Lipidomic profiling of healthy and Alzheimer's disease mouse brains by using DESI Imaging Mass Spectrometry (IMS): regional lipid dyshomeostasis in Alzheimer's disease

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ABSTRACT

Alzheimer's disease (AD) is one of the biggest health challenges that we face worldwide, which causes millions of deaths annually and costs reach many billions. Yet, the cause of the disease is not fully understood and therefore no effective treatment is available up to date. Lipidomic data from autopsy brain, human plasma and animal models highlight severe lipid dyshomeostasis in AD. The importance of lipid metabolism in AD is supported by GWAS studies which have identified multiple lipid modifying enzymes and interacting proteins. Thus, the regional disruption of lipid metabolism and homeostasis are likely to play a crucial role in the development of Alzheimer's pathology. It is clear that specific pathways in lipid metabolism underlie AD disease mechanisms leading to behavioral impairment. Specifically, previous studies have shown that the loss of polyunsaturated fatty acids among multiple phospholipid classes is common in AD affected human brain and mouse models. Therefore, it is of high importance to identify the highly specific and precise regionally dysregulated lipid species in both healthy and AD affected human and mouse brains. By applying Imaging Mass Spectrometry (IMS) using Desorption Electrospray Ionization (DESI) Synapt G2-Si (Waters), we have developed a workflow for high-content regionally specific lipidomics profiling for healthy and AD affected brains. We have shown regional dysregulation of specific lipid species in different brain areas including hippocampus, a brain region known to be vulnerable in early in AD. As supported by our preliminary data, the IMS will allow us to detect broad range of versatile lipid species by applying targeted and Untargeted analysis, Ion Mobility Separation, and DESI Imaging. Such analysis will allow insight into disease susceptibility, progression and perhaps allow identification of novel therapeutic strategies.
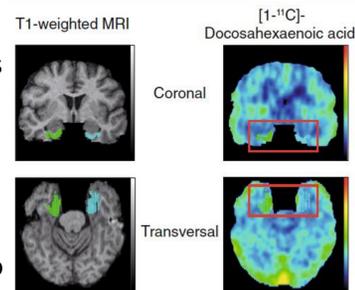
Fig. 1. DHA brain uptake and APOE4 status: a PET study with [1-^{11}C]-DHA. Greater DHA brain uptake in APOE4 carriers by age 30 with 7x higher risk of development of AD. Yassine *et al.*, Alz Res & Therapy. 2017
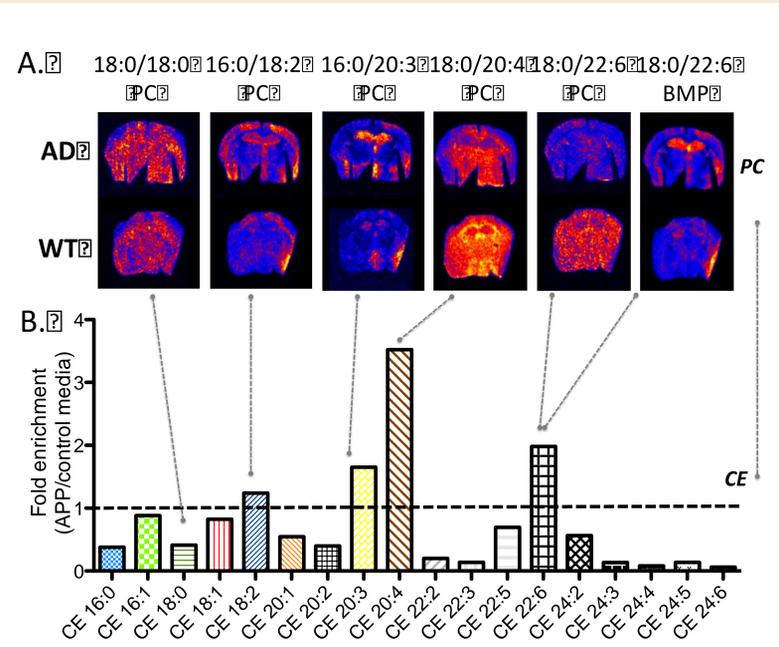

Fig. 2. Pathologically enriched lipids in Aβ immuno-isolated particles suggest acyl chain coordination between phosphatidylcholine (PC) and cholesteryl ester (CE) species.
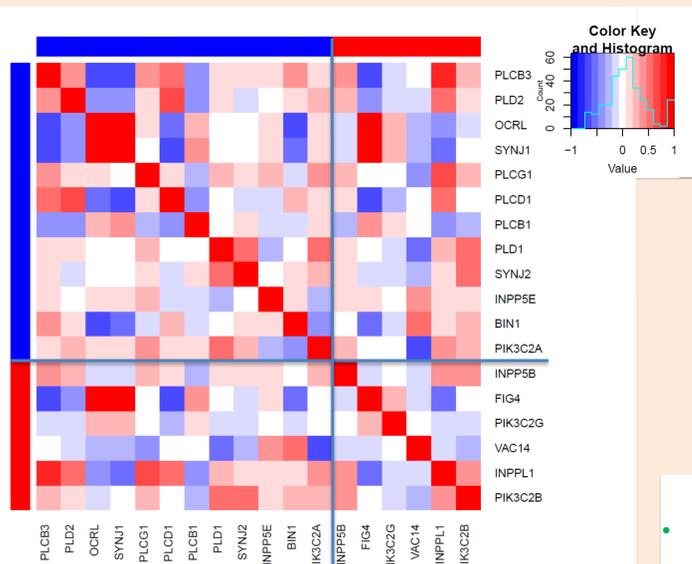
Fig. 3. Expression co-variance analysis using pairwise correlation coefficients calculated across all relevant genes using bulk RNA-seq from Religious Order Study/Rush Memory and Aging Project (ROS-MAP) identified co-varying modules PLCb3/PLD2 and Synj1/Ocrl associated with AD/dementia.
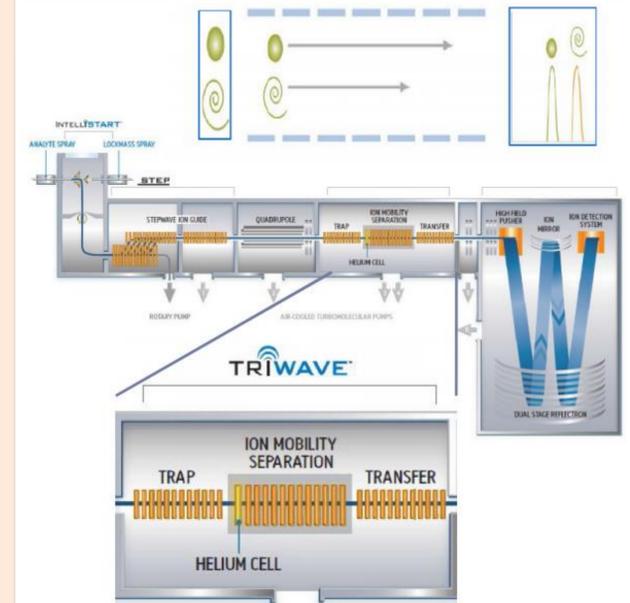
DESI-MS WORKFLOW, DATA ACQUISITION & PROCESSING

- The data acquired by the MS are processed by SCiLS Lab software (Bruker)
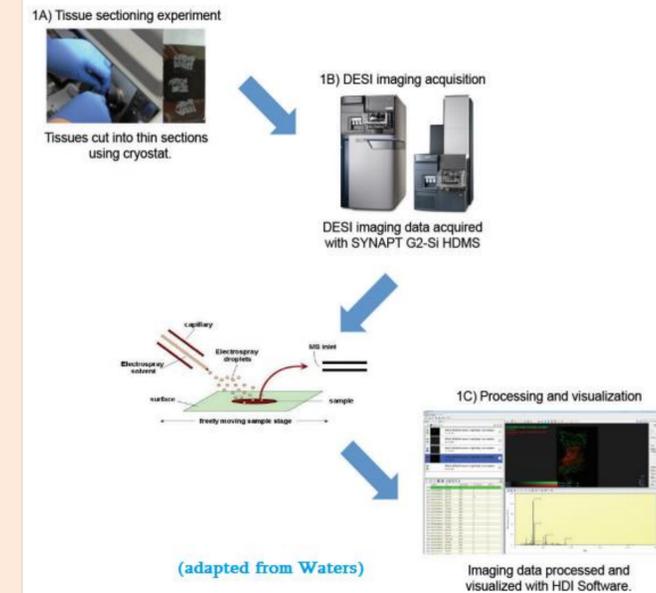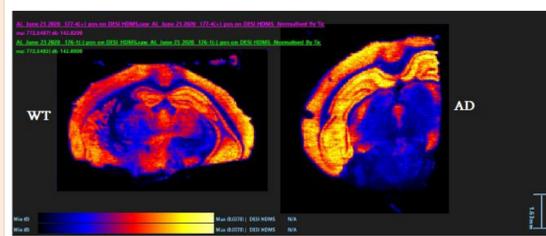

Fig. 4. General workflow of DESI-MSI.

- SCiLS Lab extracts ions peak list from whole brain or region of interest, i.e. hippocampus.

Fig. 5. The schematic view of Synapt G2-Si Mass Spectrometer (Waters) MS (Ion Mobility Separation).
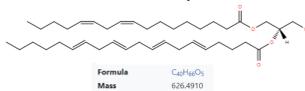
- The m/z list of precursor ions is 'translated' into possible lipid candidates using www.lipidmaps.org database.

Fig. 6. DESI-MS images of brain sections of WT and AD mice acquired in positive mode for the ion m/z=772.5; Scale bar 1.63 mm. Images are visualized by HDI software.

A candidate structure DG 37:6 lipid

m/z (±0.01)	AD±SD, ppm	WT±SD, ppm	AD/WT	P-value	Possible lipid candidates
610.5384	0.808±0.15	1.824±0.01	0.44	0.01	DG 34:2
617.5106	68.991±27.37	171.378±25.97	0.4	0.02	DG 36:4 / DG 34:1 / DG 35:2
630.6157	1.417±0.63	3.106±0.23	0.46	0.05	Cer 42:2;O2 / Cer 40:0;O
630.6183	1.198±0.45	3.841±0.79	0.31	0.02	Cer 42:2;O2 / Cer 40:0;O
635.514	46.315±1.46	96.239±4.1	0.48	0.001	CerP 34:1;O2 / CE 14:0 / DG 37:5
638.5634	3.462±0.53	7.413±0.67	0.47	0.003	DG 36:2
638.5687	2.022±0.58	4.821±0.33	0.42	0.008	DG 36:2
640.5809	1.681±0.51	4.141±0.72	0.41	0.02	DG 36:1
644.5259	7.64±1.88	20.704±3.49	0.37	0.02	FA 40:7;O3 / Cer 36:0;O4 / DG 37:6
645.5351	26.57±6.16	66.296±8.61	0.4	0.008	SM 31:0;O2 / DG 36:1
648.6243	0.745±0.35	3.087±0.55	0.24	0.01	Cer 42:2;O2 / Cer 42:1;O3
648.6265	1.499±0.68	4.715±0.83	0.32	0.01	Cer 42:2;O2 / Cer 42:1;O3
671.5491	2.398±0.42	7.417±1.65	0.32	0.04	PE-Cer 36:1;O2 / SM 33:1;O2 / DG 38:2
681.4824	43.593±5.72	135.651±23.99	0.32	0.03	PA O-36:5 / PA 36:3 / PA O-34:2 / PS O-28:1 / DG 38:5
691.5206	3.562±0.06	9.64±0.75	0.37	0.007	PA 35:0 / DG 42:9 / PG O-32:0 / DG 40:6 / TG 37:0 / DG 38:3 / PA O-36:3
816.6522	303.44±101.57	645.495±110.01	0.47	0.03	PC 38:1/PE 41:1 / HexCer40:1;O4 / PS O-40:0 / PA 43:2 / PE O-42:4
817.6465	130.69±52.41	299.841±62.74	0.44	0.04	PC 37:2 / PE 40:2

Table 1. Lipids of the hippocampus region of WT and AD mouse brains showing depletion in the AD brain. The WT/AD ratios are obtained from the averages of N=3 biological replicates. DESI-MS detection mode is positive; the m/z values include the adducts.

- In our preliminary results, we successfully set up a DESI-MS Imaging workflow and identified several putative lipid ions showing depletion in the hippocampus region of brain from AD mouse model. The brain sections were scanned by Synapt G2-Si Mass Spectrometer using Ion Mobility Separation (HDMS) in both positive and negative modes. The data was processed by SCiLS Lab software.
- In future work, we will target candidates listed in Table 1 for targeted lipidomics [LC-MS/MS] analysis to identify the molecular structure of putative lipid ions. This will allow us to assess how the lipid structure (acyl chain length, saturation state, etc.) correlates with the AD pathogenesis.