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Holographic control of brain signaling

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The optogenetics revolution began with the discovery of microbial opsins and their sensitivity to light (1971-on) and continued with the demonstration of their utility and function in neuronal cells (2005-on). Light-induced conformational changes in opsins allow direct transduction of photonic energy into electrical currents, thereby activating or inhibiting neuronal signals in a non-invasive manner.
So far most of the optogenetics experiments have used relatively simple illumination methods, where visible light is delivered non- specifically to large brain regions and genetic targeting strategies are used to 'isolate' a specific cell type (and therefore a specific neural circuit) and measure the effects produced to be able to correlate them to the type of cells activated. This approach has enabled brain function to be mapped with unprecedented anatomical and cell type specificity and, to cite a few examples, to identify the neurons linked to memory and learning, as well as to identify the neurons governing behaviour parental or involved in addiction or depression.
However, wide-field illumination can only synchronously activate entire populations of neurons, thereby controlling them as a whole –a highly unnaturalistic state, given that neurons fire in very complex patterns and sequences as they compute. Indeed, if one examines the activity of a neuronal circuit under physiological conditions, this is characterized in most cases by the fact that even genetically identical cells can have completely independent patterns of activity: each cell in the circuit has its own spatiotemporal signature. Mimicking and manipulating neuronal activity with this degree of precision therefore requires the development of new optical methods capable of illuminating one or more cells independently in space and time.
We have solved this challenge by sculpting the illumination light with computer generated holography, temporal focusing and two-photon excitation and have shown that this combination of approaches that we termed circuits optogenetics enables to selectively activate specific neuronal ensembles with single cell resolution and sub millisecond temporal precision, an arguably key step towards the methodological foundation of computational neuroscience.
Here, we will review the most recent configurations that we developed for circuits optogenetics and we will show examples where we have used these approaches for the investigation of visual circuits in head restraint and freely moving mice.

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