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State of the art imaging of neurotransmission in animal models

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The wide range of nervous system functions underlying animal physiology and behaviors is ultimately encoded by the coordinated activity of neural cells, chiefly neurons and astrocytes. A principal aspect of neural coordination is electrical and chemical transmission between neural cells that occur over a vast panel of spatial and temporal scales. The high density and intricate connectivity of neuronal circuits within brain tissue also provides a great challenge for the investigation of neurotransmission. Technological development has been key for Neuroscience to tackle with increasing depth and details the diverse facets of activity and signaling encoding specific information within the brain. This *Special Issue* focuses on recent technological developments that enable imaging precise aspects of neurotransmission at different and complementary spatial and temporal resolutions.

At the core of this *Special Issue,* the invited authors describe important and recent advances in the toolbox of genetically encoded sensors for imaging neural activity and neurotransmission. Many of these tools leverage decades of research initiated at the end of the past century. For example, several genetically encoded sensors utilize fluorescent proteins as means of detecting calcium ions in cells. The conceptual design of these tools seeds in the initial work pioneered by Roger Tsien in 1999 (Baird et al., 1999). Through constant evolution over many years and by many research laboratories, and in combination with sophisticated multiphoton imaging modalities that evolved in parallel, genetically encoded sensors have become incredibly sensitive tools, to the point that they allow the detection of calcium or neurotransmitter activity in individual dendritic spines during animal behavior (Kerlin et al., 2019). Broadly speaking, tools like these have truly revolutionized our ability to investigate cellular activity and communication within the brain, and have become a mainstay in modern Neuroscience.

In this *Special Issue*, **Broussard et al.** review recent developments and applications of calcium imaging using genetically-encoded sensors with particular emphasis on neuronal axons and the tools specifically developed to aid axonal calcium imaging. Complementarily, **Serrat et al.** describe approaches and tools for imaging calcium in mitochondria, where

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they compare the advantages and disadvantages of using calcium-sensitive dyes versus genetically encoded calcium indicators.

No matter whether dyes or genetically encoded probes are utilized for imaging neural activity, the issue of light scattering in brain tissue remains a fundamental barrier for deep tissue imaging. **Scherbakova** presents a review of state-of-the-art genetically encoded tools that can be used for imaging calcium or voltage at near-infrared wavelengths, which offers promising opportunities for investigating deeper tissues, as well as for combinatorial approaches by multiplexing spectrally orthogonal sensors. In this same Issue, we also present a complementary review by **Liu et al.,** which focuses on the broader spectrum of hybrid voltage indicators developed so far.

Although calcium signal has been the main ion targeted to monitor neural activity, probes allowing to record the changes in the concentration of other ions have also been developed. **Lodovichi et al.**, review new approaches developed to specifically monitor chloride ions and how these approaches catalyzed our understanding of the role of chloride ions in neural cells' excitability.

Even with the ability to detect calcium or voltage changes within specific cell types in the brain, our understanding of the communication between these cells is limited because several other biochemical and signaling events are actively being used to tune cell activity and responses, but remain invisible to the eye (or to the microscope). To address this limitation, genetically encoded tools and systems have also been developed to monitor other aspects of neural signaling. This *Special Issue includes* several articles presenting sensors monitoring individual aspects of neurotransmission, other than calcium or voltage. **Hao et al.** present a review of recent developments for sensing glutamate at central synapses. **Dudok et al.**, discuss the tools needed to detect endocannabinoid signaling, a powerful modulator of synaptic communication and neuronal activity. **Massengil et al.,** present a review of tools for imaging cyclic AMP, an important intracellular second messenger that regulates excitability and gene expression in neural cells. Along this line, the article by **Vincent et al.**, provides additional in-depth context on how cyclic nucleotides can be detected and can carry out different signaling functions in different types of neurons. **Lee et al.**, provide an overview of the techniques and tools that can be utilized for detecting neuropeptides, in particular oxytocin, in the living brain. Given that neuropeptides carry out their message by activating G-protein coupled receptors (GPCRs) on target cells, it is also important to study how these receptors function. **Jullié et al.**, present a review describing how genetically encoded tools, in particular nanobody-based tools, can be utilized as biosensors of GPCR activation both at the cell surface and in intracellular microdomains of neural cells.

As a very useful complement to genetically encoded tools, neurochemicals can be sensed directly also by utilizing synthetic strands of RNA or DNA. In this Special Issue, we present two separate and complementary reviews, by **O'Donnel et al.**, and **Moraldo et al.** Here the authors nicely and comprehensively summarize the state of the art synthetic nanosensors and approaches utilizing them to detect neurotransmitters *in vitro* and *ex vivo* (in brain slice) with optical readouts.

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The neuroscientific toolbox described so far can mostly provide direct optical access to cellular and subcellular events, but is not yet compatible with whole-brain imaging approaches. As a *trait d'union* between cellular-level and whole-brain imaging, in this Special Issue, **Wei et al.** review state of the art functional magnetic resonance (fMRI) approaches for the direct and brain-wide detection of neurochemical release in living animals.

We hope that this comprehensive collection of reviews on molecular, genetically encoded and hybrid tools for the investigation of neural activity at multiple spatial and temporal scales will provide a useful reference for neuroscientists that are interested in utilizing these state-of-the-art approaches in their research.

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