Inhibitory circuit plasticity and homeostasis in sensory cortex

Dan Feldman, PhD, Prof.
Dept. of Molecular & Cell Biology, Helen Wills Neuroscience Institute
University of California, Berkeley

Inhibitory circuits in sensory cortex exhibit robust plasticity in response to changes in sensory experience, but the mechanisms and functional roles of such plasticity are only beginning to be understood. In somatosensory cortex, feedforward inhibition through PV interneuron circuits rapidly weakens during whisker deprivation, altering excitation-inhibition (E-I) ratio in a manner that stabilizes synaptic potentials in feedforward circuits. This plasticity appears to act as a rapid homeostat to stabilize cortical activity in response to transient changes in sensory drive. We have recently identified some of the molecular and cellular mechanisms for this plasticity in PV interneurons. Reduced inhibition and elevated E-I ratio are also implicated in autism, where they are proposed to drive circuit hyperexcitability and excess spiking which may underlie sensory and cognitive phenotypes. However, while feedforward inhibition is reduced and E-I ratio is increased in several well-validated mouse models of autism ($Fmr1^{-/y}$, $Cntnap2^{-/-}$, $16p11.2^{del/+}$, and $Tsc2^{+/}$), synaptic depolarization and whisker-evoked spiking remain surprisingly normal under standard sensory physiology conditions. This suggests that E-I ratio changes in these autism models represent a homeostatic, compensatory response to circuit perturbation, rather than a source of hyperexcitability. Current experiments indicate that while homeostasis successfully normalizes cortical activity under sparse sensory conditions, it fails in dense sensory conditions, leading to a degradation in the neural code. Thus, some forms of autism may reflect insufficient homeostasis under noisy or complex environmental conditions.