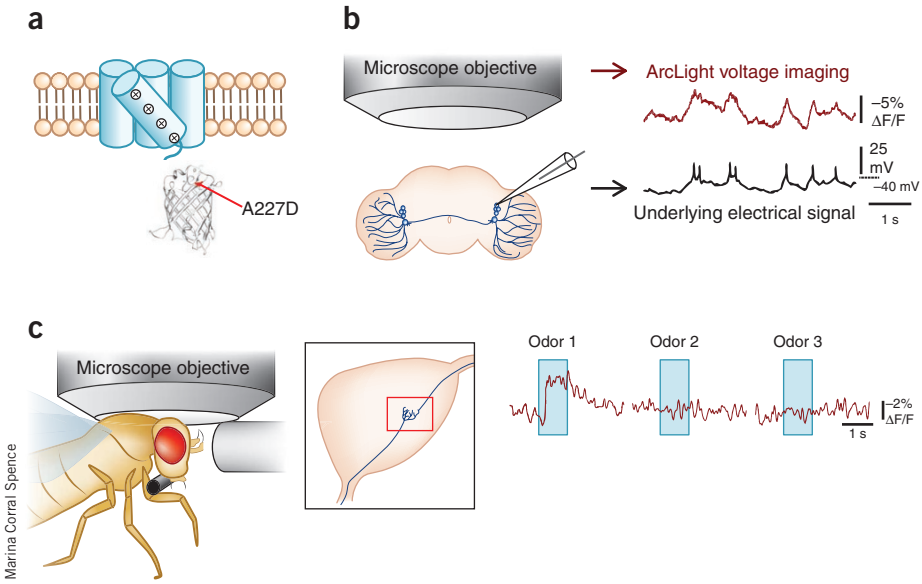

Figure 1 Cao *et al.*[1] demonstrate genetically targeted, single-trial voltage imaging in the intact brain of *Drosophila in vivo*. (**a**) Schematic diagram of the ArcLight molecule embedded in the plasma membrane of a neuron. The molecule reports changes in membrane voltage as changes in the fluorescence (ΔF/F). Signals from ArcLight are several-fold larger in amplitude than previous voltage sensor proteins thanks to a key mutation (A227D) in the ecliptic pHlourin. (**b**) The imaged fluorescence from ArcLight (top) reliably follows changes in membrane voltage of single, circadian clock neurons, as confirmed by simultaneous whole-cell recordings performed with a standard electrode in whole-brain explants (bottom) of *Drosophila*. The ArcLight signal (red) closely tracks the underlying electrical signal (black), including action potentials, with tens-of-milliseconds temporal resolution. (**c**) Demonstrating the key milestone of single-trial, *in vivo* voltage imaging, the authors imaged neurons and neurites in the living *Drosophila* (left panel), including imaging presynaptic terminals of genetically tagged olfactory sensory neurons within the antennal lobe (middle panel, in this case targeting sensory neurons expressing Or56a), which showed sharply tuned electrical activity to specific odors, including geosmin, methyl hexanoate and 3-octanol, respectively (different odors are labeled as odors 1–3 in the right panel).

matched previous data generated by electrode recordings. These sharply tuned responses to one or a few odors contrasted with the broadly tuned responses to many odors observed when ArcLight was expressed in all olfactory sensory neurons, suggesting that signals recorded from the location of one neuron were a summation of responses from nearby neurons of varying cell type. Moreover, restricting ArcLight expression to specific cell types produced signals that appeared to contain higher frequency information—that is, the signals were less smooth and more granular. This observation suggests a cleaner recording from the neuron of interest, without the temporal smoothing expected from contamination between neural signals in multiple adjacent cells. Thus, by targeting specific cell types in the *Drosophila* brain, the authors revealed cell type–specific voltage activity with minimal contamination even when imaging by wide-field microscopy.

As this example shows, the appropriate application of ArcLight can lead to new biological insight. Cao *et al.*[1] revealed odor-elicited, pre- and postsynaptic membrane activity between genetically defined olfactory sensory neurons and projection neurons in glomeruli of the antennal lobe *in vivo*. They also detected daily rhythmic activity in secretory terminals of lateral ventral circadian clock neurons (LN_vs), which are not accessible by traditional electrophysiology, indicating the first direct evidence for greater electrical activity in neuropeptide pigment dispersing factor PDF-secreting terminals in the morning than in the evening. Furthermore, they demonstrated with low-resolution (not single-cell) imaging that brain regions containing LN_v somata and distal terminals of small LN_vs have substantial synchrony within the ipsilateral hemisphere of the brain but show very little synchrony with the contralateral hemisphere.

Looking toward future developments in ArcLight technology, important milestones may include single-trial utility, high signal and good signal-to-noise ratios for two-photon microscopy. These capabilities would greatly expand the repertoire of possible experiments and model organisms for *in vivo* imaging. It would also be desirable to improve the temporal dynamics so that ArcLight could follow fast electrical events on a hundreds-of-microseconds timescale, beyond the tens-of-milliseconds timescale of the current probe[2], while maintaining sensitivity, as has been achieved with voltage-sensitive dyes[11].

COMPETING FINANCIAL INTERESTS
The authors declare no competing financial interests.

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