TARGETING NEUROTRANSMITTER ALTERATIONS FOLLOWING DRUG TREATMENT USING MASS SPECTROMETRY IMAGING AND CLOUD-BASED DATA ANALYSIS USING WEAVE

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Introduction

Understanding neurotransmitter distribution in the brain and how it is altered by CNS-targeting compounds is critical for drug discovery in neurodegeneration and mental health. MALDI mass spectrometry imaging (MALDI-MSI) is a powerful tool for analyzing neurotransmitters due to its capacity to detect multiple compounds and metabolites simultaneously, especially with chemical derivatization techniques for low-abundance target molecules.

In this study, we used MALDI-MSI to investigate neurotransmitter spatial distributions in rat brain regions after treatment with tetrabenazine, a reversible blocker of VMAT2, that depletes neuroactive monoamines (serotonin, norepinephrine and dopamine) in nerve terminals. Data integration and differential analysis were performed using Weave, a cloud-based spatial multi-omics software platform, enabling collaborative annotation, metadata management, and easy sharing of insights.

Methods:

Adult male rats were injected with tetrabenazine (0.25 mg/kg; 0.75 mg/kg or 1.5 mg/kg) or vehicle and sacrificed 1.5 hours post-injection. Coronal brain sections were mounted on conductive slides, and coated with 2-fluoro-1-methyl pyridinium (FMP-10) matrix (1.82 mg/ml). FMP-10 is a reactive matrix that modifies amine and hydroxy groups of target compounds and facilitates their detection. MSI data was acquired on a timsTOF flex (Bruker Daltonics) in positive ion mode (m/z 50-1500).

MALDI-MSI and accompanying histology data were imported into Weave, which allowed for extraction of individual tissues as separate assets, creation of a sample database, and import of accompanying metadata for downstream analysis. A total of seven neurotransmitters and associated metabolites were analyzed: serotonin and its main metabolite 5-Hydroxyindole-3-acetic acid (5HIAA); dopamine and its metabolites 3,4-dihydroxyphenylacetic acid (DOPAC), 3-Methoxytyramine and homovanillic acid (HVA); adrenaline and methanephrine (MN); noradrenaline and metabolites 3-methoxy-4-hydroxyphenylglykol (MHPG), 3,4-dihydroxymandelic acid (DHPG), 3,4-hydroxymandelic acid (DHMA), and vanillylmandelic acid (VMA); histamine and metabolite 1-methylhistamine; and gamma amino butyric acid (GABA).

Results

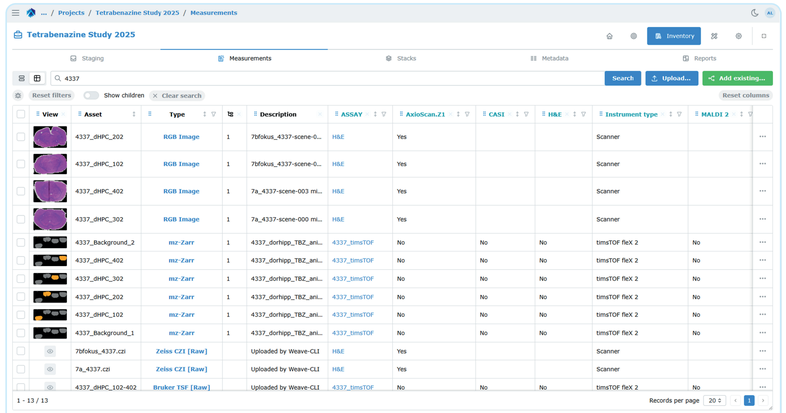

Figure 1: Weave measurement database.
In large-scale, high-throughput MSI studies, it is common practice to mount multiple sections onto a single glass slide to limit inter-measurement variability. Data ingestion into Weave splits the data from each section into individual measurements (i.e., assets) and deposits them into a repository. This functionality additionally enables measurements spread across multiple slides over time to be readily arranged into a variety of combinations for data analysis.

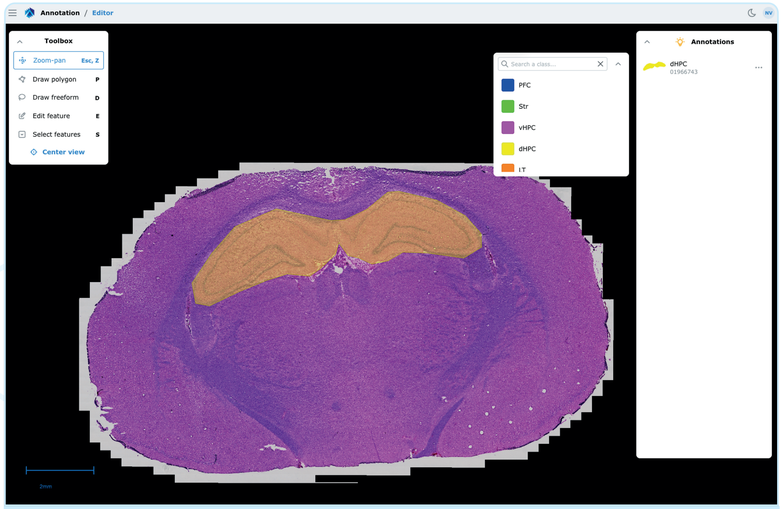

Figure 2: Tissue annotations performed in Weave.
Histological annotations of signification brain regions were performed within the Weave platform on post-measurement H&E images. With the non-rigid co-registration of MSI datasets with H&E images, the annotated regions of interest are seamlessly transferred from microscopy images to the MSI data.

Figure 3: Peak picking tool.
Weave enables users to manage peak lists and apply these to cohorts of MALDI-MSI datasets directly from the measurement database. This facilitates efficient feature extraction, promotes data re-use, and supports consistent analysis across experiments. Users can inspect intensity distributions across peaks to evaluate signal consistency and biological relevance.

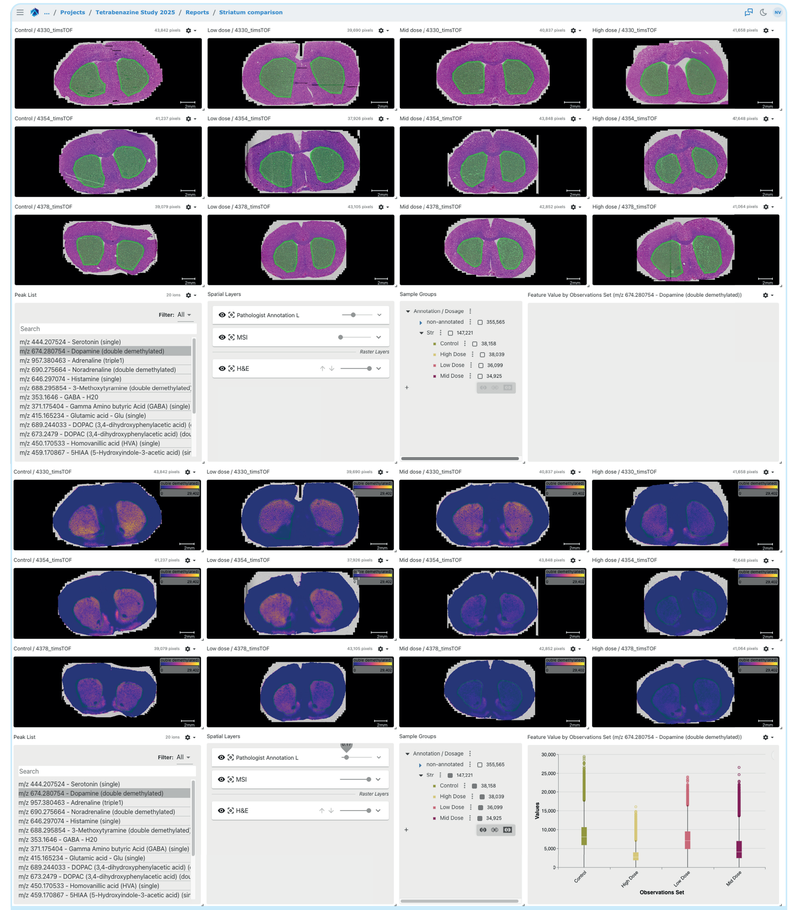

Figure 4: Web-based interactive reports to explore data on a cohort level.
Top: Weave allows simultaneous viewing of a cohort of MSI measurements overlaid onto their respective H&E images, and associated data analysis results. The cohort sample metadata is used to create intuitive layouts.

This report shows twelve samples, three control samples (far left columns) and nine samples treated with a range of tetrabenazine concentrations. Individual panels can be resized or repositioned according to user preference, e.g. resizing a specific sample for closer investigation. All reports are web-based, which allows findings to be readily shared with study collaborators (e.g. pathologists), facilitating collaborative analysis.

Bottom: Analysis shows selective expression of neurotransmitters in discrete brain regions. As an example, dopamine is highly expressed in the striatum, with differential analysis showing a decreased dopamine expression with increasing tetrabenazine concentrations.

Conclusion & Outlook

- We describe the ability to store, organize, and analyze MSI and histological data collaboratively in a cohort study, enabling robust and reproducible insights.
- Integration of MSI data with annotated regions of interest allowed identification of spatial patterns, furthering understanding of the impact of CNS-targeting drugs on neurotransmitter dynamics.
- The scalable nature of Weave supports long-term data re-use, enabling cross-study comparisons and longitudinal analyses.

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