Integrative single-plaque analysis reveals signature Aβ and lipid profiles in the Alzheimer's brain

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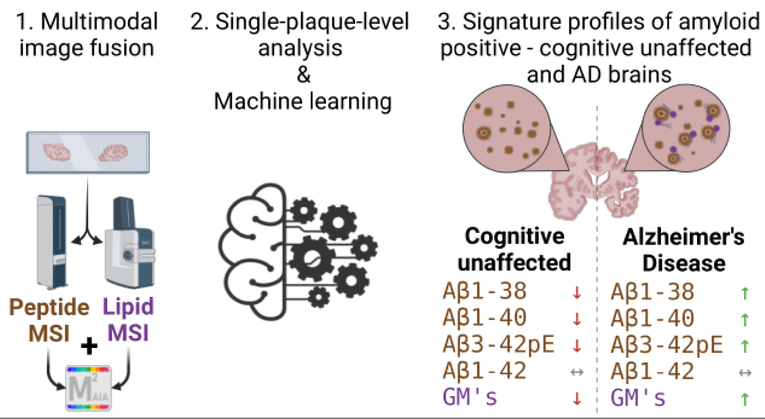
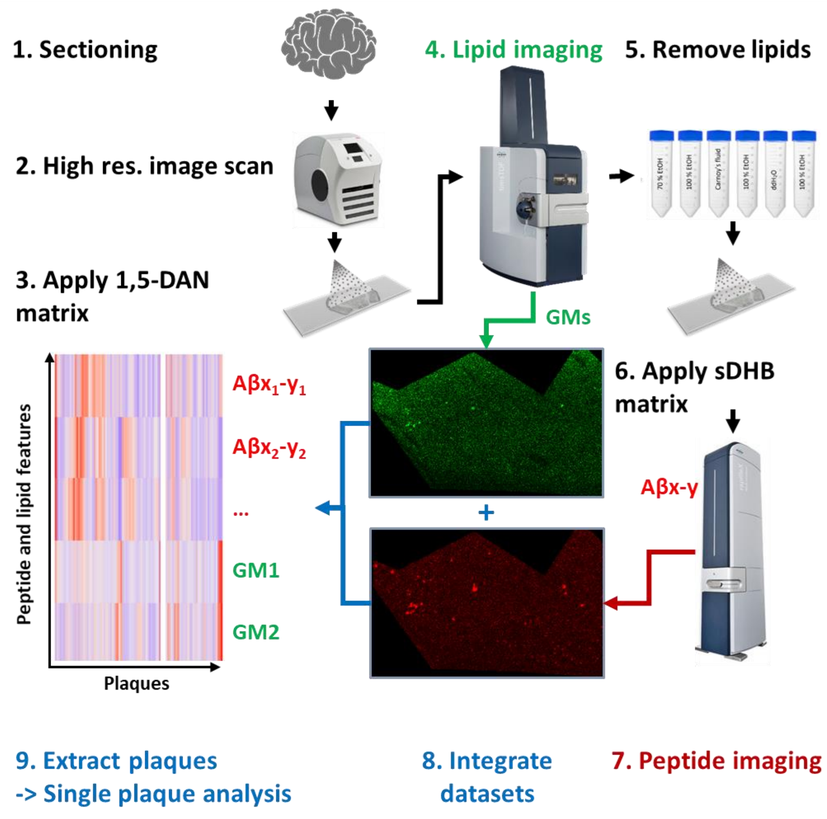
Introduction

Utilizing multimodal mass spectrometry imaging (MSI) combined with machine learning techniques, this study investigates the molecular heterogeneity of amyloid-β (Aβ) plaques and associated lipid profiles in post-mortem brain samples from Alzheimer's disease (AD) and amyloid-positive cognitively unaffected (AP-CU) individuals. Our analytical approach permitted investigation of large populations of plaques at the single-plaque level, revealing distinct populations of amyloid plaques characterized by differential Aβ and lipid compositions. Notably, the integration of MSI data with machine learning based feature extraction enabled the identification of Aβ38 and ganglioside GMx(36:1) as molecular markers differentiating AD from AP-CU pathology.



Method



Results

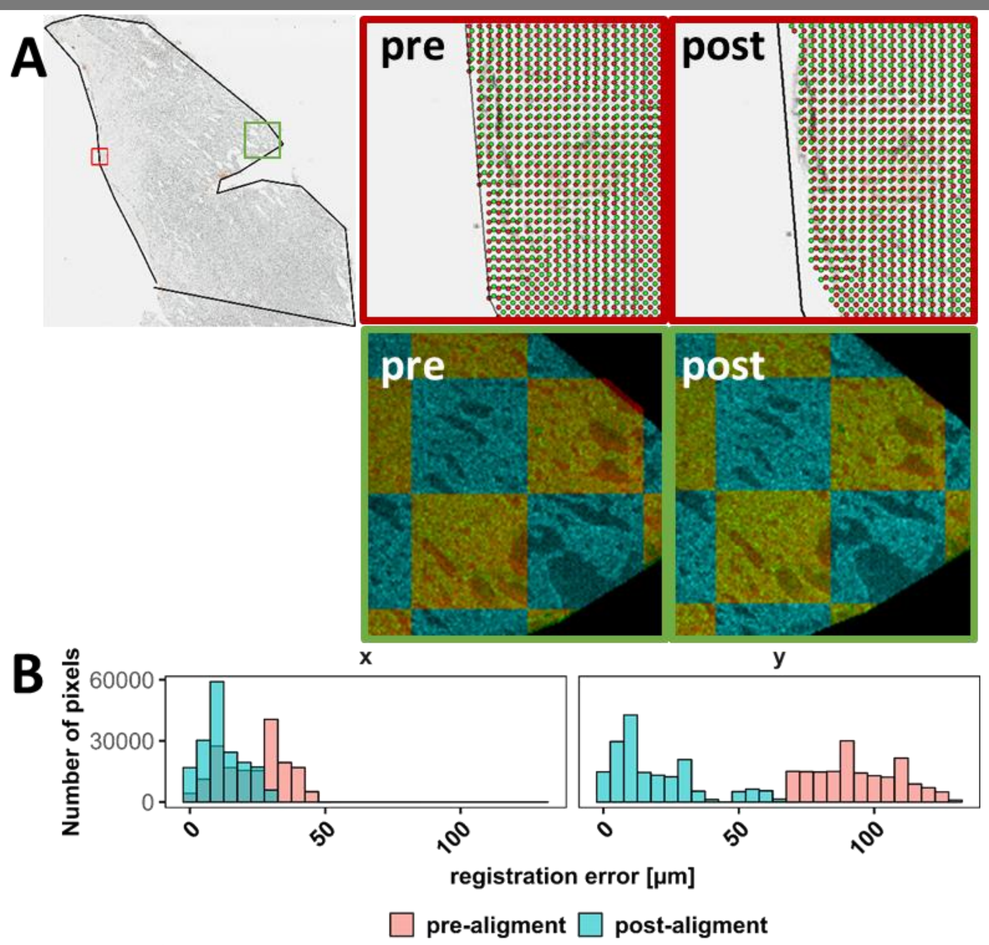


Figure 4 Peptide/Lipid-MSI alignment evaluation.

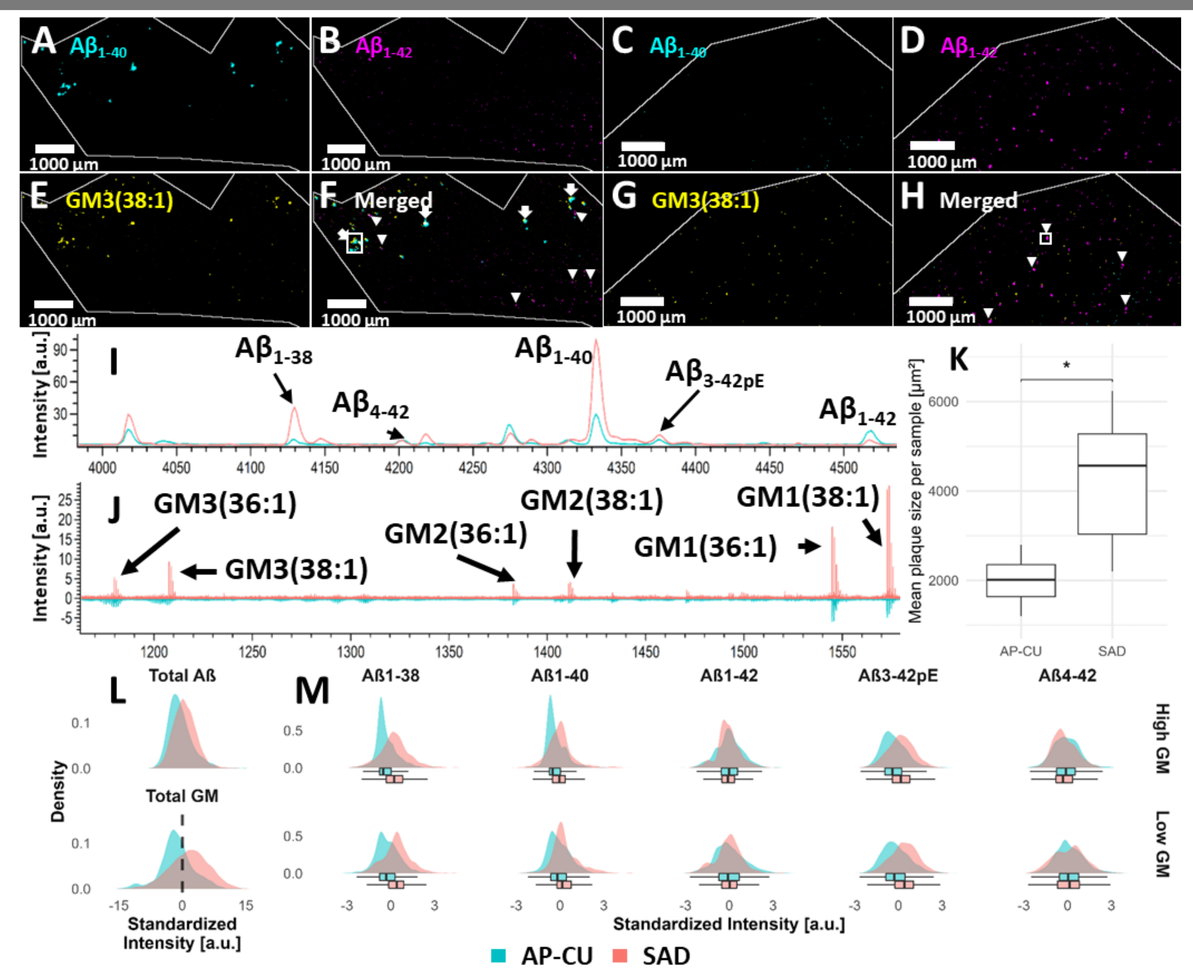


Fig. 1: Ganglioside isoforms are enriched in a subset of plaques from sporadic Alzheimer's disease (SAD) patients but less so in plaques from AP-CU cases.

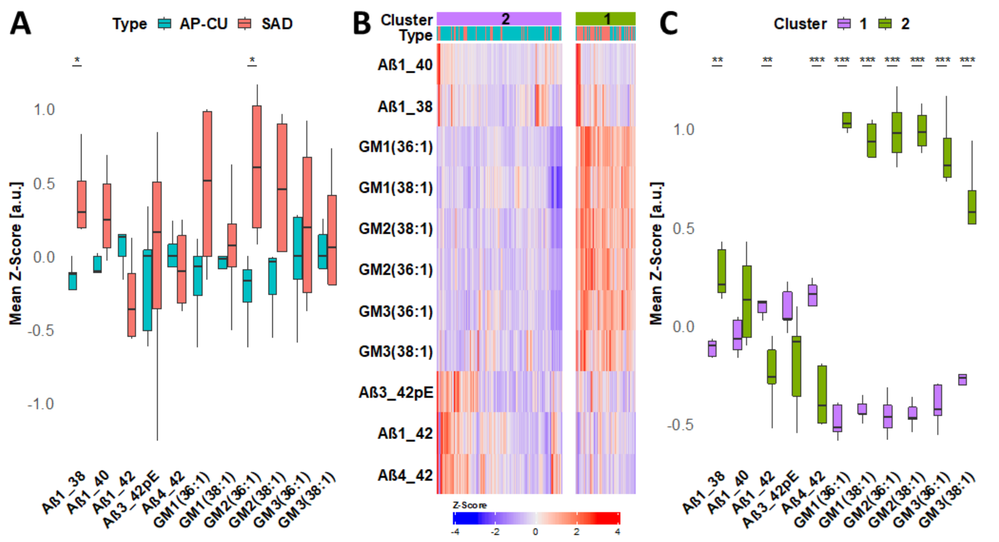


Figure 2. Single plaque analysis reveals accumulation of gangliosides in a subgroup of plaques from sporadic Alzheimer's disease (SAD) but not AP-CU cases.

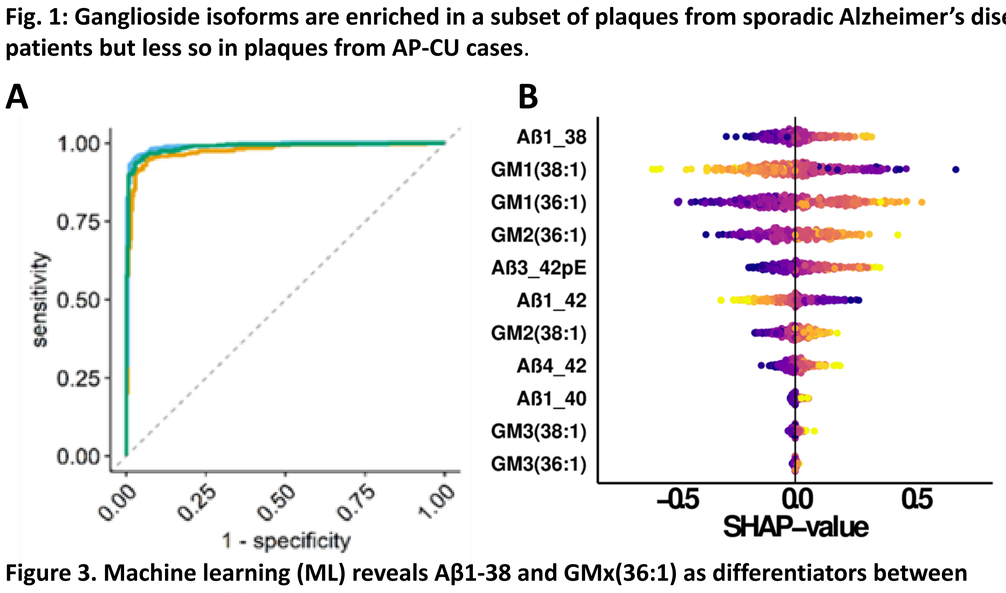


Figure 3. Machine learning (ML) reveals Aβ1-38 and GMx(36:1) as differentiators between SAD and AP-CU conditions.

Conclusion

The integration of MSI data with machine learning based feature extraction enabled the identification of Aβ1-38 and ganglioside GM1/GM2 as molecular markers differentiating AD from AP-CU pathology. These findings suggest that the heterogeneity in Aβ metabolism and lipid homeostasis is a key factor in the pathogenesis of AD and implies that total amyloid burden alone is an insufficient marker for the disease.

Acknowledgements

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