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Spatial biology brings Alzheimer's disease into sharper focus

As researchers delve into the pathogenesis of Alzheimer's disease, a cutting-edge suite of spatial biology tools is revealing new details.

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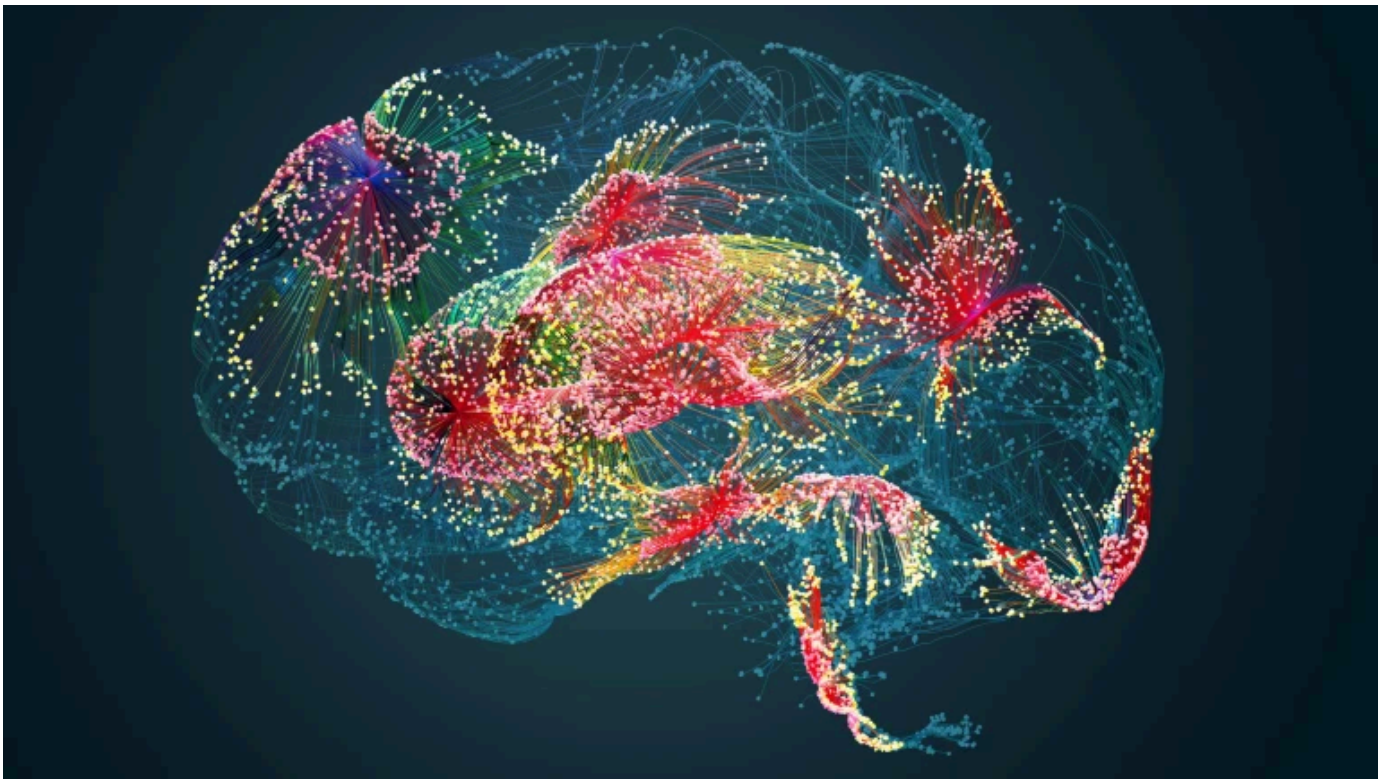


Studying the link between Alzheimer's disease and ageing requires spatial biology tools that can distinguish between different protein phosphorylation levels within individual cells. *Credit: nopparit/ Getty Images*

A hallmark of Alzheimer's disease (AD) is the deposit of phosphorylated tau proteins that form neurofibrillary tangles inside neurons. While they're known biomarkers of AD, researchers still have questions about tau deposits.

"We don't yet understand how and why this is happening," says Miranda Orr, associate professor of gerontology and geriatric medicine at Wake Forest University and research health scientist at the Salisbury VA Health Care System.

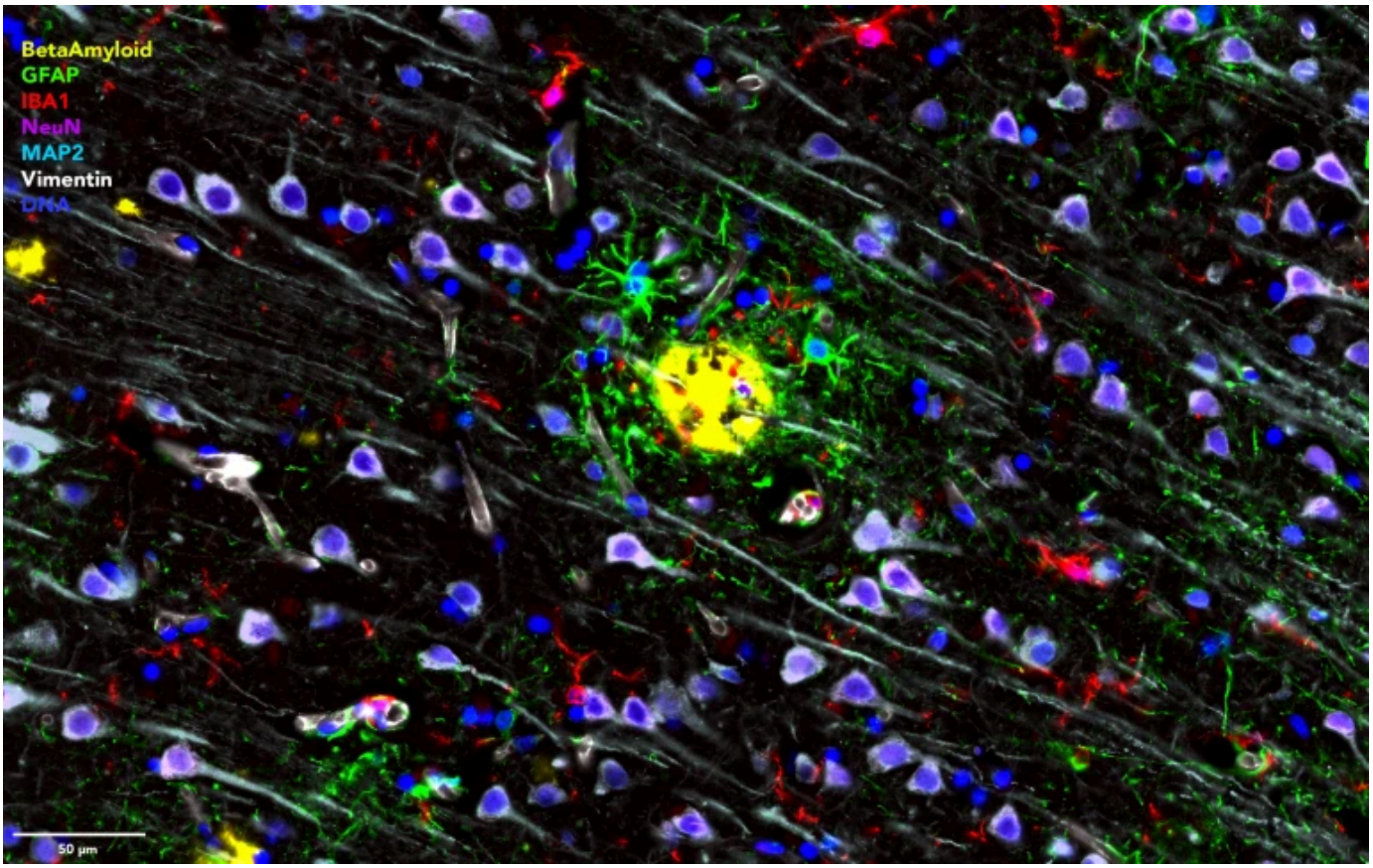
One mystery is how AD is linked to ageing, so Orr uses spatial biology to explore how tau is associated with cellular senescence. "Not only is the expression of tau important to our work, but also its phosphorylation state," she says. Tau phosphorylation and cellular senescence reinforce each other in AD; because some brain regions and cell types exhibit higher levels of both senescence and tau pathology, a spatial approach is necessary to unravel the mechanisms behind the disease.

A comprehensive toolkit for spatial biology

Orr's team follows protein expression across multiple tissues in human brain samples of different ages. "Studying the link between tau deposits and ageing requires evaluating the coordinated expression of multiple genes and proteins within a cell, and their environments," says Orr. The challenge calls for technologies that can discern transcriptomics and proteomics data within the spatial context of a cell and its surroundings.

One such technology is the GeoMx Digital Spatial Profiler (DSP), which Orr's group uses to select cells or regions for analysis of the whole transcriptome and more than 600 protein targets, including different isoforms and phosphorylation states of tau. After the fast and high-plex data acquired with GeoMx DSP, Orr's team selected 68

biomarkers for single-cell spatial analysis with the CosMx Spatial Molecular Imager (SMI).



An image of a plaque from a brain affected by Alzheimer's disease, captured by Miranda Orr's lab using the CellScape platform. *Credit: Bruker Spatial Biology*

"Both instruments provide transcriptomic data, but the subcellular resolution and ability to image every cell makes CosMx SMI appealing to evaluate cellular niches," Orr explains.

Finally, she evaluated a subset of the most interesting targets from the earlier studies using the CellScape platform — a spatial proteomics technology featuring high-resolution and high-dynamic-range imaging — to get an even closer view of those proteins.

The right tools for unique needs

Life science instrument manufacturer Bruker recently acquired NanoString Technologies, the company behind GeoMx DSP and CosMx SMI. These tools join those of Bruker Spatial Genomics and CellScape developer Canopy Biosciences

under the umbrella of Bruker Spatial Biology. “Under one roof, these companies can work together to advance each of their technologies, as they offer unique strengths,” says Orr.

GeoMx, CosMx and CellScape complement each other at different stages, balancing higher throughput for some analyses with higher resolution or ease of adding new protein targets for others. For Orr, the combination has been illuminating.

“These technologies are teaching us about the molecular signatures of neurons with tau deposits, about senescent cells and their environments, and about other neuropathologies in Alzheimer’s disease,” she says. Combining all three spatial biology technologies exposes the spatial relationships between phosphorylated tau and other pathologies, such as amyloid plaques, enabling discoveries that are impossible with a single methodology.

“We can profile neurons with different phospho-tau profiles and where they are located in the tissue to learn how they interact with their environment,” says Orr. It's another step towards understanding tau pathogenesis and cellular senescence, and their links to Alzheimer’s — insights that could influence the diagnosis and treatment of the disease.

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