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Recent applications of superresolution microscopy in neurobiology

Katrin I Willig[1,2] and Francisco J Barrantes[3]

Chemical synapses in brain are structural differentiations where excitatory or inhibitory signals are vectorially transmitted between two neurons. Excitatory synapses occur mostly on dendritic spines, submicron sized protrusions of the neuronal dendritic arborizations. Axons establish contacts with these tiny specializations purported to be the smallest functional processing units in the central nervous system. The minute size of synapses and their macromolecular constituents creates an inherent difficulty for imaging but makes them an ideal object for superresolution microscopy. Here we discuss some representative examples of nanoscopy studies, ranging from quantification of receptors and scaffolding proteins in postsynaptic densities and their dynamic behavior, to imaging of synaptic vesicle proteins and dendritic spines in living neurons or even live animals.

Addresses
[1] Center for Nanoscale Microscopy and Molecular Physiology of the Brain, Göttingen, Germany
[2] Department of NanoBiophotonics, Max Planck Institute for Biophysical Chemistry, Am Faßberg 11, 37077 Göttingen, Germany
[3] Laboratory of Molecular Neurobiology, BIOMED, Faculty of Medical Sciences, Catholic University of Argentina, UCA-CONICET, 1107 Buenos Aires, Argentina

Corresponding authors: Willig, Katrin I (kwillig@gwdg.de) and Barrantes, Francisco J (rtfjb1@gmail.com)

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Introduction

The new methodologies encompassed under the general terms 'superresolution microscopy' and 'nanoscopy' (e.g. stimulated emission depletion microscopy (STED), reversible saturable optical fluorescent transition microscopy (RESOLFT), stochastic optical reconstruction microscopy (STORM), photoactivated localization microscopy (PALM), fluorescent photoactivation localization microscopy (FPALM), structured-illumination microscopy (SIM), and others) are currently one of the most rapidly developing research fields, having revolutionized optical microscopy at large. They combine the strength of light microscopy, i.e. the very specific labeling of immunohistochemistry or genetically encoded tags, the live cell and tissue compatibility and the relative simple use with a resolution below the diffraction limit which is usually reserved for electron microscopy. The reader is referred to other chapters in this Volume for the physical principles behind superresolution techniques, and for a more comprehensive treatment of the methodological aspects see Ref. [1]). Their applications in the biological sciences continue to grow and the Neurosciences in particular constitute one of the most fertile and challenging grounds for progress on this turf. Contemporary to these developments, unprecedented advances are also being made in unraveling the intricacies of brain organization. One of the avenues opened up by this expansive progress is connectomics, a topic which could be described as the attempt to decipher the connections of different regions of the brain at the mesoscale in structural and, hopefully, functional terms (for a couple of general overviews see [2,3]). Because synapses are the ultimate link in the connectivity meshwork of neurons, and because their substructure cannot be resolved by conventional light microscopy, in our view they constitute one of the critical test objects for superresolution microscopy in the Neurosciences.

Most excitatory synapses in the central nervous system occur on dendritic spines, the postsynaptic specialization envisaged as the smallest known processing unit in brain, and as reviewed in this work, the subject of intense scrutiny by superresolution microscopy. Spines exist in an assortment of morphologies and such structural variants appear to be directly associated with synaptic function. Briefly, the spine possesses a head region connected to the dendritic shaft through a neck region [4]. The head of the spine contains the postsynaptic density (PSD), the most prominent spine microdomain, which in turn contains a dense concentration of neurotransmitter receptors, largely glutamatergic receptors (AMPA and NMDA types), the predominant chemical substances responsible for excitatory transmission in brain [5]. Spine morphology has been shown to change along different functional processes — e.g. in long-term potentiation (LTP), the paradigmatic correlate of synaptic plasticity and learning (see e.g. [6•] for a review) — or under disease conditions (reviewed by Penzes at al. [7•]). In the following section we briefly discuss recent work in which superresolution microscopy has been used to address an important topic in the Neurosciences or played a key role in the experimental approach.