

Distinct lipid profiles of hippocampal subregions and plaque microenvironments in an Alzheimer's Disease mouse model revealed by high-spatial resolution MALDI-imaging

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Introduction

Lipids are increasingly implicated in age-related neurodegenerative diseases, such as Alzheimer's disease (AD). Abnormal lipid accumulation was described by Alois Alzheimer in 1907; however, this observation was largely overlooked due to limited methodologies for studying lipids. Modern mass spectrometry imaging (MSI) enables characterization of lipids with high structural and spatial resolution. Recent advances such as routine sub-10-micron spatial resolution now enable deeper characterization of lipids in AD. Here, we used 5-micron spatial resolution MALDI-MSI to examine lipid accumulations associated with AD plaques in the hippocampus of the 5x*FAD* mouse model of AD. By registering the data to the Allen Mouse Brain Atlas, we associated MSI signals with fine morphological subregions that were previously unmappable at lower MSI resolutions.

Methods

Cryosections of 3 5x*FAD* and 3 C57BL/6 mouse brains (10µm; 15 months; n=3/sex) were collected through the center of the hippocampal formation (HF) and thaw-mounted on superfrost slides. Autofluorescence images were obtained prior to MALDI-MSI analysis. Sections were coated with 2,5-DHA via sublimation and then recrystallised. Tissues were analysed using a timsTOF flexX (Bruker), in positive (MALDI-2) and negative (MALDI) mode at 5µm spatial resolution. After MALDI-MSI analysis, tissues underwent H&E staining and digitised. MALDI-MSI and imaging data were analysed using Weave (Aspect Analytics). The data were spatially mapped using a non-rigid registration algorithm, and then integrated into a single combined dataset for downstream analysis and subsequent registration to the Allen Mouse Brain Atlas (AMBA). MALDI-MSI data underwent peak picking using a 15 ppm peak window. Peaks were extracted through aggregation of the maximum signal per tissue, filtered according to signal-to-noise ratio and the number of pixels expressing the signal. This resulted in ~1100 and ~2100 extracted features in negative and positive mode respectively.

Results

Reading direction

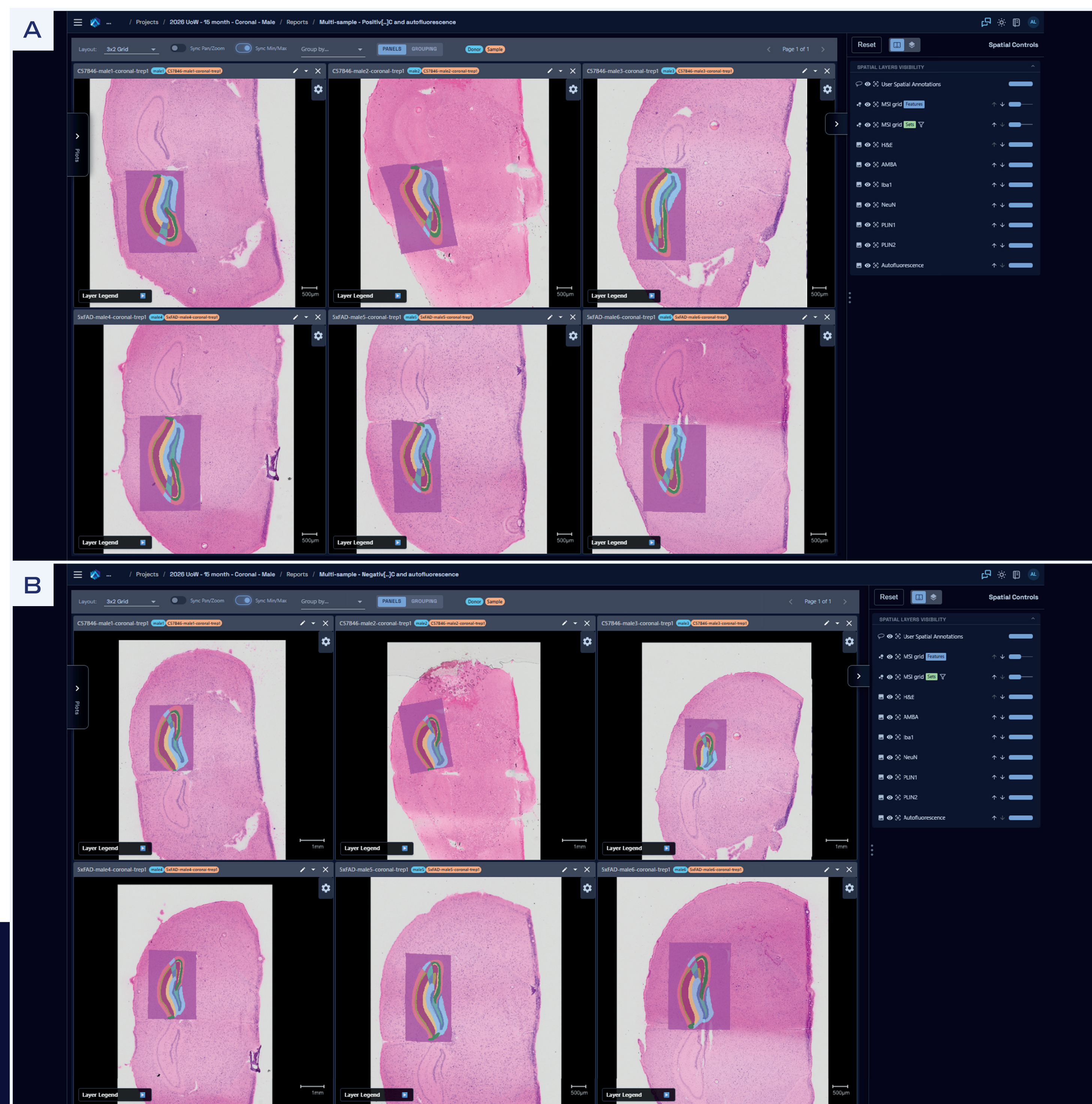
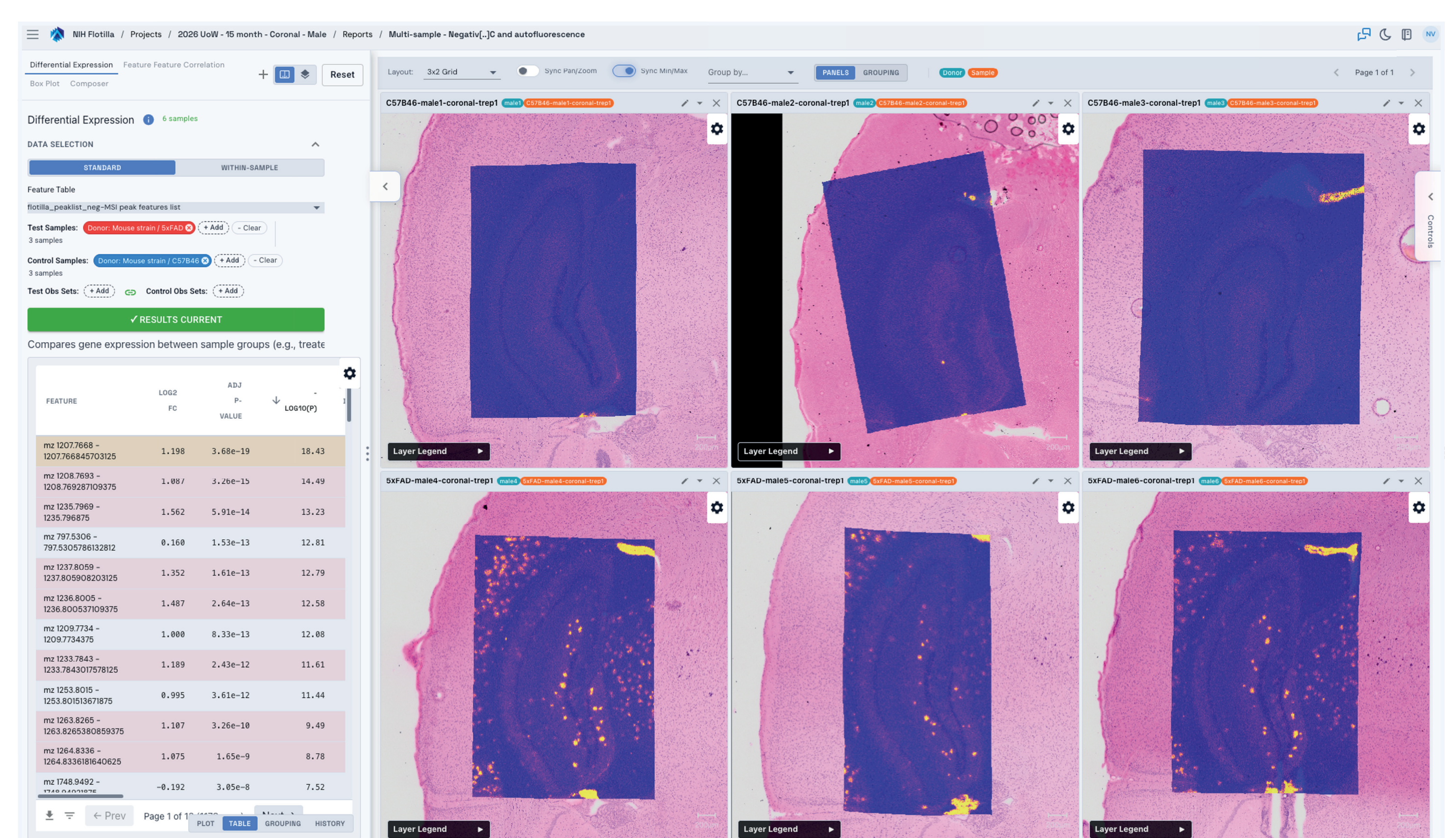
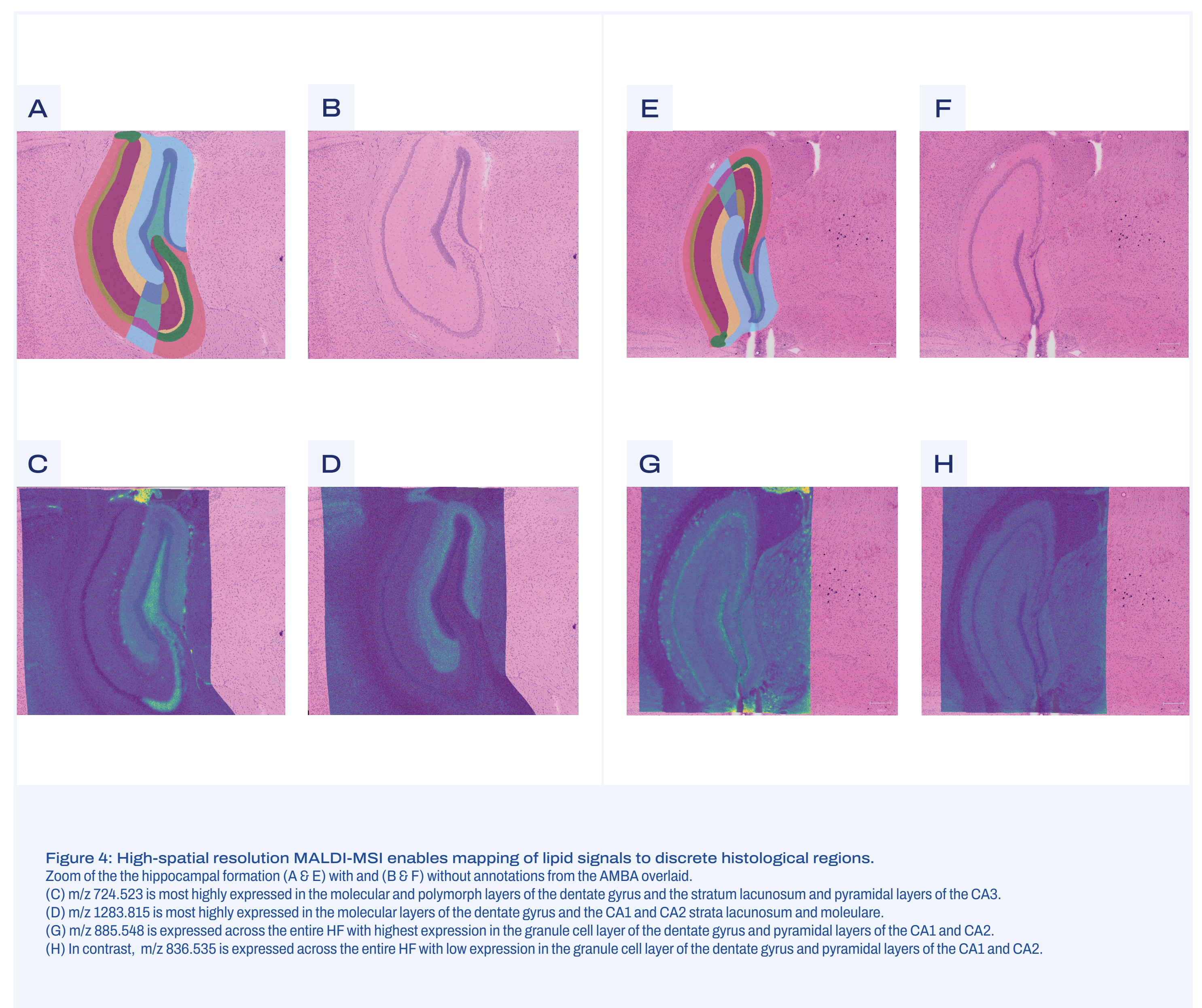
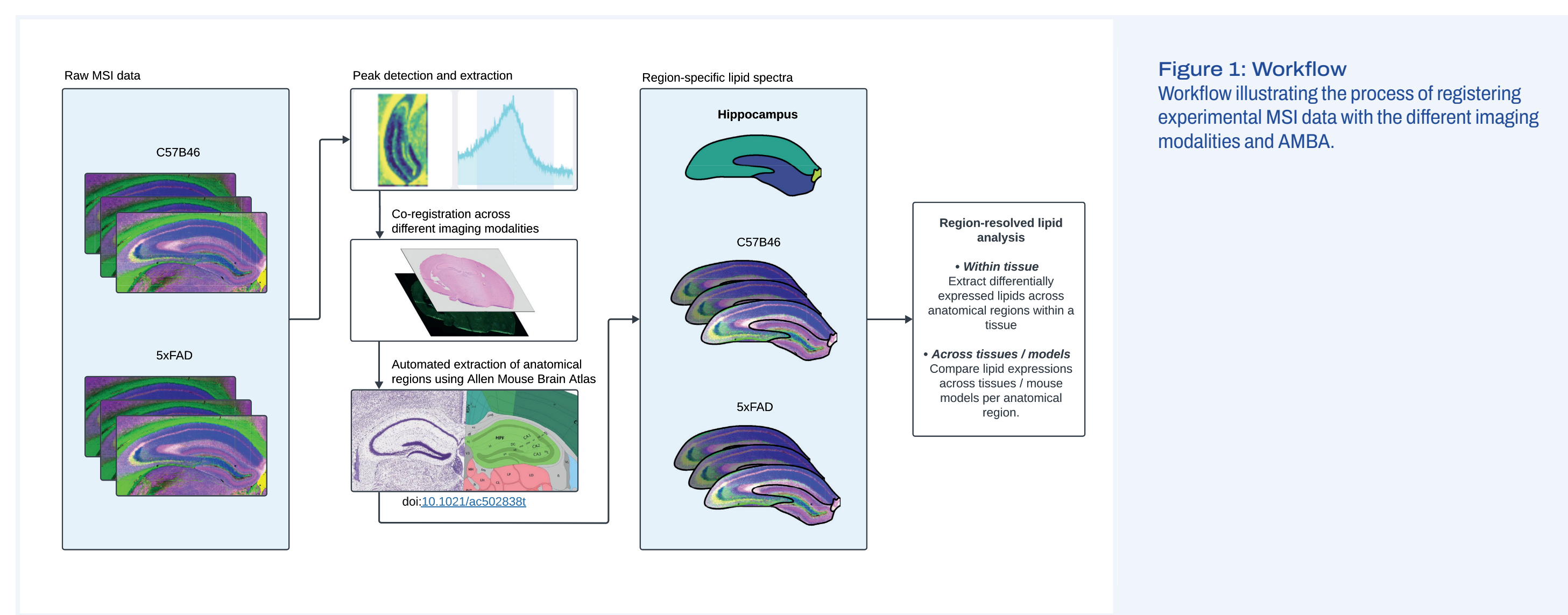


Figure 3: Web-based interactive reports to explore data on a cohort level.
Weave allows simultaneous viewing of a sample cohort with associated datasets. The cohort sample metadata is used to create intuitive layouts. All reports are web-based, which allows findings to be readily shared with study collaborators (e.g. neurobiologists, pathologists), facilitating collaborative analysis. These reports show six samples; three C57BL/6 control samples (top row) and three 5x*FAD* samples (bottom row) for (A) positive mode and (B) negative mode measurements, with AMBA annotations of the HF overlaid onto the sample H&E images.

Figure 5: Amyloid-β plaque microenvironment of the HF in 5x*FAD* mice have a distinct lipid signature.
Comparison of control and AD mice identified a number of significantly differentially expressed lipids with punctate distribution patterns matching those of AD plaques.

Conclusions

- 5-micron MALDI-MSI resolves distinct lipid signatures in hippocampal subregions and plaque microenvironments in mouse model of AD.
- Weave's peak detection pipeline allows interactive, in-depth extraction of MSI features, scaling for large cohorts and datasets.
- Allen Mouse Brain Atlas integration allows direct, standardized comparison of lipid signals in fine-grained spatial regions, both within and across tissues and animals.

With the support of