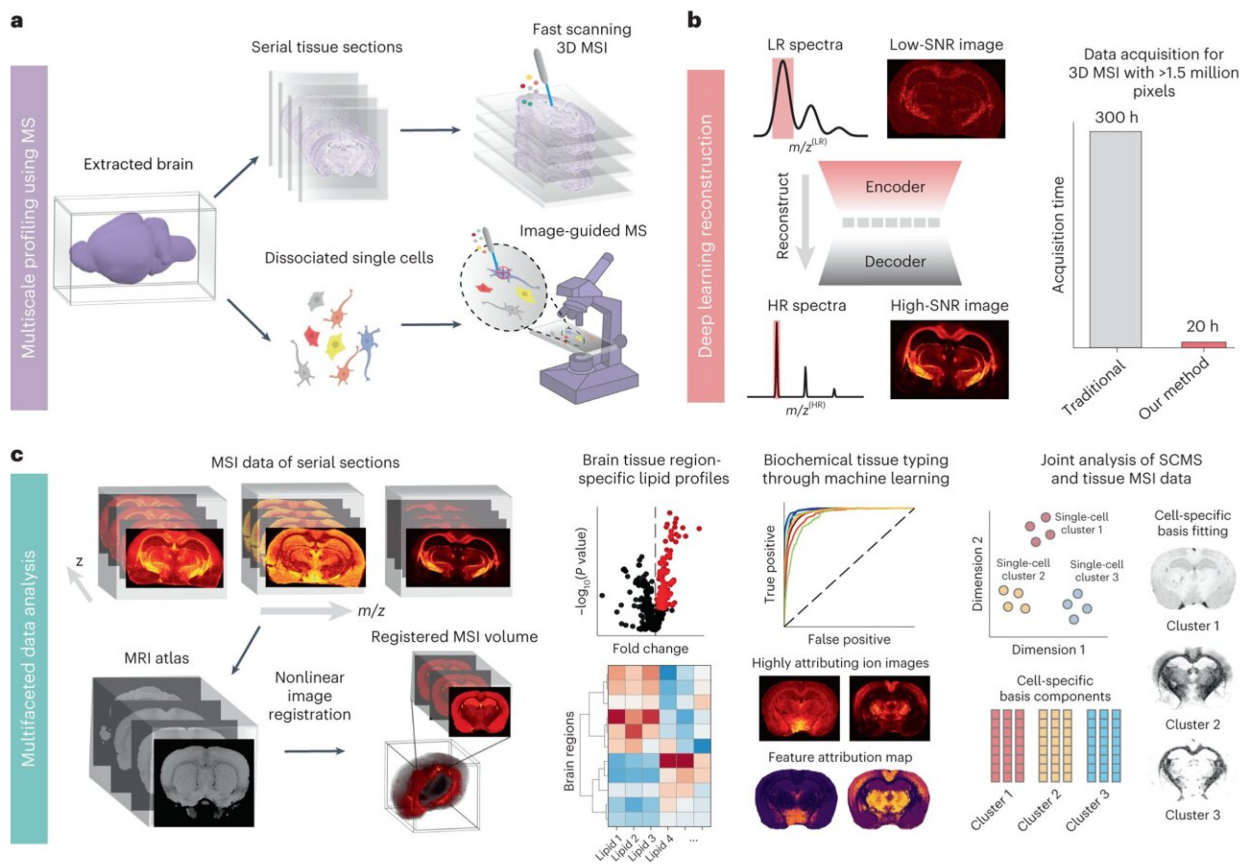
Painting a molecular portrait of the brain with mass spectrometry and deep learning

March 5 2024, by Samantha Jones Toal



The MEISTER framework for multiscale biochemical profiling using high-mass-resolution MS enhanced by computational methods. a, Obtained from surgically extracted brain, serial tissue sections are imaged for 3D MSI using a fast acquisition strategy, and single-cell populations prepared by tissue dissociation are probed with high-throughput image-guided MS. b, A deep-learning model reconstructs high-mass-resolving and high-SNR MS data from the low-mass-resolution measurements acquired with fast acquisitions by exploiting a lowdimensional manifold structure for high-dimensional MS data, producing large datasets with millions of pixels, which was previously time-prohibitive with the conventional acquisition. LR, low resolution; HR, high resolution. c, Our multifaceted data analysis pipeline uses various data-driven methods for multimodal image registration to align MSI with 3D anatomical MRI for volumetric reconstruction, identifying differential lipid distributions, tissue typing using MS data and integrating MSI and SCMS data for joint analysis and resolving cell-type-specific contributions at the tissue level across the brain. Credit: *Nature Methods* (2024). DOI: 10.1038/s41592-024-02171-3

Beckman Institute for Advanced Science and Technology researchers Jonathan Sweedler, a professor of chemistry, and Fan Lam, a professor of bioengineering, have outlined how spatial omics technologies can reveal the molecular intricacy of the brain at different scales.

Their research appears in *Nature Methods*.

The researchers and their colleagues used a biochemical imaging framework integrated with deep learning to create 3D molecular maps with cell specificity to better understand how the brain functions in health and disease.

"If you look at the brain chemically, it's like a soup with a bunch of ingredients," Lam said. "Understanding the biochemistry of the brain, how it organizes spatiotemporally, and how those chemical reactions support computing is critical to having a better idea of how the brain functions in health as well as during disease."

To understand how the brain's chemical ingredients interact with one another, the researchers used a new imaging technique called mass spectrometry imaging to collect and analyze massive amounts of high-resolution data. They also used single-cell metabolomics and computational tools to extract data about individual molecules in single brain cells, which enabled data acquisition at unprecedented speeds and scales.

"Most people have a feeling that brain diseases such as depression and Alzheimer's are caused by neurochemical imbalances," Sweedler said. "But those imbalances are really hard to study and it's difficult to understand how chemicals interact at different scales (for example, at the tissue level and individual cell level) during problems in the brain."

According to Sweedler, creating 3D maps of chemical distributions with cell-type specificity enables researchers to further understand the complicated biochemistry within the brain, which in the long term should help address currently intractable neurological diseases.

Single-cell metabolomics, a technology critical to the researchers' findings, was named as one of *Nature*'s "Seven technologies to watch in 2023" along with CRISPR and the James Webb Space Telescope, speaking to the high impact these tools will continue to have as it relates to looking at cell-specific data, Sweedler said.

The research wouldn't have been possible without the collaborative nature of the Beckman Institute.

"It truly amazes me how small interactions can turn into interesting research conversations and eventually into large-scale collaborative studies," said first author Richard Xie, a Beckman Institute Graduate Fellow. "The key is to be open-minded and interdisciplinary, as you may draw inspirations from another field. I feel very excited about the progress on leveraging different expertise across groups to engineer tools to better depict the biochemical landscape of the brain."

Lam and Sweedler met at Xie's behest to discuss his work on single-cell and tissue mass spectrometry imaging. The team had a breakthrough in how informatics and computational methods could lead to a new kind of multimodal, multiscale biochemical imaging that is highlighted in their recent *Nature Methods* paper.

More information: Yuxuan Richard Xie et al, Multiscale biochemical mapping of the brain through deep-learning-enhanced high-throughput mass spectrometry, *Nature Methods* (2024). DOI: 10.1038/s41592-024-02171-3

Provided by Beckman Institute for Advanced Science and Technology