All-optical interrogation of neural circuits

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Neural circuits display complex spatiotemporal patterns of activity on the millisecond timescale during behavior. Understanding how these activity patterns drive behavior is a fundamental problem in neuroscience, and remains a major challenge due to the complexity of their spatiotemporal dynamics. The ability to simultaneously image and manipulate patterns of activity in neural circuits at cellular resolution would open up new frontiers in neuroscience. I will describe a strategy for "all-optical" interrogation of neural circuits in vivo with single-spike and single-neuron precision. Two-photon calcium imaging is combined with two-photon optogenetic activation using coexpression of a red-shifted opsin and a genetically encoded calcium indicator. A spatial light modulator allows tens of user-selected neurons to be targeted for spatiotemporally precise optogenetic activation, while simultaneous fast calcium imaging provides high-resolution network-wide readout of the manipulation with negligible optical cross-talk. Proof-of-principle experiments in mouse barrel cortex and visual cortex demonstrate interrogation of the same neuronal population during different behavioral states and targeting of neuronal ensembles based on their functional signature. This approach extends the optogenetic toolkit beyond the specificity obtained with genetic or viral approaches, enabling high-throughput, flexible and long-term optical interrogation of functionally defined neural circuits in vivo.