Table S3. Activity Readouts for Functional Neural Circuit Analysis

Selected techniques currently available for achieving brain activity readouts and covering a broad range of capabilities are summarized. Three main categories are listed: electrophysiological, optical, and immediate early gene (IEG)-based. We also list fMRI as an important method for achieving whole-brain activity readouts, especially given compatibility with small mammals and optogenetics. For recent discussion of other activity readouts available for use in humans, beyond the scope of this review, see Poldrack and Farah (2015).

	Method	Species Compatibility	Compatibility with Awake Behavior	Major Applications/ Advantages	Major Caveats	References
Electrophysiological Readouts	Whole-cell in slice	primarily mice, rats	not compatible	• Experimenter control over ion concentrations • Easily controlled pharmacological manipulation • Intracellular access • Single cell resolution	• No behavioral context • Full circuits and circuit dynamics may not be preserved in slice	Walz et al., 2002 (Neuromethods textbook)
	Whole-cell in vivo	widely compatible	compatible	• Intracellular access in an intact circuit • Intracellular access during behavior • Single cell resolution	• Low throughput, technically demanding approach • Not currently compatible with behavior over days	Lee et al., 2006 Kitamura et al., 2008 ("shadow patching" of unlabeled cells) Kodandaramaiah et al., 2012 (automation) Munoz et al., 2014 (channelrhodopsin-assisted cell targeting)
	Extracellular in vivo	widely compatible	compatible	• Well-established method for monitoring neuronal activity during free behavior • Excellent temporal resolution • Multi- or single-unit recordings • Action potential collision tests can be used to establish projection targets	• Cell type identification (e.g. using juxtacellular labeling) is low throughput • Biased towards isolating active cells	Chorev et al., 2009 (review) Lipski et al., 1981 (collision testing)
	Extracellular in vivo with optotagging	mice	compatible	• Combines a well-established method for monitoring neuronal activity with a potentially higher throughput method of cell type identification	• Although cell type identification is higher throughput than juxtacellular labeling, it can be difficult to definitively ID cells. Arbitrary cutoffs are often employed.	Lima et al., 2009 Cardin et al., 2010
Optical Readouts	Voltage imaging	flies, mice	not yet tested	• An optical readout of neuronal activity that permits single cell resolution from many, even densely packed cells • Good temporal resolution • Access to subthreshold membrane voltage dynamics • Compatible with in vivo or slice preparations	• Sensors are still largely under development	Gong et al., 2015 (recent indicator improvement) St.-Pierre et al., 2014 (recent indicator improvement) Knopfel, 2012 (indiciator review) Hamel et al., 2015 (recent brain imaging review)
	Calcium imaging	widely compatible	compatible	• An optical readout of neuronal activity that permits single cell resolution from many, even densely packed cells • Compatible with in vivo or slice preparations • High signal-to-noise sensors available in green and red	• No access to subthreshold membrane voltage dynamics • Relatively slow kinetics compared to electrophysiology	Hamel et al., 2015 (recent brain imaging review)
	Fiber photometry	mice, rats	compatible	• An optical readout of neuronal activity from a genetically defined population of neurons • An easy-to-implement technique that is highly comptabile with freely moving behavior • Compatible with any optical indicator	• Lack of single cell resolution	Lutcke et al., 2010 Schulz et al., 2012 Cui et al., 2013 Gunaydin et al., 2014 (deep brain axonal signals relevant to ODEs) Lerner et al., 2015 (isosbestic control excitation wavelength) Guo et al., 2015 Kim et al., 2016 Zalocusky et al., 2016 (rat)
Immediate Early Gene (IEG) Readouts	IEG histology	widely compatible	compatible	• Allows a broad readout of recently activated neurons	• Poor temporal resolution (hours) • Post-mortem fixed-tissue readout	Guzowski et al., 2005 (review)
	IEG transgenic reporters (Fos-GFP, Arc-GFP)	mice	compatible	• Allows a broad readout of recently activated neurons • Compatible with whole brain measurement, in vivo imaging, slice electrophysiology	• Poor temporal resolution (hours)	Barth et al., 2007 (review)
	TRAP (FosTRAP, ArcTRAP)	mice	compatible	• Allows a broad readout of recently activated neurons • Compatible with whole brain measurement, in vivo imaging, slice electrophysiology • Readout occurs during a chemically-defined window	• Poor temporal resolution (hours)	Guenthner et al., 2013
	fMRI	Human, non-human primate, rodent	compatible with awake, but still, subjects	• Whole brain readout visible in a live subject • Non-invasive, compatible with human studies • in non-human studies, can be combined with optogenetic manipulation (ofMRI)	• Poor temporal resolution (seconds) • Lack of single cell resolution	Poldrack and Farah, 2015 (review) Lee et al., 2010 (ofMRI)

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