History Matters: Illuminating Metaplasticity in the Developing Brain

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DOI 10.1016/j.neuron.2009.10.012

Metaplasticity refers to an activity-dependent regulation of the plastic state of neurons. In this issue of *Neuron*, Dunfield and Haas demonstrate that in intact developing brain circuits, specific patterns of visual stimulation drive functional plasticity of individual neurons with variable outcomes, predisposed by time-averaged postsynaptic activity recent to visual training.

Activity-dependent synaptic plasticity, including long-term potentiation (LTP) and long-term depression (LTD), has been implicated as important cellular mechanisms underlying learning and memory, as well as activity-dependent development of neural circuits. The plastic state of neurons, i.e., the capability to generate plastic changes and the level of changes that can be expressed, can be affected by prior patterns of pre- and postsynaptic activity. This activity-dependent modification of subsequent synaptic plasticity has been termed "metaplasticity" (Abraham and Bear, 1996), which refers to plasticity at a higher level, or the plasticity of synaptic plasticity. The best-known examples of metaplasticity are those where prior activity that induces LTP inhibits further induction of LTP and facilitates the induction of LTD by subsequent stimuli (Barrionuevo et al., 1980; Staubli and Lynch, 1990). Priming activity that does not result in changes in synaptic efficacy can also induce metaplasticity (Huang et al., 1992; Christie and Abraham, 1992). A prominent theoretical model that directly relates to metaplasticity is the Bienenstock, Cooper, and Munro (BCM) model, which was designed to account for the plasticity of visual cortical synapses during development (Bienenstock et al., 1982). This model has two main features (Figure 1). First, synaptic modification varies as a nonlinear function of postsynaptic activity, such that low levels of afferent activity (above the resting level) lead to LTD of the active synapses, while higher levels of afferent activity result in LTP. Second, the point of crossover from LTD to LTP is termed the modification threshold, θ_M, which is not fixed but varies according to a time-average of prior postsynaptic activity. A critical component of the BCM model is that high levels of postsynaptic activity increase the LTP threshold for subsequent induction of plasticity, while low levels of prior activity lower the threshold. Such a "sliding" modification threshold can prevent saturation of synaptic potentiation, and conversely a downward spiral of LTD to zero strength, keeping synapses functioning within a useful dynamic range.

Experimental results from the hippocampus and visual cortex have supported the BCM theory. For example, compared to control rats, in the visual cortex of light-deprived rats, LTP is enhanced and LTD is diminished (Kirkwood et al., 1996). Most of these previous studies have been carried out in adult animals or in brain slices of young animals with drastically altered visual experience. However, it remains unclear whether metaplasticity regulates synaptic plasticity during normal brain development in vivo. In this issue of *Neuron*, Dunfield and Haas (2009) set out to address this issue by taking advantage of a simple in vivo model for studying developmental plasticity, the retinotectal system of *Xenopus* tadpoles. In this system, electrically induced LTP and LTD can be established by conventional electrophysiological methods (Zhang et al., 1998; Tao et al., 2001). These synaptic modifications are similar to those induced in the hippocampus and visual cortex. Natural visual stimuli can also induce synaptic modifications similarly to electrical induction (Zhang et al., 2000; Engert et al., 2002; Zhou et al., 2003). Dunfield and Haas (2009) take a functional imaging approach to probing neuronal plasticity. They load tectal neurons of intact, awake tadpoles with membrane permeable Ca^{2+} dyes and simultaneously image Ca^{2+} responses of hundreds of neurons before and after inducing plasticity with natural visual stimuli. Ca^{2+} events caused by both endogenous brain activity and visual stimulus probing are recorded. The level of postsynaptic activity is quantified by both the frequency and amplitude of Ca^{2+} events, since the amplitude of Ca^{2+} transients scales with the number of action potentials fired in a burst, and the frequency reflects slow firing rates. A limitation of this imaging method is that it does not distinguish the origin of plasticity, since changes of both synaptic strength and intrinsic excitability of neurons can result in changes of Ca^{2+} responses. In addition, small changes in synaptic strength may not be detectable. Nevertheless, Ca^{2+} imaging is currently the best noninvasive in vivo approach to probing functional plasticity.

To induce functional plasticity, the authors use a training paradigm containing repeated trains of high-frequency OFF visual stimuli (spaced training). Spaced induction has been shown to be able to overcome the reversal of synaptic modifications by spontaneous activity under in vivo condition, leading to more stabilized synaptic modifications (Zhou et al., 2003). The authors find that spaced training induces a long-lasting potentiation of mean population OFF responses, as evidenced by the significantly increased amplitude of the ensemble average Ca^{2+} transients post training. In contrast to the spaced training, the invariant training paradigm, during which

light with constant intensity is applied to the immobilized eye, induces a long lasting depression of the ensemble OFF responses. Since retinal ganglion cells (RGCs) usually do not respond robustly to steady states of uniform illumination, invariant training results in much weaker tectal cell activity than spaced training. Thus, the plasticity outcomes of ensemble responses appear to be in accordance with the BCM model: low levels of postsynaptic activity (caused by low levels of presynaptic activity) depress synapses (and/or excitability), while high levels of postsynaptic activity lead to synaptic strengthening.

Ca^{2+} imaging allows for probing of activity at single-cell resolution. When individual cells are examined, the authors find that plasticity outcomes are in fact highly variable. In response to spaced training, neurons can exhibit long-lasting potentiation, short-term potentiation, no change, or even long-lasting depression. Neurons that have undergone long- or short-lasting potentiation constitute the largest portion of the cell population, so that the mean response exhibits LTP. Plasticity of individual neurons in response to invariant training is similarly variable, except that the majority of cells undergo LTD. Therefore, the same training paradigm produces various types and amounts of plasticity across the tectal circuit, with specific patterns of stimulation driving the majority of neurons toward potentiation or depression. Intriguingly, while OFF responses exhibit variable plasticity outcomes after training with OFF stimuli, the ON responses are largely unchanged. In addition, the amplitude of OFF response plasticity appears to be correlated with the level of OFF dominance in the neuron's receptive field property. These results suggest that training-induced plasticity is specific to the characteristics of training stimuli and receptive field types of neurons.

How can one explain the variable plasticity outcomes in individual cells? The authors hypothesize that the activity history prior to visual training may affect the plasticity outcome. According to the BCM model, high levels of prior activity increase the modification threshold, making it easier for neurons to undergo LTD. Conversely, low levels of prior activity make neurons prone to undergo LTP. The authors thus measure spontaneous Ca^{2+} events (visually evoked events are excluded) during the pretraining period. Indeed, they find that for spaced training, there is a strong correlation between the level of prior activity and the type of plasticity induced. While the frequencies of pretraining spontaneous Ca^{2+} transients are similar among plasticity groups, the amplitudes do indeed differ. Neurons having undergone LTD display significantly larger amplitudes of average pre-training Ca^{2+} transients than those exhibiting other plasticity types, while neurons that exhibit LTP display the smallest amplitudes of pretraining Ca^{2+} transients. A plausible explanation for these results is that the retinotectal synapses of neurons with high levels of prior activity may undergo short-term depression more easily during high-frequency stimulation, resulting in net low levels of postsynaptic activity during spaced training, which lead to LTD. Conversely, synapses of neurons with low levels of prior activity may undergo facilitation during spaced training, resulting in high activity levels and LTP. If this is the case, there will be a negative correlation between the activity level in the pretraining period and during the training. However, such correlation is not observed by the authors, indicating that it is the activity history that predisposes expression of training-induced plasticity.

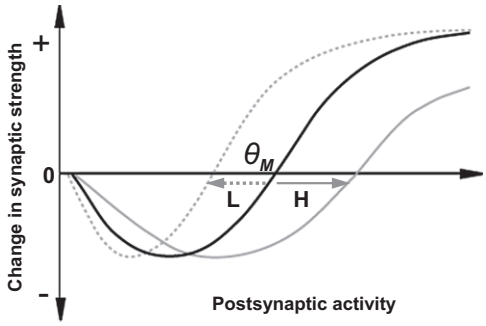

Figure 1. BCM Model for Activity-Driven Synaptic Plasticity

The change in synaptic strength depends on the level of postsynaptic activity during plasticity inducing stimulation. "+" indicates potentiation and "−" indicates depression. θ_M is the crossover point from depression to potentiation. High levels of prior activity (H) shift θ_M rightward, while low levels of prior activity (L) shift θ_M leftward. (Adapted by permission from Macmillan Publishers Ltd: Nature Rev. Neurosci. Abraham, 2008, copyright 2008.)

To further demonstrate the metaplastic control of functional plasticity, the authors carry out an elegant experiment to manipulate the level of pretraining activity. They apply a type of white-noise stimulation for 1 hr prior to spaced training, which enhances firing activity of tectal neurons but is insufficient to induce plasticity by itself. Increasing pretraining activity by white-noise stimulation indeed shifts spaced training-induced plasticity outcomes toward LTD, as can be predicted by BCM metaplasticity.

What signaling mechanisms underlie the metaplastic control of functional plasticity? Previous studies have suggested that activation of N-methyl-D-aspartate (NMDA) receptors can elevate the threshold for LTP (Huang et al., 1992). Notably, activation of NMDA receptors itself is required for the induction of many forms of synaptic plasticity. The authors examine the involvement of NMDA receptors in metaplasticity by injecting a NMDA receptor blocker, APV, into the tectum of tadpoles at the beginning of white-noise stimulation. They demonstrate earlier that injections of APV just before the spaced training can block the induction of functional LTP and largely reduce the level of functional LTD, consistent with previous studies of synaptic plasticity in the same system (Zhang et al., 1998, 2000; Tao et al., 2001; Zhou et al., 2003). The presence of APV in the tectal circuit during white-noise stimulation impairs the metaplastic effect. Compared to white-noise stimulation without APV, there are many more neurons exhibiting LTP and much fewer neurons exhibiting LTD after spaced training. Interestingly, LTP is not severely affected upon injection of APV during white-noise stimulation. This may be explained by the potential washout of APV during the 1 hr pretraining period. These results pinpoint NMDA receptors as an important signaling component for experience-dependent metaplasticity.

The demonstration of metaplastic control of functional plasticity in the intact developing circuits by Dunfield and Haas (2009) leads to many important questions. The form of metaplasticity demonstrated may be a mechanism for the neuron to

continuously adjust its plasticity threshold according to its recent global activity level, keeping the overall level of synaptic drive within a range that allows expression of plasticity. In this sense, the metaplasticity ought to be a transient, cell-wise mechanism. For how long does the neuron need to integrate its firing activity in order to determine its future plasticity threshold? How long does metaplasticity induced by a bout of prior activity persist? How does activation of NMDA receptors lead to a change in plasticity threshold? By altering the function or trafficking of NMDA receptors themselves, or the functional state of kinases and phosphatases central to plasticity processes (Abraham, 2008)? Or membrane voltage-dependent conductances are altered so that the voltage threshold for plasticity is affected? Future experiments will help elucidate the mechanisms underlying metaplasticity.

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A Stretch from the Periphery Helps Brain Clocks Feel the Daily Heat

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DOI 10.1016/j.neuron.2009.10.013

In this issue of *Neuron*, Sehadova et al. show that synchronization of circadian clocks in the brains of *Drosophila* by daily temperature changes requires chordotonal organs, mechanosensory structures that function as stretch receptors in insects. This is strikingly different from the more direct path by which brain clocks perceive light.

Circadian (≅24 hr) pacemaker neurons situated in the brain are usually considered the central clocks in animals as they drive what is undoubtedly the behavioral rhythm at the top of the hierarchy in the temporal organization of an animal's life, namely its daily wake-sleep cycle. Light-dark cycles resulting from the Earth's rotation on its axis are likely the main environmental cue in nature that synchronizes (entrains) most, if not all, circadian clocks to local time. However, diurnal changes in temperature are also potent synchronizers of circadian rhythms in many life forms, from bacteria to plants and animals (Rensing and Ruoff, 2002). Strong progress has been made toward understanding the cellular and molecular bases for circadian photoentrainment in diverse model organisms, but how clocks are synchronized by daily temperature cycles is much less clear. Using *Drosophila melanogaster* as a model system, Sehadova et al. (2009) report in this issue of *Neuron* that the way a brain clock "sees the light" and "feels the heat" can exhibit some remarkable differences. While light is thought to directly penetrate through the head into the fly brain, where it stimulates photoreceptors expressed in clock cells, the authors show that chordotonal organs in the periphery, specialized structures involved in insect sensory mechanotransduction (Kernan, 2007), are required to transduce daily temperature cues to brain clocks. Thus, mechanoreceptor neurons in insects not only function in such fundamental senses as hearing and proprioception (Kernan, 2007) but might also regulate the *timing* of behavioral programs by working as thermal sensors.

A role for temperature in modulating circadian systems would seem especially relevant in poikilothermic organisms like *Drosophila*. Indeed, flies exposed to daily temperature cycles (e.g., 12 hr at 16°C followed by 12 hr at 25°C) manifest one main activity component during the warm