Is oppositely directed motor learning implemented with inverse plasticity mechanisms?

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Most models of the cerebellar contribution to motor learning have focused on a single plasticity mechanism, long-term depression (LTD) at parallel fiber-Purkinje cell synapses ("parallel fiber LTD"). However, carefully calibrated motion requires bi-directional adjustment of the amplitude of learned movements, to match the circumstances of the body and the environment. Such bi-directional adjustment would be straightforward to implement in a model with an additional plasticity mechanism that could invert parallel fiber LTD. Thus we consider an alternative model, with both LTD and LTP at the parallel fiber synapse.

These two models make different predictions about what would happen during reversal of prior learning. If parallel fiber LTD mediated both increases and decreases in the amplitude of a given movement, new learning could only mask the effects of old learning, as learning caused more and more synapses to undergo LTD. On the other hand, having both LTD and LTP at a synapse could allow new learning to erase the effects of old learning, which could allow more flexible use of synapses in storing memories.

To distinguish between these two models for cerebellum-dependent motor learning, we studied motor memory reversal in a simple behavior, the vestibulo-ocular reflex (VOR). The gain of the VOR can be adaptively increased or decreased with appropriate training paradigms, which we refer to as gain-up and gain-down respectively. To test whether erasure or masking occurred during reversal of learning in the VOR, we concatenated gain-up and gain-down stimuli in sequence. We found a striking asymmetry in the reversibility of these opposite behavioral changes. Increases in VOR gain could be rapidly reversed by gain-down stimuli, whereas decreases in VOR gain were not readily reversed by gain-up stimuli. These results are not consistent with increases and decreases in VOR gain both being mediated by the same plasticity mechanism, since their reversal properties were different. The asymmetry suggests that increases and decreases in VOR gain are mediated by different plasticity mechanisms, which reverse each other with unequal efficacy (Boyden and Raymond, 2003).

Asymmetric reversibility of the different plasticity mechanisms could arise in several ways. One specific model is that parallel fiber LTD may contribute to storage of increases in VOR gain, whereas parallel fiber LTP may contribute to decreases in VOR gain. In this model, asymmetry could result from the known properties of the plasticity mechanisms at the parallel fiber to Purkinje cell synapse.

One prediction of this model is that increases and decreases in VOR gain would be differentially affected by manipulations that affect parallel fiber LTD or LTP. We are now beginning to test this model with experiments on mice lacking a molecule important for the late phase of parallel fiber LTD, Ca^{+2}/Calmodulin-dependent-kinase IV (CaMKIV). Acquisition of motor learning is normal for both increases and decreases in VOR gain in the CaMKIV knockout. However, these mice have impaired retention of increases, but not decreases, in VOR gain (Boyden et al., 2003). Therefore, long-term memory for an increase in gain is dependent upon a CaMKIV-dependent process, whereas long-term memory for a decrease in gain is not. These results are consistent with the model suggested by the experiments on reversal of learning, and suggest that models of cerebellum-dependent motor learning should be revised to consider the role of bidirectional plasticity, in particular at the parallel fiber-Purkinje cell synapses.

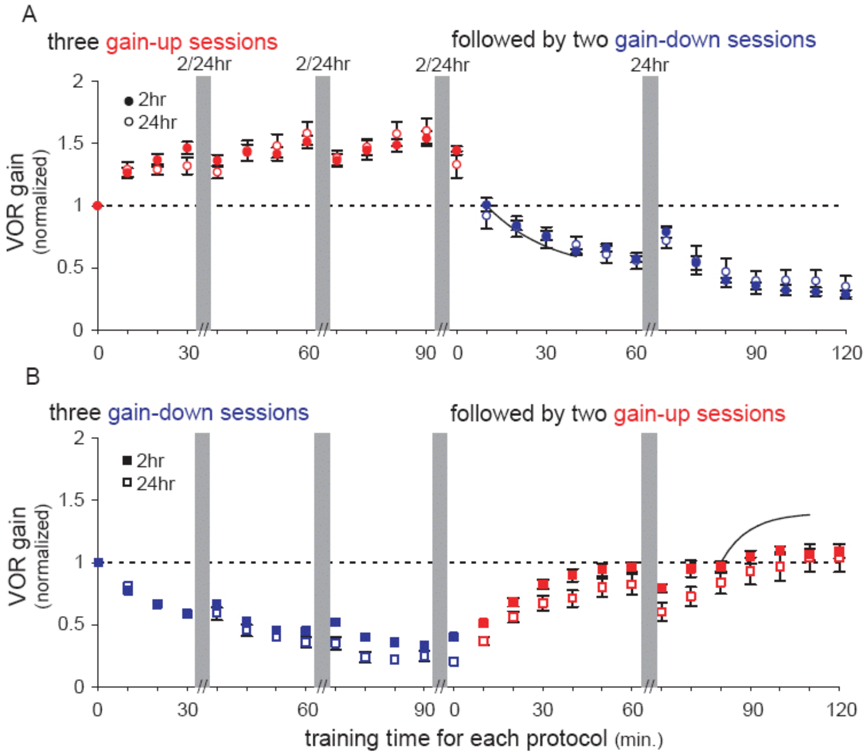

Figure 1. Changes in VOR gain induced when gain-up and gain-down training sessions are concatenated.
(A) Mice were trained with three 30-minute gain-up training sessions (red symbols), followed by two 1-hour gain-down training sessions (blue symbols). Between training sessions, there were either 2-hour (filled circles) or 24-hour (open circles) rest periods in darkness, indicated by shaded bars. The x-axis time is reset to zero when the gain-down protocol begins. The solid curve starting at the 10-minute point in gain-down training is the exponential fit to gain-down training from the naïve state, for comparison to the timecourses shown here. During reversal, the decrease in VOR gain parallels that seen in naïve mice, consistent with complete reversal of changes induced by prior gain-up training.
(B) Mice were trained with three 30-minute gain-down training sessions (blue symbols), followed by two 1-hour gain-up training sessions (red symbols). The solid curve beginning at the 80-minute point in gain-up training is the exponential fit to gain-up training from the naïve state. Even after VOR gain is restored to normal, the mice are not capable of learning normally in response to the gain-up stimulus. Thus the changes induced by the initial gain-down training were not fully reversed.

References

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