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Title: Toward noninvasive imaging of neural activity with acoustic reporter genes

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Abstract: Imaging technologies enabling noninvasive observation of specific neural signals represent a “holy grail” of tools for neuroscience. While widely used neuroimaging approaches based on fluorescent reporter genes and biosensors have enabled major neuroscience discoveries, they fall far short of providing whole-brain recordings of neural activity due to the limited tissue penetration of light. In contrast, ultrasound-based imaging techniques overcome this limitation and enable imaging of deep brain regions with high spatiotemporal resolution. To connect ultrasound to specific neural signals, we take advantage of gas vesicles (GVs), microbially derived gas-filled protein nanostructures, which our group introduced as the first genetically encodable acoustic reporters. Building on these advances, we are developing two approaches to visualize neural activity deep inside the brain. Our first technique is based on the transcriptional induction of immediate early genes (IEGs) by neural activity. We show that we can capture different levels of activity in model cell lines by linking GV expression to IEG transcriptional events and quantifying activation-evoked ultrasound signal. Our second technique is based on the development of GVs that produce enhanced ultrasound contrast upon calcium binding, which we demonstrate by imaging intracellular calcium dynamics in model cell lines. Both approaches are facilitated by a modular viral delivery platform that efficiently integrates acoustic reporter genes into mammalian cells and tissues. These results illustrate the feasibility and potential of noninvasive imaging of neural activity with acoustic reporter genes.