LTD window, and pairing presynaptic spikes with exogenous CB1 agonists drives LTD (Sjostrom et al., 2003). In a second model, the spike order and timing detector for LTD is either phospholipase C (PLC), which is a known molecular coincidence detector that detects joint mGluR activation and VSCC-derived cytosolic calcium, or the IP3 receptor, which is activated by synergism between PLC-produced IP3 and cytosolic calcium (Berridge et al., 2003; Manita and Ross, 2009; Nakamura et al., 1999; Sarkisov and Wang, 2008). Acting through these or other mechanisms, mGluRs and calcium synergistically facilitate eCB synthesis, release, and synaptic plasticity (Chevaleyre et al., 2006; Hashimotodani et al., 2005, 2007). In this model, presynaptic spikes activate mGluRs, postsynaptic spikes drive VSCC calcium entry, and appropriately timed activation of both pathways is required for sufficient eCB release. This eCB signal then instructs LTD at presynaptic terminals at which preNMDARs have been recently active (Bender et al., 2006b).

Recent evidence suggests that Hebbian STDP can also involve two other forms of LTP. Retinotectal synapses in *Xenopus laevis* and immature hippocampal mossy fibers exhibit spike timing-dependent LTD that is presynaptically expressed and is thought to use brain-derived neurotrophic factor (BDNF) as a retrograde signal (Mu and Poo, 2006; Sivakumaran et al., 2009; Zhou et al., 2003). BDNF has also been implicated in postsynaptic structural changes associated with STDP LTP (Tanaka et al., 2008). STDP LTP at L4–L2/3 synapses in the mature somatosensory cortex appears to require retrograde signaling by nitric oxide (Hardingham and Fox, 2006).

9.5.2 Biochemical Signaling Pathways for Anti-Hebbian and All-LTD STDP

Excitatory synapses onto inhibitory cartwheel cells in dorsal cochlear nucleus exhibit STDP that consists only of presynaptic CB1-mediated LTD at pre-leading-post time intervals (Figure 9.2(i)). Strikingly, at higher stimulation frequencies, these cells express postsynaptic NMDAR-dependent LTP, echoing the coexistence of these mechanisms in Hebbian STDP (Tzounopoulos et al., 2007). All-LTD STDP at parallel fiber–Purkinje cell synapses also involves postsynaptic mGluRs, VSCCs, IP3Rs, and presynaptic CB1 receptor activation but is expressed postsynaptically by AMPAR internalization (Safo and Regehr, 2005; Steinberg et al., 2006). Strong evidence suggests that the IP3 receptor is the order-dependent coincidence detector for this form of STDP (Berridge, 1993; Sarkisov and Wang, 2008; Wang et al., 2000). At other synapses, all-LTD STDP involves postsynaptic mGluR signaling (Birtoli and Ulrich, 2004; Egger et al., 1999; Lu et al., 2007) and sometimes IP3R signaling (Lu et al., 2007).

Overall, no unique cellular mechanisms have been discovered that differentiate STDP from previously known, non-spike timing-dependent forms of LTP and LTD. Instead, STDP at a given synapse seems to be a combination of a classical LTP mechanism (primarily NMDA-dependent, postsynaptic LTP) plus a known LTD mechanism (either postsynaptic NMDA-dependent LTD or mGluR/CB1-dependent presynaptic LTD). Therefore, the time-dependent features of STDP must result from previously unknown, short-timescale temporal dependence of these signaling pathways.

9.5.3 Dendritic Excitability and STDP

For postsynaptic somatic spikes to control STDP, they must backpropagate from the axonal initiation site to the synapse, where they relieve Mg^{2+} blockade of

glutamate-bound NMDA receptors at active synapses or open nearby VSCCs. Backpropagation is governed by voltage-dependent sodium, potassium, and hyperpolarization-activated cyclic nucleotide-gated (HCN) channels in dendrites (Spruston, 2008). Dendritic excitability therefore critically governs STDP. A major feature is that bAPs backpropagate decrementally so that in distal dendrites, they do not provide sufficient depolarization, when paired with a small EPSP for STDP. In the most distal branches, bAPs fail completely (Spruston, 2008). As a result, STDP in distal dendrites requires additional dendritic depolarization in addition to the bAP: either summated EPSPs from nearby convergent inputs (Sjostrom and Hausser, 2006; Sjostrom et al., 2001) or a brief burst of postsynaptic spikes at sufficiently high frequency (Froemke and Dan, 2002; Markram et al., 1997; Nevian and Sakmann, 2006; Sjostrom et al., 2001; Tzounopoulos et al., 2004; Wittenberg and Wang, 2006). These supralinearly boost the level of depolarization at the synapse and can activate dendritic sodium channels to allow bAPs to propagate more effectively to the synapse (Sjostrom and Hausser, 2006; Stuart and Hausser, 2001). This additional depolarization can also evoke local sodium or calcium spikes in the dendrite, which strongly promote STDP and other forms of plasticity (Golding et al., 2002; Kampa et al., 2006; Zhou et al., 2005). The dependence of STDP at many synapses on postsynaptic firing rate and postsynaptic bursts likely reflects this requirement for additional dendritic depolarization in addition to the bAP.

Dendritic filtering of bAPs appears to establish dendritic zones for STDP in pyramidal neurons (Kampa et al., 2007; Spruston, 2008; Figure 9.3(c)). Synapses on proximal dendrites, which experience strong bAPs, may exhibit STDP in response to single presynaptic and postsynaptic spikes. Somewhat more distal synapses require bAPs plus large EPSPs from multiple nearby synapses, or postsynaptic spike bursts, to drive STDP, perhaps with local dendritic spikes as intermediaries. Synapses on the most distal dendrites are likely to be outside the influence of bAPs so that STDP governed by somatic spikes is absent. These synapses instead exhibit plasticity based on strong local EPSPs that elicit dendritic sodium or calcium spikes or regenerative NMDA spikes (Golding et al., 2002; Gordon et al., 2006). The different magnitude and kinetics of depolarization in proximal versus distal dendrites can result in dramatically different STDP rules (Froemke et al., 2005; Letzkus et al., 2006). Thus, dendritic filtering of bAPs, plus other specializations (e.g., gradients of voltage-activated K^+ channels), leads to distinct dendritic 'plasticity zones' in which different rules for synapse modification exist. These may contribute to activity-dependent stabilization of different functional classes of synapses within these regions (Froemke et al., 2005).

As a result, dynamic modulation of dendritic excitability is predicted to strongly influence the magnitude and spatial extent of STDP. Local network states (e.g., UP states) and recent somatic depolarization can increase bAP amplitude (Tsubokawa et al., 2000; Waters and Helmchen, 2004), which may enhance STDP. Neuromodulators that alter bAP propagation (e.g., muscarinic acetylcholine receptors) could similarly increase or decrease the power of somatic spikes in controlling synaptic plasticity (Sourdet and Debanne, 1999; Tsubokawa and Ross, 1997). GABAergic inhibition increases the threshold for bAP backpropagation, which may suppress STDP (van den Burg et al., 2007), although STDP clearly occurs in networks with inhibition intact (Jacob et al., 2007; Meliza and Dan, 2006). Background activity, neuromodulation, and inhibition represent global factors that when added to mathematical STDP rules are likely to generate new adaptive capabilities in large recurrent networks of neurons (Clopath et al., 2010; Legenstein et al., 2008; Pfister and Gerstner, 2006).

9.5.4 Neuromodulatory Control of STDP

Many forms of plasticity are strongly regulated by behavioral state, including attention, vigilance, and reinforcement (e.g., Ahissar et al., 1992; Bao et al., 2001). These behavioral variables are mediated in the brain by acetylcholine, dopamine, noradrenaline, and other neuromodulators (Aston-Jones et al., 1991; Devauges and Sara, 1990; Sarter and Bruno, 2000; Sarter et al., 2005; Schultz, 2002). Substantial evidence shows that neuromodulation (particularly by acetylcholine) is required for use-dependent sensory plasticity in primary sensory cortex *in vivo*, both in juveniles (Bear and Singer, 1986; Kasamatsu and Pettigrew, 1976; Weinberger, 2003) and adults (Bakin and Weinberger, 1996; Delacour et al., 1990; Edeline et al., 1994a,b; Hars et al., 1993; Juliano et al., 1991; Metherate et al., 1988; Molina-Luna et al., 2009; Rasmusson and Dykes, 1988; Webster et al., 1991). Correspondingly, pairing sensory stimulation with microstimulation of cholinergic or dopaminergic afferents or focal application of acetylcholine induces robust long-term plasticity of sensory responses (Ego-Stengel et al., 2001; Kilgard and Merzenich, 1998; Shulz et al., 2000, 2003). These pairing effects can be temporally asymmetric: during pairing of auditory stimuli with microstimulation of the dopaminergic ventral tegmental area (VTA), responses to auditory stimuli that preceded VTA activity are enhanced in auditory cortex, while responses to stimuli that followed VTA activity are reduced (Bao et al., 2001). Thus, neuromodulators powerfully regulate cortical plasticity and can selectively reinforce sensory responses depending on their timing relative to neuromodulatory supervising signals. This

suggests that neuromodulation may be a third parameter (besides pre- and postsynaptic spiking) that governs the outcome of synaptic plasticity, including STDP (Ahissar et al., 1996; Crow, 1968; Kety, 1970; Pawlak et al., 2010; Reynolds and Wickens, 2002).

Neuromodulatory signals may affect STDP induction via a number of cellular and network parameters. On the network level, attention-related modulatory signals alter the sparseness of cortical activity (Vinje and Gallant, 2002) potentially rendering the system more sensitive to STDP induction. For instance, noradrenaline release in the visual cortex produces a reduction in the level of spontaneous and evoked activity (Ego-Stengel et al., 2002) which may lead the system into an optimized range of activity for STDP induction. However, no direct experimental evidence for this hypothesis is available yet.

On the cellular level, acetylcholine could dynamically regulate STDP by modifying the biophysical properties of dendrites and the amplitude and extent of bAPs (Sandler and Ross, 1999; Tsubokawa and Ross, 1997), whose backpropagation into the dendritic tree is required for STDP (Engelmann et al., 2008; Sjostrom et al., 2008). bAP backpropagation is well known to be modulated by the network state (Waters and Helmchen, 2004) and dendritic depolarization (Sjostrom and Hausser, 2006), both of which are modulated by ascending cholinergic signals (Colbert and Johnston, 1998; Hoffman and Johnston, 1998). Direct evidence for neuromodulatory control of STDP was shown by Seol et al. (2007), who discovered that acetylcholine and noradrenaline synergistically regulate STDP in the visual cortex *in vitro*: combined application of a muscarinic M1 agonist and a beta-adrenergic agonist enabled bidirectional STDP, while separate application of these agonists enabled spike timing-dependent LTD only and LTP only. Strong evidence also shows that dopamine (DA) modulates STDP in several brain structures (Bissiere et al., 2003; Couey et al., 2007; Lin et al., 2008; Pawlak and Kerr, 2008; Seol et al., 2007; Shen et al., 2008; Zhang et al., 2009; reviewed in Pawlak et al., 2010). Dramatic changes in the shape of the STDP curve were observed, for example, in CA1 hippocampal neurons in the presence of DA (Zhang et al., 2009) with a widening of the LTP side of the rule for pre–post pairings and an inversion of plasticity for the post–pre pairings.

Most, if not all, of the studies exploring the effect of neuromodulatory agents on STDP have been done *in vitro* (but see Cassenaer and Laurent, 2012 for an *in vivo* example of neuromodulation of the STDP rule by octopamine in the olfactory system of the locust). One cannot exclude that the timing of drug application relative to the conditioning stimuli and/or the local concentration of the neuromodulator at relevant synapses, both parameters not under control in the *in vitro* studies, are of particular importance *in vivo* (Ahissar et al., 1996). Further *in vivo* experiments combining STDP induction protocols and selective activation of neuromodulatory ascending systems are needed to explore how local rules of synaptic plasticity are regulated by global factors acting on several spatial and temporal scales.

9.6 IS STDP RELEVANT *IN VIVO*?

Neuronal networks in the intact brain show an activity regime radically different from that in the *in vitro* quiescent slice or cell culture. This includes differences in the levels of neuromodulation and inhibition and the presence of spontaneous network activity that generates strong ongoing synaptic bombardment *in vivo*. Because all these factors powerfully regulate STDP induction, the relevance of STDP *in vivo* has been questioned. Of particular importance is whether backpropagating somatic action potentials are the major source of dendritic depolarization for plasticity *in vivo* (Lisman and Spruston, 2005). Strong inhibition and intense background synaptic activity reduce the ability of backpropagating action potentials to invade the dendritic tree (Sjostrom and Hausser, 2006), possibly preventing STDP induction (van den Burg et al., 2007). Instead, it has been proposed that the primary drivers of synaptic plasticity *in vivo* are locally generated dendritic spikes, which implement local associative plasticity within each dendritic branch or compartment (Golding et al., 2002; Gordon et al., 2006). Such plasticity would be computationally distinct from STDP because it is driven purely by local synaptic associations, rather than associations between synaptic input and somatic spiking.

To evaluate whether STDP is relevant *in vivo*, the evidence that STDP is induced *in vivo* under experimental conditions tailored to elicit it is discussed first and, second, whether STDP is likely to be a prominent learning rule during natural (nonexperimental) conditions. The current evidence is suggestive, but not yet compelling, that STDP does occur *in vivo* under experimental conditions tailored to elicit STDP. This section summarizes this evidence, which is discussed in more detail in Sections 9.7 and 9.8.

The strongest evidence comes from studies in which sensory stimuli are carefully timed with respect to evoked spikes in single recorded neurons, and STDP is assessed at the level of subthreshold synaptic responses (Bell et al., 1997; Cassenaer and Laurent, 2007; Engert et al., 2002; Jacob et al., 2007; Levy and Steward, 1983; Meliza and Dan, 2006; Mu and Poo, 2006; Zhang et al., 1998). The first evidence was from Levy and Steward (Levy and Steward, 1983), who electrically stimulated pre- and postsynaptic neurons in the hippocampus in the anesthetized rat and showed that associative

induction of potentiation and depression depended on the temporal order of stimulation. A series of studies in the retinotectal system of *X. laevis* tadpoles showed that natural visual motion stimuli elicit STDP at tectal synapses, measured from changes in visually evoked synaptic currents in tectal neurons (Engert et al., 2002; Mu and Poo, 2006; Zhang et al., 1998). In visual and somatosensory cortex of anesthetized rats, pairing sensory stimuli with postsynaptic spiking induced by intracellular current injection causes STDP of sensory-evoked postsynaptic potentials (Jacob et al., 2007; Meliza and Dan, 2006), although this plasticity is of substantially lower amplitude and more variable than in cortical slices (Feldman, 2000; Froemke and Dan, 2002).

Additional evidence comes from studies that infer STDP indirectly from changes in extracellularly recorded spiking and sensory perception following precisely timed presentation of sensory stimuli. In visual cortex of young and adult cats, pairing visual and/or electrical stimulation at precise time intervals induces changes in neural tuning (e.g., in orientation selectivity and receptive field location) that are compatible with STDP at horizontal, cross-columnar synapses (Fu et al., 2002; Yao and Dan, 2001; Yao et al., 2004) and the corresponding reorganization of cortical maps (Schuett et al., 2001). These same sensory stimulation protocols drive shifts in perception of orientation and position in humans with order and interval dependence consistent with STDP. This strongly suggests that STDP or STDP-like plasticity occurs in the intact brain under attentive conditions (Fu et al., 2002; Yao and Dan, 2001). Similar neurophysiological results were observed in primary auditory cortex of adult ferrets (Dahmen et al., 2008). However, these effects are much smaller and variable than STDP in brain slices, despite large numbers of pairings (Fu et al., 2002; Jacob et al., 2007; Meliza and Dan, 2006; Yao and Dan, 2001). In somatosensory cortex of adult rats, pairing spontaneous action potentials with subsequent whisker deflection drives selective depression of neural responses to the paired whisker consistent with STDP (Jacob et al., 2007). The magnitude of plasticity is again rather small, which may reflect the complex neural network activity that occurs in response to sensory stimuli and which may affect the probability of STDP induction (see Frégnac et al., 2010 for a critical review of these data). Nevertheless, the temporal specificity and the sign of plasticity observed in these studies are in agreement with STDP.

Some properties of plasticity induced *in vivo* are not identical to STDP *in vitro*. For example, STDP *in vivo*, in addition to being smaller and more variable than in brain slices, persists for just 10–15 min before being reversed by ongoing spontaneous activity (Yao and Dan, 2001; Zhou et al., 2003). In addition, the range of synaptic delays that drives synaptic depression *in vivo* is often narrower than *in vitro* (e.g., Cassenaer and Laurent, 2007; Dahmen et al., 2008; Fu et al., 2002; Jacob et al., 2007; Yao and Dan, 2001). Importantly, evidence for spike timing-dependent potentiation in mammalian cortex is weaker than for depression. Only a few studies have attempted to measure potentiation separately from depression in mammalian cortex, but these have found depression to be consistently induced, while potentiation is rarer and may be absent on average (Jacob et al., 2007; Meliza and Dan, 2006). In contrast, spike timing-dependent potentiation does clearly occur at developing retinotectal synapses (Engert et al., 2002). Thus, spike timing-dependent depression may be more robust in the cortex *in vivo* than potentiation, although more studies are needed to evaluate this. One difficulty in comparing STDP between *in vivo* and *in vitro* models is the heterogeneity in experimental protocols applied to induce STDP (Shulz, 2010; Shulz and Jacob, 2010). These include pairing sensory or synaptic stimulation with intracellular current injection to elicit one postsynaptic spike, pairing stimulation with a vigorous postsynaptic spike burst, pairing sensory–sensory stimulation, and differences in the number of pairings and anesthetic state. Neural networks react radically differently under these conditions, making comparisons of plasticity difficult.

While these studies suggest that STDP or STDP-like plasticity can occur *in vivo*, the functional importance of STDP relative to other synaptic learning rules during natural sensory input is unclear (reviewed in Caporale and Dan, 2008; Dan and Poo, 2006; Shulz and Jacob, 2010). That is, is STDP a major learning rule under natural conditions *in vivo*? This question is almost entirely untested and depends critically on both the availability of STDP mechanisms at the cellular level *in vivo* and the temporal patterns of spiking induced by natural sensory stimulation. In the primary visual cortex of the anesthetized adult cat, imposed covariance of pre- and postsynaptic spiking drives plasticity more robustly than presynaptic theta burst stimulation, which is thought to evoke postsynaptic spikes with a pre-leading-post spike order. This has been interpreted to suggest that firing correlations drive plasticity more efficiently than STDP (Frégnac et al., 2010). In contrast, evidence strongly suggests that spike order drives STDP during natural visual stimulation in the developing *Xenopus* optic tectum (Section 9.7.3). A major complication in all *in vivo* tests of STDP is the use of anesthesia, except for demonstration of small STDP-like effects on visual perception in humans (Fu et al., 2002; Yao and Dan, 2001). Additional work in awake animals will be required to assess the prominence of STDP under natural conditions.

9.7 FUNCTIONS OF STDP IN DEVELOPMENT

STDP is an increasingly prominent candidate mechanism to mediate activity- and experience-dependent components of neural circuit development. However, proof that it plays a causal role in circuit development is limited to a few brain regions. Here, evidence for this developmental role for STDP is summarized. The focus is on three questions: (1) Are developing synapses capable of STDP? (2) What are the predicted functions of STDP in development, based on theory and simulation? (3) What developmental functions have been empirically demonstrated to result from STDP *in vivo*?

9.7.1 Are Developing Synapses Capable of STDP?

Most studies of STDP at the synaptic and mechanistic levels have been performed in brain slices from juvenile, 2–3-week-old rats and mice or from developing *Xenopus* or chicks (Egger et al., 1999; Feldman, 2000; Froemke and Dan, 2002; Lu et al., 2007; Markram et al., 1997; Nevian and Sakmann, 2006; Sjostrom et al., 2001; Tzounopoulos et al., 2004; Wittenberg and Wang, 2006; Zhang et al., 1998). This is a period of robust circuit development and activity- and experience-dependent synapse refinement. Thus, STDP operates during activity-dependent development. Indeed, Hebbian STDP has been demonstrated *in vivo* at these ages, by pairing sensory stimulation with postsynaptic spikes evoked by extracellular or intracellular current injection or by sensory stimulation (discussed in detail below) (Engert et al., 2002; Jacob et al., 2007; Meliza and Dan, 2006; Mu and Poo, 2006; Schuett et al., 2001; Vislay-Meltzer et al., 2006; Zhang et al., 2000).

At older ages, STDP rules may change, though the evidence is somewhat conflicting. In brain slice experiments in L2/3 pyramidal cells in mouse S1, STDP LTD cannot be induced after P25, while STDP LTP persists into adulthood (Banerjee et al., 2009; Hardingham and Fox, 2006). In L2/3 of V1, STDP LTD similarly becomes more difficult to elicit after P23 but can be rescued if gamma-aminobutyric acid receptor type A (GABA-A) receptors are blocked during LTD induction (Corlew et al., 2007). These findings support a prevalent view that LTD is primarily a developmental phenomenon, but LTP is robust throughout life (Bear and Abraham, 1996). At odds with this view, STDP LTD can occur in L2/3 and L5 of adult S1 *in vivo* by pairing spontaneous postsynaptic spikes with whisker stimulation (Jacob et al., 2007), though this effect is weaker than in juveniles. It remains possible that LTD is robust in adults with appropriate neuromodulation (Seol et al., 2007).

Despite its prevalence in developing circuits, STDP is not universal, and is confined to specific synapses and dendritic locations, and requires specific spike train patterns to be activated (as reviewed in Sections 9.3 and 9.4). As a result, it is an empirical question whether STDP is a dominant force shaping neural circuit development, relative to other activity-dependent forms of synaptic plasticity.

9.7.2 What Are the Predicted Functions of STDP in Development, Based on Theory and Simulation?

In the activity-dependent phase of neural circuit development, coarse initial circuits that were specified by innate molecular cues are refined and optimized by sensory-driven and spontaneous neural activity. This occurs prominently during early postnatal life. It has been studied extensively in developing sensory maps, where early sensory experience shapes neuronal sensory responses, stimulus selectivity (sensory tuning), and microcircuit topography (Feldman and Brecht, 2005; Hensch, 2005; Ruthazer, 2005; White and Fitzpatrick, 2007). Computational studies over the past 25 years have shown that key features of activity-dependent development and plasticity can be explained by classical CDP, working together with additional mechanisms that implement activity-dependent competition between inputs (Miller, 1994). More recent computational studies show that Hebbian STDP drives realistic circuit development and plasticity, including features not predicted by CDP.

STDP has been shown in computational models to drive six common features of network development and experience-dependent plasticity (reviewed in detail in Abbott and Nelson, 2000; Gilson et al., 2010a). These include: (1) Basic Hebbian strengthening of coactive inputs that associatively evoke postsynaptic spikes and weakening of inputs with later or uncorrelated firing that fails to evoke postsynaptic spikes. This is illustrated in Figure 9.4(A). (2) Segregation of inputs onto target neurons based on temporal correlations of input spiking (Clopath et al., 2010; Gilson et al., 2010b; Gutig et al., 2003; Song and Abbott, 2001; Song et al., 2000). This property can explain both experience-dependent development of sensory receptive fields and gross segregation of inputs into distinct zones within a target region. Correlation-driven input segregation occurs in both networks with initially random connection strength and networks with coarse preexisting structure, corresponding to *de novo* emergence of circuit structure and plasticity of early innate circuits (Song and Abbott, 2001). (3) Selectivity for experienced spatiotemporal patterns (sequences) of input, including direction-selective responses in vision and spatial trajectories in the

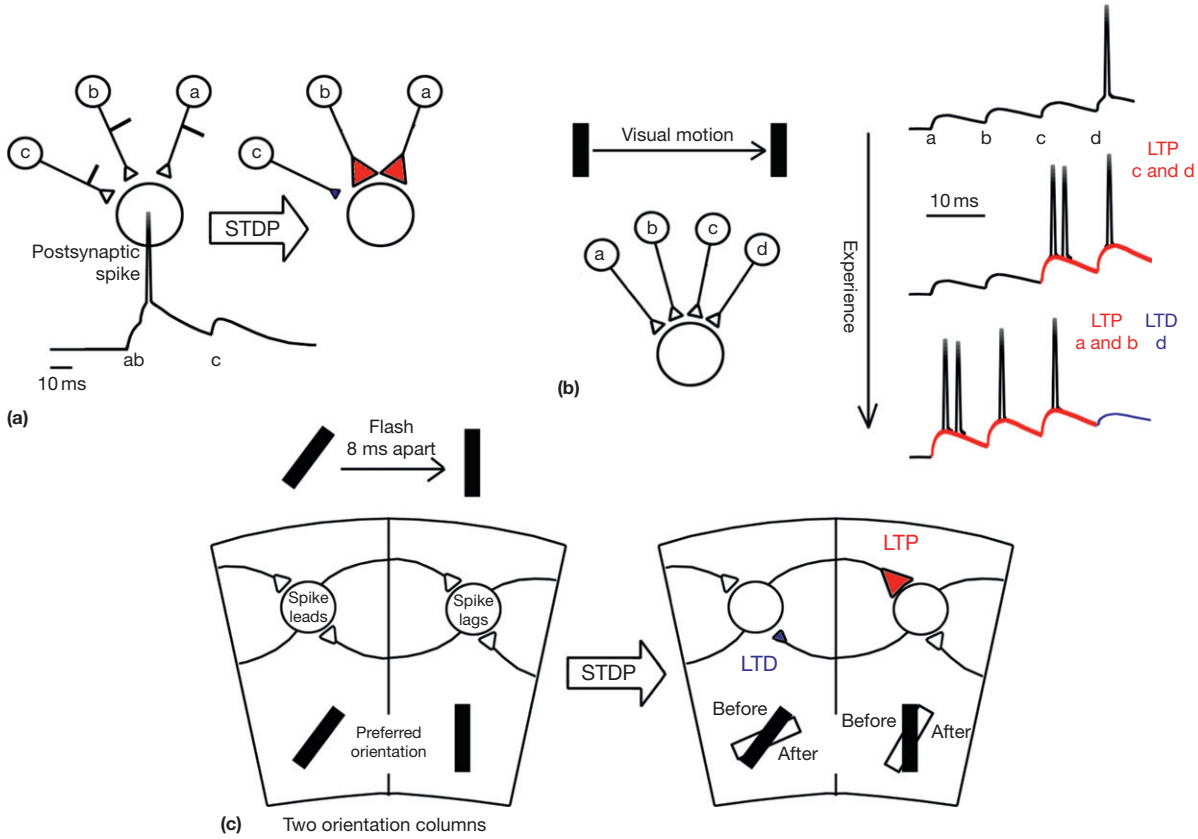

FIGURE 9.4 Some roles of STDP in synapse development and adult plasticity. (A) STDP strengthens initially weak synapses that show correlated firing (a, b) and weakens synapses with later or uncorrelated firing (c). Trace shows EPSPs mediated by each synapse and an evoked postsynaptic spike, prior to STDP. LTP is in red; LTD is in blue. (B) Development of motion direction-selective responses by STDP. Four presynaptic cells (a–d) are imagined to be driven sequentially by a rightward moving visual stimulus. Traces show visual motion-evoked EPSPs and spikes in the postsynaptic cell prior to visual experience (top) and with increasing experience. Synapses are initially weak (black EPSPs). Visual experience causes synapses active before postsynaptic spikes to strengthen (red) and synapses active after postsynaptic spikes to weaken (blue). This increases responses to motion stimuli and shifts the receptive field to 'upstream' locations. (C) Hypothesis for plasticity of orientation tuning induced by flashing two oriented bars at a precise time delay. When an oblique bar is flashed before a vertical bar, cells in the oblique orientation column spike before the vertical column. This induces STDP at intracolumnar synapses between columns. These changes in intracolumnar projection efficacy cause orientation tuning to shift toward the first orientation and away from the second.

hippocampal place system (Blum and Abbott, 1996; Buchs and Senn, 2002; Mehta et al., 2000; Rao and Sejnowski, 2001). This reflects emergence of directional connections within recurrent networks, which does not occur by CDP (Clopath et al., 2010). In motor networks, this sequence learning mechanism causes the emergence of spontaneous repeated spike train sequences, which are useful in motor patterning (Fiete et al., 2010). (4) Competition between inputs, in which strong correlated activity in one set of inputs weakens other inputs (Kempter et al., 1999; Song et al., 2000; van Rossum et al., 2000; Zhang et al., 1998). Competition is a common feature of developmental plasticity but is not inherent in CDP (Miller, 1994). Competition emerges in STDP because correlated inputs summate to drive short-latency postsynaptic spikes, which in turn weaken subsequent, noncorrelated inputs. (5) Emergence of stable, physiologically realistic firing rates and naturalistic irregular spike trains (Kempter et al., 2001; Song et al., 2000). See Section 9.3 for explanation. (6) Establishment of coincidence detection by neurons (Fontaine and Peremans, 2007; Gerstner et al., 1996) and enhancement of temporal synchrony across neurons (Masuda and Kori, 2007). While submillisecond coincidence detection is a unique property of some auditory neurons, ~10-ms timescale coincidence detection is a basic feature of sensory neocortex and could be tuned, in part, by STDP (Azouz and Gray, 2003; Roy and Alloway, 2001).

Because of these findings, Hebbian STDP has emerged as a strong candidate mechanism for activity-dependent development of neural circuits. A detailed comparison between STDP and specific CDP models is beyond the scope of this review, but one major competing model is the Bienenstock, Cooper, and Munro (BCM) model that incorporates firing rate-dependent LTP and LTD with activity-dependent metaplasticity (Bienenstock et al.,

1982). This model explains many features of activity-dependent development and plasticity in sensory cortex (Smith et al., 2009). Remarkably, several implementations of STDP have been shown to be functionally equivalent to BCM, suggesting that they may reflect equivalent cellular processes (Clopath et al., 2010; Izhikevich and Desai, 2003; Senn et al., 2001).

While STDP may play a significant role in development, it cannot be universal. In some early developing networks, postsynaptic neurons are too immature to generate somatic sodium spikes (e.g., in L2/3 of S1 cortex in the first few days of whisker use) (Stern et al., 2001). STDP cannot guide development of synapses onto these neurons, but may function a few days later, as sensory-evoked spikes increase (Bureau et al., 2004). Likewise, brain regions that generate relatively few, precisely timed spikes in response to sensory input may be most likely to utilize STDP, whereas regions with high sensory-driven or spontaneous firing rates that are modulated at slow timescales are likely to use other forms of plasticity. For example, ON and OFF retinal ganglion cells exhibit prolonged spontaneous spike bursts (retinal waves) with ~1 s temporal offset between these cell populations. Development of segregated ON and OFF input zones in the lateral geniculate nucleus requires a burst-dependent learning rule that is sensitive to longer timescale correlations, rather than STDP, which is sensitive to ms-scale correlations (Gjorgjieva et al., 2009).

9.7.3 What Developmental Functions Have Been Empirically Demonstrated to Result from STDP *In Vivo*?

Experimental studies testing how STDP contributes to circuit development have focused primarily on three areas: use-dependent development of visual response properties in the optic tectum of *X. laevis*, use-dependent development of visual response properties in the mammalian visual cortex (V1), and deprivation-induced plasticity in the mammalian sensory cortex, primarily the rodent somatosensory cortex (S1). These are reviewed here.

9.7.3.1 STDP in Emergence of Direction Selectivity in Xenopus tectum

STDP can store information about spatiotemporal patterns of input activity (Blum and Abbott, 1996; Clopath et al., 2010; Mehta et al., 2000; Rao and Sejnowski, 2001). In vision, a highly relevant spatiotemporal pattern is visual motion, and many neurons in adults are selective (tuned) for visual motion direction. In the retinotectal system of *X. laevis*, strong evidence indicates that early visual experience with moving stimuli causes neurons to develop motion direction tuning via STDP.

In young *Xenopus* tadpoles, tectal neurons initially lack selectivity for visual motion direction. When a bar is repeatedly moved in a consistent direction across a young neuron's receptive field, excitatory synaptic responses evoked by the trained movement direction are selectively increased, causing tectal neurons to become tuned for the trained direction (Engert et al., 2002). Several lines of evidence show that this is due to STDP at retinotectal synapses. First, retinotectal synapses exhibit robust Hebbian STDP *in vivo*, by pairing either electrically or visually evoked presynaptic spikes with postsynaptic spikes (Zhang et al., 1998, 2000). Second, successful motion training occurs only when visual motion stimuli elicit postsynaptic spikes, and training causes retinal inputs active before evoked tectal spikes to be potentiated, while inputs active after tectal spikes are depressed. This is the hallmark of Hebbian STDP (Engert et al., 2002; Mu and Poo, 2006). The mechanics of this process have been determined using three sequentially flashed bars at different spatial positions to simulate visual motion. When sequentially flashed bars are paired with postsynaptic spikes that occur just after the center bar stimulus (either evoked by this stimulus or by current injection), responses to the first and second bars are increased, while responses to the third bar are decreased, as predicted by Hebbian STDP. Moreover, training with both real and simulated motion increases visual responses to flashed stimuli at spatial locations that are active prior to the receptive field center (i.e., locations that are 'upstream' in the trained movement direction). This asymmetrically expands the receptive field toward earlier-activated spatial locations (Engert et al., 2002), as predicted by computational models of Hebbian STDP driven by moving stimuli (Blum and Abbott, 1996; Mehta et al., 2000). In a recent computational model, STDP at retinotectal synapses was shown to explain all these findings (Honda et al., 2011). These results strongly suggest that natural motion stimuli drive emergence of motion direction tuning via STDP. This phenomenon is illustrated in Figure 9.4(B).

Several studies show that nonmoving visual stimuli also shape tectal visual receptive field properties via STDP. Pairing a small flashed bar or spot with a postsynaptic spike evoked by intracellular current injection induces LTP or LTD of visually evoked synaptic currents according to Hebbian STDP rules (Mu and Poo, 2006; Vislay-Meltzer et al., 2006). This increases or decreases visual responses to stimuli within the trained subregion of the tectal cell's visual receptive field, causing a systematic shift in receptive field location (Vislay-Meltzer et al., 2006). When repetitively flashed stationary stimuli are strong enough to evoke tectal spikes on their own, visual responses are enhanced. This is likely to reflect STDP LTP because strengthening occurs only when stimuli successfully evoke postsynaptic spikes, which imposes the pre-leading-post spiking order within the

20-ms temporal window for STDP LTP at this synapse (Zhang et al., 2000). This suggests that visually driven STDP mediates the activity-dependent increase in visual response strength during normal tectal development and may also contribute to the normal developmental decrease in receptive field size (Tao and Poo, 2005).

A final feature of tectal development that may be driven by STDP is the development of synchronous spiking mediated by recurrent excitation between tectal neurons. Visual stimulation elicits rapid, direct retinotectal excitation of tectal neurons, plus slower, longer-lasting excitation via recurrent synapses, which mediate sustained spiking to visual stimuli. Recurrent excitation is long lasting and temporally variable early in development and becomes rapid and synchronous with experience (Pratt and Aizenman, 2007). Sensory training with optic nerve stimulation or visual flashes strengthens recurrent inputs that are active prior to the mean spike time of tectal cells and weakens recurrent inputs active after this time. As a result, recurrent inputs become more rapid and temporally precise (Pratt and Aizenman, 2007), as predicted by Hebbian STDP (Cassenaer and Laurent, 2007; Suri and Sejnowski, 2002; Zhigulin et al., 2003). However, this behavior has not been proven to reflect STDP directly.

9.7.3.2 STDP in Experience-Dependent Development of Sensory Tuning in V1 Cortex

In mammalian V1, retinotopic and ocular dominance maps are already well developed at eye opening but are strongly modified by visual experience in the first weeks of life. In contrast, tuning for orientation and motion direction are weak or absent at eye opening and are induced by early visual experience (White and Fitzpatrick, 2007). Some evidence suggests that STDP contributes to each of these aspects of development. Arguably, the weakest evidence is for retinotopy. In developing kitten V1, pairing a focal visual stimulus with postsynaptic spiking elicited by current injection during whole-cell recording strengthens or weakens visually evoked responses, with temporal dependence consistent with Hebbian STDP. While this 'stimulus timing-dependent plasticity' modulates response strength, it does not shift receptive field location (Meliza and Dan, 2006). Stimulus timing-dependent plasticity of retinotopy has been observed in adult cats, where repeated sequential presentation of two neighboring retinotopic stimuli (with <20-ms delay) shifts the spatial location of V1 receptive fields toward the retinotopic location activated first. The direction and timing dependence of this plasticity is consistent with Hebbian STDP at intracortical connections (Fu et al., 2002). Retinotopic map plasticity also occurs in adults in response to focal retinal lesions that binocularly deprive a small V1 region of visual input. Postlesion visual experience causes neurons in the deprived V1 region to acquire novel receptive fields outside the deprived region of visual space (Gilbert and Wiesel, 1992). This reflects functional and anatomical reorganization of intracortical horizontal connections (Yamahachi et al., 2009). A computational study found that the spatial pattern of acquired receptive fields was consistent with intracortical reorganization via STDP, but not with classical CDP (Young et al., 2007). However, whether these mechanisms contribute to retinotopic refinement during development is unknown.

Stronger evidence links STDP to development of motion direction selectivity. Like in *Xenopus*, motion direction tuning is absent at eye opening and develops soon thereafter as a result of visual experience (White and Fitzpatrick, 2007). Training with visual motion stimuli immediately after eye opening induces motion direction tuning in V1 of young ferrets (Li et al., 2008). This is consistent with STDP driven by spatiotemporal spike patterns evoked in V1 inputs (Buchs and Senn, 2002). However, whether STDP is the causal mechanism, and whether it explains the emergence of direction selectivity during normal development, is unclear. Some support for this hypothesis derives from a careful analysis of motion-selective properties of receptive fields in V1 complex cells in adult cats (Fu et al., 2004). Fu et al. found that complex cells received stronger rightward (leftward) motion input from visual field locations to the left (right) of receptive field center. This anisotropy in intracortical circuits is exactly as predicted by STDP driven by natural visual motion and suggests that STDP was active during the development of the circuits for motion direction tuning (Fu et al., 2004). However, cellular studies that demonstrate that STDP is the causal process for development of motion selectivity are lacking.

Similar evidence exists for plasticity of orientation tuning. Orientation tuning exists at eye opening but is robustly plastic in response to early postnatal sensory experience, with experienced orientations gaining representation in the orientation map (Hirsch and Spinelli, 1970; Sengpiel et al., 1999). To test whether orientation tuning could by altered via STDP, Schuett et al. paired oriented visual stimuli with extracellular electrical stimulation to elicit postsynaptic spikes in V1 in anesthetized kittens. When visually evoked responses preceded electrical stimulation, cortical neurons shifted their orientation toward the presented orientation; when visually evoked responses followed electrical stimulation, orientation shifted away from the presented orientation, characteristic of Hebbian STDP. The effect, which required several hundreds of pairings to be induced, occurred predominantly in L2/3 and L5–6, suggesting a locus in intracortical connections (Schuett et al., 2001). In a similar study in adults, stimulus timing-dependent plasticity was induced by flashing a conditioned oriented stimulus <20 ms before or after the presentation of the preferred orientation. This training caused the peak of the orientation tuning to shift toward or away from the conditioned orientation, respectively. The temporal order and timing

dependence was consistent with Hebbian STDP at horizontal projections between neurons tuned to the trained orientations (Yao and Dan, 2001; Yao et al., 2004). This effect is illustrated in Figure 9.4(C). Thus, carefully controlled sensory experience can alter orientation tuning in a timing-dependent manner consistent with STDP at intracortical connections. However, whether natural visual experience uses this method to refine or maintain orientation tuning during development is unknown.

STDP may contribute to experience-dependent refinement of whisker receptive fields in developing rodent S1, but evidence is weaker than for V1. In anesthetized juvenile rats, STDP LTD occurs in L2/3 pyramidal cells in response to pairing whisker deflection with intracellularly evoked postsynaptic spikes: postsynaptic spikes that precede whisker-evoked subthreshold potentials ($\Delta t < 30$ ms) cause weakening of whisker-evoked responses, which lasts for 5–10 min. Conversely, when postsynaptic spikes follow whisker-evoked potentials, no depression, or sometimes potentiation, is observed, suggestive of Hebbian STDP (Jacob et al., 2007). In adults, spike timing-dependent depression of whisker-evoked spiking responses was observed in L2/3 and L5–6 pyramidal cells (Jacob et al., 2007). However, whether STDP is engaged by natural whisker stimuli to drive receptive field plasticity during normal development is not known. One possible role for STDP is to generate whisker direction tuning in L2/3 of S1 from natural wave fronts of whisker deflection (Andermann and Moore, 2006; Leger et al., 2009).

9.7.3.3 STDP in Deprivation-Induced Plasticity in S1 and V1 Cortex

During postnatal development, sensory deprivation drives rapid depression of cortical sensory responses to deprived inputs, followed more slowly by increased responses to spared inputs. The overall effect is to bias neural selectivity toward the most active inputs. This deprivation-induced plasticity can be explained by Hebbian weakening of synapses mediating deprived inputs, coupled with some form of competition that strengthens synapses mediating spared inputs (Feldman, 2009). It is commonly hypothesized that such plasticity utilizes the same synaptic mechanisms that drive emergence or refinement of sensory response properties during normal development. Substantial evidence indicates that deprivation-induced plasticity involves LTP and LTD at cortical synapses, coupled with synapse formation, remodeling, and removal (Feldman, 2009).

STDP appears to be one of the mechanisms driving deprivation-induced weakening of sensory responses in rodent somatosensory (S1 or barrel) cortex. Rodent S1 contains a somatotopic map of the whiskers, each represented by a cortical column. Deflection of a single whisker drives spikes in L4, followed by L2/3, of the corresponding column, due to feedforward, column-specific excitatory projections from thalamus to L4 to L2/3. In addition, whisker deflection drives weaker responses in neighboring columns via horizontal cross-columnar projections (Lubke and Feldmeyer, 2007). In juvenile rats, trimming or plucking a subset of whiskers weakens and shrinks the representation of deprived whiskers in L2/3, mediated in part by weakening L4–L2/3 excitatory synapses (Feldman and Brecht, 2005). This deprivation-induced weakening appears to represent CB1-LTD induced *in vivo* by sensory deprivation because it occludes subsequent CB1-LTD, is expressed presynaptically by reduced release probability, and is prevented by CB1 antagonist treatment *in vivo* during whisker deprivation (Allen et al., 2003; Bender et al., 2006a; Feldman, 2009; Li et al., 2009).

L4–L2/3 synapses in rat S1 exhibit LTD-biased STDP consisting of NMDAR-dependent LTP and CB1-LTD (Bender et al., 2006b; Feldman, 2000; Nevian and Sakmann, 2006). This STDP rule drives net LTD in response to either uncorrelated spiking or systematic post-leading-pre spiking (Feldman, 2000). Deprivation is likely to drive LTD *in vivo* via STDP because whisker deprivation acutely alters mean L4 and L2/3 firing rate in S1 of awake rats only modestly but powerfully alters L4–L2/3 spike timing. This was shown in anesthetized animals, where simultaneous deflection of all whiskers (to mimic normal whisking) evokes L4 spikes reliably before L2/3 spikes, whereas deflection of all but one whisker (to mimic acute whisker deprivation) immediately causes L4–L2/3 firing in the deprived column to decorrelate and firing order to reverse. These spike timing changes are quantitatively appropriate to drive spike timing-dependent LTD (Celikel et al., 2004). These findings suggest that spike timing, not spike rate, may be the key parameter driving synapse weakening in response to whisker deprivation.

STDP has also been hypothesized to drive ocular dominance plasticity in developing V1, but there is currently little direct evidence for this hypothesis. V1 neurons exhibit characteristic ocular dominance, which is a measure of the relative response to stimuli in the right versus left eye. Ocular dominance is already mature at eye opening but is highly plastic to visual experience in a defined developmental critical period (19–32 days of age in mice). During this period, closure of one eye (monocular deprivation) causes a rapid loss of responses to the deprived eye, followed by a slower gain of responses to the open eye, thus shifting ocular dominance (Wiesel and Hubel, 1963). Ocular dominance plasticity involves both rapid physiological changes in excitatory synaptic strength (e.g., LTP and LTD) and structural rearrangement of V1 synapses (Hensch, 2005; Hofer et al., 2006). While CDP can explain the basic features of ocular dominance plasticity, an STDP model has been proposed. In this model, monocular deprivation alters the precise temporal patterning of V1 spikes, thus inducing STDP

in deprived-eye or open-eye pathways (Hensch, 2005; Hofer et al., 2006). Direct evidence that STDP causally drives ocular dominance plasticity is lacking, but the dynamics of plasticity in one cell class (fast-spiking interneurons) may be consistent with STDP (Yazaki-Sugiyama et al., 2009). In addition, the STDP model may explain why, during development, the critical period does not begin until inhibitory basket cells mature sufficiently to provide an 'optimal' balance between inhibition and excitation (Katagiri et al., 2007). Basket cells make dense perisomatic synapses on pyramidal cells that potently control spike timing (Huang et al., 2007; Pouille and Scanziani, 2001). Sufficient inhibition may be required to enable the precise timing of visually evoked spikes so that experience-dependent changes in spike timing can engage STDP (Hofer et al., 2006; Kubota and Kitajima, 2010; Kuhlman et al., 2010). Similar inhibitory gating of plasticity occurs in *Xenopus*, where tectal inhibitory circuits are required to ensure that visual motion stimuli evoke precise spatiotemporal patterns of spiking in the tectum. When GABAergic transmission is blocked, precise encoding of motion stimuli is lost and spikes become highly correlated between neurons. Under these conditions, training with visual motion stimuli does not cause development of motion direction tuning (Richards et al., 2010).

Thus, STDP is a strong candidate for driving deprivation-induced weakening of synapses in S1 and may play a similar role in V1, but for this, substantially less evidence exists. Inhibitory gating of plasticity may reflect the need for optimal inhibitory–excitatory balance to precisely time spikes and enable STDP.

In summary, STDP is well suited to explain activity-dependent development of network connectivity and stimulus selectivity during initial circuit formation. Experimentally, the best evidence that STDP is involved in circuit development is in experience-dependent development of direction selectivity in the *Xenopus* retinotectal system. STDP may also contribute to deprivation-induced plasticity in developing S1 and possibly to experience-dependent development of stimulus selectivity in V1. However, direct evidence that STDP is the relevant synaptic plasticity rule for circuit development or developmental plasticity outside of the retinotectal system remains largely lacking. In contrast, stronger evidence exists for STDP in adult circuit plasticity (see Section 9.8).

9.8 FUNCTIONS OF STDP IN ADULT PLASTICITY AND LEARNING

Theoretical work suggests that STDP could mediate several forms of learning, including shaping of neuronal selectivity (Guyonneau et al., 2005), coordinating transformations of multimodal information (Davison and Fregnac, 2006), tuning of auditory response delays (Gerstner et al., 1996), reinforcement learning (Farries and Fairhall, 2007), temporal difference learning (Rao and Sejnowski, 2003), input pattern detection (Masquelier et al., 2009), and learning of temporal sequences (Fiete et al., 2010). However, whether STDP plays these roles *in vivo* in the behaving animal is not yet clear (Letzkus et al., 2007). Evidence for the involvement of STDP in sensory learning in the primary sensory cortex and in the electrosensory lobe of electric fish is strong; for other forms of learning, however, its involvement remains primarily theoretical.

9.8.1 Sensory Learning and Primary Sensory Cortex Plasticity

The occurrence of STDP has been indirectly studied in the visual cortex *in vivo* by sequentially presenting two visual stimuli at time intervals suitable for inducing STDP (Fu et al., 2002; Yao and Dan, 2001; Yao et al., 2004). The two stimuli differ in spatial location or orientation. Sensory stimulation increases the firing probability of neurons within a defined window of time, and thus the pairing of two stimuli increases the occurrence of the imposed spike timing interactions. In these studies of stimulus timing-dependent plasticity using sensory–sensory associations, pairing causes modifications of neuronal tuning that are rather small but have a temporal specificity and sign expected from STDP (see also Dahmen et al. (2008) for a similar study on the auditory cortex). These results support the idea that STDP could mediate experience-dependent modulation of receptive fields in the visual cortex *in vivo*. Parallel psychophysical experiments using similar plasticity protocols show perceptual changes that are compatible with the induced neurophysiological effects, indicating that sensory-induced STDP may drive plasticity of human visual perception (Fu et al., 2002; Yao and Dan, 2001).

In the *in vivo* somatosensory cortex of the rat, cortical map reorganization can be induced by whisker deprivation. This procedure modifies the relative timing of thalamic and cortical action potentials within a range compatible with STDP (Allen et al., 2003; Celikel et al., 2004). Thus, STDP could underlie modifications of cellular responses during experience-driven network reorganizations, although these observations should be confirmed in the adult rat. Evidence for STDP in the somatosensory cortex of adult animals *in vivo* is still scarce but Jacob et al. (2007) have shown that pairing spontaneously emitted postsynaptic spiking with subsequent whisker deflections within a brief time window leads to synaptic and functional depression specific to the paired whisker, consistent with spike timing-dependent LTD.

9.8.2 Sensory Image Cancellation in Electric Fish

Anti-Hebbian forms of STDP have been described in cerebellum-like structures containing comparable cell types to mammalian cerebellum (Bell et al., 1997; Tzounopoulos et al., 2004) and in some corticostriatal connections (Fino et al., 2005). In the electrosensory lobe of three distinct groups of electric fish, anti-Hebbian STDP at parallel fiber synapses on Purkinje-like cells has been proposed to generate a representation of predictable electrosensory input arising from motor commands. The comparison of this 'negative' image with the actual sensory inflow suppresses the expected sensory consequences of a motor act, facilitating the detection of unexpected stimuli (reviewed in Bell, 2001; Bell et al., 1999).

9.8.3 Hippocampus and Memory

The hippocampus shows prominent STDP (Bi and Poo, 1998; Wittenberg and Wang, 2006), which has been proposed to be involved in the modification of hippocampal spatial receptive fields (place fields) (O'Keefe and Dostrovsky, 1971) during exploration of novel environments (Wilson and McNaughton, 1993). Place fields of hippocampal CA1 pyramidal cells are spatially skewed such that firing is asymmetric across the spatial extent of the place field, with lower firing rates when the animal enters the field and higher firing rates when it exits. In addition, the center of gravity of place fields expands backward as an animal repetitively explores a track. These features of place fields are experience-dependent (Mehta et al., 2000). As proposed on the basis of computational models of CA3 to CA1 plasticity, these modifications of CA1 receptive fields could result from NMDA-dependent STDP of synaptic inputs to CA1 cells (Ekstrom et al., 2001; Mehta et al., 2000; Shouval et al., 2002, 2010) (see also Yu et al., 2008 for alternative biophysical models). These receptive field shifts are similar to those observed in the primary visual cortex during stimulus timing-dependent plasticity (Fu et al., 2002; Yao and Dan, 2001).

9.8.4 Olfactory Learning

Olfactory learning in the insect represents one of the most robust examples of STDP induction. In the beta-lobe of the mushroom body, a central structure of the locust olfactory system, spiking activity elicited by odor presentation associated with postsynaptic spiking of intrinsic neurons (known as the Kenyon cells) triggers STDP. This form of STDP facilitates the transmission of odor-specific information through the olfactory system by synchronizing the target neurons of the Kenyon cells, thus improving the readout of the sparse olfactory code in Kenyon cells (Cassenaer and Laurent, 2007). In moths, an appetitive associative procedure induces a conditioned response to an odor. This conditioned response is reduced, however, if the reward delivery overlaps with Kenyon cell activity induced by the odor (Ito et al., 2008). Thus, changing the temporal interval between odor and reward modifies the probability of induction of the conditioned response. This was considered as evidence that STDP in Kenyon cells alone cannot underlie the olfactory learning. However, STDP has not been directly measured in this study. An alternative possibility is to reinterpret these results within the theoretical framework of reinforcement learning where in addition to pre- and postsynaptic activity, a third element (here, an appetitive reward) provides a behavioral validation of the network state during the presentation of the odor but does not in itself induce postsynaptic action potentials (see Cassenaer and Laurent, 2012). Its permissive action is rather mediated through activation of metabotropic receptors and second messenger cascades that might interact with a sustained response (Drew and Abbott, 2006) or with some intracellular signature left by the sensory input (Izhikevich, 2007), but not with the early sensory-driven activity.

9.8.5 STDP in Human Cortex

In humans, paired association of transcranial magnetic stimulation over the somatosensory cortex (S1) and median nerve stimulation induces bidirectional changes of the median nerve somatosensory evoked potential (SSEP) (Wolters et al., 2005). See Wolters et al. (2003) for a similar study on the motor cortex. The changes were confined to the P25 component of the SSEP, which is believed to originate in the upper cortical layers of S1. Interestingly, the direction of the changes depended on the timing of the stimuli. Enhancement of the P25 component was induced by a pre–post arrangement of stimulation-induced events, while a depression was noted with a reversal of events. These observations may constitute a signature of STDP in human S1. Litvak et al. (2007) further confirmed the regional and laminar location of neuroplastic changes induced by the paired associative stimulation and reported congruent behavioral consequences of the STDP-like plasticity in human S1.

In summary, theory indicates that STDP could mediate multiple features of learning. Currently, the strongest experimental evidence for Hebbian STDP in natural learning in adults is during sensory perceptual learning in the primary sensory cortex, where it may store associations and temporal sequences in response to precisely timed sequential sensory stimuli. For anti-Hebbian STDP, evidence strongly supports a role in learning and cancelling expected sensory patterns in the

electrosensory lobe of electric fish. Additional work is needed to evaluate the biological role of STDP in other forms of adult learning and plasticity.

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Glossary

AMPAR Alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid subtype of ionotropic glutamate receptor.
bAP Backpropagating action potential, that is, action potential that propagates from soma to dendrites.
CB1 Cannabinoid receptor type 1.
Correlation-dependent plasticity Form of LTP and LTD in which plasticity is determined by magnitude of correlated pre- and postsynaptic activity, but not precise pre–post timing and order.
eCB Endocannabinoid.
GABA-A receptor Gamma-aminobutyric acid receptor type A, the primary fast inhibitory receptor in the central nervous system.
IP3 Inositol trisphosphate.
LTD Long-term depression, or activity-dependent, long-term decrease in functional synapse strength.
LTP Long-term potentiation, or activity-dependent, long-term increase in functional synapse strength.
mGluR Metabotropic glutamate receptor.
NMDAR *N*-Methyl-D-aspartate subtype of ionotropic glutamate receptor.
PLC Phospholipase C.
S1 Primary somatosensory cortex.
Spike timing-dependent plasticity Form of LTP and LTD in which the magnitude and sign of plasticity are determined by the precise (10–100-ms scale) timing of pre- and postsynaptic action potentials.
V1 Primary visual cortex.
VSCC Voltage-sensitive calcium channel.

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