

Metaplasticity: A new frontier in the neural representation of memory

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Abstract

Synaptic plasticity, the modification of the strength of connections between neurons, is widely accepted to be essential for information storage in the brain and is thought to form the basis of learning and memory. However, in order for the richness of learning and memory to emerge from the long-term potentiation and depression of synapses, regulatory mechanisms must exist. Metaplasticity, the phenomenon of previous synaptic activity modulating the future synaptic plasticity of a neuron, might answer questions about how synaptic plasticity is regulated in order to create meaningful, coordinated changes in neural activity. There are many different proposed contributors to metaplasticity, including the NMDA and AMPA receptors, epigenetics, and neurotrophins. Although the way in which all these factors interact remains enigmatic, metaplasticity appears to play a role in learning, possibly by serving to control neuronal 'learning modes.'

Keywords: *metaplasticity, plasticity, memory, learning, long-term potentiation*

The seemingly simple question, “how is information stored in the nervous system?” has proven difficult to answer in the nearly five decades in which the biological basis of memory has been studied. Behavioural observation of learning and memory has been successful in characterizing many of the functional aspects of memory; short-term memory, long-term memory, and conditioning have all been well studied. However, due to technological constraints and the complexity of neural systems, knowledge of the neurobiological underpinnings behind learning and memory is severely lacking. Synaptic plasticity, the

ability of neural connections to change by strengthening or weakening, is revolutionary in its potential to provide a physiological explanation for learning, but its mechanisms have yet to be fully understood. How the complexity of learning and memory can arise from such simple changes is one of the most fascinating questions in neuroscience.

For the purposes of this review, synaptic plasticity is defined as long-term potentiation (LTP) and the complementary process of long-term depression (LTD) of connections between neurons. First discovered in rat hippocampal experiments in 1964, LTP is the process by which high

frequency electrical stimulus delivered to a bundle of axons results in increased sensitivity or 'potentiation' of those neurons to stimulation. Between two synapsed cells, this means that if one neuron repeatedly stimulates another, the first neuron can more easily excite the second neuron. This results in the strengthening of synaptic transmission between these two communicating neurons. Because this potentiation was observed to last for days (up to an entire year in one study), it was believed to be the primary process through which memory traces were encoded in neural structures (Abraham, 2002). This effect, which was first discovered by Bliss and Lomo in 1964, caused great excitement because it supported an important idea that had been circulating—that persistent changes in the strength of connections between neurons form the basis of learning and memory.

LTD is the reverse of LTP; wherein synapses are depressed and exhibit reduced sensitivity following long-term, low-frequency stimulation. Less extensively studied, LTD is believed to be critical in the ability of neural systems to refine their circuits for efficiency.

Although the brain's ability to learn, remember, and adapt to stimuli cannot be explained entirely in terms of synaptic plasticity, most memory research today is based on the assumption that plasticity is the foundation from which all these abilities arise. For a comprehensive review on the role of LTP and LTD in learning and memory see Lynch (2004).

This review will address the basic mechanisms of synaptic plasticity and describe metaplasticity, a recently discovered and exciting phenomenon which regulates and integrates synaptic plasticity over time. Metaplasticity is the process in

which high or low frequency stimulation affects the extent with which a neuron will undergo LTP or LTD in the future. Between two synapsed neurons, this could manifest as a greater frequency of stimulation required to induce LTP in a neuron that has already been potentiated. The specific mechanisms and functions of metaplasticity remain unclear, but it appears to be critical in maintaining synaptic memory traces and keeping synaptic plasticity occurring within a tight, dynamic range. If synaptic plasticity is the neural representation of firing history, then metaplasticity is the neural history of that plasticity.

Synaptic Plasticity: Potentiation and Depression

Neurons can form thousands of connections with neighbouring cells between specialized cell junctions called synapses. Neurons transmit information through action-potentials (APs), large waves of electrical activity that travel down the neuron's axon and stimulate the awaiting dendrites of that neuron's synaptic partners. Importantly, action potentials are all-or-none responses; once the threshold level of stimulation of the neuron is reached, the action potential will fire with the exact same intensity, regardless of the magnification of the triggering stimuli. This means that the frequency, not the intensity, of action potential firing becomes the primary way through which out-going signal strength is encoded in neural systems.

The synapse is the primary junction of information transfer. When an AP reaches the synapse of the transmitting or presynaptic neuron, neurotransmitters are released which stimulate much smaller electrical signals of variable strength in the receiving, or postsynaptic, neuron. Unlike APs, these postsynaptic potentials (PSPs) can

vary in strength depending on a number of factors, such as the number and sensitivity of postsynaptic neurotransmitter receptors. These PSPs then travel to the cell body and, much like how smaller waves in the ocean combine to form larger waves, summate into large membrane potentials which push the total membrane depolarization towards or away from the threshold at which an AP is created (Pinel, 2007). With hundreds of these incoming signals converging with different strengths and frequencies, there exists a staggering amount of computational power within each neuron.

Synaptic plasticity is simply the process by which the sensitivity of these synaptic connections alters according to their level of activity. “Those that fire together, wire together” is a common expression describing this process in which the synapses between neurons that often fire together are strengthened, such that it becomes easier for the presynaptic neuron to activate the postsynaptic neuron. This is accomplished by a change in synaptic efficacy, defined as the amplitude of the PSP generated upon activation by presynaptic firing. LTP strengthens PSPs and LTD weakens them. In this way, the brain is able to adapt to organize its firing and adapt to new patterns of stimulation.

How does LTP occur? When researchers first set out the answer this question, they hoped to pinpoint either presynaptic or postsynaptic changes as leading to changes in synaptic efficacy; however, it appears that both presynaptic and postsynaptic changes are involved. Because primarily postsynaptic changes appear to be involved in metaplasticity, only postsynaptic LTP mechanisms will be discussed here and readers interested in presynaptic mechanisms should consult Castillo (2012). In the synapse, the generation of PSPs

primarily occurs through the rapid flow of ions through ion-permeable, ionotropic receptors. At glutamate-based synapses in the hippocampus, which are known to be critical in learning and memory, there are two important types of ionotropic receptors: NMDA (N-methyl-D-aspartate) and AMPA (α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid). These receptors, though both responsive to glutamate, have several important functional differences. AMPA receptors (AMPA receptors), will always allow ion flow and cause local PSPs when glutamate binds to them, while NMDA receptors (NMDARs) possess a voltage-dependent magnesium gate and will only open when binding is coupled with a significant amount of postsynaptic depolarization (Pinel, 2007). The interplay of these two of receptors is crucial for many neuronal functions, including synaptic plasticity

During high-frequency stimulation, glutamate binding to AMPA receptors causes a large number of ions to enter the postsynaptic neuron, which initiates PSPs and opens NMDAR channels by depolarizing the postsynaptic environment. With their channels open, NMDARs are free to allow the influx of calcium ions into the synapse. Calcium (Ca^{2+}) influx leads to the phosphorylation of regulatory protein kinases, initiating both an early and a late-phase of LTP. First, in early-phase LTP, these protein kinases (e.g calcium-dependent protein kinase II (CaMKII)), increase the sensitivity of existing AMPARs and recruit new receptors to the synapse (Malenka & Bear, 2004). This almost immediate increase in both AMPAR density and sensitivity leads to a stronger postsynaptic response to the same presynaptic stimulus, effectively creating a memory trace within the neuron. In what is known as late-phase LTP, a

cascade of secondary messengers travel to the cell nucleus, initiating gene expression and protein synthesis, facilitating increased production of AMPAR proteins and other synaptic proteins (Lynch, 2004). Late-phase LTP often results in an increased postsynaptic surface area and a greater number of synaptic vesicles, which further amplifies the ability of the presynaptic neuron to excite the postsynaptic neuron (Desmond & Levy, 1988). Both early- and late-phase LTP are implicated in learning and memory by enhancing retention of a task for the first few minutes after it is learned while also making arrangements for the persistent retention of that learning.

Long-term depression, the weakening of synaptic efficacy following prolonged low-frequency stimulation, has not been studied as extensively as LTP, but its basic mechanics appear similar. During low-frequency stimulation, there is a relatively low degree of postsynaptic depolarization and thus a much smaller amount of NMDAR activation and Ca^{2+} influx. Interestingly, rather than simply leading to a reduced degree of LTP, low levels of Ca^{2+} appear to have the opposite effect entirely. While high levels of Ca^{2+} phosphorylate regulatory kinases, low Ca^{2+} levels promote their dephosphorylation. This leads to a decrease in synaptic efficacy via AMPAR

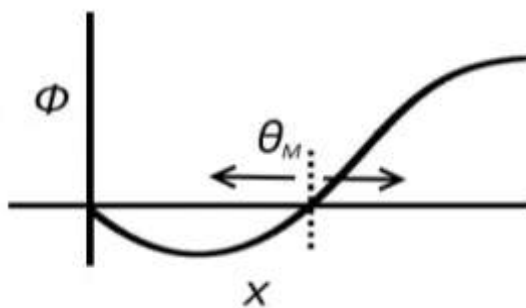


Figure 1. The BCM model function depicting postsynaptic activity (X), change in postsynaptic efficacy (Φ), and plasticity threshold (θ_M).

desensitization and removal (Malenka & Bear, 2004). The selective weakening of synapses through LTD is believed to be important for the constructive use of LTP. Indeed, if synapses continued to increase in strength, they would ultimately reach a ceiling level of synaptic efficacy which would prevent the encoding of new information. It is important to note that the complete picture of these mechanisms, including the involvement of other supplementary mechanisms, is much more complex than described here and despite being an area of active research, is beyond the scope of this article. For further detail on LTD mechanisms, readers should consult Collingridge (2010).

The BCM Theory: Thresholds of Plasticity

In order to describe how metaplasticity affects the induction of synaptic plasticity, it is appropriate to first address the BCM theory of plasticity thresholds. During synaptic firing, increases in postsynaptic Ca^{2+} cause changes in synaptic efficacy: but if Ca^{2+} is the stimulus for both LTP and LTD, then what determines whether LTP or LTD will be induced? Because the effect of Ca^{2+} is concentration-dependent, there seems to be a threshold concentration that determines whether potentiation, depression, or no change in synaptic efficacy will occur. The Bienenstock-Cooper-Munro (BCM) model best characterizes this threshold.

The BCM model (see figure 1) describes a relationship between postsynaptic response (x -axis on figure) and change in postsynaptic strength (Φ) with two key features. First, a threshold exists (θ_M) above which the synapse will be strengthened (LTP), and below which it will be weakened (LTD). Second, this threshold is not static, but shifts in response to the average

frequency of presynaptic stimulation (Bienenstock, Cooper, & Munro, 1982). In this way, an increase in sensitivity following LTP induction will not cause even more LTP in a cycle of positive feedback and lead to excitotoxicity (cellular toxicity involving overactivation of glutamate receptors), and a loss of meaningful input from the synapse. A sliding threshold allows synaptic plasticity to function as a synaptic 'novelty detector', with the threshold being equal to the average level of activity so that LTP and LTD are only induced during significant bursts of in stimulation frequency.

The BCM model was constructed based on observation and mathematical analysis of synaptic plasticity with little explanation for physical mechanisms. However, following the discovery of metaplasticity, it has become clear that synaptic plasticity regulation is not as simple as the BCM model proposes.

Metaplasticity: Making Plasticity Make Sense

In an early experiment on LTP, researchers were surprised to find that increasing the permeability of NMDARs to Ca^{2+} paradoxically seemed to prevent LTP induction (Coan, Irving, & Collingridge, 1989). This conflicted with what was known about LTP at the time; NMDAR activation leads to LTP so it was expected that greater NMDAR permeability, and thus greater Ca^{2+} influx, would strengthen LTP. These researchers correctly concluded that NMDAR activation could somehow have an inhibitory effect on LTP despite its central role in LTP induction, but were unable to specify how. Research by Huang et al. in 1992 clarified this effect when they demonstrated that induction of LTP by a strong stimulus could be inhibited if a weak stimulus had been previously delivered to

the same pathway (Huang, Colino, Selig, & Malenka, 1992). This effect lasted for upwards of thirty minutes, was dependent on NMDAR activation, and seemed to represent a shift in the BCM plasticity threshold since the inhibition could be overcome eventually by increasing the intensity of stimulation. These experiments were the first to demonstrate that 'priming' stimuli, whether it induces LTP or not, can cause covert changes in the synapse which will affect subsequent plasticity responses. This effect was dubbed "metaplasticity" because of its higher-order nature and was met with much excitement because of its implications for a mechanism of synaptic plasticity control similar to what had been proposed by the BCM theory.

Metaplasticity is often defined as "the plasticity of synaptic plasticity." In other words, synaptic plasticity itself is plastic (capable of change), and metaplasticity is its modulation by a cell's prior history of activity. Metaplastic changes are subtle yet enduring, and allow synaptic events at a single point in time to regulate synaptic processing minutes, hours, or even days later. For example, if a synapse has just undergone LTP, the same stimulus delivered only minutes later will fail to elicit the same degree of potentiation, and may even cause depression. Importantly, metaplasticity can be monosynaptic, effective at one synapse only, or heterosynaptic, effecting neighbouring synapses as well (Abraham, 2008).

Functionally, metaplasticity allows neurons to integrate plasticity-relevant signals over time, encouraging gradual and meaningful neural change. Furthermore, metaplasticity maintains plasticity within a dynamic range and prevents destructive feedback cycles that may lead to either excessive or insufficient activation. The

higher-order, 'meta', nature of this effect is exciting not only because of its importance to organized functioning of plasticity, but also because it suggests that neurons retain a trace of their own activity.

Mechanisms of Metaplasticity

NMDAR: LTP Inhibition. Much like synaptic plasticity itself, metaplasticity can either have potentiating or depressing effects. As described by the BCM model, a decrease in successive LTP (a shift of the threshold θ_M to the right, Figure 1) appears to be based on NMDA activity, and lasts from 30-90 minutes (Huang et al., 1992). There have been two proposed mechanisms for how NMDAR activation may lead to an increase in the plasticity threshold. One theory was based on the observation that NMDARs themselves will occasionally become desensitized after stimulation due to nitric oxide feedback mechanisms (Sobczyk & Svoboda, 2007). It was proposed that this decrease in NMDAR sensitivity leads to a reduced postsynaptic Ca^{2+} response and thus inhibits LTP (Murphy & Bliss, 1999). As attractive as this hypothesis is, metaplastic LTP inhibition has been shown to occur independently of this NMDAR-specific desensitization (Moody, Carlisle, & O'Dell, 1999). Although it may be important in NMDAR function, this pathway cannot be directly mediating NMDAR-dependent metaplasticity.

The most promising explanation for NMDAR-dependent metaplasticity is the long-term alteration of the regulatory enzyme CaMKII by previous synaptic 'priming' (Bear, 1995). Manipulation of CaMKII phosphorylation sites has been shown to replicate the effect of NMDAR priming and increases the amount of postsynaptic activity needed to induce LTP without any prior high-frequency stimulation

(Zhang et al., 2005). This is plausible since CaMKII is crucial in both early- and late-phase LTP; however, it is unclear whether the activation of CaMKII during metaplasticity is involved or conflicts with its transient phosphorylation during LTP induction. Recent electrostatic imaging studies have revealed that CaMKII is an impressively complex enzyme possessing two sets of six binding domains, so it is quite possible that it may be activated at multiple sites independently (Craddock, Tuszynski, & Hameroff, 2012). This is a fascinating area for further research, not only to clarify CaMKII's involvement in metaplasticity, but also because these multiple binding domains may be another site of information storage in the nervous system.

mGluR: LTP Facilitation. The idea that metaplasticity facilitates LTP is exciting. Might there be some way our neurons can direct themselves to learn faster and more efficiently?

Certain types of priming stimulation have indeed been shown to enhance LTP, though the mechanisms by which this occurs appear to be more mysterious and complex than LTP inhibition. The lowering of the LTP threshold, decreasing the amount of stimulation needed in order to elicit LTP response, appears not to be based on NMDARs but on an entirely different type of receptor, the metabotropic glutamate receptor.

In addition to fast-acting ionotropic receptors, there also exists a different class of receptors that are slower acting, with profoundly different structure and effects. These receptors, known as metabotropic or G-protein coupled receptors, do not open ion channels in response to neurotransmitter binding but instead activate secondary messenger proteins on

the inside of the postsynaptic membrane. These secondary messengers can then effect long-term changes within the cell, such as influencing gene expression and protein translation (Simon, 2007).

Metabotropic glutamate receptors (mGluRs) appear alongside NMDA and AMPA receptors in the postsynaptic membrane and are involved in LTP facilitation (Cohen & Abraham, 1996). The activation of mGluRs has been shown to both facilitate the induction of LTP and lengthen its persistence (Bortolotto, Bashir, Davies, & Collingridge, 1994; Bortolotto et al., 1995). This enhancing effect can last up to an hour and appears to be related to the down-regulating effect that mGluR activation has on the After-Hyperpolarization Period (AHP): the length of time neurons take to return to their resting potential after firing. A decrease in the AHP could lead to an increase in whole-cell neuronal excitability and an increase in postsynaptic depolarization due to back-propagation of action potentials from the cell body (Saar, Grossman, & Barkai, 1998). Additionally, mGluR activity may also enhance LTP by trafficking AMPARs to the synaptic membrane, preparing them for involvement in subsequent plasticity events (Oh, Derkach, Guire, & Soderling, 2006). Despite these promising findings, the involvement of mGluRs in metaplastic events has proven difficult to completely describe. For instance, mGluR activation appears to have an inhibitory effect on LTP in the dentate gyrus, and it is unknown how this effect could be reconciled with their usual role in enhancing LTP (Gisabella, Rowan, & Anwyl, 2003).

Epigenetics. In addition to synaptic receptor activity, there are a number of other factors that can effect long-term modulatory

changes on synaptic plasticity. For instance, environmentally induced changes in gene expression (epigenetics) have been shown to be associated with increased LTP during learning tasks. Histone acetylation is an epigenetic process by which certain stretches of DNA are made more accessible to transcription proteins, leading to the increased production of the proteins encoded therein. High levels of histone acetylation have been found in relevant brain regions during learning tasks in rats, and experimental manipulation of this acetylation was shown to affect plasticity thresholds (Levenson et al., 2004). This not only implicates epigenetics as yet another possible mechanism of metaplasticity, but also suggests that a learning event in one synapse could promote LTP to other synapses throughout the neuron. By increasing the availability of proteins involved in late-phase LTP, epigenetics could provide a fertile environment for LTP to occur and thereby enhance learning.

BDNF. The protein known as Brain-Derived-Neurotrophic-Factor (BDNF) has recently been suggested to be involved in metaplasticity, although it is uncertain whether it can effect metaplastic changes its own, or whether it is simply a necessary factor in LTP induction. BDNF's primary role in the brain is developmental: it is involved in the promotion of neural cell survival, differentiation, and the establishment and maintenance of newly formed synapses (Huang & Reichardt, 2001). Because of its stimulatory effect on most neuronal processes, it is not surprising that artificial introduction of BDNF can induce LTP (Ying et al., 2002). However, research has revealed that BDNF may also alter the plasticity threshold in conjunction with PKM ζ , another critical protein for LTP induction (Sajikumar

& Korte, 2011). Furthermore, BDNF appears to be upregulated during certain learning tasks (Naimark et al., 2007). BDNF's role in synaptic plasticity is far from being completely understood and the persistence of its effect on LTP induction has yet to be demonstrated. Metaplasticity entails a temporal component where synaptic events at one point in time affect later synaptic plasticity; this property has yet to be demonstrated with BDNF, though its presence does appear to amplify LTP. Nevertheless, it does provide a promising avenue of research and serves to illustrate just how many different factors are involved in regulating synaptic plasticity.

Metaplasticity and Learning

Metaplasticity is critical for maintaining synaptic plasticity within a dynamic range, but could it have a more direct role in learning? Research on the link between metaplasticity and learning is still in its infancy, yet what has been found is exciting and seems to implicate metaplasticity in both the facilitation and inhibition of learning. For example, it is well known that stress can impair learning, and now research has demonstrated that NMDAR-related metaplasticity triggered by stressful events may be the reason why (Sacchetti et al., 2002). Metaplasticity may also increase neural plasticity during learning periods, leading to more efficient learning. An exciting study demonstrated that during olfactory-discrimination training in mice, the AHP period of pyramidal neurons in the hippocampus was significantly decreased, suggesting the presence of mGluR-mediated metaplastic LTP facilitation. Importantly, this effect was present during the learning period but disappeared once the learning rule had been acquired, and was even correlated with enhanced ability to learn a

different task in which the same neurons were involved. This suggests that mGluR-mediated metaplasticity may act as a 'learning switch', providing an improved cellular environment for learning to occur (Zelcer et al., 2006). Similar learning-related reductions in AHP have also been observed in reflexive eye-blink conditioning and water maze tasks (Lebel, Grossman, & Barkai, 2001; Moyer, Thompson, & Disterhoft, 1996).

Within the limited body of behavioural research on metaplasticity, an important observation has arisen which calls into question the accuracy of the BCM model and previous conceptions about synaptic plasticity regulation. The presence of multiple mechanisms of metaplasticity (NMDARs, mGluRs), often leads to a failure of a single sliding threshold model to predict or explain changes in synaptic plasticity. For example, when decreases in the AHP are observed, there is almost always a simultaneous reduction in LTP as well. This suggests that NMDAR-mediated LTP inhibition may occur in dynamic balance with mGluR sensitization and illustrates an important point: these processes are by no means exclusive. With multiple metaplastic processes occurring simultaneously, it is challenging to develop a single model of metaplasticity that is accurate in all situations. At this point, there is no unifying explanation for how these different mechanisms work together. They may be cooperating, competing, or involved in some complex memory encoding process we have yet to discover. Explaining the interactions between discrete metaplastic mechanisms is a critical question — how do all these pieces of the puzzle fit together?

Conclusion

Metaplasticity, the modulation of synaptic plasticity based on previous firing history, is critical for the emergence of learning and memory. Like memory itself, metaplasticity appears to be composed of many different complex processes working together. NMDAR-mediated metaplasticity inhibits future LTP through CaMKII phosphorylation while mGluR-mediated metaplasticity facilitates LTP via AHP downregulation. Histone acetylation enhances LTP by increasing transcription of synaptic proteins and BDNF may play a role in metaplasticity as well. Together, these processes allow neurons to maintain synaptic plasticity within a dynamic range. There is also mounting evidence that metaplasticity is involved directly in learning processes through up-regulation of neural plasticity in task-relevant neurons and that a dynamic balance between mechanisms may exist in order to regulate these 'learning modes'. Further research on metaplasticity could elaborate on this involvement in learning, leading to new discoveries about how we learn and providing knowledge to fill the considerable gap between psychological and neurobiological understanding of memory.

Although the stated goal of this review was to dissect metaplasticity into a simple, unified, understandable phenomenon, it is clear that metaplasticity cannot be reduced to a single process. NMDARs, mGluRs, neurotrophins, epigenetics – all these factors are involved and inter-related in ways we do not yet understand, forming a very complex phenomenon which is only superficially cohesive. These phenomena are not neat, orderly, or amenable to a unified label. Instead, they constitute a complex adaptation to endow organisms with the flexibility to adapt in a chaotic and unplanned world.

Declaration of Conflicting Interests

The author declared they have no conflicts of interests with respect to their authorship or the publication of this article.

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