Investigation of Lipid Biomarkers in Amyotrophic Lateral Sclerosis Using Mass Spectrometry Imaging

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Objective

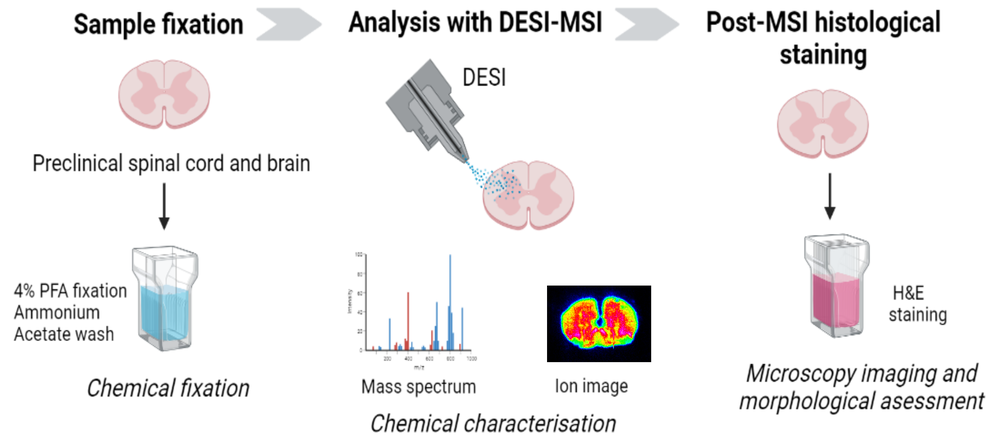
The application of Mass Spectrometry Imaging (MSI) can be used for the investigation of lipid metabolism dysregulation. Preclinical mouse brain and spinal cord tissues were analysed prior to human tissue from patients with slow and fast ALS progression to assess the link between altered metabolism of lipids and the progression of ALS.

Desorption Electrospray Ionisation Mass Spectrometry Imaging (DESI-MSI)

DESI-MSI provides the surface analysis of biological samples for the visualisation of molecular information *in-situ*. DESI-MSI is a label-free, soft ionisation technique carried out under atmospheric pressure conditions. At MDC, the DESI source is attached to a SYNAPT G2-Si system as part of our bespoke multimodal Mass Spectrometry laboratory.

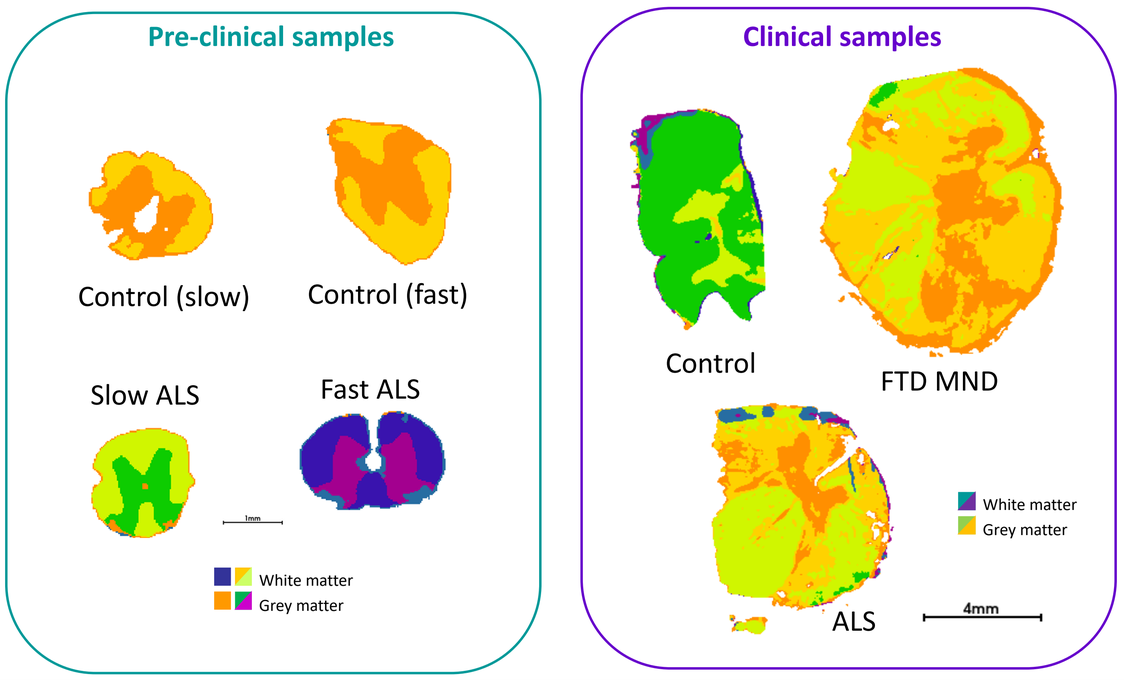
Methodology

Coronal sections from brain and spinal cord were obtained from four mouse models: control slow ALS, control fast ALS, fast ALS and slow ALS. Human coronal spinal cord sections from three different patients diagnosed with Amyotrophic lateral sclerosis (ALS), Frontotemporal dementia TDP Motor Neuron Disease (FTD-TDP-MND) or non-dementia (control) were obtained from the tissue biobank.
Each section was chemically fixed with paraformaldehyde (PFA) and washed with ammonium acetate. Thereafter, each sample was analysed with DESI-MSI and subsequently stained with H&E for histological assessment and image overlay (not presented here).

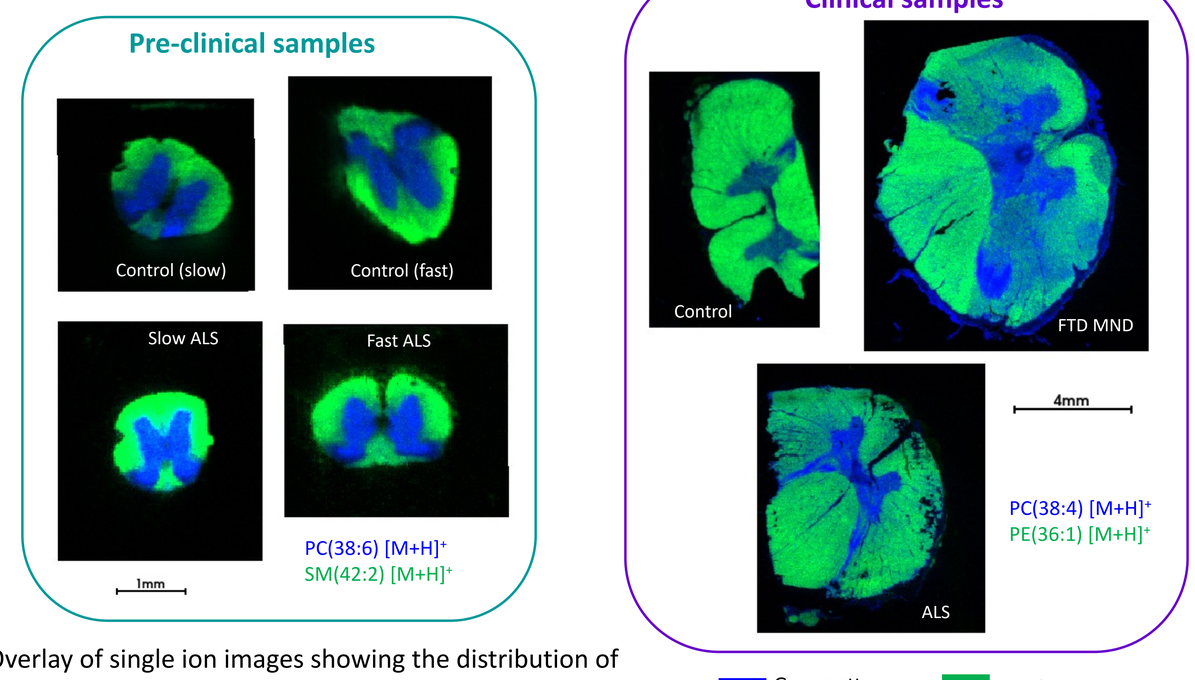


Lipid Biomarkers Identified Clinical and Pre-clinical Spinal Cord Sections

Image Segmentation Bisecting k-means

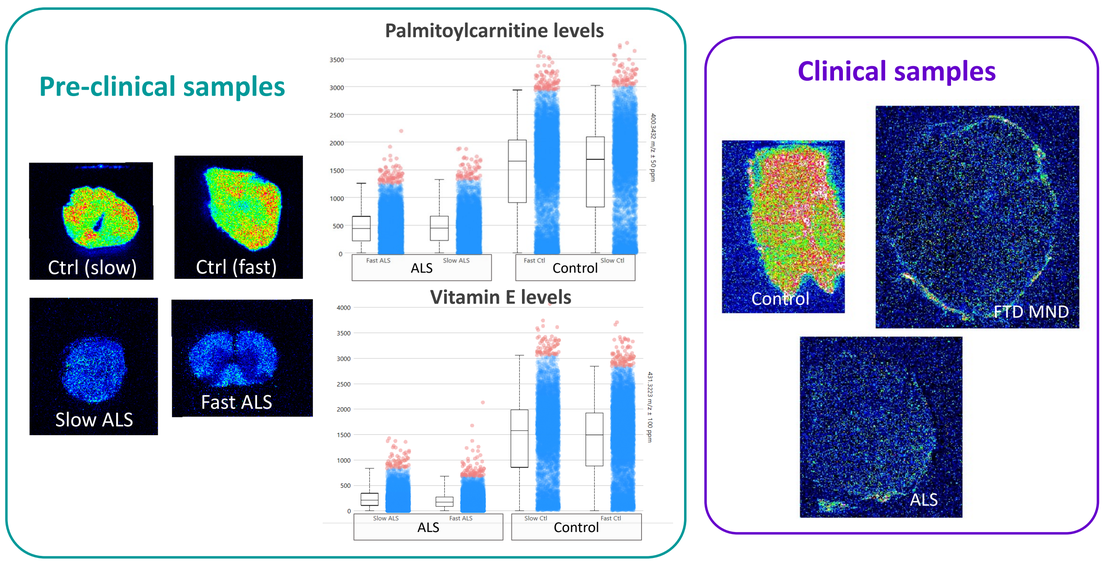


Distribution of Structural Lipids



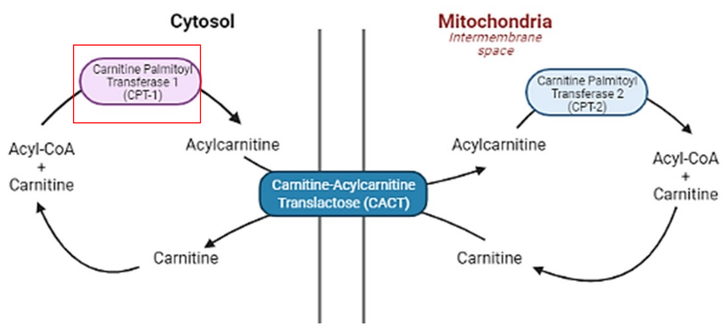
Overlay of single ion images showing the distribution of structural lipids in grey and white matter of the spinal cord.

Grey matter White matter



Single ion images acquired with DESI-MSI showing the distribution of O-palmitoylcarnitine $[M+H]^+$

Decreased Signal from Vitamin E and Acyl Carnitines as a Consequence of Mitochondrial Insufficiency an During ALS



Carnitine shuttle system. Acyl-CoA cannot penetrate the mitochondrial membrane and therefore has to be conjugated to a carnitine to enter. Carnitines bond to a long chain fatty acid via the action of Carnitine Palmitoyl Transferase 1 (CPT-1) to be transported inside the mitochondria.

Palmitoylcarnitine may be down-regulated in ALS as a consequence of mitochondrial degeneration. This leads to a dysregulation of the beta-oxidation of fatty acid metabolic pathway during the progression of central nervous system disorders. Downregulation of vitamin E has been previously linked to the ageing process as it thought to play a role in modulating cellular energy production through the carnitine shuttle system.

Conclusions

Potential lipid biomarkers were identified in ALS samples with DESI-MSI. These findings support a link between altered metabolism of lipids and the progression of ALS. Further MSI experiments will provide insight into the translational nature of the MSI methods implemented and into the role of highlighted biomarkers and their potential application in drug discovery.

References

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