Neuron
Perspective

Ubiquitous Plasticity and Memory Storage

Sang Jeong Kim[1,*] and David J. Linden[2,*]
[1]Department of Physiology, Seoul National University College of Medicine, 110-799 Seoul, Korea
[2]Department of Neuroscience, Johns Hopkins University School of Medicine, Baltimore, MD 21205, USA
*Correspondence: dlinden@jhmi.edu (D.J.L.), sangjkim@snu.ac.kr (S.J.K.)
DOI 10.1016/j.neuron.2007.10.030

To date, most hypotheses of memory storage in the mammalian brain have focused upon long-term synaptic potentiation and depression (LTP and LTD) of fast glutamatergic excitatory postsynaptic currents (EPSCs). In recent years, it has become clear that many additional electrophysiological components of neurons, from electrical synapses to glutamate transporters to voltage-sensitive ion channels, can also undergo use-dependent long-term plasticity. Models of memory storage that incorporate this full range of demonstrated electrophysiological plasticity are better able to account for both the storage of memory in neuronal networks and the complexities of memory storage, indexing, and recall as measured behaviorally.

If an extraterrestrial neuroscientist managed to obtain a badge and abstract book and attend the Society for Neuroscience annual meeting, she could be forgiven for concluding that humans believe that memory storage is solely accomplished through LTP/LTD of fast (ionotropic) neurotransmission at excitatory, glutamatergic synapses. Indeed, the vast majority of presentations would support this conclusion. She might not realize that many additional aspects of glutamatergic neurotransmission can undergo LTP/LTD including slow neurotransmission (mediated by mGluRs) and glutamate reuptake. Furthermore, it might not be obvious that nonglutamatergic synapses, both chemical and electrical, express LTP/LTD. And she might be similarly surprised to learn that many of the voltage-sensitive ion channels in the dendrites and soma that underlie and modulate signal integration and spiking are similarly plastic (Figure 1).

We suggest that, in time, all electrophysiological functions of neurons will be shown to undergo long-term use-dependent modulation. However, while electrophysiological plasticity is ubiquitous, not all plasticity is *directly* involved in constituting the memory trace, what we call mnemonic plasticity. Rather, some non-mnemonic forms of plasticity are homeostatic (Turrigiano, 1999; Abbott and Nelson, 2000; Desai, 2003) and thereby are permissive for memory storage in neuronal networks. Other non-mnemonic forms of electrophysiological plasticity are metaplastic (Huang et al., 1992; Abraham and Bear, 1996), impacting the probability of inducing subsequent mnemonic plasticity and thereby supporting high-order aspects of memory such as savings, blocking, or generalization.

A Little Recent History

When long-term potentiation (LTP) was first reported at the glutamatergic perforant path-dentate gyrus granule cell synapse by Bliss and Lomo (1973), neuroscientists were excited, not just because LTP seemed like a useful cellular memory mechanism, but also because it was reported in the hippocampal formation, a structure known to be important in the storage of memories for facts and events (declarative memories). The dominant thought at that time, and one that persisted for many years, was that LTP, and later long-term depression (LTD, which was first described at the glutamatergic Schaffer collateral-CA1 pyramidal cell synapse of the hippocampus by Lynch et al. [1977]), were unusual phenomena that would only be found in the few brain regions then thought to be involved in memory storage. Now, we know that memory storage involves many additional brain regions and that LTP and LTD are widespread, having been found at glutamatergic synapses from the spinal cord to the neocortex.

In the last 35 years or so, great strides have also been made in uncovering the molecular underpinnings of these phenomena and, to a lesser degree, in testing their roles in learning and memory tasks. Part of what has emerged in this process is an appreciation that LTP and LTD of fast, monosynaptic EPSCs can be triggered and expressed by a variety of different mechanisms. There are synapses where LTP and LTD are expressed presynaptically, as a change in the probability of neurotransmitter release, and others where LTP and LTD are expressed postsynaptically, as changes in the number or unitary conductance of AMPA and/or NMDA receptors in the postsynaptic density. There are many synapses where multiple forms of LTP and LTD expression occur simultaneously.

Glutamate is the major excitatory neurotransmitter in the central nervous system, and fast glutamatergic EPSCs are a fundamental mode of neuronal communication. There have been many attempts to test the hypothesis that persistent, use-dependent changes in the electrical properties of neurons underlie memory storage in the brain. These tests have mostly used drugs, transfection, or mutant mice to interfere with (or occasionally to enhance) the induction and expression of LTP/LTD of fast glutamatergic EPSCs, with the hope that these manipulations would also change performance in memory tasks. While this approach has sometimes been fruitful, it has largely ignored the diversity of long-term use-dependent

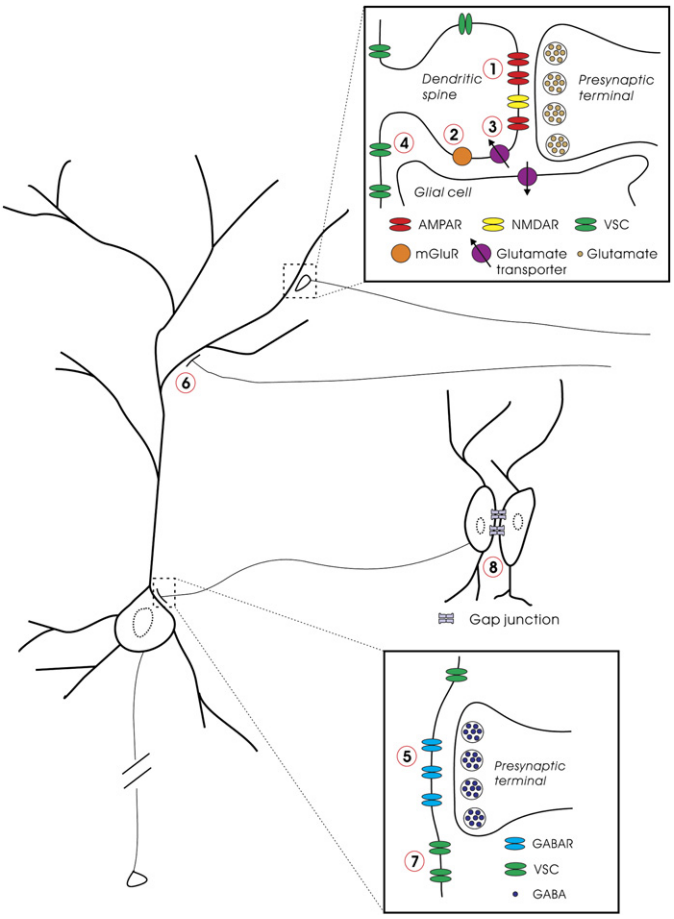

Figure 1. Diverse Forms of Long-Term Use-Dependent Electrophysiological Plasticity

This diagram is meant to present a portion of generic brain neural circuitry in which a principal neuron receives an excitatory glutamatergic synapse in its distal apical dendrite (expanded box in upper right corner) and inhibitory GABAergic synapses in both distal apical dendrite and somatic regions (the latter shown by an expanded box). The axon forming the somatic inhibitory synapse derives from an interneuron that is part of a network, synchronized by gap junctions. To date, the following forms of long-term use-dependent plasticity have been reported: (1) conventional, input-specific synaptic LTP and LTD. The form illustrated here is expressed by changes in AMPA receptors, but there are other forms as well, both presynaptically and postsynaptically expressed. (2) LTP and LTD of mGluR1 function triggered by postsynaptic Ca transients. (3) LTP of neuronal glutamate transporter function. This could potentially attenuate the glutamate transient seen by neuronal perisynaptic mGluRs. (4) Local intrinsic plasticity of voltage-sensitive channels (VSCs) in the dendrite. Here, we have indicated VSC function with a single aggregate symbol, but, of course, this actually represents many different conductances. (5) LTP and LTD of somatic GABAergic synapses. This will have a global effect on excitatory synaptic throughput. (6) LTP and LTD of distal, dendritic GABAergic synapses will have a more localized effect on excitatory synaptic throughput, restricted to neighboring synapses on the same dendritic branch. (7) Intrinsic plasticity of voltage-sensitive ion channel function in the somatic (or axonal) region will have a global effect on excitatory synaptic throughput. (8) LTD of electrical synapses between interneurons. This can attenuate the synchrony of interneuron networks.

plasticity that electrophysiologists have uncovered in recent years.

We shall give a brief overview of some of the diverse ways in which experience has been shown to produce long-term changes in the electrical function of neurons and consider whether this collection of plastic mechanisms can help us refine our models of memory storage. In so doing, we will need to define some terminology. Here, LTP and LTD will be defined by their mode of expression, not induction. So, LTP(mGluR1) indicates LTP expressed by mGluR1, not LTP triggered by mGluR1 activation and expressed as an upregulation of, say, AMPA receptors.

Unconventional Experience-Driven Plasticity at Glutamatergic Synapses

LTD and LTP of mGluR1 Function

In many synapses, bursts (but not single spikes) activate both an AMPA/NMDA receptor-mediated fast EPSC (time to peak ~2 ms) and an mGluR1/5-mediated slow EPSC (time to peak ~400 ms). Activation of mGluR1/5 is an important trigger of many cellular events in addition to the slow EPSC, including Ca mobilization from internal stores (via IP_3 receptors) and activation of protein kinase C (PKC), MEK, and endocannabinoid signaling pathways (via phospholipase activation). Activation of mGluR1/5 is crucial for certain conventional forms of LTP and LTD expressed by AMPA receptors (Anwyl, 1999). At a behavioral level, mGluR1/5 have been implicated in seizures (Wong et al., 1999), addiction (Chiamulera et al., 2001), and several forms of memory storage (Riedel et al., 2003) involving the hippocampus, amygdala, neocortex, striatum, and cerebellum. If mGluR1/5 activation were itself modulated, then this might have a profound metaplastic effect, changing the set point for the induction of some conventional forms of LTP and LTD.

Recently, it has been shown that mGluR1 function can undergo profound use-dependent LTD (Jin et al., 2007). Burst stimulation of parallel fibers releases glutamate which activates perisynaptic mGluR1 in the dendritic spines of cerebellar Purkinje cells in brain slices. The mGluR1-mediated slow EPSC activated by parallel fiber bursts was completely and persistently depressed by Ca influx triggered by strong depolarization of Purkinje cells. This depolarization-evoked depression of the slow EPSC had no effect on the fast EPSC at this same synapse which is mediated by AMPA-type glutamate receptors. LTD of

the slow EPSC was also observed when slow synaptic current was evoked by exogenous application of an mGluR1-mediated agonist, implying a postsynaptic mechanism of expression. Ca imaging showed that this depression, called LTD(mGluR1), was expressed as coincident attenuation of both limbs of mGluR1 signaling: the TRPC1-medaited slow EPSC and the phospholipase C/IP_3-mediated dendritic Ca mobilization.

When cultured Purkinje cells were treated with an external saline supplemented with 50 mM KCl to produce strong depolarization (5 min duration), this did not trigger LTD(mGluR1), but rather resulted in an increase in surface mGluR1 immunoreactivity and a corresponding increase in the Ca transient and inward current evoked by puffs of mGluR1 agonist, LTP(mGluR1) (Minami et al., 2003). It remains to be seen if LTP(mGluR1) and LTD(mGluR1) can be expressed at the same synapses in a slice preparation and if they can reverse each other, thereby achieving bidirectional modulation.

What is the function of LTD(mGluR1) and LTP(mGluR1) in Purkinje cells? One clue comes from the observation that LTD(mGluR1) blocked subsequent induction of conventional mGluR1-dependent LTD of AMPA receptors (Jin et al., 2007). Thus, various forms of neuronal activity can evoke LTD of both fast ionotropic neurotransmission and/or slow mGluR1-mediated transmission at a glutamatergic synapse and the latter can have a metaplastic effect.

A similar metaplastic mGluR effect may be induced in the CA1 region of the hippocampus by seizures. When chronic, recurring seizures were produced in rats following a single pilocarpine injection, this resulted in a downregulation of mGluR5 protein as assessed in hippocampal tissue using Western blots. Brain slices derived from pilocarpine-treated rats (4–10 weeks later) lacked an mGluR5-dependent form of LTD at Schaffer collateral-CA1 pyramidal cell synapses (Kirschstein et al., 2007).

LTP of Glutamate Transporters

The cerebellar climbing fiber-Purkinje cell synapse is an advantageous model system for the study of neuronal glutamate transporter currents. Most Purkinje cells are innervated by a single climbing fiber axon, which ramifies to form ~1500 release sites. Each of these sites appears to release multiple vesicles of glutamate with each action potential invasion (Wadiche and Jahr, 2001). A single shock delivered to the climbing fiber axon results in the activation of AMPA and kainate receptors (Huang et al., 2004), and when these receptors are blocked with drugs, a synaptic glutamate transporter current is revealed. This current is mediated by the transporter EAAT4 (Huang et al., 2004), which is strongly expressed in the perisynaptic membranes of climbing fiber-Purkinje cell synapses.

Tetanic stimulation of climbing fiber-Purkinje cell synapses resulted in LTP of climbing fiber-evoked EAAT4 current (Shen and Linden, 2005). This LTP(EAAT4) required activation of an mGluR1/PKC cascade and an LTP(EAAT4)-like effect produced by exogenous PKC activators could be observed using glutamate uncaging test pulses in place of climbing fiber volleys, indicating a postsynaptic locus of expression.

In cerebellar Purkinje cells, blockade of glial and neuronal EAATs with the drug TBOA, produced a large increase in mGluR1 activation, presumably by increasing the amplitude of the glutamate transients at perisynaptic mGluR1 receptors. Brasnjo and Otis (2001) showed that this manipulation could reduce the threshold for induction of mGluR1-dependent LTD of AMPA receptors at the parallel fiber-Purkinje cell synapse. It will be interesting to determine whether LTP(EAAT4) will produce the converse effect: raising the threshold for conventional cerebellar LTD of AMPA receptors.

Use-Dependent Long-Term Plasticity at Nonglutamatergic Synapses

GABAergic Synapses

At present, the vast majority of studies examining the synaptic substrates of memory storage have involved LTP/LTD of excitatory glutamatergic synapses. Although inhibitory synapses are widespread and crucial to nervous system function, long-term alterations of these synapses have received much less attention. Inhibitory synapses exert powerful control over synaptically-driven neuronal firing. In part, this control derives from the spatial distribution of excitatory versus inhibitory synapses. Inhibitory synapses are often found on the soma, proximal dendrites, and axon initial segment of a target neuron, whereas excitatory synapses are more likely to be found on the distal dendrites. This interposed configuration allows a single proximal inhibitory synapse to negate hundreds of integrated EPSPs by a shunting conductance and thereby influence spike frequency and timing.

In a number of brain regions, including neocortex, hippocampus, and cerebellum, strong depolarization of postsynaptic neurons can give rise to LTP or LTD of GABAergic IPSCs (Gaiarsa et al., 2002). One well-established example involves the synapses between molecular layer interneurons and cerebellar Purkinje cells, where strong postsynaptic depolarization give rise to LTP(GABA) (Kano et al., 1992) through a postsynaptic signaling cascade involving Ca influx and CaMKII (Kano et al., 1996). At the GABAergic synapses between cerebellar Purkinje cells and the neurons of the deep cerebellar nuclei, either LTD(GABA) (Morishita and Sastry, 1996) or LTP(GABA) may be induced, depending upon the degree of postsynaptic activation (Aizenman et al., 1998).

In the neocortex, cell-pair recordings of synapses between fast spiking interneurons and pyramidal cells have shown that LTP(GABA) or LTD(GABA) can be induced in a spike timing-dependent fashion: LTD(GABA) in induced by near-coincident pre- and postsynaptic firing while LTP(GABA) is induced by greater temporal mismatch (Holmgren and Zilberter, 2001). A separate study examined LTP(GABA) in inhibitory synapses from fast-spiking basket cells to star pyramidal neurons in layer 4 of primary visual cortex (Maffei et al., 2006). LTP(GABA) could be induced by pairing of fast-spiking basket cell firing with

subthreshold depolarization of star pyramidal neurons. In this case, correlated presynaptic and postsynaptic firing prevented LTP(GABA).

Dopaminergic Synapses

In the ventral tegmental area, stimulation of dopaminergic neurons can evoke dendritic dopamine release and consequent activation of D2 receptors at dendrodendritic synapses. These D2 receptors activate a GIRK conductance via $G_{i/o}$ proteins, resulting in a slow IPSC (time to peak ~300 ms; Beckstead et al., 2004). Following low-frequency conditioning stimulation, LTD of the slow dopamine IPSC was observed that is likely mediated by desensitization of postsynaptic D2 receptors (Beckstead and Williams, 2007). Thus, LTD has now been observed at both slow metabotropic (dopamine) and fast ionotropic (GABA-A) inhibitory synapses, further expanding the repertoire of use-dependent plasticity.

Electrical Synapses

It has become clear that there are large groups of neighboring inhibitory neurons that are electrically connected by gap junctions in both the neocortex and the thalamus. These connections promote synchronized firing of inhibitory networks. One such location where this occurs is the thalamic reticular nucleus, where the probability of electrical coupling between adjacent inhibitory neurons is ~50%. These neurons also receive powerful glutamatergic drive from the neocortex that is received by synapses bearing postsynaptic mGluR1/5. Landisman and Connors (2005) performed dual whole-cell recordings from adjacent inhibitory neurons in this structure and measured the strength of electrical synapses (by passing a hyperpolarizing current step into one cell while recording from its neighbor). They found that the strength of electrical coupling was consistent when monitoring with low-frequency test pulses for >20 min. However, when conditioning stimulation, consisting of brief bursts applied to glutamatergic synapses, was delivered, this produced an attenuation of the electrical synapses that resulted in an ~25% depression of the coupling coefficient and which lasted for the duration of the recording (Figure 2). This LTD(electrical) could be blocked by an mGluR1/5 antagonist and mimicked by an agonist. Importantly, induction of LTD(electrical) was accompanied by a reduction in the correlation coefficient of spike firing between the two cells. It remains to be seen whether the converse phenomenon, LTP(electrical), will be found in the mammalian brain. This seems likely, given that LTP(electrical) has been previously reported at mixed electrical/chemical club ending synapses on goldfish Mauthner cells (Yang et al., 1990; see Pereda et al., 2004, for review).

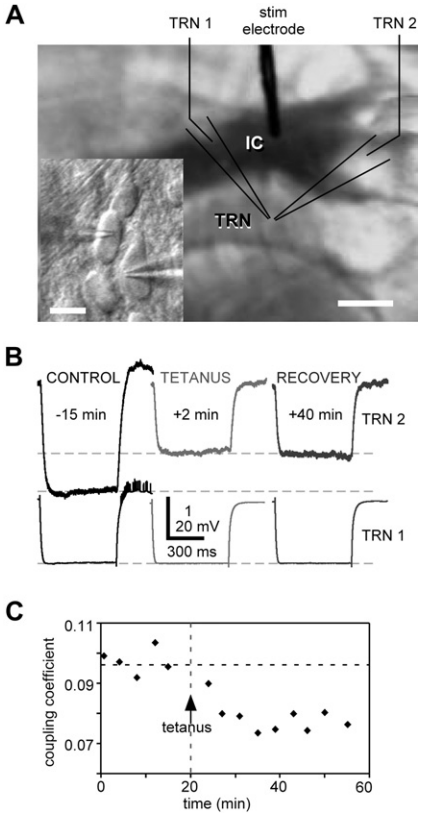

Figure 2. LTD at Electrical Synapses between Neurons in the Thalamic Reticular Nucleus

(A) Infrared DIC images showing the recording configuration. Simultaneous recordings were made from a pair of electrically coupled neurons in the thalamic reticular nucleus (TRN1 and 2). A stimulating electrode was placed to activate corticothalamic fibers running in the internal capsule (IC). Scale bars indicate 1 mm and 20 μm (inset).

(B) Large hyperpolarizing current injections into TRN1 evoked electrical coupling responses in TRN2. This constituted the test stimulation. Conditioning stimulation involved tetanic activation of corticothalamic fibers, which impinged upon both TRN1 and TRN2. Following conditioning stimulation, LTD(electrical) was observed.

(C) A time course graph shows LTD(electrical) as a persistent decrease in coupling coefficient.

From Landisman and Connors (2005). Reprinted with permission of AAAS.

Intrinsic Plasticity

In recent years, a number of reports have demonstrated that patterns of brief synaptic stimulation, particularly bursts, can give rise to persistent changes in postsynaptic voltage-sensitive ion channel function (see Zhang and Linden, 2003; Frick and Johnston, 2005, for review). One nice example comes from the sensorimotor neocortex, in which high-frequency stimulation of glutamatergic fibers from layer II/III produced a persistent increase in the intrinsic excitability of layer V pyramidal cells. This phenomenon required activation of mGluR5 and produced an increase in the number of spikes recorded in response to a constant injection of depolarizing current in the soma (Sourdet et al., 2003). It was also manifest as a reduction in the medium-duration after hyperpolarization that followed a spike burst, produced in part by the action of SK-type Ca-sensitive K channels. Many other examples of synaptically evoked changes in intrinsic excitability have been reported and they have involved a number of different induction mechanisms (NMDA receptor activation, Ca influx via voltage-gated channels) and expression

mechanisms (various Na, K, Cl, and Ca conductances have all been altered).

Almost all of the studies that have examined intrinsic plasticity have relied upon somatic recording, which reflects conductances in the soma, proximal axon, and the dendrites (with the proximal dendrites contributing most of the dendritic signal). One limitation of this recording mode is that it does not pinpoint the location of the plastic ion channels. If a group of K channels near the site of synaptic activation in the dendrite were modulated, this could not be distinguished from a smaller but more widespread effect on K channels. In a seminal report, Frick et al. (2004) combined patch-clamp recording from dendrites with Ca imaging to address this question. They stimulated a group of Schaffer collateral synapses that impinged upon the distal dendrite of a hippocampal CA1 pyramidal cell. This stimulation produced conventional NMDA receptor-dependent LTP of AMPA receptors, but it also produced a local enhancement of excitability in an ~100 μm long segment of distal dendrite (Figure 3). This was mediated in part by a hyperpolarizing shift in the steady-state inactivation of the K conductance I_A measured in distal dendrite. This intrinsic plasticity was also seen as an accompanying local increase in the amplitude of single back-propagating spikes and their associated Ca transients. This result is important because it shows that local, persistent changes in a dendritic voltage-sensitive conductance can be evoked in a use-dependent manner. It opens the door to the possibility that these localized changes can constitute a portion of memory traces by modulating dendritic integration in a subset of the synaptic array. In addition, it points out that there may be units of integration in the dendrite that are intermediate between the single synapse (as modulated by conventional LTP/LTD) and the entire neuron (as modulated by intrinsic changes of axo-somatic conductances that would affect throughput from all synapses). Interestingly, it appears as if the same pattern of stimulation can produce both local and global changes in dendritic intrinsic conductances. For example, theta burst pairing can produce both the local increases in intrinsic excitability mediated by I_A, as discussed previously (Frick et al., 2004), and a superimposed decrease in dendritic excitability that is spread across the dendritic arbor and mediated by an upregulation of a different conductance, I_h (Fan et al., 2005).

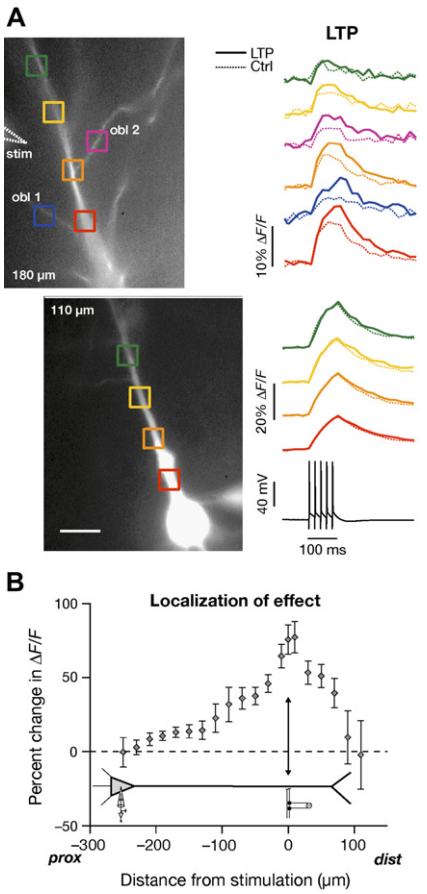

Figure 3. Long-Term Intrinsic Plasticity in a Local Subdomain of Hippocampal CA1 Pyramidal Neuron Apical Dendrite

(A) Left: a fluorescent image of a dye-loaded CA1 pyramidal neuron showing the main apical dendrite and smaller oblique dendrites (obl1 and obl2 are two examples). The colored boxes indicate regions of interest for dynamic free Ca measurements. "stim" indicates the position of the stimulating electrode used to activate Schaffer collateral axons. Right: Ca transients were evoked by somatic current injection which produced a burst of five back-propagating spikes. The Ca transients were measured before (dotted lines) and after (solid lines) the induction of conventional synaptic LTP from theta-burst pairing of a bundle of Schaffer collateral axons.

(B) Persistent changes in the peak Ca transient evoked by backpropagating spikes are plotted, normalized to the distance from the site of synaptic stimulation. This shows that the persistent increase in intrinsic excitability is not widespread, but rather is confined to a segment of dendrite. Reprinted with permission from Macmillan Publishers Ltd.: *Nature Neuroscience*. Frick et al. (2004). Copyright, 2004.

Everything, All the Time

In the beginning (1973, actually), there was LTP of fast glutamatergic EPSPs (Bliss and Lomo, 1973). Interestingly, even in the original report of LTP, it was also noted that at least one additional form of plasticity was present. The increase in population spike was greater than could be accounted for by the increase in the population EPSP caused by LTP. In fact, in some cases, population spike potentiation occurred in the absence of potentiation of the population EPSP. This phenomenon was termed the "nonsynaptic component of LTP" and later came to be known as EPSP-spike or E-S potentiation. Amazingly, the mechanism underlying E-S potentiation is still controversial with some investigators, suggesting that E-S potentiation is due to an increase in the ratio of excitatory to feed-forward inhibitory drive while others implicate an increase in the intrinsic excitability of the postsynaptic neuron (see Zhang and Linden, 2003, for review). In either case, plasticity mechanisms other that glutamatergic synapse LTP are required.

A few years later, LTD of fast glutamatergic EPSPs emerged (Lynch et al., 1977), followed, in the 1990s by LTP and LTD of fast GABAergic IPSPs (Kano et al.,

1992; Morishita and Sastry, 1996). LTP and LTD have also been found at electrical synapses (Landisman and Connors, 2005). More recently, at glutamatergic synapses, slow metabotropic EPSCs have been shown to undergo LTP and LTD (Minami et al., 2003; Jin et al., 2007) and LTP of a neuronal glutamate transporter has also been reported (Shen and Linden, 2005). In a parallel track of discovery, beginning in 1980 (Brons and Woody, 1980), voltage-sensitive ion channels underlying synaptic integration and spike generation have also been shown to undergo persistent use-dependent modulation. At present, many species of ion channel have been shown to express rapidly-induced long-term use-dependent plasticity (see Zhang and Linden, 2003; Frick and Johnston, 2005, for review).

What can we take from these recent discoveries? One simple conclusion is that when neuroscientists examine an electrophysiological function long enough, they will find it to undergo long-term use-dependent plasticity. This progress in identifying new forms of electrophysiological plasticity in the brain suggests the following prediction: in time, every electrophysiological function of neurons will be shown to express long-term use-dependent plasticity. Let's be clear about the details of this hypothesis. It doesn't mean that every *individual molecular species* of ion channel, receptor, transporter, exchanger, docking molecule, pump, etc. must be subject to long-term plasticity. What it does suggest is that every main *class* of molecule underlying neuronal electrical function is fundamentally plastic. For synaptic transmission, this might include neurotransmitter transporters responsible for vesicular loading; some, but not all, molecules involved in vesicular docking, priming, and fusion; a subset of ionotropic and metabotropic receptors; and neuronal and possibly glial neurotransmitter transporters. For signal integration, this might include a subset of dendritic and somatic voltage-sensitive ion channels that control membrane excitability. For spike generation, a subset of ion channels involved in triggering and propagating action potentials might be modulated. In this way, every electrical *function* of neurons might be plastic, even if only a subset of the total complement of *molecules* underlying these functions are plastic.

Too Much of a Good Thing?

To the experimentalist in search of the engram, this ubiquitous plasticity is a mixed blessing. Many experiments designed to test the link between a particular form of plasticity (usually conventional LTP or LTD of AMPA receptors) and memory disrupt these forms of plasticity by targeting receptors, with drugs or mutant mice, and then assess performance in a learning task, like the Morris water maze, associative eyelid conditioning, or cued fear conditioning. The problem is that inhibition of these receptors often blocks multiple forms of plasticity. For example, deletion or antagonism of NMDA receptors blocks not only certain forms of conventional LTP and LTD of AMPA receptors, but also long-term use-dependent modulation of voltage-sensitive ion channels that control spiking (intrinsic plasticity). Similarly, interfering with group I mGluRs (mGluR1 and 5) not only blocks the induction of LTD of AMPA receptors in many brain regions, but in also blocks LTP(EAAT4), LTD(mGluR1), and certain forms of intrinsic plasticity.

This problem of off-target effects is not substantially reduced by interfering with second messengers. For example, CaMKII inhibition has been a popular experimental strategy because CaMKII activity is necessary for LTP of AMPA receptors at many synapses. However, CaMKII is also required for certain forms of use-dependent modulation of intrinsic excitability (such as attenuation of SK-type Ca-sensitive K-current; Sourdet et al., 2003) as well as a postsynaptically expressed form of LTP at GABAergic synapses (Kano et al., 1996). Similar divergent signaling has been found for many other protein kinases, phosphatases, and phospholipases in neurons. It is important to stress that genetic techniques to target mutations to certain populations of neurons will not solve the off-target effect problem, as most individual neurons express multiple forms of plasticity, triggered by a limited number of signaling cascades. Ubiquitous plasticity makes it very difficult to ascribe particular behavioral phenotypes to disruption of a single form of use-dependent modulation.

Is ubiquitous plasticity a limitation for creating engrams in the brain? If every electrophysiological function of neurons is subject to long-term experience-dependent modulation, how can neural circuits balance the requirements for plasticity and stability? It is now appreciated that brains have systems for storing both memories of facts and events, declarative memory, and also nondeclarative memory which includes rules, procedures, habits, and reflex modulation. To some degree, the neural circuits for these two classes of memory are nonoverlapping. Nonetheless, both types of memory are subject to some similar design requirements. The storage capacity for both declarative and nondeclarative memories is very large. Furthermore, at least some memories must persist for the entire lifespan. Perhaps most importantly, memory storage is a dynamic process. Memory is most useful when it can be adaptively generalized. Memories for facts and events are triggered by sensory experiences that may be very different from those that were present when the memory trace was originally encoded. Nondeclarative memories must generalize to appropriately similar situations to those that laid down the memory trace. Perhaps, the known diversity of experience-driven plasticity can help us to construct models of memory that incorporate these dynamic properties.

A Taxonomy of Long-Term Use-Dependent Plasticity

Too much of a good thing… can be wonderful.
—Mae West

If a certain pattern of activity rapidly and persistently alters a certain electrical function of neurons, then we can

simply conclude that this plasticity is a candidate memory storage mechanism? Probably not. Not all experience-driven changes in electrophysiological function directly constitute the memory trace, what we call *mnemonic plasticity*. Other forms of plasticity, while they do not constitute the memory trace per se, may be permissive for memory storage within neuronal networks (*homeostatic plasticity*) or may support higher-order aspects of memory such as savings, blocking or generalization (*metaplasticity*).

Mnemonic Plasticity

The brain stores a large number of memory traces. There are ~5000-fold more synapses than neurons in the brain, so conventional LTP and LTD of fast glutamatergic synapses, which are mostly synapse-specific phenomena, have been attractive in formulating models of memory storage. In this scheme, memory is stored as an array of synaptic weights, encompassing both presynaptic and postsynaptic changes. This type of model is useful, but limited. It does not consider that "synaptic weight" is an insufficiently detailed parameter for capturing dendritic function. EPSPs at the synapse must be propagated to the spike initiation zone and so the ultimate *throughput* for a given synapse is a function of both synaptic properties and the intrinsic conductances that influence forward dendritic EPSP propagation and spike generation (see Marder et al., 1996, for a nice discussion of this and related points).

Crucially, if we are to imagine that memory is stored as an array of synaptic throughput values, then the engram itself must be encoded by local changes. These could include not only the well-known forms of fast glutamatergic LTP and LTD, but also other local plastic phenomena (Figure 4). For example, the local changes in dendritic voltage-sensitive ion channels reported by Frick et al. (2004) could alter the throughput of a subset of synapses in the dendritic array and thereby constitute a portion of the memory trace. Likewise, changes in distal inhibitory synapses could also produce local changes in the dendritic array and thereby constitute mnemonic plasticity.

However, changes that affect the throughput of the entire synaptic array have a highly reduced informational content. These changes are exemplified by plasticity of axosomatic voltage-sensitive ion channels or proximal shunting inhibitory synapses. These phenomena, while they can change the throughput function of the entire neuron, cannot alter the relative throughput values associated with individual synapses (Figure 4). As a consequence, these global plastic mechanisms are less likely to constitute mnemonic plasticity, but may have other roles.

Homeostatic Plasticity

To this point, we have discussed forms of plasticity, both synaptic and nonsynaptic, that are rapidly triggered (by patterns of activation lasting from tens of milliseconds to tens of seconds). In recent years, it has been appreciated that neurons also have forms of plasticity that integrate activity over a longer time scale (hours to days). These phenomena have been grouped together under the term *homeostatic plasticity* because they tend to boost or attenuate the average level of electrical activity to bring it back within a particular target range. It has been suggested that, without homeostatic plasticity, conventional LTP and LTD of glutamatergic synapses, by reinforcing the probability of their own induction, could drive synapses to their absolute maximum and minimum, respectively. In this situation, neural circuits become unusable and further information storage is precluded. Portions of these ideas were formulated in early theoretical works, particularly those that sought to explain the development of the primary visual cortex (Stent, 1973; von der Malsburg, 1973; Bienenstock et al., 1982). However, it was not until some years later that more detailed models of homeostatic plasticity appeared, which incorporated the growing descriptive literature on LTP/LTD at glutamatergic synapses (Bear, 1996; Turrigiano, 1999) together with clear electrophysiological evidence for homeostatic plasticity.

In neuronal cultures, chronic treatments that block spiking, like tetrodotoxin or antagonism of fast glutamatergic neurotransmission, result in a suite of slow compensatory changes that include delivery of synaptic AMPA receptors, an increase in the average size of synapses, an increase in the probability of neurotransmitter release, and changes in voltage-sensitive conductances that serve to lower the spike threshold and increase firing frequency. These changes typically take 1–4 days to develop. Chronic treatments that initially increase excitatory drive and spike firing (like blockade of $GABA_A$ receptors) generally produce the opposite changes in these same electrophysiological parameters, ultimately resulting in a downward correction of mean firing frequency (see Turrigiano, 1999; Abbott and Nelson, 2000; Desai, 2003, for review).

Homeostatic plasticity has been described as a process by which neuronal activity is integrated over a long period (hours to days) and compensatory changes in the electrical properties result to slowly restore a neuron to an optimal mean firing rate. However, it is also possible that homeostatic changes can be triggered by brief patterns of activity and then rapidly expressed. For example, if LTD of some excitatory glutamatergic synapses were accompanied by global increase in intrinsic excitability produced by modulation of axosomatic K channels, the latter might serve a homeostatic function by normalizing mean spiking rates. Likewise, if LTP of a group of excitatory synapses were accompanied by LTP of proximal GABAergic inhibitory synapses, this might also serve to normalize the mean spiking rate of the postsynaptic neuron. The central point here is that homeostatic plasticity (of either the slow or the fast integrating variety) can alter the mean firing rate of a postsynaptic neuron, but, by virtue of its spatial expression pattern and its multiplicative computation, does not change the relative throughput values for the synaptic array in the dendrites (Turrigiano, 1999). In this fashion, mnemonic plasticity, acts locally to set synaptic throughput and thereby constitute the memory trace per se, while homeostatic plasticity acts globally to modulate the throughput function of the entire array. Thus, homeostatic plasticity has the capacity to prevent the saturation of neuronal signaling (at either maximum or minimum values) in

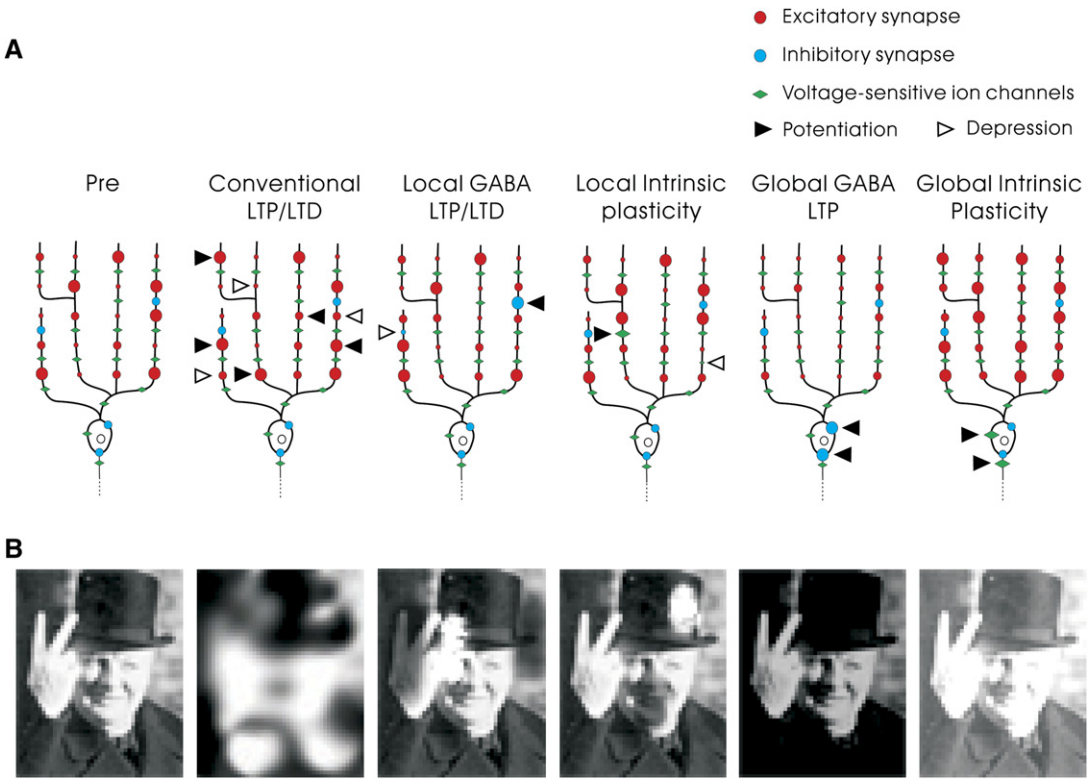

Figure 4. A Model of Memory Storage Incorporating Ubiquitous Electrophysiological Plasticity

(A) In this diagram of a generic principal neuron in the brain, excitatory synapses are indicated in red, inhibitory synapses in blue, and voltage-sensitive ion channels (considered as an aggregate of all voltage-sensitive conductances) are shown in green. Importantly, the size of each excitatory synapses does not indicate its "synaptic strength," but rather its "synaptic throughput," that is, the probability that its activation will trigger an action potential at the axon hillock. The throughput of an excitatory synapse is determined by several factors, including the strength of the excitatory synapse, the strength of inhibitory synaptic drive that is interposed between the excitatory synapse and the axon hillock, and the status of voltage-sensitive ion channels that will participate in actively propagating the EPSP through this same interposed region. The "Pre" neuron has a random array of synaptic throughput values assigned to its excitatory synapses. If conventional LTP and LTD are applied pseudorandomly across the excitatory synaptic array (this is done here by eyeball, not following any rule or simulation), then this will change the arrays throughput function in a manner that can store large amounts of new information. At distal GABAergic inhibitory synapses, local LTP (filled arrowhead) or LTD (hollow arrowhead), can produce local changes in the throughput function of adjacent excitatory synapses. These changes occur in intermediate-size dendritic domains that are neither strictly synapse specific nor cell wide. Likewise, local intrinsic plasticity that either promotes (filled arrowhead) or attenuates (open arrowhead) forward EPSP propagation, can produce intermediate-domain level changes in excitatory synapse throughput. However, when LTP of somatic GABAergic inhibitory synapses occurs, this will produce a global attenuation of throughput, impacting the entire dendritic array of excitatory synapses. Similarly, upregulation of voltage-sensitive ion channel function in the soma that promotes forward EPSP propagation will produce a global upregulation of excitatory synaptic throughput.

(B) As another way to express this same idea, we have taken an image of a well-known historical figure and imagined that the grayscale of each pixel corresponds to the throughput function of an excitatory synapse (black pixels are minimum and white pixels are maximum). In this way, the array of synaptic throughput functions, as read out by spiking at the axon hillock, can encode the image. The manipulations of each image are designed to illustrate the corresponding modes of long-term use-dependent plasticity and the local and global changes that can result. In this manner, LTP and LTD of glutamatergic synapses distributed across the dendrite gives rise to a fundamentally new distribution of relative throughput values across the synaptic array and thereby can store new information, yielding a major disruption in the image. Local GABA LTP/LTD and local intrinsic plasticity also change relative synaptic throughput values, but this is limited to a particular subsection of the array, resulting in a local disruption of the image (brighter and darker patches representing increased and decreased throughput, respectively) Finally, while global GABA LTP and global intrinsic plasticity change the overall range of synaptic throughput values, they maintain the relative weights of these values across the array.

a manner that retains the relative throughput values in the synaptic array and thereby preserves the informational content of the memory trace.

Metaplasticity

In addition to simple recall, there are a group of higher-order processes that allow memory to be adaptively generalized. One fine example is called "rule learning." This can be observed in an operant conditioning task in which thirsty rats are trained to discriminate between two odors for a water reward. Typically, rats require 6–7 days of training to learn to reliably discriminate between odor A and odor B. However, after learning the A/B discrimination, the same rats tested the next day will be able to learn to discriminate odor C from odor D in only 1–2 days (Saar and Barkai, 2003). This is a temporary effect: if an interval of 7 days is interposed between the two training series, then the rat will approach the second discrimination task (odors C and D) as if it had no prior experience (requiring

6–7 days to master it.) In this situation, the rat has temporarily learned something general from the training with odors A and B which can be applied to subsequent odor C and D discrimination trials.

What might be the neural substrate of temporary rule learning in the odor discrimination task? Barkai and coworkers have made recordings from layer 2 pyramidal cells in the piriform cortex (which receives olfactory information) and have found a transient increase in intrinsic excitability in trained but not pseudo-trained rats (see Saar and Barkai, 2003, for review). This change was manifest as a decrease in the afterhyperpolarization following postsynaptic spike bursts and a decrease in spike accommodation in response to a sustained somatic current injection. The time course of this intrinsic plasticity roughly followed that of rule learning: it was present 1–3 days but not 5–7 days after training. It has been suggested that this phenomenon has a cell-wide metaplastic effect: by increasing postsynaptic spiking in response to synaptic bursts, it could facilitate the induction of LTP and LTD of fast glutamatergic transmission, thereby underlying the rapid acquisition of new associations that constitutes rule learning.

Other forms of adaptive generalization can be found in classical conditioning tasks. When a rabbit (or mouse or human) receives a weak periorbital shock as an unconditioned stimulus, a reflexive eyeblink is elicited (this is called the unconditioned response). When a neutral conditioned stimulus, such as a tone, is presented, no eyeblink results. However, when tone and shock are repeatedly presented together, such that the tone is predictive of the shock, an association is made. Then, presentation of the tone-conditioned stimulus alone will reliably evoke an eyeblink, called the conditioned response. Following acquisition of associative eyeblink conditioning, without further training, the conditioned response will very slowly fade away over a period of weeks to months. However, if, following training, the tone conditioned stimulus is repeatedly presented alone, the animal rapidly learns that the tone is no longer predictive of the shock and will generally stop blinking in response to tones within ~80 trials (this is called extinction). If, in a subsequent training session, this animal is then trained by pairing shock with a new conditioned stimulus, like a light, it will fail to blink to the first light presentation. However, it will acquire reliable conditioned responses ~5-fold faster than if it had had no prior training. This rapid relearning to a new cue is called *conditioned stimulus generalization* and is a robust phenomenon that has been observed in a number of classical conditioning tasks, not just eyelid conditioning.

What are the requirements for plastic mechanisms that might underlie conditioned stimulus generalization? These alterations must not directly change the relative throughput values in the synaptic array that encodes the response to the new conditioned stimulus: recall that the animal fails to respond to the first presentation of the new conditioned stimulus. Like the case of rule learning in olfactory discrimination, metaplasticity is called for. Conditioned stimulus generalization requires metaplastic changes that alter the probability of subsequent local changes in the synaptic array throughput at those synapses that convey the new conditioned stimulus. Metaplastic changes could include increases in intrinsic excitability. However, other forms of plasticity are also potentially metaplastic.

In fact, one of the first examples of metaplasticity in the mammalian brain was an activity-dependent short-term attenuation of NMDA receptor function in hippocampal slices (Huang et al., 1992). Since NMDA receptor activation is required for induction of several forms of mnemonic plasticity, LTP and LTD of NMDA receptor function (or changes in receptor subunits or localization) are thereby candidate metaplastic phenomena (Abraham and Bear, 1996). Other potential metaplastic mechanisms include LTP(mGluR1) (Minami et al., 2003), which could increase the probability of subsequently inducing mGluR1-triggered forms of LTP and LTD of AMPA receptors.

While not directly applicable to conditioned stimulus generalization, it is worth noting that metaplasticity can work both positively and negatively. Recall that LTD(mGluR1) in cerebellar Purkinje cells can function to suppress subsequent mGluR1-dependent LTD of AMPA receptors. It is possible that LTP(EAAT4) (Shen and Linden, 2005) may serve a similar negative metaplastic function by restricting the diffusion of synaptically released glutamate to perisynaptic mGluR1. In these ways, neurons may limit the rapid overwriting of memory with new information (Abraham and Bear, 1996).

One interesting unresolved point concerns the duration of metaplasticity. Olfactory discrimination rule learning decays in days. While some memories must last for the life of the organism, it is likely that adaptive generalization of memory occurs on a shorter time scale. It will be useful to determine the time-course of those forms of plasticity which we propose to be metaplastic.

Coda

Recent work from a number of laboratories has significantly expanded the repertoire of long-term experience-driven plasticity available to neurons. There is reason to believe that there are still more forms of plasticity to be uncovered in neurons and perhaps in glial cells as well (Bellamy and Ogden, 2006; Ge et al., 2006). We propose that, while every *molecular species* involved in electrical signaling in the brain will not undergo plasticity, in time, every major *electrical function* of neurons will be shown to be plastic.

If every major electrical function of neurons is plastic, is the end result that the balance between stability and plasticity necessary for memory storage in neurons becomes impossible? Clearly, the brain accomplishes memory storage in the face of ubiquitous plasticity. This can be understood by constructing a taxonomy of plasticity in which rapidly triggered *local*, long-duration plastic changes, in either synaptic or intrinsic properties, constitute the engram itself (mnemonic plasticity). In addition, both slowly and rapidly triggered *global* plastic changes set the overall signaling range (homeostatic plasticity) and both slowly

and rapidly triggered changes determine the probability of subsequent mnemonic plasticity (metaplasticity). In this way, we suggest that ubiquitous plasticity is necessary to account for the rich phenomenon of memory as measured behaviorally.

ACKNOWLEDGMENTS

This study was supported by a grant of Korea Science & Engineering Foundation (R01-2006-000-10990-0) to S.J.K., and NIH MH51106 and MH07769 to D.J.L. D.J.L. is supported by the Develbiss Fund and a Silvio O. Conte Center Grant from the NIH. Thanks to Gareth Thomas, Jung Hoon Shin, Hiroshi Nishiyama, Wei Zhang, and Joo Min Park for helpful comments.

REFERENCES

Abbott, L.F., and Nelson, S.B. (2000). Synaptic plasticity: taming the beast. Nat. Neurosci. Suppl. *3*, 1178–1183.

Abraham, W.C., and Bear, M.F. (1996). Metaplasticity: the plasticity of synaptic plasticity. Trends Neurosci. *19*, 126–130.

Aizenman, C., Manis, P.B., and Linden, D.J. (1998). Polarity of long-term synaptic gain change is related to postsynaptic spike firing at a cerebellar inhibitory synapse. Neuron *21*, 827–835.

Anwyl, R. (1999). Metabotropic glutamate receptors: electrophysiological properties and role in plasticity. Brain Res. Brain Res. Rev. *29*, 83–120.

Bear, M.F. (1996). A synaptic basis for memory storage in the cerebral cortex. Proc. Natl. Acad. Sci. USA *93*, 13453–13459.

Beckstead, M.J., and Williams, J.T. (2007). Long-term depression of a dopamine IPSC. J. Neurosci. *27*, 2074–2080.

Beckstead, M.J., Grandy, M.K., Wickman, K., and Williams, J.T. (2004). Vesicular dopamine release elicits an inhibitory postsynaptic current in midbrain dopamine neurons. Neuron *42*, 939–946.

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

Bellamy, T.C., and Ogden, D. (2006). Long-term depression of neuron to glial signalling in rat cerebellar cortex. Eur. J. Neurosci. *23*, 581–586.

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

Brasnjo, G., and Otis, T.S. (2001). Neuronal glutamate transporters control activation of postsynaptic metabotropic glutamate receptors and influence cerebellar long-term depression. Neuron *31*, 607–616.

Brons, J.F., and Woody, C.D. (1980). Long-term changes in excitability of cortical neurons after Pavlovian conditioning and extinction. J. Neurophysiol. *44*, 605–615.

Chiamulera, C., Epping-Jordan, M.P., Zocchi, A., Marcon, C., Cottiny, C., Tacconi, S., Corsi, M., Orzi, F., and Conquet, F. (2001). Reinforcing and locomotor stimulant effects of cocaine are absent in mGluR5 null mutant mice. Nat. Neurosci. *4*, 873–874.

Desai, N.S. (2003). Homeostatic plasticity in the CNS: synaptic and intrinsic forms. J. Physiol. (Paris) *97*, 391–402.

Fan, Y., Fricker, D., Brager, D.H., Chen, X., Lu, H.C., Chitwood, R.A., and Johnston, D. (2005). Activity-dependent decrease of excitability in rat hippocampal neurons through increases in I(h). Nat. Neurosci. *8*, 1542–1551.

Frick, A., and Johnston, D. (2005). Plasticity of dendritic excitability. J. Neurobiol. *64*, 100–115.

Frick, A., Magee, J., and Johnston, D. (2004). LTP is accompanied by an enhanced local excitability of pyramidal neuron dendrites. Nat. Neurosci. *7*, 126–135.

Ge, W.P., Yang, X.J., Zhang, Z., Wang, H.K., Shen, W., Deng, Q.D., and Duan, S. (2006). Long-term potentiation of neuron-glia synapses mediated by Ca^{2+}-permeable AMPA receptors. Science *312*, 1533–1537.

Gaiarsa, J.L., Caillard, O., and Ben-Ari, Y. (2002). Long-term plasticity at GABAergic and glycinergic synapses: mechanisms and functional significance. Trends Neurosci. *25*, 564–570.

Holmgren, C.D., and Zilberter, Y. (2001). Coincident spiking activity induces long-term changes in inhibition of neocortical pyramidal cells. J. Neurosci. *21*, 8270–8277.

Huang, Y.Y., Colino, A., Selig, D.K., and Malenka, R.C. (1992). The influence of prior synaptic activity on the induction of long-term potentiation. Science *255*, 730–733.

Huang, Y.H., Dykes-Hoberg, M., Tanaka, K., Rothstein, J.D., and Bergles, D.E. (2004). Climbing fiber activation of EAAT4 transporters and kainate receptors in cerebellar Purkinje cells. J. Neurosci. *24*, 103–111.

Jin, Y., Kim, S.J., Kim, J., Worley, P.F., and Linden, D.J. (2007). Long-term depression of mGluR1 signaling. Neuron *55*, 277–287.

Kano, M., Rexhausen, U., Dreessen, J., and Konnerth, A. (1992). Synaptic excitation produces a long-lasting rebound potentiation of inhibitory synaptic signals in cerebellar Purkinje cells. Nature *356*, 601–604.

Kano, M., Kano, M., Fukunaga, K., and Konnerth, A. (1996). Ca^{2+}-induced rebound potentiation of gamma-aminobutyric acid-mediated currents requires activation of Ca^{2+}/calmodulin-dependent kinase II. Proc. Natl. Acad. Sci. USA *93*, 13351–13356.

Kirschstein, T., Bauer, M., Müller, M., Rüschenschmidt, C., Reitze, M., Becker, A.J., Schoch, S., and Beck, H. (2007). Loss of metabotropic glutamate receptor-dependent long-term depression via downregulation of mGluR5 after status epilepticus. J. Neurosci. *27*, 7696–7704.

Landisman, C.E., and Connors, B.W. (2005). Long-term modulation of electrical synapses in the mammalian thalamus. Science *310*, 1809–1813.

Lynch, G.S., Dunwiddie, T., and Gribkoff, V. (1977). Heterosynaptic depression: a postsynaptic correlate of long-term potentiation. Nature *266*, 737–739.

Maffei, A., Nataraj, K., Nelson, S.B., and Turrigiano, G.G. (2006). Potentiation of cortical inhibition by visual deprivation. Nature *443*, 81–84.

Marder, E., Abbott, L.F., Turrigiano, G.G., Liu, Z., and Golowasch, J. (1996). Memory from the dynamics of intrinsic membrane currents. Proc. Natl. Acad. Sci. USA *93*, 13481–13486.

Minami, I., Kengaku, M., Smitt, P.S., Shigemoto, R., and Hirano, T. (2003). Long-term potentiation of mGluR1 activity by depolarization-induced Homer1a in mouse cerebellar Purkinje neurons. Eur. J. Neurosci. *17*, 1023–1032.

Morishita, W., and Sastry, B.R. (1996). Postsynaptic mechanisms underlying long-term depression of GABAergic transmission in neurons of the deep cerebellar nuclei. J. Neurophysiol. *76*, 59–68.

Pereda, A.E., Rash, J.E., Nagy, J.I., and Bennett, M.V. (2004). Dynamics of electrical transmission at club endings on the Mauthner cells. Brain Res. Brain Res. Rev. *47*, 227–244.

Riedel, G., Platt, B., and Micheau, J. (2003). Glutamate receptor function in learning and memory. Behav. Brain Res. *140*, 1–47.

Saar, D., and Barkai, E. (2003). Long-term modifications in intrinsic neuronal properties and rule learning in rats. Eur. J. Neurosci. *17*, 2727–2733.

Shen, Y., and Linden, D.J. (2005). Long-term potentiation of neuronal glutamate transporters. Neuron *46*, 715–722.

Sourdet, V., Russier, M., Daoudal, G., Ankri, N., and Debanne, D. (2003). Long-term enhancement of neuronal excitability and temporal

fidelity mediated by metabotropic glutamate receptor subtype 5. J. Neurosci. *23*, 10238–10248.

Stent, G.S. (1973). A physiological mechanism for Hebb's postulate of learning. Proc. Natl. Acad. Sci. USA *70*, 997–1001.

Turrigiano, G.G. (1999). Homeostatic plasticity in neuronal networks: the more things change, the more they stay the same. Trends Neurosci. *22*, 221–227.

von der Malsburg, C. (1973). Self-organization of orientation sensitive cells in the striate cortex. Kybernetik *14*, 85–100.

Wadiche, J.I., and Jahr, C.E. (2001). Multivesicular release at climbing fiber-Purkinje cell synapses. Neuron *32*, 301–313.

Wong, R.K., Bianchi, R., Taylor, G.W., and Merlin, L.R. (1999). Role of metabotropic glutamate receptors in epilepsy. Adv. Neurol. *79*, 685–698.

Yang, X.D., Korn, H., and Faber, D.S. (1990). Long-term potentiation of electrotonic coupling at mixed synapses. Nature *348*, 542–545.

Zhang, W., and Linden, D.J. (2003). The other side of the engram: experience-dependent changes in neuronal intrinsic excitability. Nat. Rev. Neurosci. *4*, 885–900.