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Brainwide optical circuit interrogation guided by online analysis of neuronal function

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Understanding the brain requires measuring and perturbing neuronal activity. Tools for this are typically applied locally, but behavior is generated by the coordinated activity of neurons widely distributed across the brain. Thus, ideally we want to measure activity patterns of all neurons in the brain during behavior, use this information to decide which neurons to perturb, and record the brainwide effects of the perturbation.

We introduce an experimental and computational system that enables such experiments at the brainwide scale. In behaving larval zebrafish, we measure neuronal activity in the entire brain during behavior using light-sheet imaging. Concurrently, through fast distributed computational analysis, we generate whole-brain functional maps relating neuronal activity to stimuli/behavior. Any subset of neurons can be selected from the maps and then optically ablated with a two-photon laser. The resulting changes in whole-brain activity and behavior are subsequently analyzed, all in the same animal.

We apply this method to brainwide neuronal responses during visually-evoked swimming and find that a widely distributed set of nuclei mediate the behavior. Deleting specific functional neuron types from any of these nuclei has profound effects on brainwide responses consistent with a distributed implementation of the sensorimotor transformation.

We extend the method to cellular-resolution targeted optogenetic activation during whole-brain imaging. These methods allow for concurrent whole-brain activity and causality mapping in the same animal, which will enable delineating the contributions of neurons to brainwide circuit dynamics and behavior.

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