Amyloid Plaque Polymorphism is Associated with Distinct Lipid Accumulations Revealed by Trapped Ion Mobility (TIMS) Mass Spectrometry Imaging

Wojciech Michno[1, 2, 3], Patrick Wehrli[1], Srinivas Koutarapu[1], Christian Marsching[4, 5], Sven Meyer[6], Henrik Zetterberg[1, 7, 8, 9], Kaj Blennow[1, 7], Corinna Henkel[6], Janina Oetjen[6], Carsten Hopf[4], Jörg Hanrieder[1, 7, 10]

[1]University of Gothenburg, Göteborg, Sweden; [2]Department of Neuroscience, Physiology and Pharmacology; University College London, London, United Kingdom; [3]Stanford University, Stanford, CA; [4]Center for Mass Spectrometry and Optical Spectroscopy (CeMOS), Mannheim Technical University, Mannheim, Germany; [5]Bruker Daltonics GmbH & Co. KG, Bremen, Germany; [6]Bruker Daltonics GmbH & Co.KG, Bremen, Germany; [7]Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital, Gothenburg, Sweden; [8]Department of Neurodegenerative Disease, Institute of Neurology, University College London, London, United Kingdom; [9]UK Dementia Research Institute, University College London, London, United Kingdom; [10]Department of Neurodegenerative Disease, Institute of Neurology, University College London, London, United Kingdom

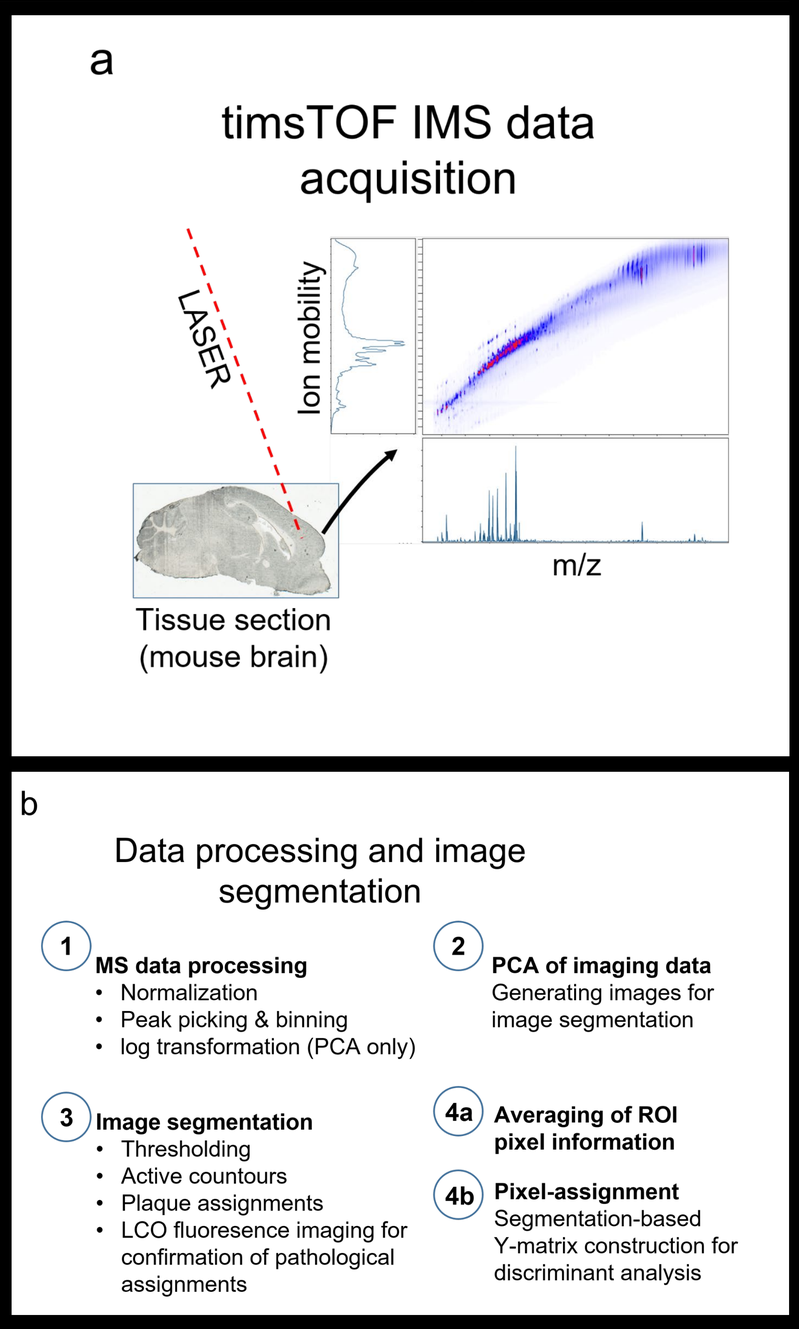
Background

Understanding of Alzheimer's disease (AD) pathophysiology requires molecular assessment of how key pathological factors, specifically amyloid β (Aβ) plaques, influence the surrounding microenvironment. Here, neuronal lipids are of interest as these are implicated in pathological- and neurodegenerative processes in AD. The exact molecular characteristics of the cellular environment in direct proximity to Aβ plaques are still unknown. One of the reasons being the high molecular complexity of lipid species but also the lacking spatial resolution, sensitivity, and specificity of analytical approaches. Likewise, it has been a challenge to investigate how such microenvironmental changes differ across structurally polymorphic Aβ features. Complemental multimodal imaging approaches are required to gain knowledge about these structural and molecular changes at a microenvironmental scale.

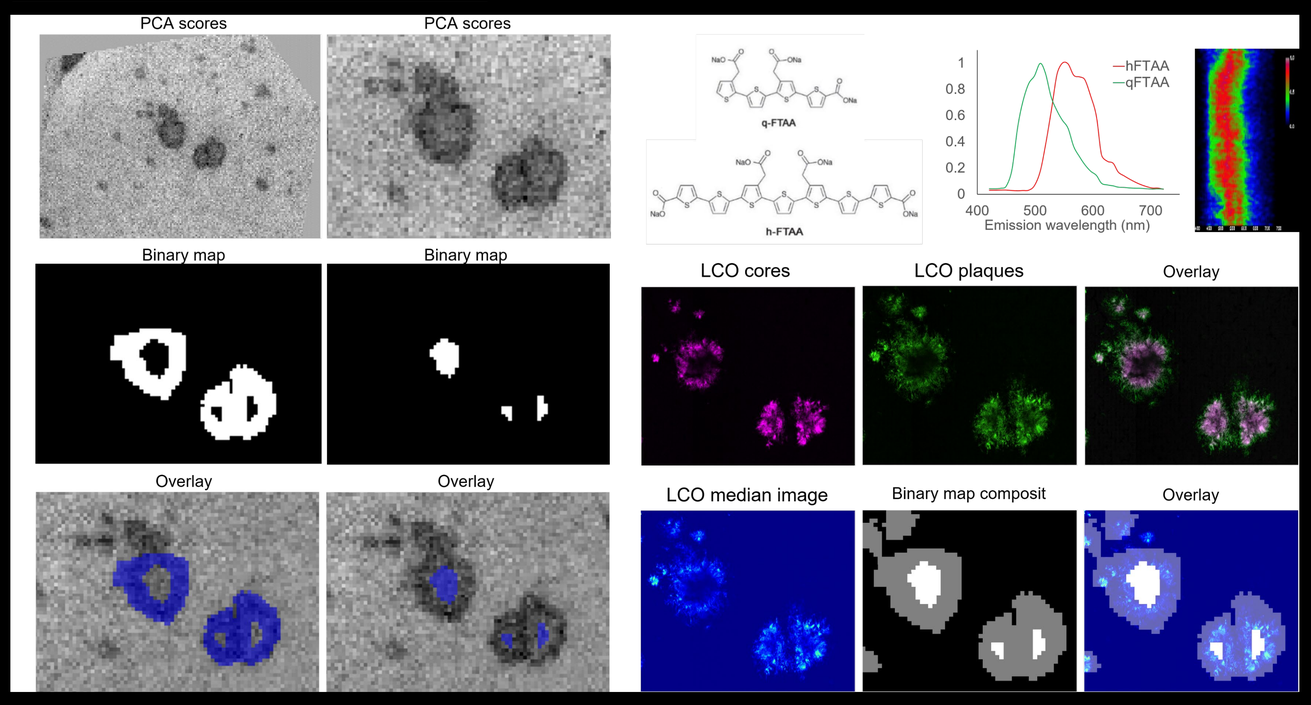
Herein, we used matrix assisted laser desorption/ionization mass spectrometry imaging (MALDI-MSI) trapped ion mobility Time-of-Flight (TIMS TOF) in combination with hyperspectral microscopy to probe the lipidomic microenvironment associated with structural polymorphism of Aβ plaque in transgenic mouse model of Alzheimer's disease (tgAPPSWE).

Experimental

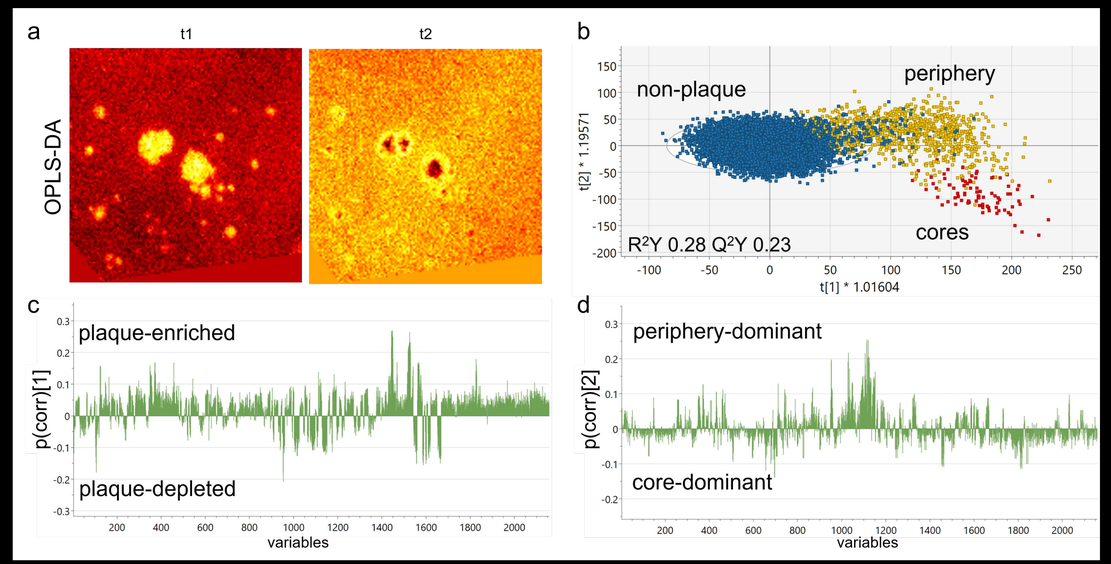
Schematic workflow for processing of timsTOF IMS data



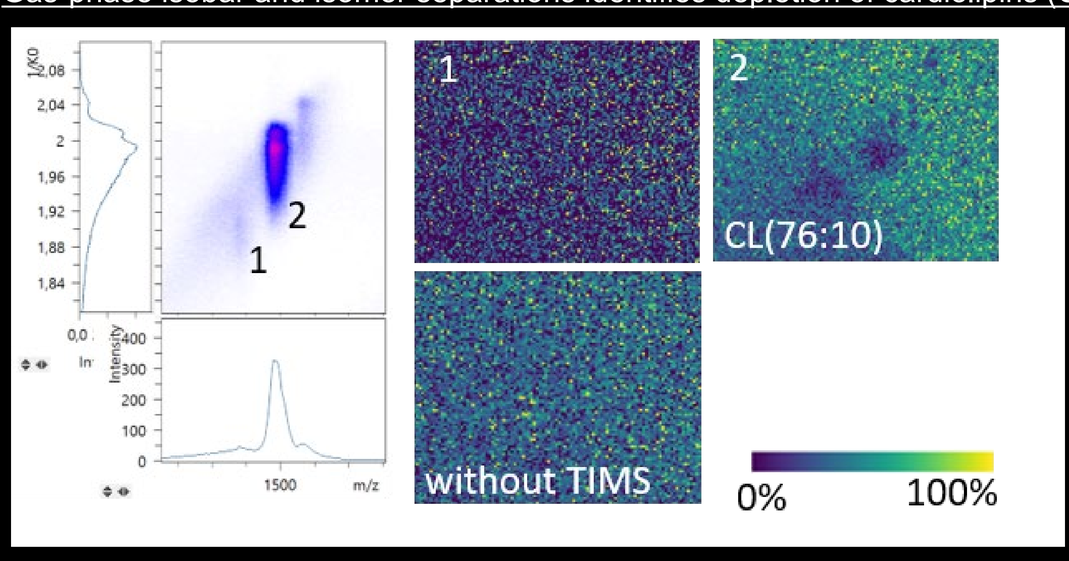
Multimodal Image Segmentation



OPLS-DA modeling of timsTOF IMS data on image basis



Gas-phase isobar and isomer separations identifies depletion of cardiolipins (CLs)



Results

- The integrated multimodal imaging analysis demonstrated alteration of multiple lipid classes
- There exists both a uniform Aβ associated enrichment/depletion, but also unique distribution of PAs and PIs to more/less aggregated Aβ fibrillary structures present within individual Aβ plaques.

Conclusions

Multimodal imaging approaches overcome limitations associated with conventional advanced molecular imaging applications allowing for differentiation of both, distinct components in complex mixtures of compounds, as well as their correlation to disease relevant Aβ proteoforms.