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Review Article

The need for calcium imaging in nonhuman primates: New motor neuroscience and brain-machine interfaces

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ABSTRACT

A central goal of neuroscience is to understand how populations of neurons coordinate and cooperate in order to give rise to perception, cognition, and action. Nonhuman primates (NHPs) are an attractive model with which to understand these mechanisms in humans, primarily due to the strong homology of their brains and the cognitively sophisticated behaviors they can be trained to perform. Using electrode recordings, the activity of one to a few hundred individual neurons may be measured electrically, which has enabled many scientific findings and the development of brain-machine interfaces. Despite these successes, electrophysiology samples sparsely from neural populations and provides little information about the genetic identity and spatial micro-organization of recorded neurons. These limitations have spurred the development of all-optical methods for neural circuit interrogation. Fluorescent calcium signals serve as a reporter of neuronal responses, and when combined with post-mortem optical clearing techniques such as CLARITY, provide dense recordings of neuronal populations, spatially organized and annotated with genetic and anatomical information. Here, we advocate that this methodology, which has been of tremendous utility in smaller animal models, can and should be developed for use with NHPs. We review here several of the key opportunities and challenges for calcium-based optical imaging in NHPs. We focus on motor neuroscience and brain-machine interface design as representative domains of opportunity within the larger field of NHP neuroscience.

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1. Introduction

Neuroscientists seek to understand the function and dysfunction of the nervous system, with an eye towards ultimately comprehending and supporting the health of the human brain. In order to understand how a system like the brain operates one must measure its internal workings, much like understanding a computer requires measuring voltages and currents throughout its circuitry. For decades, a dominant approach to measuring these signals has been extracellular electrophysiology. Using sharp electrodes inserted into the brain, neuroscientists can record the spiking activity of one or many individual neurons involved in perception, cognition, and action. Decades of discoveries and fundamental insights into brain function have resulted from studying the brain using these types of electrical measurement techniques.

Traditional electrophysiology captures the spiking activity of a sparse sample of neurons, allowing the responses of individual neurons to be measured and of neural populations to be collectively visualized and modeled. However, these models remain at a level of abstraction agnostic to the microstructural details of neural circuits. These limitations of electrophysiology have motivated the development of an array of impressive technological advances that have enabled fluorescent labeling and all-optical recording and manipulation of targeted cell types in awake behaving animals. Whereas electrical measurements accurately capture neuronal spiking, optical methods can provide a complementary view of neural activity that is substantially richer in many ways, contextualizing patterns of neural activity within a genetically annotated, spatially localized, dense map linking circuit structure with function (Deisseroth and Schnitzer, 2013; Peron et al., 2015; Emiliani et al., 2015). These tools have already transformed the study of neural circuits in small animal models, including worms, zebrafish, flies, and rodents, and promise to open new avenues of research to probe a variety of neuropathologies in nonhuman primate models of

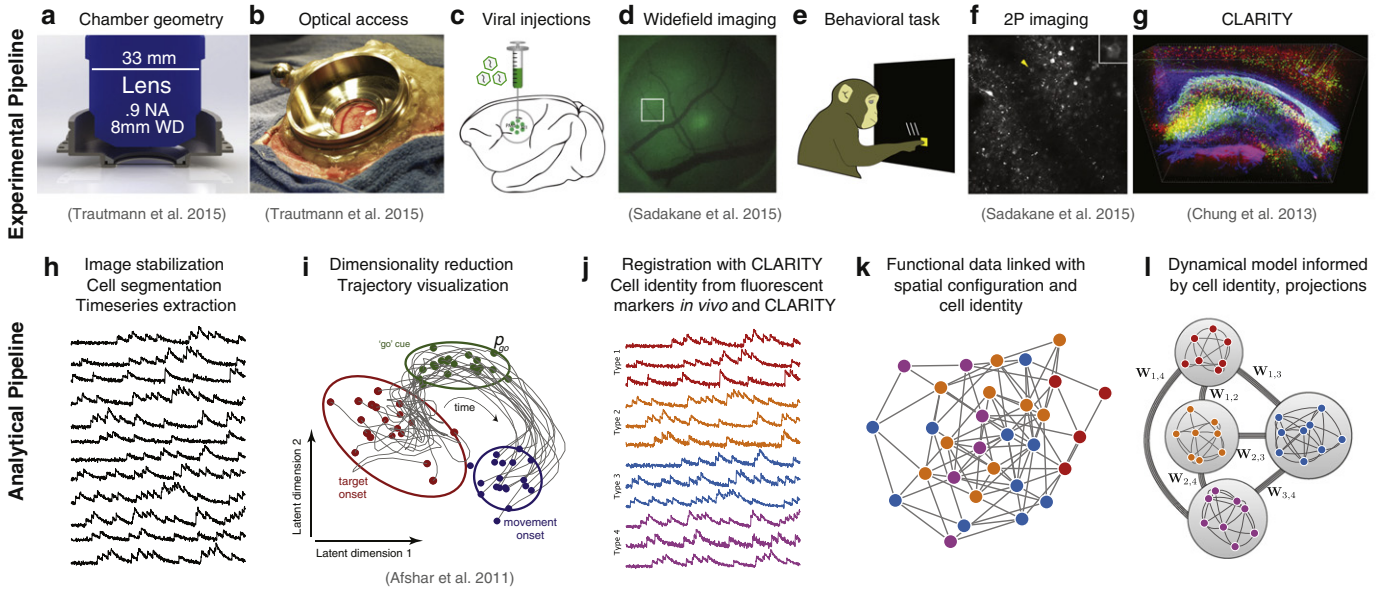

Fig. 1. Experimental and analytical pipelines for employing calcium-imaging and CLARITY for primate systems neuroscience. (a) Schematic of cross-section with high-NA multiphoton-optimized objective lens. (b) Optical chamber implanted over motor cortex. Adapted from Trautmann et al. (2015). (c) Viral constructs will be injected into cortex to deliver the calcium reporter gene and other fluorescent markers. (d) Widefield epifluorescence microscopy can be used to monitor expression and to record macro-scale functional activity. Adapted from Sadakane et al. (2015). (e) The monkey will be trained to perform a behavioral task, during which (f) two-photon microscopy can be performed through the artificial dural window. Adapted from Sadakane et al. (2015). (g) Post-mortem CLARITY can be performed on brain tissue and spinal cord to localize expression and provide more detailed information about the neurons and circuits recorded via immuno-staining. (h) Calcium imaging data can then be analyzed to extract the functional activity of each neuron as a function of time. (i) These traces can be visualized as neural state trajectories using dimensionality reduction techniques. Adapted from Afshar et al. (2011). (j) Individual cells can be registered to fluorescent markers imaged using two-photon *in vivo* or collected post hoc via CLARITY facilitating the annotation of the functional traces with cell type and projection information. (k) Spatial relationships between cells can also be used to embed models of the population activity within their 2D or 3D topography, e.g. by building a graphical model with functional (not synaptic) connectivity. (l) Combined functional, spatial, projection, and genetic information can be used to build models of the population dynamics in which cell types and circuit projections can serve distinct computational roles.