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Presentation Abstract

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Title: Adaptive timing is impaired in mice deficient in presynaptic LTP

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Authors: ***S.-L. SHIN**¹, E. S. BOYDEN², A. KATOH¹, G. Q. ZHAO¹, J. L. RAYMOND¹;
¹Stanford Univ., Stanford, CA; ²MIT, Cambridge, MA

Abstract: A candidate mechanism for cerebellum-dependent learning is plasticity of the synapses from cerebellar parallel fibers onto Purkinje cells. Many previous studies have assessed the role of postsynaptic LTD at these synapses. Here, we evaluate the role of presynaptic LTP. Mice deficient in RIM1 α , a Rab3 interacting molecule, have impaired presynaptic LTP at the parallel fiber-Purkinje cell synapses (Castillo et al, 2002). We characterized a simple form of cerebellum-dependent motor learning in RIM1 α knockout mice. The vestibulo-ocular reflex (VOR) undergoes learned changes in gain (amplitude) and/or phase (timing) in response to the appropriate visual-vestibular training. RIM1 α knockout mice were selectively impaired in the ability to modify the phase of the VOR through motor learning, with no significant impairment in the ability to modify the gain of the VOR. Additional experiments localized the requirement for RIM1 function for normal VOR phase learning to the cerebellar granule cells, the source of the parallel fibers. A line of mice with RIM1 function selectively disrupted in the granule cells was generated by crossing a conditional knockout of RIM1 α and RIM1 β (Kaiser et al., 2008) with mice expressing Cre recombinase under the control of the GABA_A receptor $\alpha 6$ subunit promoter (Fünfschilling & Reichardt, 2002). Like the global RIM1 α knockouts, the granule cell-specific RIM1 knockouts were impaired on VOR phase lead learning and phase lag learning, with sparing of VOR gain learning. Preliminary recordings from Purkinje cells in RIM1 knockout mice revealed a lower average firing rate and more variability in neighboring interspike intervals, as measured by CV₂, compared to wild-type mice, with no difference in the overall variability of interspike intervals, as measured by the CV. These results suggest that the alteration of synaptic dynamics by

presynaptic LTP supports the adaptive regulation of movement dynamics and shapes the temporal patterns of Purkinje cell spiking.

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