Unraveling the mysteries of the presynapse with super resolution microscopy

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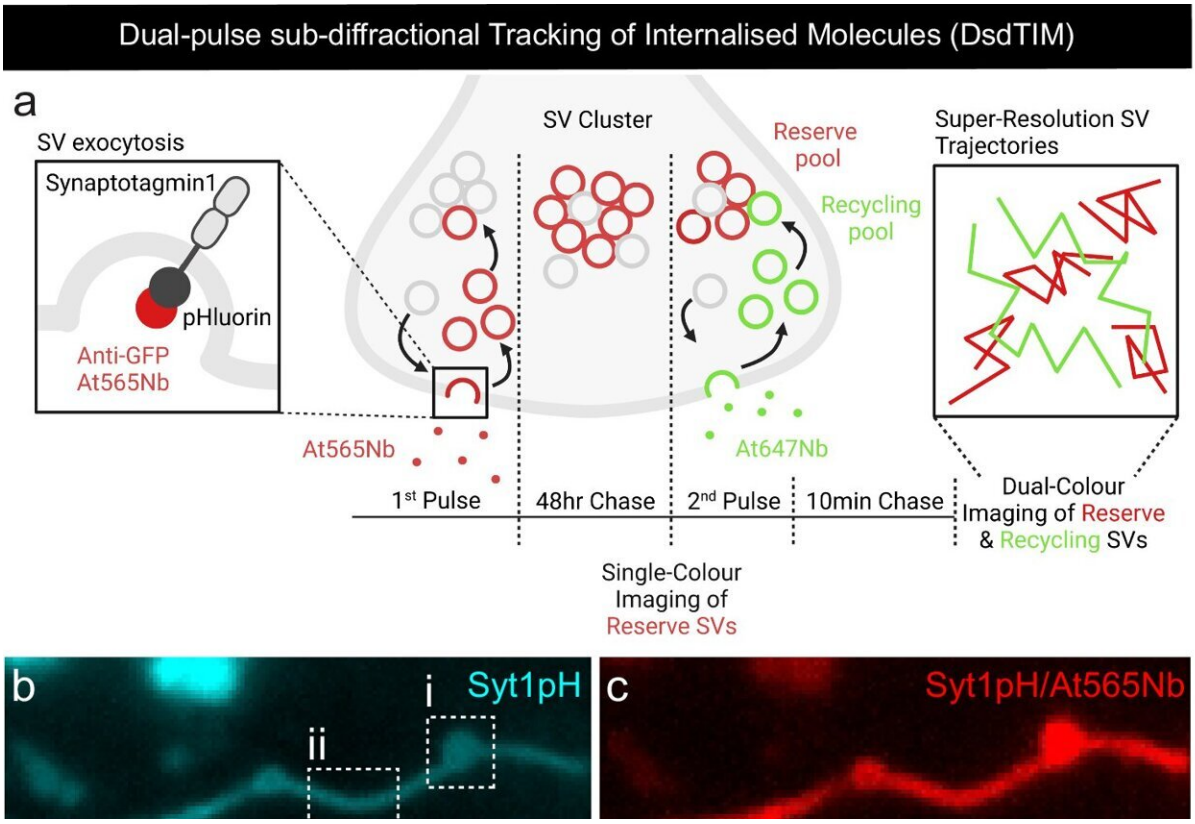

a Graphical representation of the Dual-pulse sub-diffractional Tracking of Internalized Molecules (DsdTIM) protocol. b Representative epifluorescence image of an axonal segment expressing Syt1pH acquired before incubation with At647Nb. The dashed boxes in (b) highlight (i) a presynaptic compartment and (ii) a peri-synaptic axonal segment. c–e Maximum intensity projection of (c) Syt1pH/At565Nb, (d) Syt1pH/At647Nb and (e) merged maximum intensity projection. f Trajectory map of tracked reserve SVs containing Syt1pH bound by At565Nb in the (i) presynapse and (ii) axonal segment. g Trajectory map of

tracked recycling SVs containing Syt1pH bound by At647Nb in the (i) presynapse and (ii) axonal segment. h Merged trajectory maps. Credit: *Nature Communications* (2024). DOI: 10.1038/s41467-024-46256-1

Researchers from UQ's Queensland Brain Institute (QBI) have revealed the pivotal role played by Synapsin 2a proteins in orchestrating the organization and mobility of synaptic vesicles within live neurons.

Shanley Longfield, a Ph.D. student in the Meunier lab, explained that she used super resolution microscopy, simultaneously tracking key proteins and synaptic vesicles, to make this discovery.

This study was a collaboration with the Ecole Normale Superieure (France), the University of Cambridge (UK), and the Temasek Lifesciences Laboratory (Singapore). The article was published in *Nature Communications*.

"We used a novel technique, known as dual-pulse sub-diffractional tracking of internalized molecules, developed in our lab, to peer into the inner workings of live hippocampal neurons," Longfield said.

"One of our main findings revolves around the role of Synapsin 2a tetramerization in controlling the clustering and mobility of reserve synaptic vesicles.

"The reserve synaptic vesicles, which constitute a crucial backup reservoir of neurotransmitters, display lower mobility and are less responsive to high-frequency stimulation compared to their recycling pool counterparts.

"This revelation underscores the intricate balance maintained within

neurons to ensure efficient neurotransmitter release under varying physiological conditions.

"Our study also sheds light on the distinct mobility patterns of reserve and recycling synaptic vesicles at different neuronal terminals, emphasizing the nuanced regulation of these dynamics by Synapsin proteins.

"Synapsins serve as molecular tethers, anchoring the synaptic vesicles within clusters and fine-tuning their movements, ultimately influencing neurotransmitter release and neuronal communication.

"In earlier research, we have shown that tau, a protein involved in Alzheimer's disease, controls the dynamic clustering of the important subpopulation of recycling vesicles at the presynapse critical for neuronal communication.

"We found that tau forms small and transient nanoscale biomolecular condensates that can selectively capture these vesicles at the presynapse.

"Now we have tracked the protein—Synapsin 2a—at the same time as the reserve vesicles and shown Synapsin 2a can form tetramers that cross-link synaptic vesicles at the presynapse."

Professor Fred Meunier said the next step is to study how the two mechanisms, one involving tau and the other Synapsin 2a, "talk to each other" to drive neuronal communication.

"Understanding how condensates and the cross-linking mechanisms coordinate the clustering of synaptic vesicles to allow the presynapse to communicate will be a challenging but exciting endeavor," Meunier said.

"The implications of this research extend far beyond the realm of basic

neuroscience.

"Understanding the precise mechanisms governing synaptic vesicle dynamics deepens our knowledge of fundamental brain processes and holds potential therapeutic applications for neurological disorders, such as Alzheimer's disease, characterized by disruptions in synaptic function."

More information: Shanley F. Longfield et al, Synapsin 2a tetramerisation selectively controls the presynaptic nanoscale organisation of reserve synaptic vesicles, *Nature Communications* (2024). DOI: 10.1038/s41467-024-46256-1

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