CSE511 Brain & Memory Modeling

Lect13+15+16: Synaptic Plasticity
Chapter 8 of Purves et al., 4e

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http://www.cs.sunysb.edu/~cse511 and ~lw
Figure 8.1 Forms of short-term synaptic plasticity.

(A) **Facilitation** at the squid giant synapse. A pair of presynaptic action potentials elicits two EPSPs. Because of facilitation, the second EPSP is larger than the first. (B) By varying the time interval between pairs of presynaptic action potentials, facilitation can be seen to decay over a time course of tens of milliseconds. (C) In normal physiological conditions, a high-frequency tetanus (bar) causes pronounced depression of EPSPs at the squid giant synapse (top). Lowering the external Ca\(^{2+}\) concentration to an intermediate level reduces transmitter release and causes a mixture of depression and augmentation (middle). Further reduction of external Ca\(^{2+}\) eliminates depression and leaves only **augmentation** (bottom). 

(D) Synaptic depression at the frog neuromuscular synapse increases in proportion to the amount of transmitter released from the presynaptic terminal. (E) Application of a high-frequency tetanus (bar) to presynaptic axons innervating a spinal motor neuron causes a post-tetanic **potentiation** that persists for a couple of minutes after the tetanus ends. (A,B after Charlton and Bittner, 1978; C after Swandulla et al., 1991; D after Betz, 1970; E after Lev-Tov et al., 1983.)
Figure 8.1-1 Forms of short-term synaptic plasticity

(A) Facilitation at the squid giant synapse. A pair of presynaptic action potentials elicits two EPSPs. Because of facilitation, the second EPSP is larger than the first. (After Charlton and Bittner. 1978.)

Synaptic facilitation results from prolonged elevation of presynaptic calcium levels after synaptic activity. Entry of Ca\(^{2+}\) into a presynaptic terminal occurs within a millisecond or two after an action potential invades, but the mechanisms that return Ca\(^{2+}\) to resting levels are much slower.
(B) By varying the time interval between pairs of presynaptic action potentials, facilitation can be seen to decay over a time course of tens of milliseconds (After Charlton and Bittner. 1978.)
Synaptic depression occurs when many presynaptic action potentials occur in rapid succession. It likely is caused by progressive depletion of the pool of synaptic vesicles available for release. Depression causes the strength of transmission to decline until vesicles near the presynaptic membrane can be replenished by mobilization of vesicles from a reserve pool.
(D) Synaptic depression at the frog neuromuscular synapse increases in proportion to the amount of transmitter released from the presynaptic terminal. (After Betz, 1970.)
Figure 8.1-5 Forms of short-term synaptic plasticity.

(E) Application of a high-frequency tetanus (bar) to presynaptic axons innervating a spinal motor neuron causes a post-tetanic potentiation that persists for a couple of minutes after tetanus ends. (After Lev-Tov et al., 1983.)
Figure 8.2 Short-term plasticity at the neuromuscular synapse.

(A) A train of electrical stimuli (top) applied to the presynaptic motor nerve produces changes in EPP (end plate potential) amplitude in a muscle fiber (below).

(B) Dynamic changes in transmitter release caused by the interplay of four forms of short-term plasticity. Facilitation and augmentation of the EPP occurs at the beginning of the stimulus train and are followed by a pronounced depression of the EPP. Both augmentation and potentiation enhance the ability of Ca\textsuperscript{2+} to trigger fusion of synaptic vesicles with the plasma membrane, but they work over different time scales. Potentiation begins late in the stimulus train and persists for many seconds after the end of the stimulus, leading to what is called post-tetanic potentiation. (A after Katz, 1966; B after Malenka and Siegelbaum, 2001.)
Figure 8.2-1 Short-term plasticity at the neuromuscular synapse.

(A) A train of electrical stimuli (top) applied to the presynaptic motor nerve produces changes in EPP (end-plate potential) amplitude in a muscle fiber (below). (After Katz, 1966.)
Figure 8.2-2 Short-term plasticity at the neuromuscular synapse. (B) Dynamic changes in transmitter release caused by the interplay of four forms of short-term plasticity. Facilitation and augmentation of the EPP occurs at stimulus train and are followed by a pronounced depression of the EPP. Both augmentation and potentiation enhance the ability of Ca\textsuperscript{2+} to trigger fusion of synaptic vesicles with the plasma membrane, but they work over different time scales. Potentiation begins late in the stimulus train and persists for many seconds after the end of the stimulus, leading to post-tetanic potentiation. (After Malenka and Siegelbaum, 2001.)
Figure 8.3 Short-term sensitization of the *Aplysia* gill withdrawal reflex.

(A) Diagram of the animal. (B) The abdominal ganglion of *Aplysia*. The cell bodies of many of the neurons involved in gill withdrawal can be recognized by their size, shape, and position within this ganglion. (C) Changes in the gill withdrawal behavior due to habituation and sensitization. The first time that the siphon is touched, the gill contracts vigorously. Repeated touches elicit smaller gill contractions due to habituation. Subsequently pairing a siphon touch with an electrical shock to the tail restores a large and rapid gill contraction, due to short-term sensitization. (D) A short-term sensitization of the gill withdrawal response is observed following the pairing of a single tail shock with a siphon touch. (E) Repeated applications of tail shocks causes prolonged sensitization of the gill withdrawal response. (After Squire and Kandel, 1999.)
Figure 8.3-1 Short-term sensitization of the *Aplysia* gill withdrawal reflex.  
(A) Diagram of the animal.  
(B) The abdominal ganglion of *Aplysia*. The cell bodies of many of the neurons involved in gill withdrawal can be recognized by their size, shape, and position within this ganglion.  
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Figure 8.3 Short-term sensitization of the *Aplysia* gill withdrawal reflex (Part 2)

Figure 8.3-2 Short-term sensitization of the *Aplysia* gill withdrawal reflex. (C) Changes in the gill withdrawal behavior due to habituation and sensitization. The first time that the siphon is touched, the gill contracts vigorously. Repeated touches elicit smaller gill contractions due to habituation. Subsequently pairing a siphon touch with an electrical shock to the tail restores a large and rapid gill contraction, due to short-term sensitization. Like synaptic depression, habituation is caused by synaptic vesicle depletion. Unlike potentiation, facilitation, and augmentation from reactions within a single axonal synapse, sensitization arises from interactions with interneurons. (After Squire and Kandel, 1999.)

(C)  

<table>
<thead>
<tr>
<th>Trial 1</th>
<th>Trial 6</th>
<th>Trial 13</th>
<th>Trial 14</th>
</tr>
</thead>
<tbody>
<tr>
<td>Touch siphon</td>
<td>Touch siphon</td>
<td>Touch siphon</td>
<td>Shock tail and touch siphon</td>
</tr>
</tbody>
</table>

Magnitude of gill contraction

- Touch siphon
- Touch siphon
- Touch siphon
- Shock tail and touch siphon

Time (s) 0 4 8 12 12
Figure 8.3-2 Short-term sensitization of the *Aplysia* gill withdrawal reflex. (D) A short-term sensitization of the gill withdrawal response is observed following the pairing of a single tail shock with a siphon touch. (E) Repeated applications of tail shocks causes prolonged sensitization of the gill withdrawal response. (After Squire and Kandel, 1999.)
Prior to sensitization, activating the siphon sensory neurons causes an EPSP to occur in the gill motor neurons. Activation of the serotonergic modulatory interneurons enhances release of transmitter from the sensory neurons onto the motor neurons, increasing the EPSP in the motor neurons and causing the motor neurons to more strongly excite the gill muscle.

(C) Time course of the serotonin-induced facilitation of transmission at the sensory motor synapse is nearly an hour. (After Squire and Kandel, 1999.)

**Figure 8.4 Synaptic mechanisms underlying short-term sensitization**

(A) Neural circuitry involved in sensitization. Normally, touching the siphon skin activates sensory neurons that excite interneurons and gill motor neurons, yielding a contraction of the gill muscle. A shock to the animal’s tail stimulates modulatory interneurons that alter synaptic transmission between the siphon sensory neurons and gill motor neurons, resulting in sensitization.

(B) Changes in synaptic efficacy at the sensory-motor synapse during short-term sensitization.
Figure 8.4-1 Synaptic mechanisms underlying short-term sensitization. (A) Neural circuitry involved in sensitization. Normally, touching the siphon skin activates sensory neurons that excite interneurons and gill motor neurons, yielding a contraction of the gill muscle. A shock to the animal’s tail stimulates modulatory interneurons that alter synaptic transmission between the siphon sensory neurons and gill motor neurons, resulting in sensitization. (After Squire and Kandel, 1999.)
Figure 8.4-2 Synaptic mechanisms underlying short-term sensitization. (B) Changes in synaptic efficacy at the sensory-motor synapse during short-term sensitization. Prior to sensitization, activating the siphon sensory neurons causes an EPSP (excitatory post-synaptic potential) to occur in the gill motor neurons. Activation of the serotonergic modulatory interneurons enhances release of transmitter from the sensory neurons onto the motor neurons, increasing the EPSP in the motor neurons and causing the motor neurons to more strongly excite the gill muscle. (After Squire and Kandel, 1999.)
(C) Time course of the serotonin-induced facilitation of transmission at the sensory-motor synapse is nearly an hour. (After Squire and Kandel, 1999.)
Figure 8.5 Mechanism of presynaptic enhancement underlying behavioral sensitization.

(A) Short-term sensitization is due to an acute, PKA-dependent enhancement of glutamate release from the presynaptic terminals of sensory neurons. (After Squire and Kandel, 1999.)

(B) Long-term sensitization is due to changes in gene expression, causing expression of proteins that change PKA activity and lead to changes in synapse growth. (After Squire and Kandel, 1999.)

Serotonin released by the facilitatory interneurons binds to G-protein-coupled receptors on the presynaptic terminals of the siphon sensory neurons, which stimulates production of the second messenger, cAMP (3'-5'-cyclic adenosine monophosphate). cAMP binds to the regulatory subunits of protein kinase A (PKA), liberating catalytic subunits of PKA that are then able to phosphorylate several proteins, probably including K⁺ channels. The phosphorylated K⁺ channels are less likely to open during a presynaptic action potential, prolonging Na⁺ depolarization, which opens more presynaptic Ca²⁺ channels. Finally, the enhanced influx of Ca²⁺ into the presynaptic terminals increases the amount of transmitter released onto motor neurons during sensory neuron action potentials.
Figure 8.5-1 Mechanism of presynaptic enhancement underlying behavioral sensitization.

(A) Short-term sensitization is due to an acute, PKA-dependent enhancement of glutamate release from the presynaptic terminals of sensory neurons. There are 6 steps. 1) Serotonin released by the facilitatory interneurons binds to G-protein-coupled receptors on the presynaptic terminals of the siphon sensory neurons, 2) which stimulates production of the second messenger, cAMP (3'-5'-cyclic adenosine monophosphate). 3) cAMP binds to the regulatory subunits of protein kinase A (PKA), 4) liberating catalytic subunits of PKA that are then able to phosphorylate several proteins, probably including K\(^+\) channels. 5) The phosphorylated K\(^+\) channels are less likely to open during a presynaptic action potential, prolonging Na\(^+\) depolarization, which opens more presynaptic Ca\(^{2+}\) channels. 6) Finally, the enhanced influx of Ca\(^{2+}\) into the presynaptic terminals increases the amount of transmitter released onto motor neurons during sensory neuron action potentials. (After Squire and Kandel, 1999.)
Figure 8.5-2 Mechanism of presynaptic enhancement underlying behavioral sensitization.

(B) Long-term sensitization is due to changes in gene expression, causing expression of proteins that change PKA activity and lead to changes in synapse growth. Serotonin-induced enhancement of glutamate release also underlies long-term sensitization, lasting several weeks. With repeated training shocks, the serotonin-activated PKA also phosphorylates, and thereby activates, the transcriptional activator protein CREB (cAMP response element-binding). CREB binding in regulatory regions of nuclear DNA speeds transcription of genes for an enzyme, ubiquitin hydroxylase, that degrades regulatory subunits of PKA. Some PKA stays persistently active without additional serotonin. CREB also stimulates another transcriptional activator protein, C/EBP (CCAAT/enhancer binding protein, where CCAAT is a 5 unit RNA chain of the genetic bases Cytosine, Adenine, and Thymine). C/EBP stimulates transcription of genes that add new long-lasting synaptic terminal structures between the sensory and the motor neurons. The stronger circuit connections produce a long-term enhancement in the gill withdrawal response. (After Squire and Kandel, 1999.)
Box 8A (A) The fruit fly, *Drosophila melanogaster*. (B) Performance of normal and mutant flies on an olfactory learning task. The performance of both *dunce* and *rutabaga* mutants on this task is diminished by at least 50%. Flies that are mutant at both the *dunce* and *rutabaga* loci show a larger decrease in performance, suggesting that the two genes disrupt different but related aspects of learning. (B after Tully, 1996.)
Figure 8.6 The rodent hippocampus

Figure 8.6 Diagram of a section through the rodent hippocampus showing the major regions, excitatory pathways, and synaptic connections. Long-term potentiation has been observed at each of the three synaptic connections shown here. Long-term synaptic plasticity has been most thoroughly studied at excitatory synapses in the mammalian hippocampus. The hippocampus brain area is especially important in the formation and/or retrieval of many forms of memory. The human hippocampus is activated during certain memory tasks and damage to the hippocampus results in an inability to form new declarative memories. In rats, "place cell" hippocampal neurons fire action potentials only when an animal is in certain locations and hippocampal damage prevents rats from developing proficiency in spatial learning tasks.
Figure 8.7 Long-term potentiation of Schaffer collateral-CA1 synapses. (A) Arrangement for recording synaptic transmission: two stimulating electrodes (1 and 2) each activate separate populations of Schaffer collaterals, thus providing test and control synaptic pathways. (B) Left: Synaptic responses recorded in a CA1 neuron in response to single stimuli of synaptic pathway 1, minutes before and one hour after a high-frequency train of stimuli. The high-frequency stimulus train increases the size of the EPSP evoked by a single stimulus. Right: Responses produced by stimulating synaptic pathway 2, which did not receive high-frequency stimulation, is unchanged. (C) The time course of changes in the amplitude of EPSPs evoked by stimulation of pathways 1 and 2. High-frequency stimulation of pathway 1 causes a prolonged enhancement of the EPSPs in this pathway (purple). This potentiation of synaptic transmission in pathway 1 persists for several hours, while the amplitude of EPSPs produced by pathway 2 (orange) remains constant. (D) Recordings of EPSPs from the living hippocampus reveal that high-frequency stimulation can produce LTP that lasts for more than a year. (A-C after Malinow et al., 1989; D after Abraham et al., 2002.)
Figure 8.7-1 Long-term potentiation of Schaffer collateral-CA1 synapses.

(A) Arrangement for recording synaptic transmission: two stimulating electrodes (1 and 2) each activate separate populations of Schaffer collaterals, thus providing test and control synaptic pathways. (After Malinow et al., 1989.)
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Figure 8.7-4 Long-term potentiation of Schaffer collateral-CA1 synapses.

(D) Recordings of EPSPs from the living hippocampus reveal that high-frequency stimulation can produce LTP that lasts for more than a year.

(After Abraham et al., 2002.)
Figure 8.8 Pairing presynaptic and postsynaptic activity causes LTP. Single stimuli applied to a Schaffer collateral synaptic input evokes EPSPs in the postsynaptic CA1 neuron. These stimuli alone do not elicit any change in synaptic strength. However, when the CA1 neuron’s membrane potential is briefly depolarized (by applying current pulses through the recording electrode) within 100 ms after presynaptic transmitter release caused by the Schaffer collateral stimuli, there is a persistent increase in the EPSPs, as Hebb’s 1949 memory formation postulate predicts. (After Gustafsson et al., 1987.)
Figure 8.9 Properties of LTP at a CA1 pyramidal neuron receiving synaptic inputs from two independent sets of Schaffer collateral axons. (A) Strong activity initiates LTP at active synapses (pathway 1) without initiating LTP at nearby inactive synapses (pathway 2). (B) Weak stimulation of pathway 2 alone does not trigger LTP. However, when the same weak stimulus to pathway 2 is activated together with strong stimulation of pathway 1, both sets of synapses are strengthened. This result is consistent with Donald Hebb’s 1949 postulate on learning by strengthening of synapses between neurons that repeated fire in sequence, helping form “cell assemblies”.

(A) Specificity
Pathway 1: Active
| Synapse not strengthened |
Pathway 2: Inactive
| Synapse strengthened |

(B) Associativity
Pathway 1: Strong stimulation
| Synapse strengthened |
Pathway 2: Weak stimulation
| Synapse strengthened |
Figure 8.10 The NMDA receptor channel can open only during depolarization of the postsynaptic neuron from its normal resting level. Depolarization, e.g., by Na\(^+\) admitted by local glutamate AMPA receptors, expels Mg\(^{2+}\) from the NMDA channel, allowing current with Ca\(^{2+}\) to flow into the postsynaptic cell. Ca\(^{2+}\) entry, in turn, triggers LTP. (After Nicoll et al., 1988.)
Figure 8.11 Mechanisms underlying LTP. During glutamate release, the NMDA channel opens only if the postsynaptic cell is sufficiently depolarized. The Ca\(^{2+}\) ions that enter the cell through the channel activate postsynaptic protein kinases, especially Ca\(^+/\)calmodulin kinase II (CaMKII). The CaMKII enzyme is the most abundant postsynaptic protein at Schaffer collateral synapses; blocking of CaMKII prevents LTP. These kinases may act postsynaptically to insert new AMPA receptors into the postsynaptic spine, thereby increasing the sensitivity to glutamate.
Figure 8.12 Addition of postsynaptic AMPA receptors during LTP

(A) Spatial maps of the glutamate sensitivity of a hippocampal neuron dendrite before (left) and 120 minutes after (right) induction of LTP. The color scale indicates amplitude of responses to highly localized glutamate application. LTP causes an increase in the glutamate response of a dendritic spine (arrow), due to an increase in the number of AMPA receptors on the spine membrane.

(B) Time course of changes in glutamate sensitivity of dendritic spines during LTP. Induction of LTP (at time = 0) causes elevated glutamate sensitivity for more than 60 minutes.

(C) LTP induces AMPA receptor responses at silent synapses in the hippocampus. Prior to inducing LTP, no EPSCs are elicited at -65 mV at this silent synapse (upper trace). After LTP induction, the same stimulus produces EPSCs that are mediated by AMPA receptors (lower trace).

(A, B from Matsuzaki et al., 2004; C after Liao et al., 1995.)
Figure 8.12 Addition of postsynaptic AMPA receptors during LTP (Part 1)

Figure 8.12-1 Addition of postsynaptic AMPA receptors during LTP

(A) Spatial maps of the glutamate sensitivity of a hippocampal neuron dendrite before (left) and 120 minutes after (right) induction of LTP. The color scale indicates amplitude of responses to highly localized glutamate application. LTP causes an increase in the glutamate response of a dendritic spine (arrow), due to an increase in the number of AMPA receptors on the spine membrane. (From Matsuzaki et al., 2004.)
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Figure 8.12-3 Addition of postsynaptic AMPA receptors during LTP (C) LTP induces AMPA receptor responses at silent synapses in the hippocampus. Prior to inducing LTP, no EPSCs (excitatory postsynaptic currents) are elicited at -65 mV at this silent synapse (upper trace).

After LTP induction, the same stimulus produces EPSCs that are mediated by AMPA receptors (lower trace). (After Liao et al., 1995.)
Electrophysiological evidence for silent synapses. Stimulation of some axons fails to activate synapses when the postsynaptic cell is held at a negative potential (–65 mV, upper trace). However, when the postsynaptic cell is depolarized (+55 mV), stimulation produces a robust response (lower trace). (B) Immunofluorescent localization of NMDA receptors (green) and AMPA receptors (red) in a cultured hippocampal neuron. Many dendritic spines are positive for NMDA receptors but not AMPA receptors, indicating NMDA receptor-only synapses. (A after Liao et al., 1999; B courtesy of M. Ehlers.) (C) Electron microscopy of excitatory synapses in CA1 stratum radiatum of the hippocampus from 10-day-old or 5-week-old (adult) rats double-labeled for AMPA receptors and NMDA receptors. The presynaptic terminal (pre), synaptic cleft, and postsynaptic spine (post) are indicated. AMPA receptors are abundant at the adult synapse, but absent from the younger synapse. (D) Diagram of glutamatergic synapse maturation. Early in postnatal development, many excitatory synapses contain only NMDA receptors. As synapses mature, AMPA receptors are recruited. (C from Petralia et al., 1999.)
Box 8B Silent Synapses (Part 1)

**Box8B-1** (A) Electrophysiological evidence for silent synapses. Stimulation of some axons fails to activate synapses when the postsynaptic cell is held at a negative potential (−65 mV, upper trace). However, when the postsynaptic cells is depolarized (+55 mV), stimulation produces a robust response (lower trace). (B) Immunofluorescent localization of NMDA receptors (green) and AMPA receptors (red) in a cultured hippocampal neuron. Many dendritic spines are positive for NMDA receptors but not AMPA receptors, indicating NMDA receptor-only synapses. (A after Liao et al., 1999; B courtesy of M. Ehlers.)
Box 8B Silent Synapses (Part 2)

Box8B-2 (C) Electron microscopy of excitatory synapses in CA1 stratum radiatum of the hippocampus from 10-day-old or 5-week-old (adult) rats double-labeled for AMPA receptors and NMDA receptors. The presynaptic terminal (pre), synaptic cleft, and postsynaptic spine (post) are indicated. AMPA receptors are abundant at the adult synapse, but absent from the younger synapse. (D) Diagram of glutamatergic synapse maturation. Early in postnatal development, many excitatory synapses contain only NMDA receptors. As synapses mature, AMPA receptors are recruited. (C from Petralia et al., 1999.)
**Figure 8.13** Role of protein synthesis for maintaining LTP  

(A) Repetitive high-frequency stimulation (arrows) induces LTP that persists for many hours.  
(B) Treatment with anisomycin, an inhibitor of protein synthesis (at bar), causes LTP to decay within a few hours after the high-frequency stimulation (arrows)  

(After Frey and Morris, 1997.)
Figure 8.14  Mechanisms responsible for changes in synaptic transmission during LTP. (A) The late component of LTP is due to PKA activating the transcriptional regulator CREB, which turns on expression of a number of genes that produce long-lasting changes in PKA activity and synapse structure. (B, C) Structural changes associated with LTP in the hippocampus.

(B) The dendrites of a CA1 pyramidal neuron were visualized by filling the cell with a fluorescent dye. (C) New dendritic spines (white arrows) can be observed to appear approximately 1 hour after a stimulus that induces LTP. The presence of novel spines raises the possibility that LTP may arise, in part, from formation of new synapses. (A after Squire and Kandel, 1999; B and C after Engert and Bonhoeffer, 1999.)
Figure 8.14-1 Mechanisms responsible for long-lasting changes in synaptic transmission during LTP. (A) The late component of LTP is due to PKA activating the transcriptional regulator CREB, which turns on expression of a number of genes that produce long-lasting changes in PKA activity and synapse structure. (After Squire and Kandel, 1999.)
**Figure 8.14** Mechanisms responsible for changes in synaptic transmission during LTP (Part 2)

**Figure 8.14** Mechanisms responsible for long-lasting changes in synaptic transmission during LTP.

(B, C) Structural changes associated with LTP in the hippocampus.

(B) The dendrites of a CA1 pyramidal neuron were visualized by filling the cell with a fluorescent dye. (C) New dendritic spines (white arrows) can be observed to appear approximately 1 hour after a stimulus that induces LTP. The presence of novel spines raises the possibility that LTP may arise, in part, from formation of new synapses. (After Engert and Bonhoeffer, 1999.)
Figure 8.15 Long-term synaptic depression in the hippocampus.

(A) Electrophysiological procedures used to monitor transmission at the Schaffer collateral synapses on to CA1 pyramidal neurons. (B) Low-frequency stimulation (1 per second) of the Schaffer collateral axons causes a long-lasting depression of synaptic transmission. (C) Mechanisms underlying LTD. A low-amplitude rise in Ca$^{2+}$ concentration in the postsynaptic CA1 neuron activates postsynaptic protein phosphatases, which cause internalization of postsynaptic AMPA receptors, thereby decreasing the sensitivity to glutamate released from the Schaffer collateral terminals. (B after Mulkey et al., 1993.)
Figure 8.15-1 Long-term synaptic depression in the hippocampus. (A) Electrophysiological procedures used to monitor transmission at the Schaffer collateral synapses on to CA1 pyramidal neurons. (B) Low-frequency stimulation (1 per second) of the Schaffer collateral axons causes a long-lasting depression of synaptic transmission. (B after Mulkey et al., 1993.)
Figure 8.15-1 Long-term synaptic depression in the hippocampus.

(C) Mechanisms underlying LTD. A low-amplitude rise in \( \text{Ca}^{2+} \) concentration in the postsynaptic CA1 neuron activates postsynaptic protein phosphatases, which cause internalization of postsynaptic AMPA receptors, thereby decreasing the sensitivity to glutamate released from the Schaffer collateral terminals.
Figure 8.16 Long-term synaptic depression in the cerebellum. (A) Experimental arrangement. Synaptic responses were recorded from Purkinje cells following stimulation of parallel fibers and climbing fibers. (B) Pairing stimulation of climbing fibers (CF) and parallel fibers (PF) causes LTD that reduces the parallel fiber EPSP. (C) LTD requires depolarization of the Purkinje cell, produced by climbing fiber activation, as well as signals generated by active parallel fiber synapses. (D) Mechanism underlying cerebellar LTD. Glutamate released by parallel fibers activates both AMPA receptors and metabotropic glutamate receptors. The latter produces two second messengers, DAG and IP3, which interact with Ca^{2+} that enters when climbing fiber activity opens voltage-gated Ca^{2+} channels. This leads to activation of PKC, which triggers clathrin-dependent internalization of postsynaptic AMPA receptors to weaken the parallel fiber synapse. (B after Sakurai, 1987.)
Figure 8.16-1 Long-term synaptic depression (LTD) in the cerebellum. (A) Experimental arrangement. Synaptic responses were recorded from Purkinje cells following stimulation of parallel fibers and climbing fibers. All cerebellar outputs are inhibitory (GABA) synapses from Purkinje cell axons onto neurons in the deep cerebellar nuclei. The deep nuclei and granule cells all receive indirect excitatory motor control signals from the spine, brainstem nuclei, vestibular system, and massive cerebral projections. The inferior olive nucleus lies in the brainstem between the spine and the pontine cerebellar peduncles. Climbing fiber inputs from olivary neurons likely signal motor errors. LTD of inhibitory Purkinje cells selectively excites rapid corrective motor signals from the deep nuclei.
Figure 8.16-2 Long-term synaptic depression in the cerebellum. (B) Pairing stimulation of climbing fibers (CF) and parallel fibers (PF) causes LTD that reduces the parallel fiber EPSP. (After Sakurai, 1987.)
Figure 8.16-3 Long-term synaptic depression in the cerebellum. (C) LTD requires depolarization of the Purkinje cell, produced by climbing fiber activation, as well as signals generated by active parallel fiber synapses.
Figure 8.16-4 Long-term synaptic depression in the cerebellum. (D) Mechanism underlying cerebellar LTD. Glutamate released by parallel fibers activates both AMPA receptors and metabotropic glutamate receptors. The latter produces two second messengers, DAG and IP3, which interact with Ca$^{2+}$ that enters when climbing fiber activity opens voltage-gated Ca$^{2+}$ channels. This leads to activation of PKC, which triggers clathrin-dependent internalization of postsynaptic AMPA receptors to weaken the parallel fiber synapse. (B after Sakurai, 1987.)
Figure 8.17 Spike timing-dependent synaptic plasticity in cultured hippocampal neurons. (A) The left-hand graph shows that stimulating a presynaptic neuron (pre) causes an EPSP in the postsynaptic neuron; applying a subsequent stimulus to the postsynaptic neuron (post) causes an action potential that is superimposed on the EPSP. At the right, repetitive application of the stimulus paradigm shown at left causes a long-term potentiation (LTP) of the EPSP (excitatory postsynaptic potential).

(B) Reversing the order of stimulation, so that the postsynaptic neuron is excited before the presynaptic neuron causes a long-term depression (LTD) of the EPSP. (C) Complex dependence of STDP on the interval between presynaptic and postsynaptic activity. If the presynaptic neuron is activated 40 ms or less before the postsynaptic neuron, LTP occurs. Conversely, if the postsynaptic neuron is activated 40 ms or less before the presynaptic neuron, LTD occurs. If the interval between the two events is longer than 40 ms, no STDP is observed. (After Bi and Poo, 1998.)
Figure 8.17 Spike timing-dependent synaptic plasticity in cultured hippocampal neurons (Part 1)

Figure 8.17-1 Spike timing-dependent synaptic plasticity (STDP) in cultured hippocampal neurons. (A) The left-hand graph shows that stimulating a presynaptic neuron (pre) causes an EPSP in the postsynaptic neuron; applying a subsequent stimulus to the postsynaptic neuron (post) causes an action potential that is superimposed on the EPSP. At the right, repetitive application of the stimulus paradigm shown at left causes a long-term potentiation (LTP) of the EPSP (excitatory post-synaptic potential). (After Bi and Poo, 1998.)
Figure 8.17-2 Spike timing-dependent synaptic plasticity (STDP) in cultured hippocampal neurons.

(B) Reversing the order of stimulation, so that the postsynaptic neuron is excited before the presynaptic neuron causes a long-term depression (LTD) of the EPSP. (After Bi and Poo, 1998.)
Figure 8.17-3 Spike timing-dependent synaptic plasticity (STDP) in cultured hippocampal neurons. (C) Complex dependence of STDP on the interval between presynaptic and postsynaptic activity. If the presynaptic neuron is activated 40 ms or less before the postsynaptic neuron, LTP occurs. Conversely, if the postsynaptic neuron is activated 40 ms or less before the presynaptic neuron, LTD occurs. If the interval between the two events is longer than 40 ms, no STDP is observed. (After Bi and Poo, 1998.)
Box 8C  Epilepsy: The Effect of Pathological Activity on Neural Circuitry

**Box 8C** Electroencephalogram (EEG) recorded from a patient during a seizure. The traces show rhythmic activity that persisted much longer than the duration of this record. This abnormal pattern reflects the synchronous firing of large numbers of cortical neurons.

(The designations are various positions of electrodes on the head; see text in Box 28C for additional information about EEG recordings.) (After Dyro, 1989.)