

Quantitative Imaging and Characterization of Brain Ganglioside Phenotypes in Parkinson's Disease

Kim Ekroos¹; Shadrack M Mutuku²; Reza Ranjbar Choubeh³; Nicolas Tomasiello⁴; Caine Smith⁵; Maria José Q Mantas⁶; Alice Ly⁷; Greg Sutherland⁸; Nathan G Hatcher⁹; Nico Verbeeck⁸; Shane Ellis⁹

¹ Lipidomics Consulting Ltd, Esbo, Finland
² Molecular Horizons, School of Chemistry and Molecular Bioscience, University of Wollongong, Wollongong, NSW, Australia
³ Aspect Analytics, Genk, Belgium
⁴ The University of Sydney, Sydney, NSW, Australia
⁵ Merck & Co., Inc., West Point, PA, USA

Introduction

Mutations in GBA1, which encodes lysosomal glucocerebrosidase (GCase), are a major genetic risk factor for Parkinson's disease (PD). Reduced GCase activity results in accumulation of GCase substrates glucosylceramide and glucosylsphingosine. How GCase mutations affect downstream brain gangliosides remains unclear.

Methods

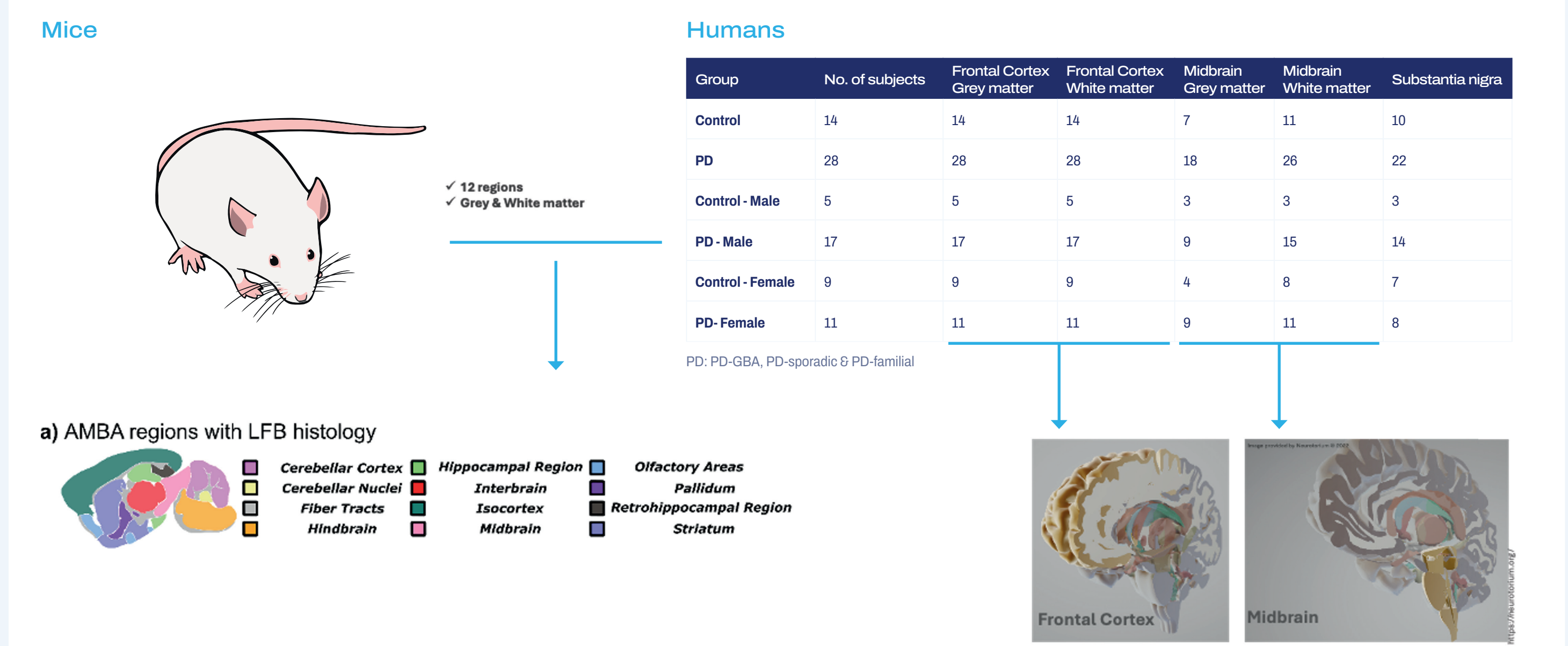
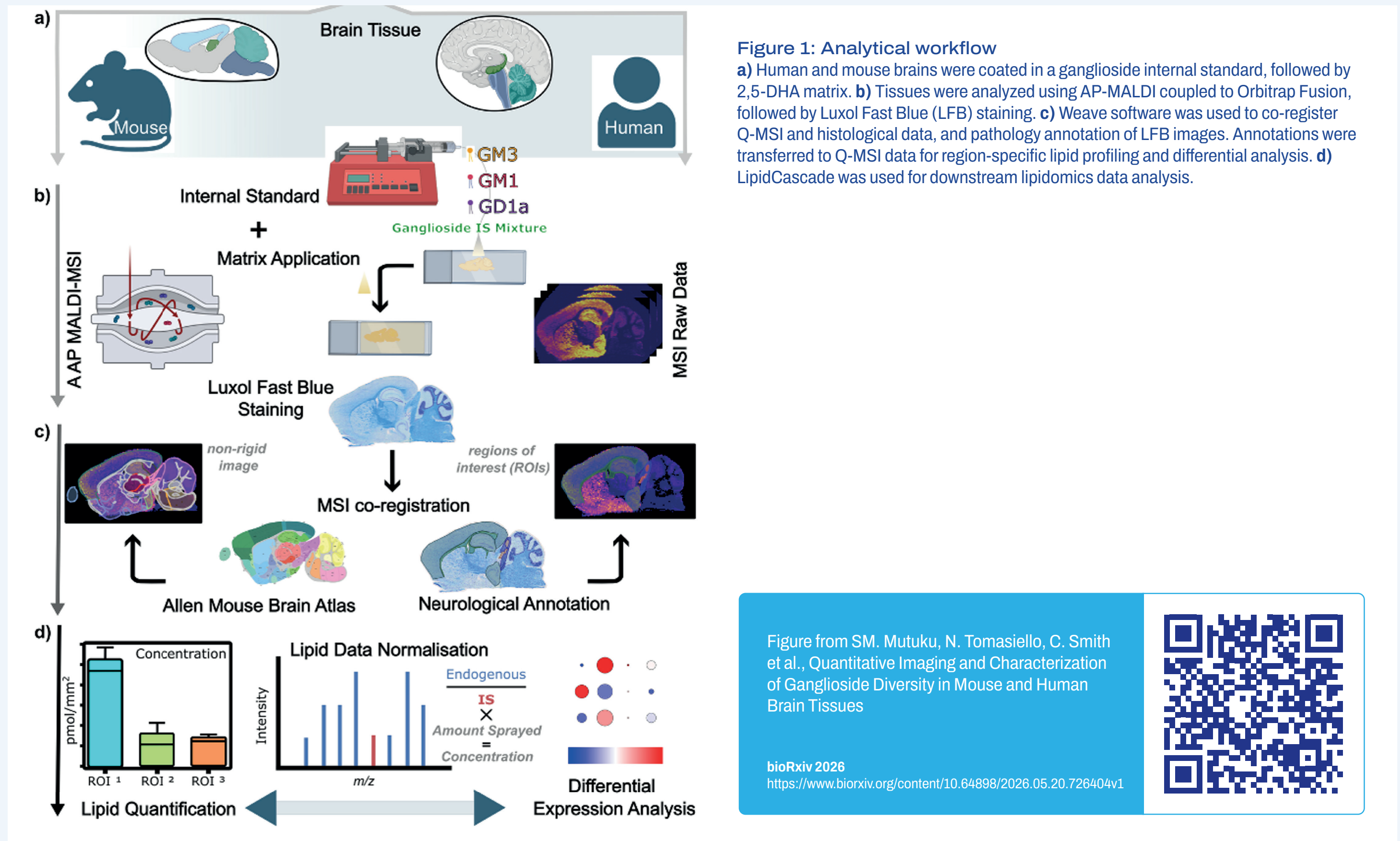


Figure 3: Summary of mouse and human samples used in this study. 12 Different mouse brain regions across both grey and white matter as defined by the Allen Mouse Brain Atlas (AMBA) were used in the analysis. Human midbrain and frontal cortex tissues (n=42: 15 control, 27 PD) encompassed grey and white matter in the frontal cortex, grey and white matter in the midbrain, and the substantia nigra.

To address this, we used quantitative mass spectrometry imaging (Q-MSI) to map ganglioside distributions across multiple brain regions in mouse models and human post-mortem brain specimens from sporadic and GBA-PD patients.

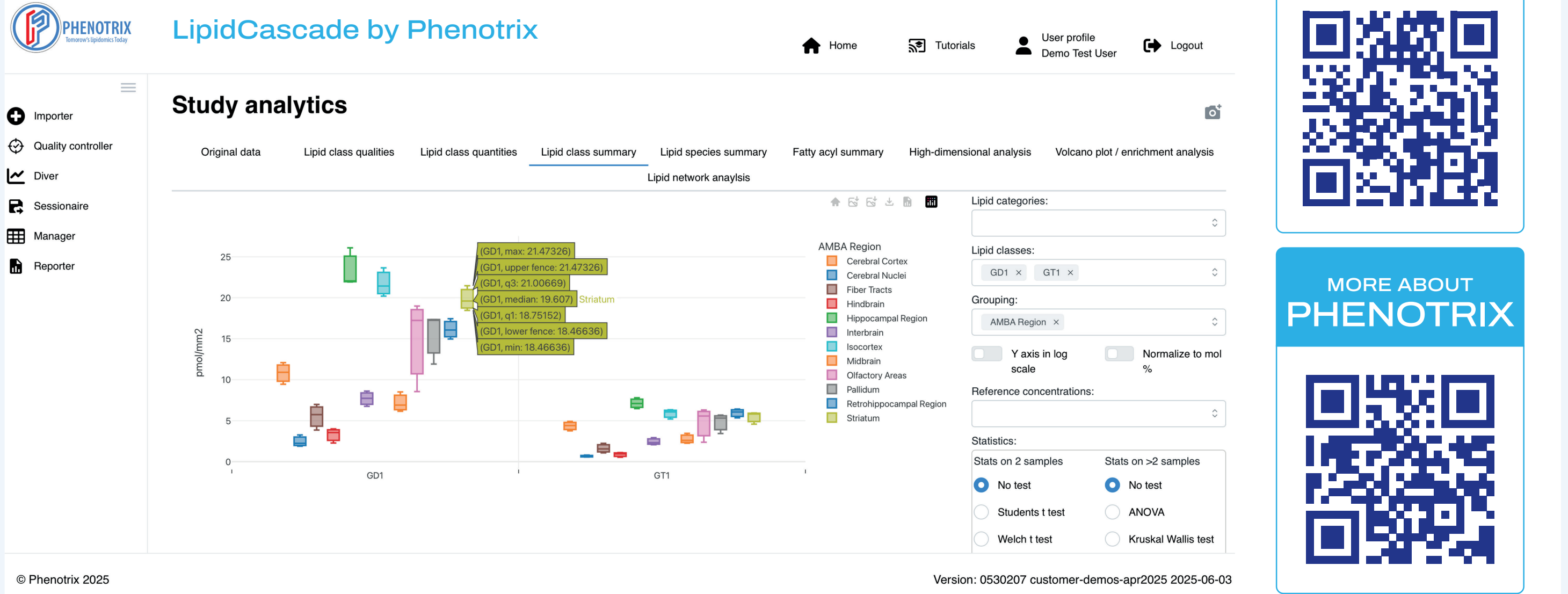
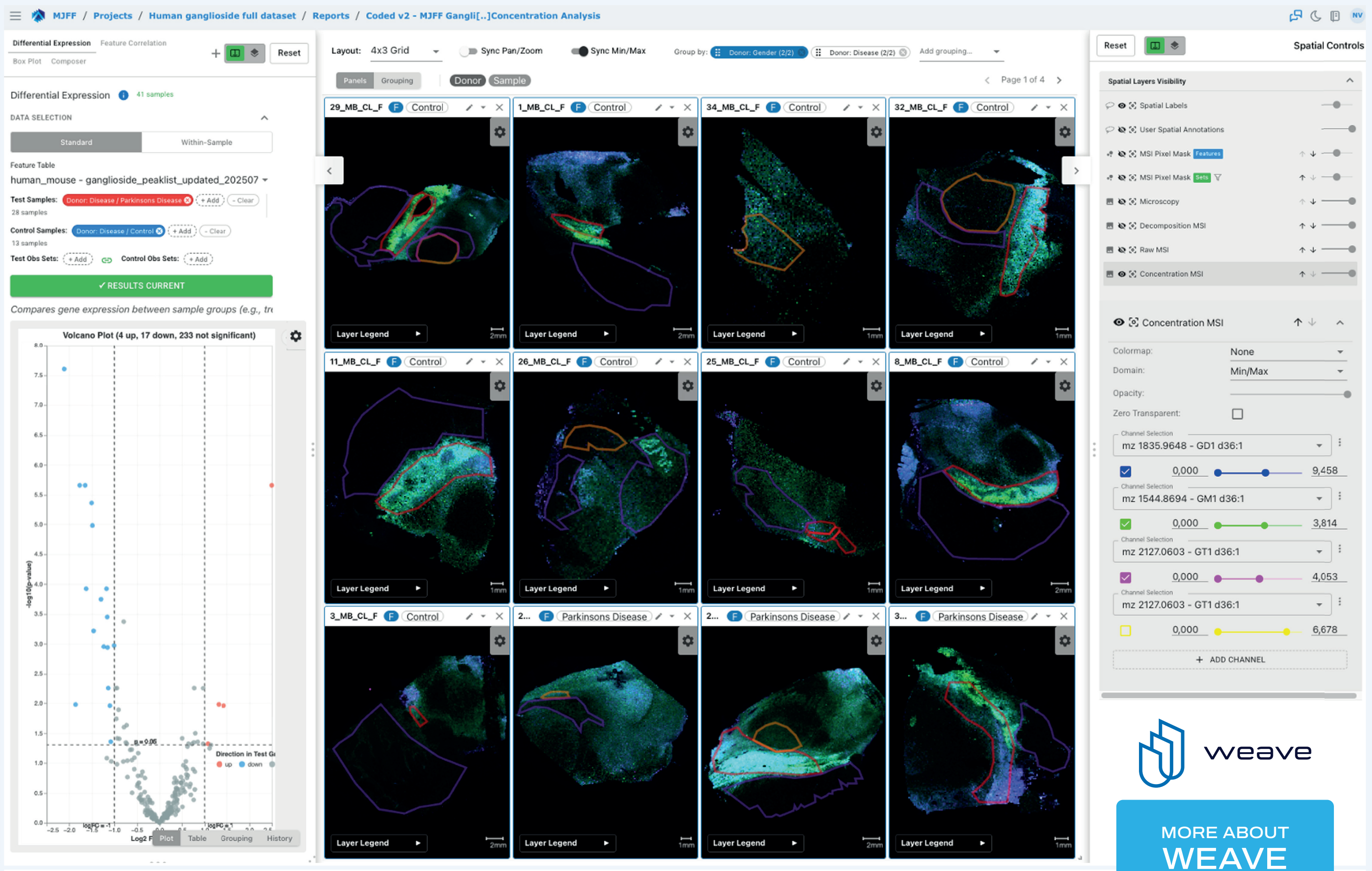


Figure 2: Cloud-based Spatial and Data Analysis Platforms. Weave (top) was used for visualization, exploration and analysis of MALDI-MSI data. This screenshot shows multi-sample view and differential analysis of different human brain samples. LipidCascade (bottom) was used for downstream lipidomics analysis.

Results

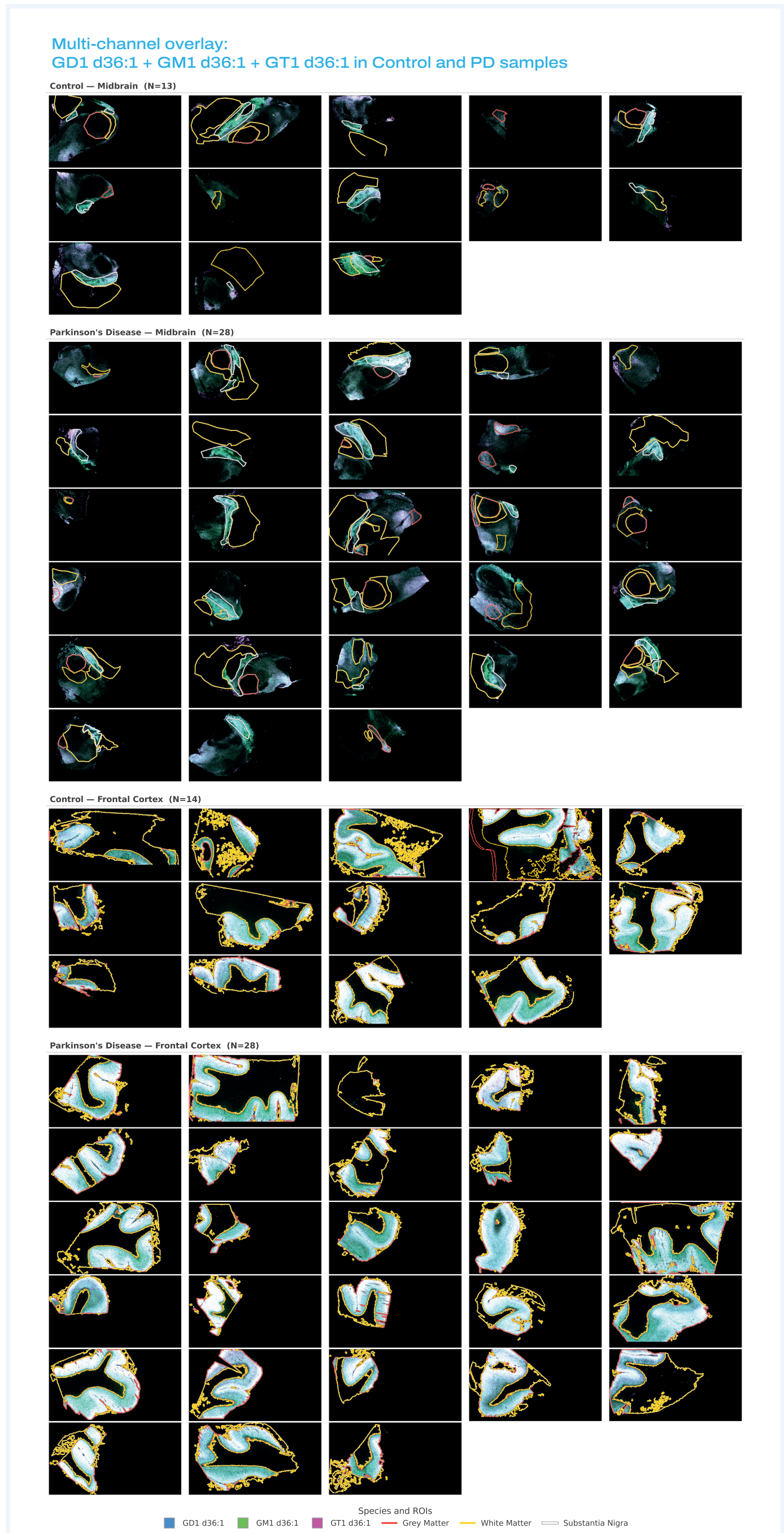


Figure 4 Composite image of GD1 d36:1, GM1 d36:1, GT1 d36:1 concentrations using the 95 pct quantile as the max, measured by Q-MSI across all 83 human tissue sections measured in this study. Midbrain tissues were manually annotated by a pathologist (Grey Matter, White Matter, Substantia Nigra). Frontal Cortex tissues were annotated using a cosine similarity classification model, segmenting the different regions (Grey Matter, White Matter), and verified by a pathologist.

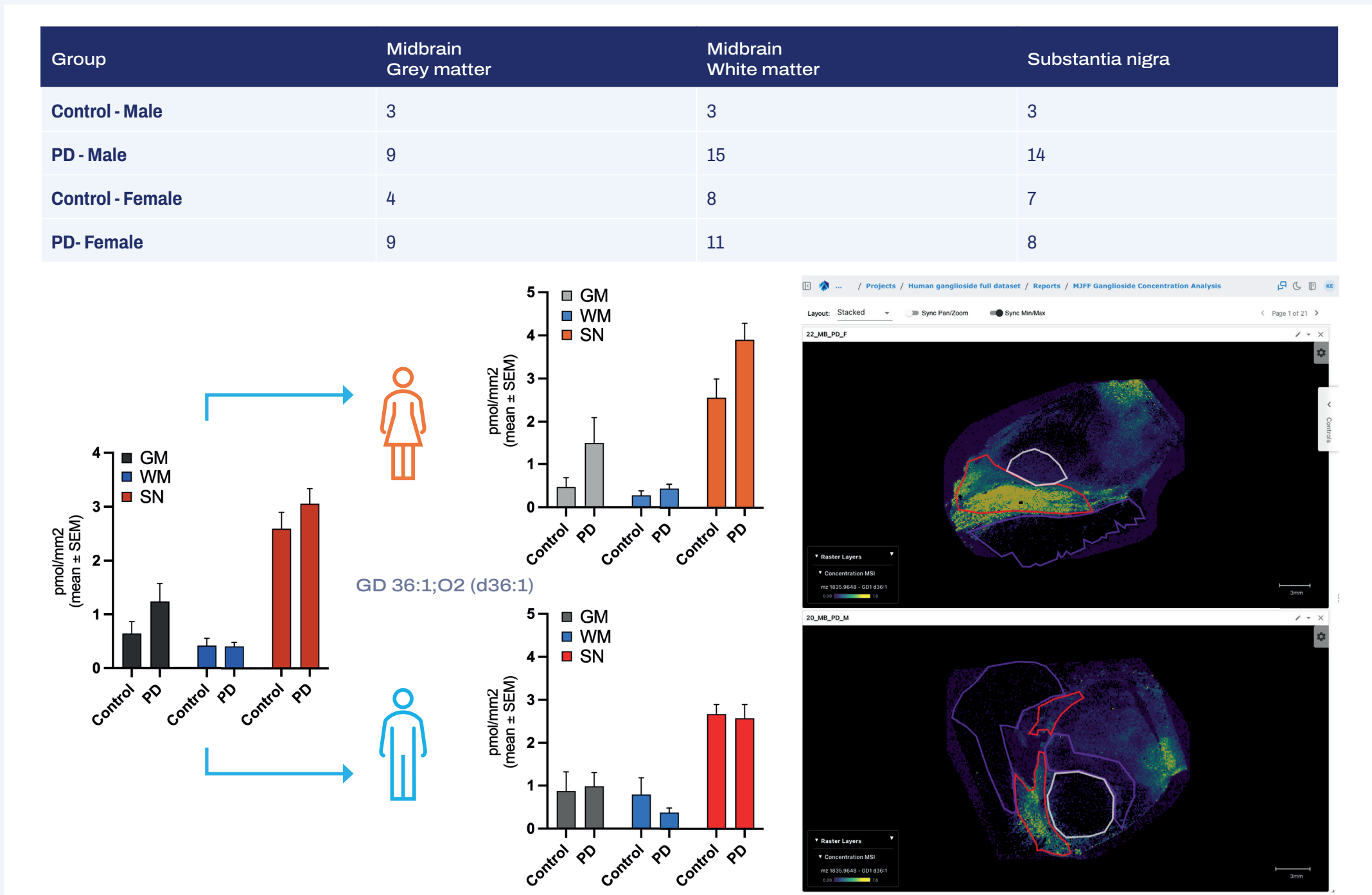
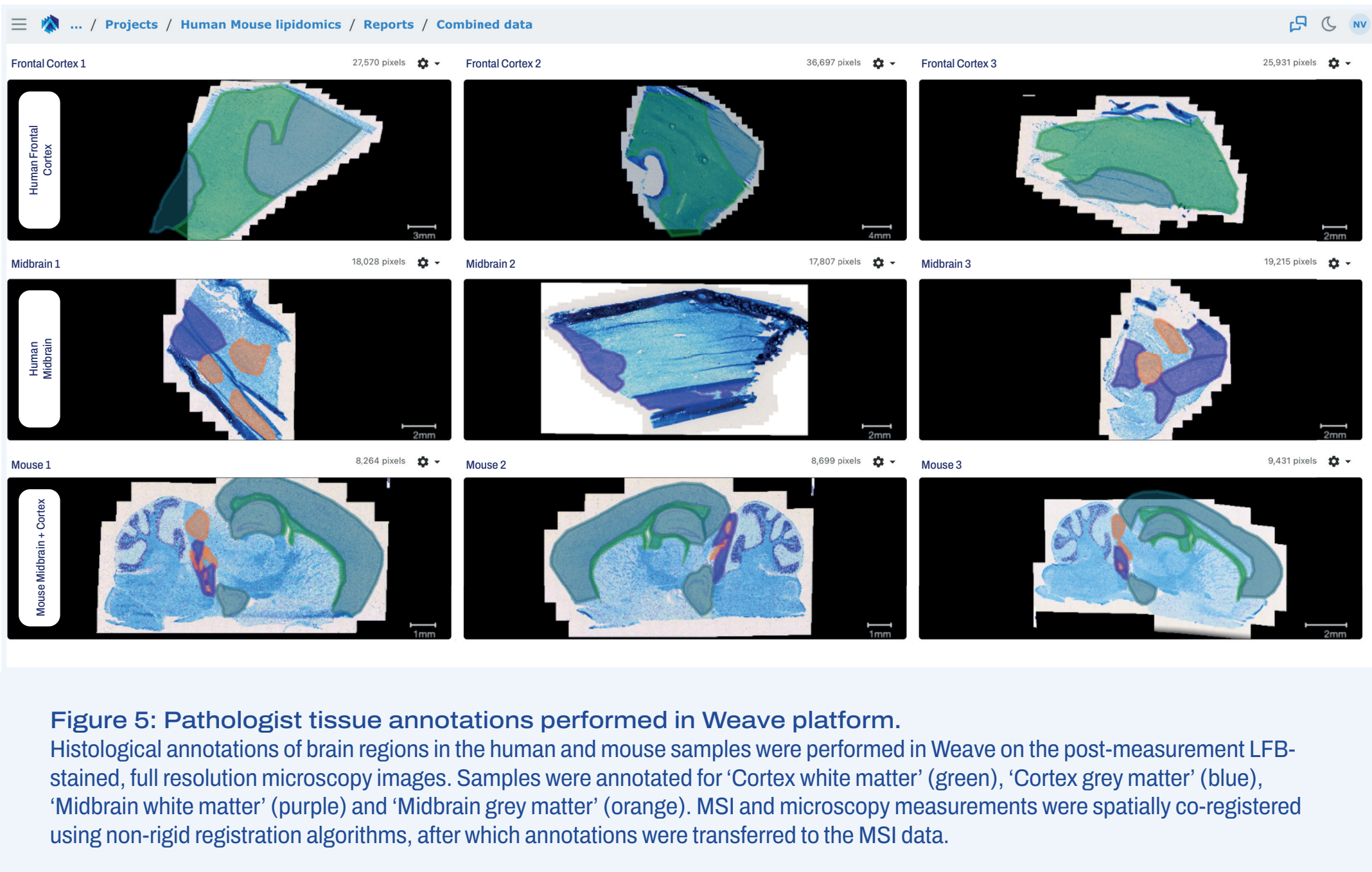


Figure 7 Concentration Changes in PD are Region- and Species-selective. When comparing all controls vs all PD samples, GD 36:1: O2 (d36:1) is slightly increased across the grey matter (GM) and substantia nigra (SN), no change is observed in the white matter (WM). When the samples are split into genders, female samples exhibit pronounced changes in the GM and SN. No change is observed in male samples.

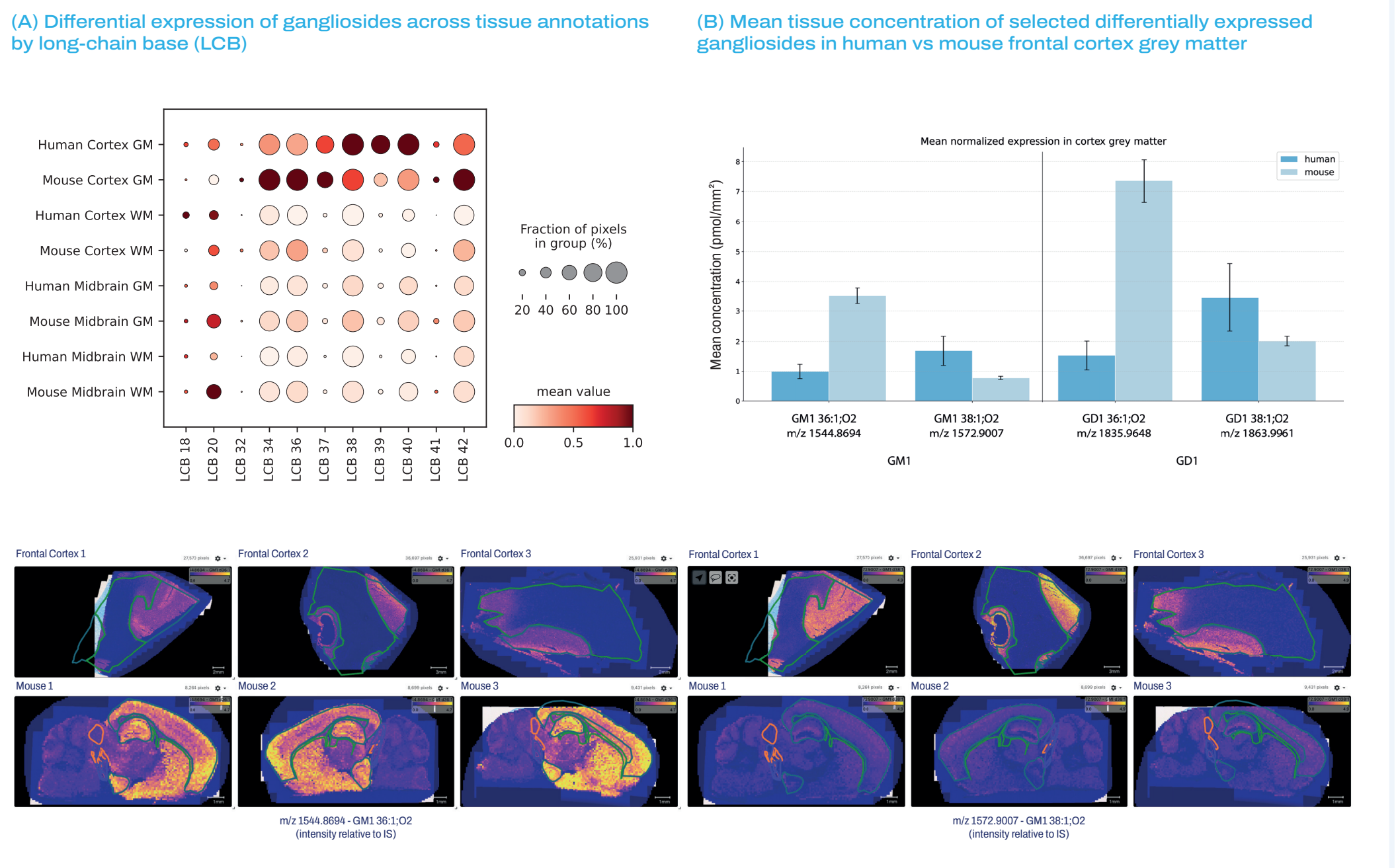


Figure 6: Differential analysis mouse-human samples. The Q-MSI workflow enables direct quantitative comparison of ganglioside expression across regions of interest between species. **Left A:** Dot plot showing mean ganglioside concentrations, grouped by long-chain base (LCB). Mean expression values are normalized (0–1) within each LCB. This analysis reveals marked differences in LCB composition between human and murine brain, particularly in the cortex grey matter. **Left B:** Mean concentration in tissue of GM1 36:1:O2 vs GM1 38:1:O2 and GD1 36:1:O2 vs GD1 38:1:O2 across regions of interest. The ratio of GM1 36:1:O2/GM1 38:1:O2 and GM1 36:1:O2/GM1 38:1:O2 respectively is inverted between mouse and human brain tissue. **Bottom:** Standard-normalized expression of GM1 36:1:O2 vs GM1 38:1:O2 in tissue. Differences in expression in the cortex grey matter (blue annotation) are visually pronounced, highlighting structural and metabolic variations between human and murine brains.

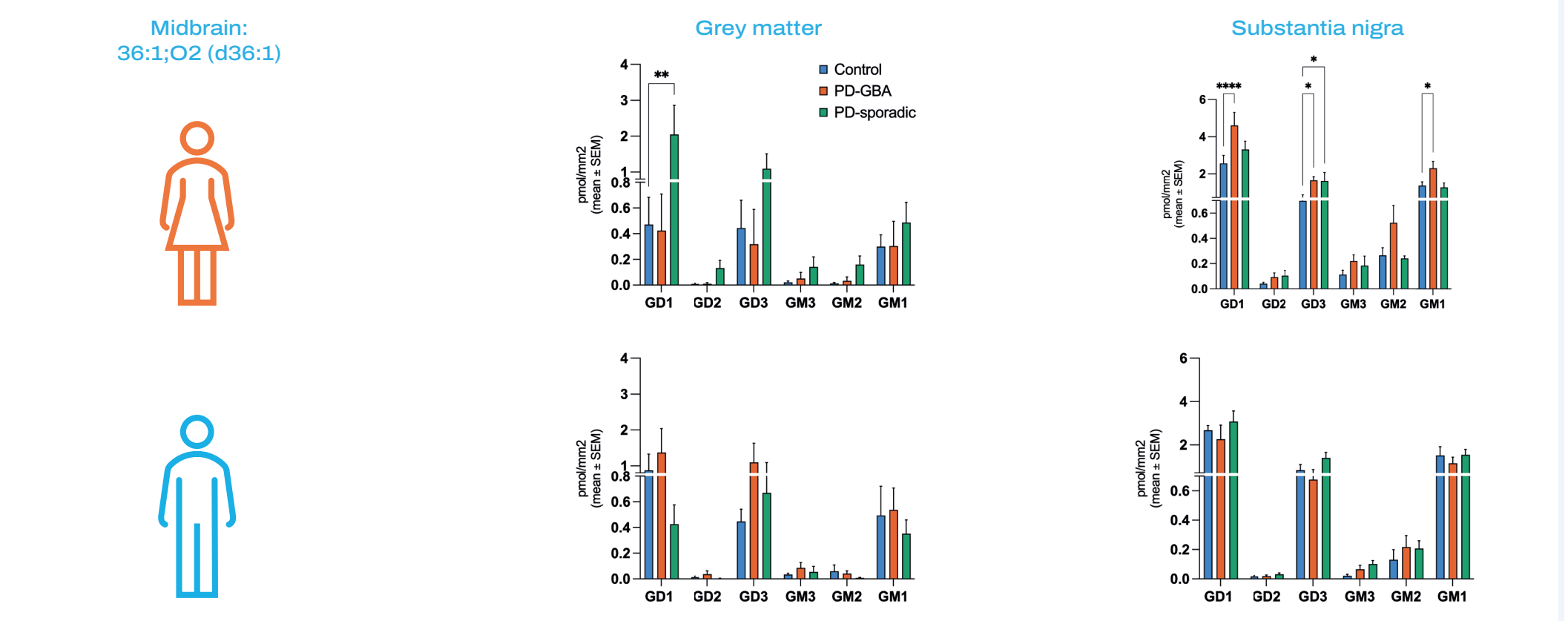


Figure 8 Remodeling of Ganglioside Pathways varies according to gender, control and PD-status, brain region and area, and ganglioside class. For GD 36:1: O2 (d36:1), females with sporadic PD exhibit overall increased ganglioside expression in the GM, with significantly increased GD1 class type. In comparison, female patients with GBA1 mutation-associated PD exhibit significantly increased GD1, GD3, and GM1 class gangliosides in the SN. No significant change is observed in male samples across GM or SN. Statistics used are 2-way ANOVA with Dunnett comparisons.

Conclusion & Outlook

- Established quantitative ganglioside concentration maps for different regions of human and mouse brain
- Human and mouse brains express distinct ganglioside landscapes that should be taken into account in translational work.
- In patient brain specimens, ganglioside pathway remodeling varies by sex, mutation status, brain region, subregional anatomy, and ceramide backbone composition.
- Brain ganglioside remodeling is more pronounced in female patients

With the support of

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