Week 11 (April 15 & 20) Plasticity and Learning

Rick Born (rborn[at]hms.harvard.edu)

As a well-studied example of the relationship between molecular mechanisms of synaptic plasticity and learning, we will study the cerebellum and motor learning. In particular, we will examine the role of cerebellar LTD in the ability of animals to adjust the gain of their vestibulo-ocular reflex. Wednesday's lecture will begin with a broad overview on eye movements followed by a more detailed description of the vestibulo-ocular reflex (VOR). Finally, I will introduce a particular form of cerebellum-dependent learning in which the *gain* of the VOR can be adjusted to adapt to changes in environmental conditions. This will lead us to the development of a general paradigm for thinking about the uses of *feedback*, both to adjust behavior "on line" as well as to induce synaptic plasticity that leads to longer term adaptive changes in the *feedforward* circuitry.

For a general overview on cerebellar learning, please read:

Raymond, J. L., S. G. Lisberger and M. D. Mauk (1996) The Cerebellum: A neuronal learning machine? *Science* **272**:1126-1131.

On Monday we will discuss the following paper:

De Zeeuw, C. I., C. Hansel, F. Bian, S. K. Koekkoek, A. M. van Alphen, D. J. Linden, and J. Oberdick (1998) Expression of a protein kinase C inhibitor in Purkinje cells blocks cerebellar LTD and adaptation of the vestibulo-ocular reflex. *Neuron* **20**:495-508.

The written assignment concerns only the De Zeeuw paper, and you should write a REFEREE's report. Keep in mind that a "critique" is not necessarily only negative—both weaknesses and particular strengths should be discussed.

I chose this paper because it is a particularly heroic example of using molecular techniques to address a specific hypothesis about the mechanism of learning in a simple circuit. It is a real attempt at a "soup-to-nuts" programme in which a particular intracellular signaling pathway is tied to a specific mechanism of synaptic plasticity, which is, in turn, tied to a specific form of learning. It brings out both the promises of such an approach and the pitfalls. In writing your critiques, you might want to consider the following issues/questions (without feeling compelled to address each and every one):

1. Limitations in the temporal and spatial specificity of the molecular manipulation. What have the authors done to improve upon previous efforts? What might be done to improve still more?

2. Relationship between *in vitro* cellular analysis and *in vivo* cellular function. How was the defect in LTD documented? What complexities might exist between an early perturbation in a cellular mechanism and its ultimate function in the adult circuit? What other experiments would you want to do to convince yourself that the behavioral result is due to a *specific* defect in LTD?

3. Relationship between the preparation in which the molecular manipulations are performed (mouse) and the preparation in which the circuit has been most studied (monkey). In the current paper, how "normal" does the behavior of the controls look? Might there be interspecies differences in the particular sites and mechanisms of plasticity? (Of course, but are there precedents?) How would you address this potential set of problems?