Modeling enhanced and impaired learning with enhanced plasticity

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The widely held belief that synaptic plasticity mediates learning suggests the tantalizing possibility that we might enhance learning by enhancing plasticity. However, many experiments involving animals with genetically enhanced LTP or LTD reveal conflicting results; some show that enhanced plasticity actually impairs learning, while others show it enhances learning. Theoretical principles allowing us to reconcile such conflicting data remain elusive.

We developed a mouse in which parallel-fiber Purkinje cell synapse LTD is enhanced by genetically knocking out the Class-I major histocompatibility molecules H2-D^b and H2-K^b. We then tested these knockout (KO) mice in a gain-up vestibular oculomotor reflex (VOR) learning task. Interestingly, we found such enhanced LTD mice showed *impaired* gain up learning. However, when such KO mice were first pre-trained using a gain down learning task, they subsequently showed *enhanced* gain up learning. However, this *same* pre-training in WT in contrast impaired subsequent gain up learning. These results indicate that whether learning is impaired or enhanced depends upon a complex interplay between plasticity rates and prior experience.

Using computational analysis, we uncovered principles of synaptic plasticity that can account for this complex learning dynamics. Importantly, we found that widely used classical models of synaptic plasticity in which LTP/LTD simply increases/decreases a scalar synaptic efficacy, are unable to account for behavior. Instead, we required more complex, metaplastic synaptic models with multiple internal states, allowing the propensity for LTP/LTD to depend upon the prior history of LTP/LTD events. In particular, we found that a form of synaptic stubbornness in which repeated LTD biases the synapse towards internal states from which further LTD or LTP becomes more difficult, could naturally account for both impaired and enhanced learning phenotypes in WT and KO.

More generally, our modeling provides a theoretical framework for resolving conflicting experimental results relating perturbations of synaptic plasticity to learning.