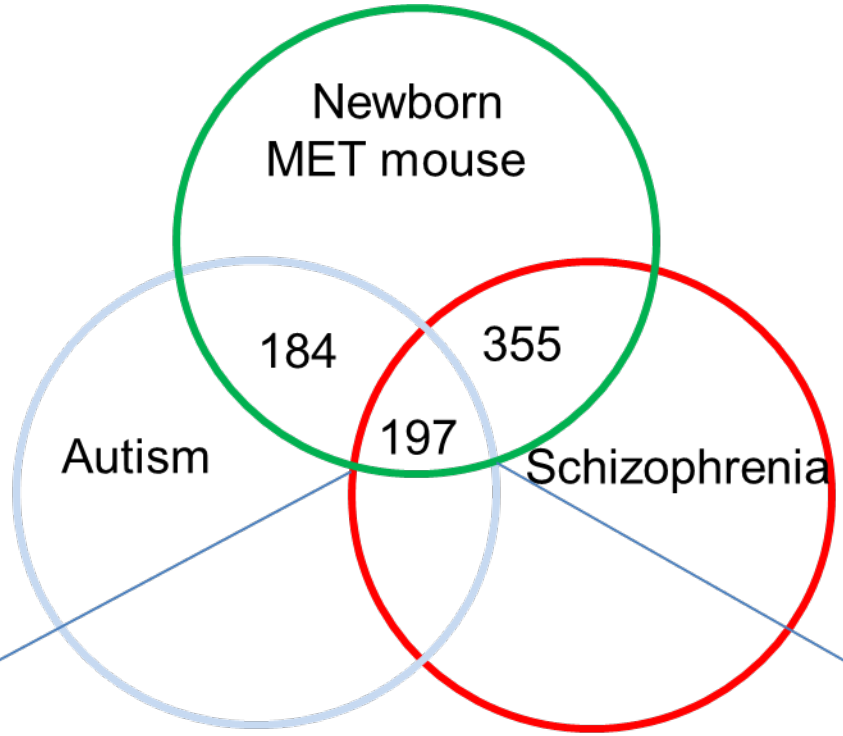
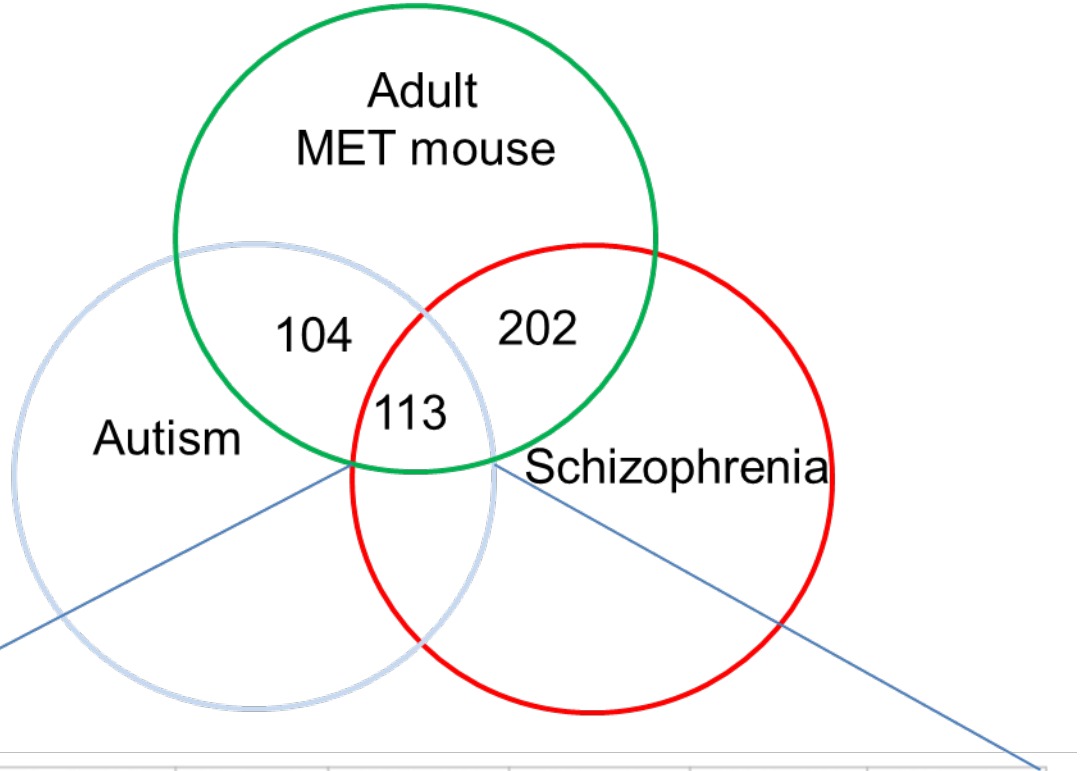
Supplementary Figure 1a




| Gene_Symbol | MET.log2FC | MET.P-val | ASD.log2FC | ASD.p.value | SCZ.log2FC | SCZ.p.value |
|---|---|---|---|---|---|---|
| SERPINA3N | 0.871843649 | 0.0002 | 1.1546822 | 0.0041541 | 0.9327256 | 1.14E-13 |
| TPD52L1 | - 0.731183242 | 5.42E-05 | 0.2569486 | 0.0048815 | 0.1262865 | 8.91E-06 |
| SESN2 | 0.687060688 | 0.0002 | 0.2334936 | 0.0023911 | 0.1124706 | 2.01E-06 |
| GFAP | 0.650764559 | 0.0002 | 0.3272682 | 0.0034481 | 0.1417304 | 9.47E-05 |
| NHP2L1 | - 0.584962501 | 0.0107 | -0.089384 | 0.0049057 | -0.020432 | 0.0438139 |
| HSPA5 | 0.565597176 | 9.20E-08 | 0.1809459 | 0.0295751 | 0.0590221 | 0.0206079 |
| FDPS | 0.475084883 | 0.0007 | -0.123438 | 0.0011553 | -0.036591 | 0.0023864 |
| HSP90B1 | 0.464668267 | 1.90E-05 | 0.1390337 | 0.0082098 | 0.0473852 | 0.003538 |
| MAP3K5 | 0.464668267 | 0.0105 | 0.1092901 | 0.0073146 | 0.0380869 | 0.0040021 |
| GPR137B | 0.432959407 | 0.0008 | 0.2148763 | 0.0003337 | 0.0451982 | 0.0191243 |

Supplementary Figure 1b




| Gene_Symbol | MET.log2FC | MET.p.val | ASD.log2FC | ASD.p.value | SCZ.log2FC | SCZ.p.value |
|---|---|---|---|---|---|---|
| TSNAX | - 0.367371 | 0.03923 | -0.17647 | 4.37E-05 | -0.0349 | 0.009231 |
| SLC11A1 | 0.31034 | 0.008124 | 0.473048 | 0.041415 | 0.354799 | 6.78E-07 |
| MC4R | - 0.275007 | 0.009921 | 0.398237 | 0.000727 | 0.244528 | 4.09E-10 |
| RPL13A | 0.275007 | 0.006816 | 0.11091 | 0.007259 | 0.030688 | 0.021933 |
| MID1 | 0.263034 | 0.030505 | 0.276535 | 0.000319 | 0.11375 | 3.26E-06 |
| PLSCR4 | 0.263034 | 0.018974 | 0.312723 | 0.000991 | 0.161755 | 1.68E-07 |
| LDLRAP1 | 0.250962 | 0.018588 | 0.20735 | 0.03451 | 0.10872 | 0.000861 |
| NXPH3 | 0.238787 | 0.014262 | -0.2556 | 0.000266 | -0.09609 | 3.24E-05 |
| PPP1R14C | 0.238787 | 0.021609 | -0.16866 | 0.001735 | -0.03953 | 0.022549 |
| NBEAL2 | 0.238787 | 0.043181 | 0.167713 | 0.003826 | 0.047478 | 0.011623 |

**Supplementary Figure 1**

**Integrated mouse-human transcriptomic analysis reveals overlap between genes changed in MET mice and schizophrenia, and autism patients**

**a.** Genes whose expressions are changed in the brains of newborn MET mice, schizophrenia patients, and autism patients

**b.** Genes whose expressions are changed in the brains of adult MET mice, schizophrenia patients, and autism patients

Supplementary Table 1. Newborn metabolite differential expressions

| Metabolite name | pVal | Fold_Change |
|---|---|---|
| Malonyl-carnitine | 1.42E-08 | 17.37784019 |
| PC(34:3) | 0.003225576 | 3.574221846 |
| LPC(20:4) | 0.009898235 | 3.175387368 |
| LPC(22:6) | 0.005861152 | 2.786656371 |
| N-Acetylalanine | 0.020758666 | 2.545295921 |
| Ceramide (d34:0) | 1.34E-05 | 2.509074836 |
| LPC(18:3) | 0.00156866 | 2.496785714 |
| FA (16:1) (palmitoleic acid) | 0.000190152 | 2.410129596 |
| PC(p-36:4)/PC(o-36:5) | 0.028178573 | 2.3496485 |
| LPC (16:1) | 0.005343272 | 2.20554044 |
| LPC(16:1) | 0.003248755 | 2.086582552 |
| LPC(20:3) | 0.000388322 | 2.059253928 |
| FA (18:1) (oleic acid) | 9.01E-05 | 2.051125414 |
| LPE (20:4) | 0.008111778 | 2.050065445 |
| FA (22:6) (docosahexaenoic acid) | 0.000259012 | 2.02644805 |
| 2-Propanamidoacetic acid | 0.046561051 | 1.999669893 |
| LPE(20:4) | 0.00354443 | 1.990588567 |
| LPE (22:6) | 0.009771699 | 1.984216306 |
| FA (20:4) (arachidonic acid) | 0.000381253 | 1.926877101 |
| Ergothioneine | 0.017048832 | 1.904308617 |
| FA (18:2) (linoleic acid) | 0.00013315 | 1.900305243 |
| FA (20:3) (homo-gamma-linolenic acid) | 2.51E-05 | 1.887569714 |
| FA (20:1) (eicosenoic acid) | 6.35E-05 | 1.852139775 |
| Cer(d42:1) | 7.73E-06 | 1.845950745 |
| GlcCer (d42:2) | 5.01E-06 | 1.819345942 |
| 1-monopalmitin (palmitoyl glycerol) | 0.014562486 | 1.800112296 |
| FA (20:2) (eicosadienoic acid) | 4.03E-05 | 1.774147029 |
| LPC(18:1) | 0.006345602 | 1.738119667 |
| FA (20:5) (eicosapentaenoic acid) | 0.00106048 | 1.731969101 |
| FA (18:3) (linolenic acid) | 0.000671825 | 1.724266992 |
| Methylglycinate | 0.047780322 | 1.714285714 |
| LPC (18:2) | 0.010863895 | 1.709048664 |
| Isoleucine | 0.02243996 | 1.701696475 |
| glutathione | 0.036729509 | 1.686834482 |
| FA (20:3) (eicosatrienoic acid) | 0.003619176 | 1.677735528 |
| Ceramide (d40:2) | 0.004406923 | 1.669829889 |
| LPE (18:2) | 0.002817457 | 1.668078859 |
| PC(42:10) | 0.035581665 | 1.658477842 |
| Pro-Gln | 0.048487458 | 1.646858033 |
| Ceramide (d42:1) | 1.99E-05 | 1.641631442 |
| LPC (18:1) | 0.022383612 | 1.638744964 |
| LPC(14:0) | 0.000919332 | 1.636602502 |
| phosphoenolpyruvate | 0.011634947 | 1.627368774 |
| ceramide(d34:1) | 0.000338275 | 1.625415475 |
| GlcCer(d34:1) | 0.018851089 | 1.625289291 |
| ceramide(d40:1) | 0.000218007 | 1.622755115 |

| | | |
|---|---|---|
| gamma-Glutamyl-L-glutamic acid | 0.00521573 | 1.606305605 |
| Ceramide (d40:1) | 0.001221676 | 1.600645327 |
| LPC (14:0) | 0.010213989 | 1.59375 |
| Ceramide (d41:1) | 0.000375285 | 1.593629132 |
| PC(37:4) | 0.044537526 | 1.58276117 |
| N,N,N trimethyllysine | 0.00528629 | 1.580642806 |
| Cytidine 5'-diphosphocholine | 0.039031493 | 1.578072208 |
| (2R)-3-Hydroxyisovaleroylcarnitine | 0.02189903 | 1.57180386 |
| FA (22:2) (docosadienoic acid) | 1.67E-05 | 1.548834558 |
| Ceramide (d33:1) | 0.000788701 | 1.542713184 |
| Ceramide (d34:1) | 0.00020458 | 1.513003873 |
| Citrulline | 0.002934252 | 1.508178487 |
| LPC(18:2) | 0.005980702 | 1.505751451 |
| Phenylalanine | 0.046352501 | 1.494811879 |
| LPE(18:0) | 0.000155769 | 1.48537659 |
| PG 34:2; PG 16:1-18:1 | 0.000740313 | 1.482888087 |
| Serine | 0.007874799 | 1.47509761 |
| Proline | 0.021629014 | 1.460093724 |
| GlcCer (d38:1) | 0.001267722 | 1.45780631 |
| Ceramide (d38:1) | 0.02988303 | 1.450890935 |
| Ceramide (d42:2) | 0.000204266 | 1.448209973 |
| glycine | 0.00249354 | 1.442933498 |
| ceramide(d42:2) | 0.007346085 | 1.439903868 |
| Betaine | 0.004378113 | 1.422000033 |
| ceramide(d38:1) | 0.019447342 | 1.419681051 |
| FA (14:1) (physeteric acid) | 0.000255794 | 1.419641477 |
| LPC (16:0) | 0.006337196 | 1.419327287 |
| Guanosine 5'-tetraphosphate | 0.01878964 | 1.381682644 |
| LPC(16:0) | 0.01926954 | 1.380779968 |
| Threonine | 0.021805471 | 1.378233512 |
| S-Adenosyl-L-methionine | 0.03780681 | 1.375611524 |
| FA (14:0) (myristic acid) | 0.000534169 | 1.352435553 |
| Uridine 5'-monophosphate | 0.038719373 | 1.338242444 |
| LPE (16:0) | 0.008000173 | 1.336140926 |
| .beta.-Nicotinamide adenine dinucleotide (N | 0.027644083 | 1.330447477 |
| N-Acetylaspartylglutamic acid | 0.031678685 | 1.318502034 |
| Guanine | 0.011415469 | 1.313997076 |
| LPC(18:0) | 0.041845937 | 1.300439441 |
| PC (35:1) | 0.001673869 | 1.299338698 |
| Uridine | 0.015460318 | 1.294951434 |
| Ceramide (d34:2) | 0.032542936 | 1.283715433 |
| PC (36:5) | 0.029199708 | 1.2761079 |
| PC (40:4) | 0.010632461 | 1.269081689 |
| hippuric acid | 0.037727235 | 1.265170038 |
| LPC (18:0) | 0.036701241 | 1.26043385 |
| PC (40:8) | 0.028178073 | 1.248804114 |
| Aspartic acid | 0.01055777 | 1.236658933 |

| | | |
|---|---|---|
| Ceramide (d32:1) | 0.017833902 | 1.233891688 |
| PC (34:4) | 0.010881093 | 1.231711656 |
| PC (35:4) | 0.019959144 | 1.202626178 |
| PC (34:3) | 0.022476296 | 1.202529123 |
| PC (38:3) | 0.004024444 | 1.201970443 |
| PC (36:1) | 0.050758861 | 1.197213048 |
| galacturonic acid | 0.016558363 | 1.196483891 |
| Inosine | 0.023737185 | 1.177160032 |
| PC (40:6) B | 0.042754477 | 1.176184338 |
| Adenine | 0.02808395 | 1.17057998 |
| PC (33:1) | 0.033295672 | 1.167377348 |
| PC (35:2) | 0.027614 | 1.166033734 |
| Creatine | 0.022912855 | 1.131943573 |
| stearic acid | 0.042024025 | -1.170770716 |
| heptadecanoic acid | 0.042367286 | -1.190333949 |
| 4-hydroxybutyric acid | 0.021800309 | -1.190575734 |
| 3-deoxyhexitol NIST | 0.01532955 | -1.192243767 |
| glutamic acid | 0.005577824 | -1.195742327 |
| isocitric acid | 0.049496068 | -1.234030309 |
| palmitic acid | 0.016621365 | -1.241368058 |
| phosphoethanolamine | 0.0340957 | -1.250177482 |
| orotic acid | 0.017171631 | -1.253148926 |
| uracil | 0.017249046 | -1.297383776 |
| fumaric acid | 0.001518153 | -1.320722296 |
| alpha-aminoadipic acid | 0.02215198 | -1.323910483 |
| leucine | 0.011370697 | -1.3252108 |
| ribonic acid | 0.002726209 | -1.339101338 |
| fucose | 9.31E-06 | -1.365242215 |
| nicotinamide | 0.001935704 | -1.372416175 |
| tyrosine | 0.005086967 | -1.385195884 |
| adipic acid | 0.008074106 | -1.414739759 |
| urea | 0.002817654 | -1.445821026 |
| glycolic acid | 0.022126295 | -1.463490404 |
| creatinine | 0.012422587 | -1.479562002 |
| lactic acid | 0.000265193 | -1.525590211 |
| SM(d36:1) | 0.042836939 | -1.564856564 |
| tartaric acid | 0.045332384 | -1.574576271 |
| tryptophan | 0.03897947 | -1.588580644 |
| methionine sulfoxide | 0.019447555 | -1.596146166 |
| DG(34:1) | 0.049989843 | -1.614326212 |
| SM (d36:1) | 0.004569146 | -1.620467284 |
| acetophenone | 0.004900414 | -1.658038825 |
| Trigonelline | 0.013151153 | -1.66828188 |
| glutamine | 0.01743561 | -1.9189826 |
| hypoxanthine | 0.001375521 | -2.009659686 |
| PG 44:12; PG 22:6-22:6; | 0.018960217 | -2.01024742 |
| PC(p-38:4)/PC(o-38:5) B | 0.006574967 | -2.069430315 |

| | | |
|---|---|---|
| guanosine | 0.000258347 | -2.104031857 |
| adenosine | 0.030525858 | -2.143022181 |
| threose | 0.000371668 | -2.208040307 |
| SM (d36:2) | 0.002192205 | -2.340853284 |
| trans-4-hydroxyproline | 0.036131287 | -3.781165819 |
| Sucrose | 0.018709327 | -4.654283145 |

Supplementary Table 2. Metaboanalyst analysis of enrichment pathways in the brains of newborn pups

| | Total Cmpd | Hits | Raw p | FDR |
|---|---|---|---|---|
| Purine Metabolism | 74 | 11 | 0.00017305 | 0.010866 |
| Arginine and Proline Metabolism | 53 | 13 | 0.00024146 | 0.010866 |
| Aspartate Metabolism | 35 | 9 | 0.0017542 | 0.045637 |
| Citric Acid Cycle | 32 | 4 | 0.0021556 | 0.045637 |
| Urea Cycle | 29 | 9 | 0.0033856 | 0.045637 |
| Carnitine Synthesis | 22 | 6 | 0.0035261 | 0.045637 |
| D-Arginine and D-Ornithine Metabolism | 11 | 1 | 0.0037003 | 0.045637 |
| Malate-Aspartate Shuttle | 10 | 2 | 0.0042442 | 0.045637 |
| Thyroid hormone synthesis | 13 | 1 | 0.005087 | 0.045637 |
| Mitochondrial Electron Transport Chain | 19 | 3 | 0.00554 | 0.045637 |
| Lysine Degradation | 30 | 1 | 0.0055778 | 0.045637 |
| Valine, Leucine and Isoleucine Degradation | 60 | 6 | 0.0068409 | 0.051307 |
| Warburg Effect | 58 | 9 | 0.010471 | 0.063719 |
| Beta-Alanine Metabolism | 34 | 3 | 0.010671 | 0.063719 |
| Amino Sugar Metabolism | 33 | 5 | 0.011008 | 0.063719 |
| Starch and Sucrose Metabolism | 31 | 5 | 0.011328 | 0.063719 |
| Ammonia Recycling | 32 | 7 | 0.016075 | 0.083697 |
| Nicotinate and Nicotinamide Metabolism | 37 | 9 | 0.017947 | 0.083697 |
| Fatty Acid Elongation In Mitochondria | 35 | 1 | 0.018619 | 0.083697 |
| Plasmalogen Synthesis | 26 | 4 | 0.018935 | 0.083697 |
| Phosphatidylcholine Biosynthesis | 14 | 7 | 0.019529 | 0.083697 |
| Threonine and 2-Oxobutanoate Degradation | 20 | 1 | 0.021805 | 0.087166 |
| Pyruvate Metabolism | 48 | 5 | 0.023119 | 0.087166 |
| Pyrimidine Metabolism | 59 | 9 | 0.023244 | 0.087166 |
| Fructose and Mannose Degradation | 32 | 4 | 0.024576 | 0.088473 |
| Arachidonic Acid Metabolism | 69 | 3 | 0.028581 | 0.094649 |
| Phenylalanine and Tyrosine Metabolism | 28 | 6 | 0.028784 | 0.094649 |
| Betaine Metabolism | 21 | 7 | 0.030446 | 0.094649 |
| Phospholipid Biosynthesis | 29 | 3 | 0.030498 | 0.094649 |
| Tryptophan Metabolism | 60 | 7 | 0.033948 | 0.10184 |
| Bile Acid Biosynthesis | 65 | 6 | 0.035603 | 0.10329 |
| Ubiquinone Biosynthesis | 20 | 3 | 0.036726 | 0.10329 |
| Galactose Metabolism | 38 | 10 | 0.042175 | 0.10767 |
| Gluconeogenesis | 35 | 6 | 0.042861 | 0.10767 |
| Methylhistidine Metabolism | 4 | 2 | 0.044104 | 0.10767 |
| Estrone Metabolism | 24 | 2 | 0.044104 | 0.10767 |
| Pyruvaldehyde Degradation | 10 | 1 | 0.044263 | 0.10767 |
| Phosphatidylethanolamine Biosynthesis | 12 | 5 | 0.049989 | 0.11839 |
| Phenylacetate Metabolism | 9 | 3 | 0.053442 | 0.12333 |
| Histidine Metabolism | 43 | 8 | 0.06765 | 0.14638 |
| Glycerolipid Metabolism | 25 | 5 | 0.068329 | 0.14638 |
| Glycolysis | 25 | 4 | 0.073444 | 0.14638 |
| Phosphatidylinositol Phosphate Metabolism | 17 | 2 | 0.074022 | 0.14638 |
| Steroid Biosynthesis | 48 | 5 | 0.075285 | 0.14638 |
| Cardiolipin Biosynthesis | 11 | 3 | 0.076353 | 0.14638 |
| Inositol Phosphate Metabolism | 26 | 1 | 0.078069 | 0.14638 |

| | | | | |
|---|---|---|---|---|
| Trehalose Degradation | 11 | 1 | 0.078069 | 0.14638 |
| De Novo Triacylglycerol Biosynthesis | 9 | 1 | 0.078069 | 0.14638 |
| Spermidine and Spermine Biosynthesis | 18 | 5 | 0.087883 | 0.16142 |
| Lactose Synthesis | 20 | 5 | 0.097734 | 0.17592 |
| Alpha Linolenic Acid and Linoleic Acid Metaboli | 19 | 1 | 0.10035 | 0.17709 |
| Porphyrin Metabolism | 40 | 2 | 0.12847 | 0.22235 |
| Inositol Metabolism | 33 | 2 | 0.14025 | 0.23375 |
| Sulfate/Sulfite Metabolism | 22 | 2 | 0.14025 | 0.23375 |
| Phytanic Acid Peroxisomal Oxidation | 26 | 2 | 0.14511 | 0.23745 |
| Ketone Body Metabolism | 13 | 1 | 0.15276 | 0.24551 |
| Biotin Metabolism | 8 | 1 | 0.17835 | 0.2816 |
| Mitochondrial Beta-Oxidation of Medium Chain | 27 | 3 | 0.19988 | 0.31016 |
| Alanine Metabolism | 17 | 6 | 0.2155 | 0.32873 |
| Fatty Acid Biosynthesis | 35 | 5 | 0.25504 | 0.38256 |
| Tyrosine Metabolism | 72 | 6 | 0.27778 | 0.40984 |
| Nucleotide Sugars Metabolism | 20 | 3 | 0.29123 | 0.42275 |
| Sphingolipid Metabolism | 40 | 4 | 0.31237 | 0.43501 |
| Transfer of Acetyl Groups into Mitochondria | 22 | 3 | 0.3153 | 0.43501 |
| Catecholamine Biosynthesis | 20 | 4 | 0.31708 | 0.43501 |
| Fatty acid Metabolism | 43 | 4 | 0.31901 | 0.43501 |
| Beta Oxidation of Very Long Chain Fatty Acids | 17 | 4 | 0.32742 | 0.43982 |
| Lactose Degradation | 9 | 3 | 0.36833 | 0.48749 |
| Propanoate Metabolism | 42 | 4 | 0.37399 | 0.48782 |
| Mitochondrial Beta-Oxidation of Long Chain Sat | 28 | 4 | 0.38578 | 0.496 |
| Butyrate Metabolism | 19 | 3 | 0.41652 | 0.52076 |
| Riboflavin Metabolism | 20 | 3 | 0.41661 | 0.52076 |
| Mitochondrial Beta-Oxidation of Short Chain Sa | 27 | 3 | 0.45525 | 0.56126 |
| Ethanol Degradation | 19 | 2 | 0.47459 | 0.57721 |
| Glycine and Serine Metabolism | 59 | 16 | 0.48242 | 0.5789 |
| Folate Metabolism | 29 | 3 | 0.54173 | 0.6284 |
| Oxidation of Branched Chain Fatty Acids | 26 | 5 | 0.5441 | 0.6284 |
| Glutamate Metabolism | 49 | 11 | 0.56274 | 0.6284 |
| Steroidogenesis | 43 | 1 | 0.56527 | 0.6284 |
| Pentose Phosphate Pathway | 29 | 2 | 0.56678 | 0.6284 |
| Thiamine Metabolism | 9 | 2 | 0.56678 | 0.6284 |
| Pterine Biosynthesis | 29 | 1 | 0.57254 | 0.6284 |
| Methionine Metabolism | 43 | 12 | 0.63032 | 0.68348 |
| Glutathione Metabolism | 21 | 6 | 0.69142 | 0.74081 |
| Selenoamino Acid Metabolism | 28 | 3 | 0.70473 | 0.74618 |
| Glucose-Alanine Cycle | 13 | 3 | 0.73977 | 0.77418 |
| Taurine and Hypotaurine Metabolism | 12 | 2 | 0.78132 | 0.80826 |
| Pantothenate and CoA Biosynthesis | 21 | 5 | 0.79057 | 0.80853 |
| Homocysteine Degradation | 9 | 2 | 0.81306 | 0.82219 |
| Cysteine Metabolism | 26 | 4 | 0.88194 | 0.88194 |

SupplementaryTable 3. Adult metabolite differential expressions

| Label | pVal | Fold_Change |
|---|---|---|
| PE (38:4); PE(19:2/19:2); | 0.0012708 | -1.323989757 |
| PE (p-38:4); PE(P-16:0/22 | 0.0033697 | -1.93443963 |
| urea | 0.005304 | -1.360062716 |
| UDP-N-acetylglucosamine | 0.0080877 | -1.397084048 |
| PE (38:4); PE(16:0/22:4); | 0.0099433 | -1.46234864 |
| PC (38:4) | 0.0110451 | -1.418304177 |
| sucrose | 0.0115212 | 1.30734767 |
| PC (o-32:0) | 0.0159487 | -1.594770029 |
| SM (d36:2) | 0.0170569 | -1.916587385 |
| PC (40:5) | 0.017285 | -1.255304313 |
| N-Octadecanoyl-1-.beta.-g | 0.0186709 | -1.848020061 |
| SM (d36:1) | 0.0204108 | -1.782202133 |
| guanosine | 0.0252246 | 1.334669339 |
| PE (38:4) | 0.0252532 | -1.512904694 |
| PI (36:4) | 0.0273519 | 2.007767354 |
| TG (52:1) | 0.0354902 | -1.248174839 |
| lyxitol | 0.0359114 | 1.283474853 |
| PE (p-36:4) or PE (o-36:5) | 0.0378509 | -1.865264077 |
| PC (p-36:3) or PC (o-36:4) | 0.0392595 | -1.332110441 |
| isoleucine | 0.0398941 | 1.341933802 |
| PC (40:5) | 0.0441218 | -1.176933406 |
| 2-hydroxyglutaric acid | 0.044591 | -1.877374169 |
| PE (38:2) | 0.0465127 | -1.234653502 |
| SM (d36:1) | 0.046723 | -1.478118762 |
| 1-Methyladenosine | 0.0489158 | -1.233539775 |

SupplementaryTable 4. Metaboanalyst analysis of enrichment pathways in the brains of adult pups

| | Total Cmpc | Hits | Statistic Q | Raw p | FDR |
|---|---|---|---|---|---|
| Oxidation of Branched Chain Fatty Acids | 26 | 4 | 18.585 | 0.046582 | 0.52975 |
| Catecholamine Biosynthesis | 20 | 3 | 21.657 | 0.054041 | 0.52975 |
| Carnitine Synthesis | 22 | 4 | 13.32 | 0.11591 | 0.52975 |
| Phytanic Acid Peroxisomal Oxidation | 26 | 3 | 14.028 | 0.11613 | 0.52975 |
| Tyrosine Metabolism | 72 | 8 | 11.214 | 0.15681 | 0.52975 |
| Glycerolipid Metabolism | 25 | 6 | 10.638 | 0.18808 | 0.52975 |
| D-Arginine and D-Ornithine Metabolism | 11 | 2 | 11.505 | 0.19504 | 0.52975 |
| Thyroid hormone synthesis | 13 | 2 | 11.367 | 0.19733 | 0.52975 |
| Vitamin B6 Metabolism | 20 | 1 | 11.549 | 0.19781 | 0.52975 |
| Vitamin K Metabolism | 14 | 1 | 11.549 | 0.19781 | 0.52975 |
| Beta Oxidation of Very Long Chain Fatty A | 17 | 2 | 11.269 | 0.20179 | 0.52975 |
| Pyruvaldehyde Degradation | 10 | 2 | 11.003 | 0.20503 | 0.52975 |
| Plasmalogen Synthesis | 26 | 5 | 9.9735 | 0.20952 | 0.52975 |
| Citric Acid Cycle | 32 | 5 | 9.8712 | 0.22459 | 0.52975 |
| Caffeine Metabolism | 24 | 2 | 9.9624 | 0.22549 | 0.52975 |
| Glycerol Phosphate Shuttle | 11 | 2 | 9.9624 | 0.22549 | 0.52975 |
| Threonine and 2-Oxobutanoate Degradati | 20 | 3 | 9.8202 | 0.22898 | 0.52975 |
| Mitochondrial Electron Transport Chain | 19 | 4 | 9.7732 | 0.23042 | 0.52975 |
| Alpha Linolenic Acid and Linoleic Acid Met | 19 | 1 | 10.026 | 0.23215 | 0.52975 |
| Porphyrin Metabolism | 40 | 3 | 9.6479 | 0.23336 | 0.52975 |
| Galactose Metabolism | 38 | 7 | 9.2093 | 0.23638 | 0.52975 |
| Pyrimidine Metabolism | 59 | 8 | 9.0564 | 0.23979 | 0.52975 |
| Folate Metabolism | 29 | 4 | 9.4127 | 0.24059 | 0.52975 |
| Lysine Degradation | 30 | 3 | 9.4143 | 0.24077 | 0.52975 |
| Glutathione Metabolism | 21 | 8 | 8.7365 | 0.2499 | 0.52975 |
| Betaine Metabolism | 21 | 9 | 8.823 | 0.25124 | 0.52975 |
| Warburg Effect | 58 | 8 | 8.8125 | 0.25666 | 0.52975 |
| Phospholipid Biosynthesis | 29 | 6 | 8.6662 | 0.25774 | 0.52975 |
| Tryptophan Metabolism | 60 | 6 | 8.7947 | 0.25807 | 0.52975 |
| Lactose Degradation | 9 | 1 | 8.8011 | 0.26453 | 0.52975 |
| Trehalose Degradation | 11 | 1 | 8.8011 | 0.26453 | 0.52975 |
| Transfer of Acetyl Groups into Mitochondı | 22 | 3 | 8.5611 | 0.26856 | 0.52975 |
| Glycolysis | 25 | 2 | 8.2028 | 0.28195 | 0.52975 |
| De Novo Triacylglycerol Biosynthesis | 9 | 2 | 8.2028 | 0.28195 | 0.52975 |
| Pterine Biosynthesis | 29 | 1 | 8.1994 | 0.28229 | 0.52975 |
| Androgen and Estrogen Metabolism | 33 | 1 | 8.1994 | 0.28229 | 0.52975 |
| Ketone Body Metabolism | 13 | 1 | 8.1994 | 0.28229 | 0.52975 |
| Retinol Metabolism | 37 | 1 | 8.1994 | 0.28229 | 0.52975 |
| Androstenedione Metabolism | 24 | 1 | 8.1994 | 0.28229 | 0.52975 |
| Estrone Metabolism | 24 | 1 | 8.1994 | 0.28229 | 0.52975 |
| Starch and Sucrose Metabolism | 31 | 3 | 8.0357 | 0.2855 | 0.52975 |
| Cardiolipin Biosynthesis | 11 | 3 | 8.0357 | 0.2855 | 0.52975 |
| Steroid Biosynthesis | 48 | 6 | 8.1944 | 0.28565 | 0.52975 |
| Nucleotide Sugars Metabolism | 20 | 2 | 8.0316 | 0.28582 | 0.52975 |
| Fructose and Mannose Degradation | 32 | 4 | 7.9475 | 0.28646 | 0.52975 |
| Steroidogenesis | 43 | 2 | 8.0334 | 0.2866 | 0.52975 |

| | | | | | |
|---|---|---|---|---|---|
| Fatty Acid Elongation In Mitochondria | 35 | 2 | 8.0024 | 0.28739 | 0.52975 |
| Inositol Phosphate Metabolism | 26 | 3 | 7.9106 | 0.28937 | 0.52975 |
| Inositol Metabolism | 33 | 4 | 7.7643 | 0.29316 | 0.52975 |
| Mitochondrial Beta-Oxidation of Long Cha | 28 | 6 | 8.0375 | 0.29415 | 0.52975 |
| Mitochondrial Beta-Oxidation of Short Cha | 27 | 5 | 7.9859 | 0.29736 | 0.52975 |
| Beta-Alanine Metabolism | 34 | 7 | 7.898 | 0.29851 | 0.52975 |
| Fatty acid Metabolism | 43 | 7 | 7.852 | 0.30346 | 0.52975 |
| Gluconeogenesis | 35 | 4 | 7.4528 | 0.30473 | 0.52975 |
| Valine, Leucine and Isoleucine Degradatio | 60 | 7 | 7.8596 | 0.3093 | 0.52975 |
| Butyrate Metabolism | 19 | 4 | 7.5989 | 0.3235 | 0.52975 |
| Mitochondrial Beta-Oxidation of Medium | 27 | 4 | 7.5989 | 0.3235 | 0.52975 |
| Nicotinate and Nicotinamide Metabolism | 37 | 9 | 7.612 | 0.32806 | 0.52975 |
| Pyruvate Metabolism | 48 | 7 | 7.4452 | 0.33103 | 0.52975 |
| Glucose-Alanine Cycle | 13 | 3 | 6.8147 | 0.33414 | 0.52975 |
| Propanoate Metabolism | 42 | 7 | 7.2838 | 0.33971 | 0.52975 |
| Histidine Metabolism | 43 | 10 | 7.1888 | 0.34529 | 0.52975 |
| Riboflavin Metabolism | 20 | 5 | 7.2281 | 0.35467 | 0.52975 |
| Methionine Metabolism | 43 | 13 | 7.0257 | 0.35604 | 0.52975 |
| Bile Acid Biosynthesis | 65 | 7 | 6.9964 | 0.35932 | 0.52975 |
| Phenylalanine and Tyrosine Metabolism | 28 | 7 | 7.0395 | 0.3642 | 0.52975 |
| Glutamate Metabolism | 49 | 16 | 6.938 | 0.37494 | 0.53513 |
| Ammonia Recycling | 32 | 11 | 6.4543 | 0.39611 | 0.53513 |
| Glycine and Serine Metabolism | 59 | 15 | 6.54 | 0.39669 | 0.53513 |
| Malate-Aspartate Shuttle | 10 | 4 | 5.6813 | 0.39678 | 0.53513 |
| Ethanol Degradation | 19 | 3 | 5.7819 | 0.39781 | 0.53513 |
| Arginine and Proline Metabolism | 53 | 13 | 6.4106 | 0.40134 | 0.53513 |
| Cysteine Metabolism | 26 | 6 | 5.6173 | 0.41402 | 0.53905 |
| Selenoamino Acid Metabolism | 28 | 6 | 5.6296 | 0.4214 | 0.53905 |
| Sulfate/Sulfite Metabolism | 22 | 2 | 4.8353 | 0.42675 | 0.53905 |
| Lactose Synthesis | 20 | 2 | 4.8353 | 0.42675 | 0.53905 |
| Ubiquinone Biosynthesis | 20 | 1 | 4.3376 | 0.43891 | 0.54019 |
| Biotin Metabolism | 8 | 1 | 4.3376 | 0.43891 | 0.54019 |
| Purine Metabolism | 74 | 17 | 6.2845 | 0.44906 | 0.54418 |
| Pentose Phosphate Pathway | 29 | 2 | 4.0852 | 0.45348 | 0.54418 |
| Aspartate Metabolism | 35 | 11 | 5.6292 | 0.48041 | 0.56938 |
| Pantothenate and CoA Biosynthesis | 21 | 4 | 3.8126 | 0.49223 | 0.57627 |
| Phenylacetate Metabolism | 9 | 3 | 3.7586 | 0.5061 | 0.58274 |
| Thiamine Metabolism | 9 | 3 | 3.7142 | 0.5099 | 0.58274 |
| Phosphatidylinositol Phosphate Metabolis | 17 | 2 | 3.3939 | 0.52327 | 0.59099 |
| Urea Cycle | 29 | 11 | 4.5972 | 0.5489 | 0.61273 |
| Taurine and Hypotaurine Metabolism | 12 | 2 | 2.7326 | 0.5577 | 0.61488 |
| Alanine Metabolism | 17 | 6 | 3.539 | 0.56364 | 0.61488 |
| Arachidonic Acid Metabolism | 69 | 3 | 3.8577 | 0.62181 | 0.67072 |
| Spermidine and Spermine Biosynthesis | 18 | 5 | 3.6026 | 0.63005 | 0.67206 |
| Homocysteine Degradation | 9 | 2 | 3.0202 | 0.66047 | 0.69676 |
| Sphingolipid Metabolism | 40 | 3 | 2.6919 | 0.70632 | 0.73703 |
| Fatty Acid Biosynthesis | 35 | 1 | 0.40413 | 0.81507 | 0.84136 |

| | | | | | |
|---|---|---|---|---|---|
| Phosphatidylethanolamine Biosynthesis | 12 | 5 | 2.6725 | 0.83729 | 0.85312 |
| Phosphatidylcholine Biosynthesis | 14 | 4 | 2.1948 | 0.84423 | 0.85312 |
| Amino Sugar Metabolism | 33 | 4 | 1.3816 | 0.90686 | 0.90686 |

Supplementary Table 5. Newborn RBPs and TFs

| Gene Symb | Fold | P-val |
|---|---|---|
| Cirbp | -1.25 | 0.0007 |
| A1cf | -1.25 | 0.0013 |
| Elavl2 | 1.17 | 0.0077 |
| Hnrnpk | -1.21 | 0.0194 |
| Khdrbs3 | 1.17 | 0.0232 |
| Pabpc5 | 1.1 | 0.0258 |
| Fus | -1.2 | 0.0259 |
| Cpeb3 | 1.14 | 0.0266 |
| Igf2bp3 | -1.08 | 0.0445 |

SupplementaryTable 6. Metaboanalyst analysis of associated diseases with metabolites set

| | Total Cmpd | Hits | Raw p | FDR |
|---|---|---|---|---|
| Rett Syndrome | 5 | 2 | 0.000101 | 0.005769 |
| Pyridoxamine 5-Prime-Phosphate | 2 | 2 | 0.000348 | 0.008649 |
| Pyruvate Dehydrogenase Deficien | 2 | 1 | 0.000455 | 0.008649 |
| Alzheimer's Diesease | 7 | 5 | 0.001064 | 0.010933 |
| Bacterial Meningitis | 9 | 4 | 0.0015 | 0.010933 |
| Leukemia | 21 | 13 | 0.001638 | 0.010933 |
| Degenerative Disc Disease | 6 | 2 | 0.001816 | 0.010933 |
| Schizophrenia | 24 | 13 | 0.002217 | 0.010933 |
| Hydrocephalus | 5 | 1 | 0.002224 | 0.010933 |
| Lesch-Nyhan Syndrome | 4 | 1 | 0.002224 | 0.010933 |
| Different Seizure Disorders | 25 | 13 | 0.002241 | 0.010933 |
| 3-Phosphoglycerate Dehydrogena | 2 | 1 | 0.002494 | 0.010933 |
| Juvenile Myoclonic Epilepsy | 3 | 1 | 0.002494 | 0.010933 |
| Hypothyroidism | 8 | 3 | 0.007577 | 0.030848 |
| Brain Injury | 8 | 4 | 0.008986 | 0.034145 |
| Canavan Disease | 4 | 4 | 0.014479 | 0.051582 |
| Transurethral Resection Of The Pr | 2 | 1 | 0.019909 | 0.066755 |
| Viral Meningitis | 5 | 1 | 0.024158 | 0.076502 |
| Epilepsy | 14 | 4 | 0.02832 | 0.076615 |
| Traumatic Brain Injury | 6 | 2 | 0.028851 | 0.076615 |
| Glut-1 Deficiency Syndrome | 2 | 2 | 0.034957 | 0.076615 |
| Aseptic Meningitis | 5 | 4 | 0.03624 | 0.076615 |
| Post Transurethral Prostatic Resec | 5 | 3 | 0.038291 | 0.076615 |
| Friedreich's Ataxia | 5 | 1 | 0.038979 | 0.076615 |
| Hereditary Spastic Paraplegia | 5 | 1 | 0.038979 | 0.076615 |
| Olivopontocerebral Atrophy | 5 | 1 | 0.038979 | 0.076615 |
| Ataxia (Assorted) | 5 | 1 | 0.038979 | 0.076615 |
| Friedreich Ataxia | 4 | 1 | 0.038979 | 0.076615 |
| Heredo-Degenerative Ataxias \| Sp | 5 | 1 | 0.038979 | 0.076615 |
| Hyperphenylalaniemia Due To Gua | 5 | 1 | 0.046353 | 0.08807 |
| Acute Tonic-Clonic Seizures | 3 | 2 | 0.053823 | 0.098965 |
| Tuberculous Meningitis | 7 | 3 | 0.064081 | 0.11414 |
| Alcoholism | 5 | 1 | 0.06619 | 0.11433 |
| Parkinson's Disease | 14 | 1 | 0.11232 | 0.18346 |
| Meningomyelocoele (Spina Bifida) | 8 | 3 | 0.1163 | 0.18346 |
| Meningitis | 15 | 4 | 0.11673 | 0.18346 |
| Febrile Seizures | 2 | 2 | 0.11909 | 0.18346 |
| Alzheimer's Disease | 51 | 18 | 0.13167 | 0.19751 |
| Spinocerebellar Degeneration | 3 | 2 | 0.15323 | 0.22395 |
| Gaba-Transaminase Deficiency | 2 | 1 | 0.19089 | 0.24729 |
| 2-Hydroxyglutaric Aciduria (D) | 2 | 1 | 0.19089 | 0.24729 |
| Gaba Transaminase Deficiency | 3 | 1 | 0.19089 | 0.24729 |
| Premenstrual Dysphoric Disorder | 2 | 1 | 0.19089 | 0.24729 |
| Pyridoxine Dependency With Seizu | 3 | 1 | 0.19089 | 0.24729 |
| Complex Febrile Seizures | 3 | 3 | 0.24101 | 0.30528 |
| Anoxia | 9 | 3 | 0.2612 | 0.32366 |

| | | | | |
|---|---|---|---|---|
| Biotinidase Deficiency | 6 | 3 | 0.26924 | 0.32653 |
| Propionic Acidemia | 7 | 2 | 0.30942 | 0.36744 |
| Early-Onset Encephalopathy And ( | 2 | 1 | 0.40094 | 0.4664 |
| Multi-Infarct Dementia | 6 | 1 | 0.43931 | 0.491 |
| Vascular Dementia | 6 | 1 | 0.43931 | 0.491 |
| Aging-Related Metabolites | 4 | 3 | 0.50945 | 0.55843 |
| Multiple Sclerosis | 13 | 3 | 0.74365 | 0.79977 |
| Dementia | 4 | 2 | 0.76811 | 0.81078 |
| Peripheral Neuropathy | 2 | 1 | 0.91069 | 0.92696 |
| Stroke | 7 | 1 | 0.91069 | 0.92696 |
| Glucose Transporter Type 1 Defici | 2 | 1 | 0.96323 | 0.96323 |

## Supplementary Methods

### Biogeneic Amines metabolites' Measurement

#### Summary

The biogenic amine HILIC analysis workflow involves analysis of polar phase of lipid extraction by ultra high pressure liquid chromatography (UHPLC) on a Waters BEH Amide Column, interfaced to a SCIEX Triple TOF 6600 mass spectrometer (high resolution, accurate mass), with a 16.8 minute total run time. Data are collected in both positive and negative ion mode, and analyzed using MS DIAL, open software for metabolome analysis

#### Sample Preparation

Extraction is carried out using a bi-phasic solvent system of cold methanol, methyl *tert*-butyl ether (MTBE), and water. In more detail, cold methanol (225 µL is added to a 5mg tissue sample aliquot, which is placed into a 1.5 mL Eppendorf tube. Then, 750 µL of cold MTBE is added, followed by vortexing for 10 s. and shaking for 6 min. at 4ºC. Phase separation is induced by adding 188 µL of mass spec-grade water. After vortexing for 20 s. the sample is centrifuged at 14,000 rpm for 2 min. The upper organic phase is collected in two 300 µL aliquots for lipid analysis polar layer is collected in two 125 µL aliquots for HILIC analysis. One is stored at -20ºC as a backup and the other is evaporated to dryness in a SpeedVac. Dried extracts are resuspended in acetonitrile.

#### LC/MS parameters

The LC/QTOFMS analyses are performed using an Agilent 1290 Infinity LC system (G4220A binary pump, G4226A autosampler, and G1316C Column Thermostat) coupled to a SCIEX Triple TOF mass spectrometer. Polar compounds are separated on an Acquity UPLC BEH Amide Column, 130Å, 1.7 µm, 2.1 mm X 150 mm maintained at 45°C at a flow-rate of 0.4 mL/min. Solvent pre-heating (Agilent G1316) was used. The mobile phases consist of: Water, 10 mM Ammonium Formate, 0.125% Formic Acid (A) and Acetonitrile: Water (95/5, v/v), 10 mM Ammonium Formate, 0.125% Formic Acid (B)

The gradient is as follows: 0 min 100% (A); 0–2 min 100% (A); 2–7.7 min 30% (A); 7.7–9.5 min 60% (A); 9.5–10.3 min 70% (A); 10.3–12.8 min 0% (A); 12.8–16.8 min 0% (A. A sample volume of 1 µL for positive mode and 3 µL for negative mode is used for the injection. Sample temperature is maintained at 4°C in the autosampler.

SCIEX Triple TOF 6600mass spectrometers are operated with electrospray ionization (ESI) performing full scan in the mass range m/z 50–1200. Number of cycles in MS1 is 1667 with cycle time of 500ms and accumulation time 475ms. Mass spectrometer parameters are as follows (positive mode) Gas Temp 300°C, gas pressures in psi units with : GS1 and GS2 50 psi, CUR: 35. ISVF is 4500V and DP and CE are 10V and 100 V.

**Supplementary References**


1. Matyash, V., et al., *Lipid extraction by methyl-tert-butyl ether for high-throughput lipidomics.* J Lipid Res, 2008. **49**(5): p. 1137-46.
2. Tsugawa, H.,et al., MS-DIAL: data-independent MS/MS deconvolution for comprehensive metabolome analysis. Nature Methods 12, p 523–526 (2015)

## Lipidomics Measurement Method

### Summary

The lipidomics workflow involves sample extraction in MTBE with addition of internal standards, followed by ultra high pressure liquid chromatography (UHPLC) on a Waters CSH column, interfaced to a QTOF mass spectrometer (high resolution, accurate mass), with a 15 minute total run time. Data are collected in both positive and negative ion mode, and analyzed using MassHunter (Agilent). Approximately 400 lipids can be identified from plasma, with additional unknowns. The method is highly stable and has been validated on large datasets (>8,000 samples) collected over long time periods (> 1 year).

### Sample Preparation

Extraction of plasma lipids is based on the “Maytash” method [1] which was subsequently modified. Extraction is carried out using a bi-phasic solvent system of cold methanol, methyl *tert*-butyl ether (MTBE), and water. In more detail, cold methanol (225 µL) containing a mixture of odd chain and deuterated lipid internal standards [lysoPE(17:1), lysoPC(17:0), PC(12:0/13:0), PE(17:0/17:0), PG(17:0/17:0), sphingosine (d17:1), $d_7$-cholesterol, SM(17:0), C17 ceramide, $d_3$-palmitic acid, MG(17:0/0:0/0:0), DG(18:1/2:0/0:0), DG(12:0/12:0/0:0), and $d_5$-TG(17:0/17:1/17:0)] is added to a 20 µL sample aliquot, which is placed into a 1.5 mL Eppendorf tube, and the tube is vortexed for 10 s. Then, 750 µL of cold MTBE containing CE(22:1) (internal standard) are added, followed by vortexing for 10 s. and shaking for 6 min. at 4ºC. Phase separation is induced by adding 188 µL of mass spec-grade water. After vortexing for 20 s. the sample is centrifuged at 14,000 rpm for 2 min. The upper organic phase is collected in two 300 µL aliquots. One is stored at -20ºC as a backup and the other is evaporated to dryness in a SpeedVac. Dried extracts are resuspended using a mixture of methanol/toluene (9:1, v/v) (60 µL) containing an internal standard [12-[[(cyclohexylamino)carbonyl]amino]-dodecanoic acid (CUDA)] used as a quality control.

**LC/MS parameters**

The LC/QTOFMS analyses are performed using an Agilent 1290 Infinity LC system (G4220A binary pump, G4226A autosampler, and G1316C Column Thermostat) coupled to either an Agilent 6530 (positive ion mode) or an Agilent 6550 mass spectrometer equipped with an ion funnel (iFunnel) (negative ion mode). Lipids are separated on an Acquity UPLC CSH C18 column (100 x 2.1 mm; 1.7 µm) maintained at 65°C at a flow-rate of 0.6 mL/min. Solvent pre-heating (Agilent G1316) was used. The mobile phases consist of 60:40 acetonitrile:water with 10 mM ammonium formate and 0.1% formic acid (A) and 90:10 propan-2-ol:acetonitrile with 10 mM ammonium formate and 0.1% formic acid. The gradient is as follows: 0 min 85% (A); 0–2 min 70% (A); 2–2.5 min 52% (A); 2.5–11 min 18% (A); 11–11.5 min 1% (A); 11.5–12 min 1% (A); 12–12.1 min 85% (A); 12.1–15 min 85% (A). A sample volume of 3 µL is used for the injection. Sample temperature is maintained at 4°C in the autosampler.

The quadrupole/time-of-flight (QTOF) mass spectrometers are operated with electrospray ionization (ESI) performing full scan in the mass range *m*/*z* 65–1700 in positive (Agilent 6530, equipped with a JetStreamSource) and negative (Agilent 6550, equipped with a dual JetStream Source) modes producing both unique and complementary spectra. Instrument paramaters are as follows (positive mode) Gas Temp 325°C, Gas Flow 8 l/min, Nebulizer 35 psig, Sheath Gas 350°C, Sheath Gas Flow 11, Capillary Voltage 3500 V, Nozzle Voltage 1000V, Fragmentor 120V, Skimmer 65V. Data (both profile and centroid) are collected at a rate of 2 scans per second. In negative ion mode, Gas Temp 200°C, Gas Flow 14 l/min, Fragmentor 175V, with the other parameters identical to positive ion mode. For the 6530 QTOF, a reference solution generating ions of 121.050 and 922.007 *m/z* in positive mode and 119.036 and 966.0007 m/z in negative mode, and these are used for continuous mass correction. For the 6550, the reference solution is introduced via a dual spray ESI, with the same ions and continuous mass correction.

Samples are injected (1.7 µl in positive mode and 5 µl in negative ion mode) with a needle wash for 20 seconds (wash solvent is isopropanol). The valve is switched back and forth during the run for washing; this has been shown to be essential for reducing carryover of less polar lipids.

**Data Analysis**

For the data processing the MassHunter software is used, and a unique ID is given to each lipid based on its retention time and exact mass (RT_mz). This allows the report of peak areas/heights or concentration of lipids based on the use of particular internal standards. Lipids are identified based on their unique MS/MS fragmentation patterns using in-house software, Lipidblast. Using complex lipid class-specific internal standards this approach is used to quantify >400 lipid species including: mono-, di- and triacylglycerols, glycerophospholipids, sphingolipids, cholesterol esters, ceramides, and fatty acids.

This approach is highly reproducible, displaying an RSD of 0.1% for the retention time and 1.7% for peak area based on replicate analysis of plasma samples (*n*=10). An average shot-to-shot carryover of less than 0.1% is observed. The described method is specifically developed to deal with high-throughput analyses, and can be used to analyze over 300 samples a week, including both positive and negative mode data acquisition.

**Supplementary References**

1. Matyash, V., et al., *Lipid extraction by methyl-tert-butyl ether for high-throughput lipidomics.* J Lipid Res, 2008. **49**(5): p. 1137-46.

**Primary metabolites measurement**

**GC-TOF Method:**

***Instruments:***

Gerstel CIS4 –with dual MPS Injector/

Agilent 6890 GC-

Pegasus III TOF MS

**Injector conditions:**

Agilent 6890 GC is equipped with a Gerstel automatic liner exchange system (ALEX) that includes a multipurpose sample (MPS2) dual rail, and a Gerstel CIS cold injection system (Gerstel, Muehlheim, Germany) with temperature program as follows: 50°C to 275°C final temperature at a rate of 12 °C/s and hold for 3 minutes. Injection volume is 0.5 µl with 10 µl/s injection speed on a splitless injector with purge time of 25 seconds. Liner (Gerstel #011711-010-00) is changed after every 10 samples, (using the Maestro1 Gerstel software vs. 1.1.4.18). Before and after each injection, the 10 µl injection syringe is washed three times with 10 µl ethyl acetate.

***Gas Chromatography conditions:***

A 30 m long, 0.25 mm i.d. Rtx-5Sil MS column (0.25 µm 95% dimethyl 5% diphenyl polysiloxane film) with additional 10 m integrated guard column is used (Restek, Bellefonte PA). 99.9999% pure Helium with built-in purifier (Airgas, Radnor PA) is set at constant flow of 1 ml/min. The oven temperature is held constant at 50°C for 1 min and then ramped at 20°C/min to 330°C at which it is held constant for 5 min.

***Mass spectrometer settings:***

A Leco Pegasus IV time of flight mass spectrometer is controlled by the Leco ChromaTOF software vs. 2.32 (St. Joseph, MI). The transfer line temperature between gas chromatograph and mass spectrometer is set to 280°C. Electron impact ionization at 70V is employed with an ion source temperature of 250°C. Acquisition rate is 17 spectra/second, with a scan mass range of 85-500 Da.