

Metabolic basis of neuronal vulnerability to ischemia; an *in vivo* untargeted metabolomics approach

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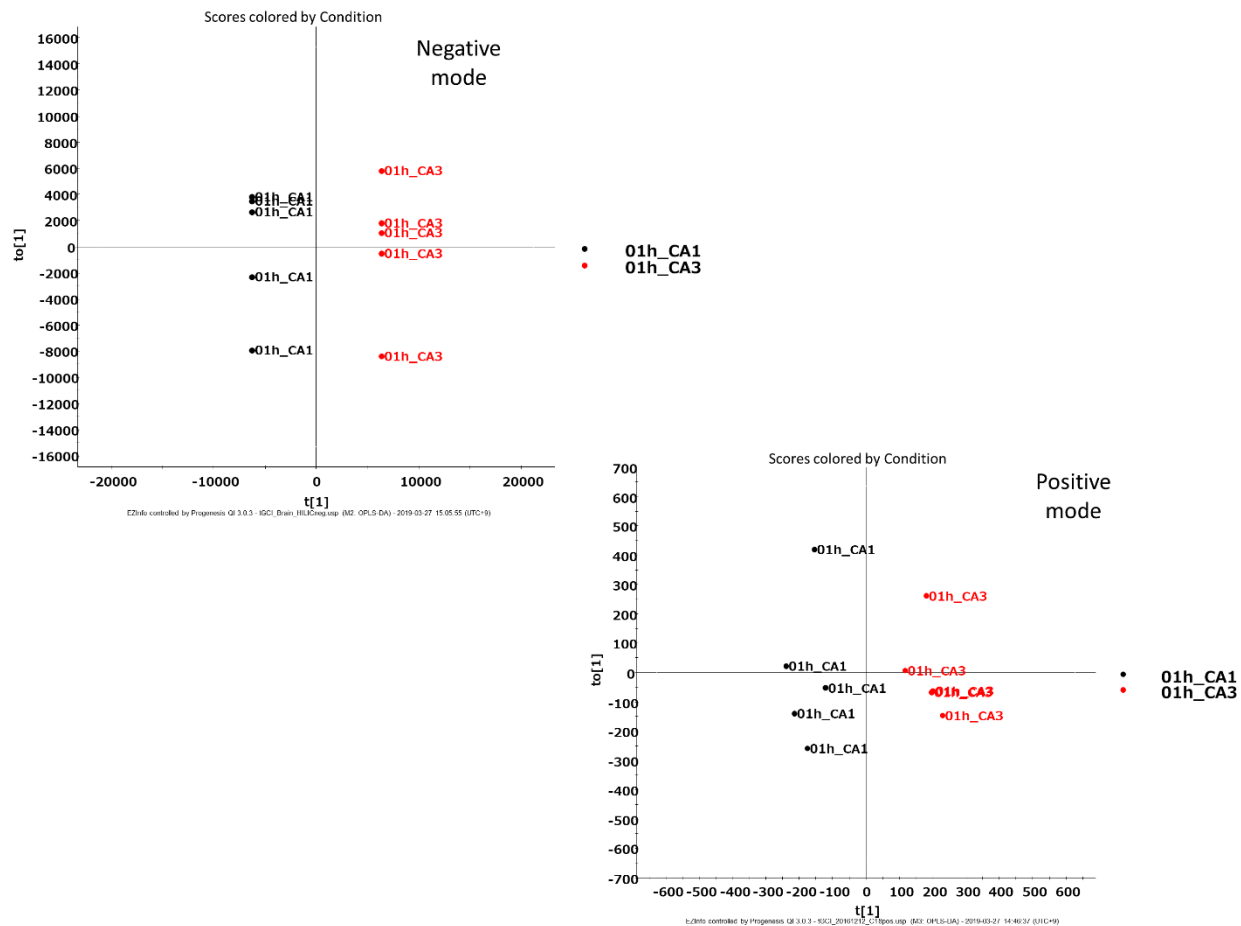
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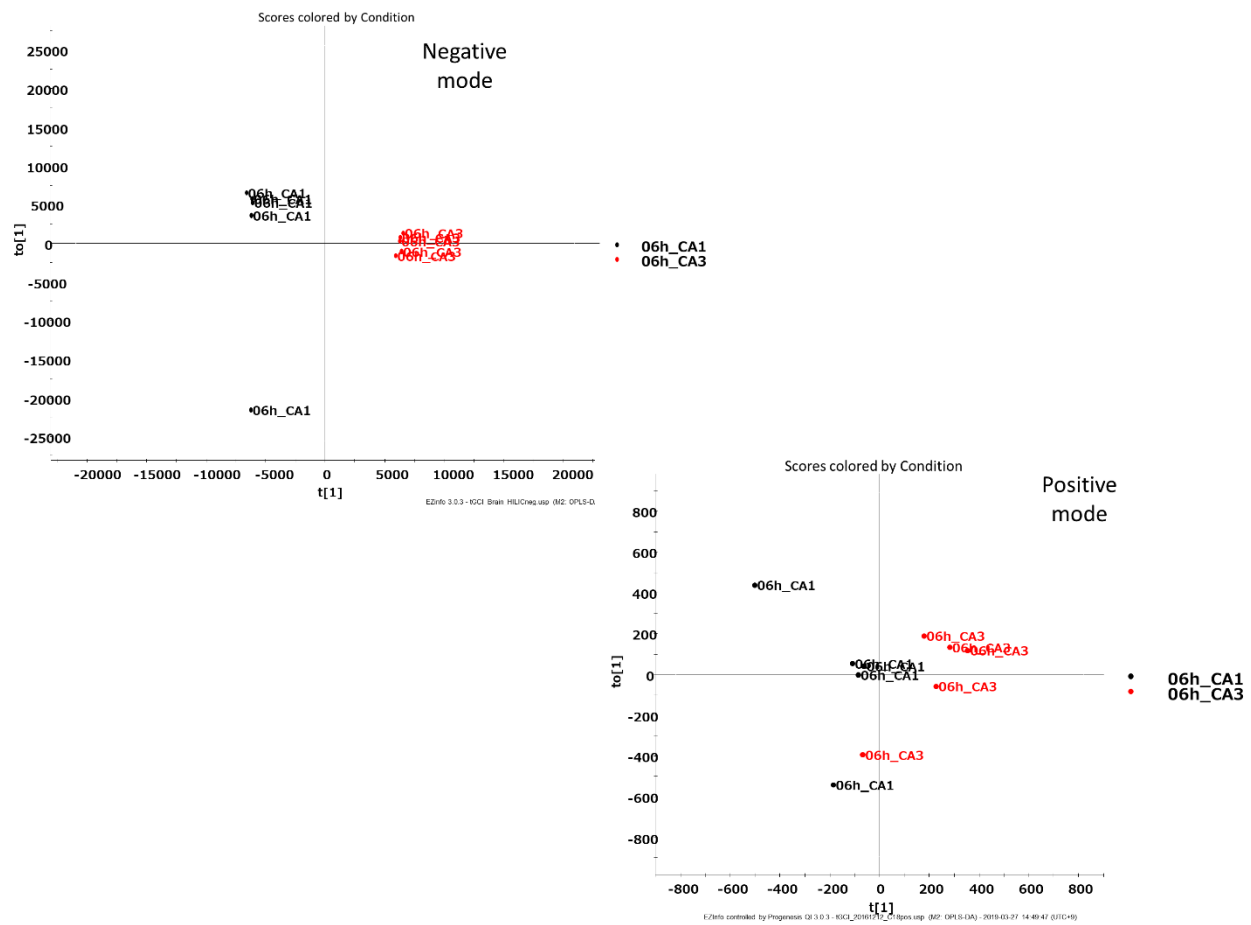
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Supplemental information

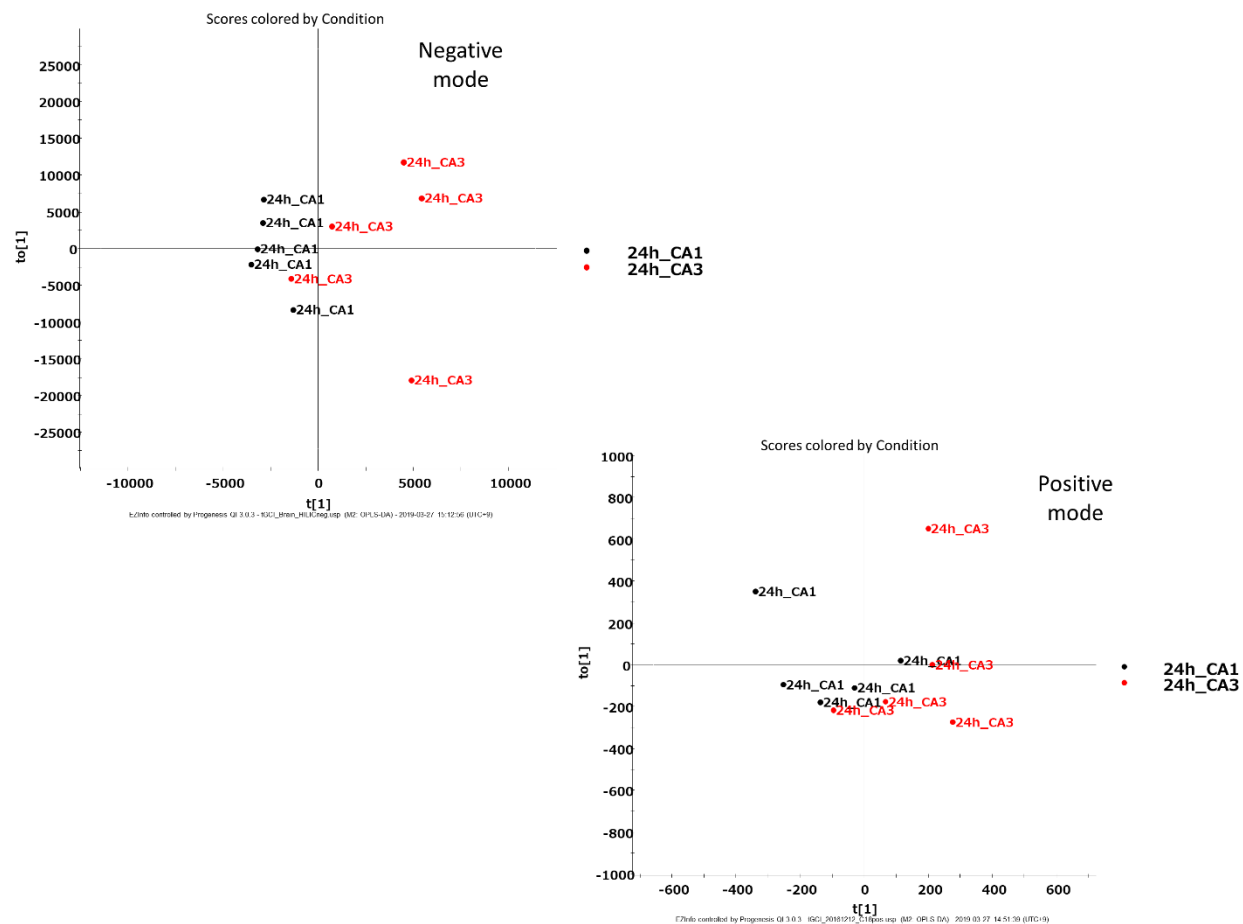
Supplementary Figure 1: Principle component analysis (PCA) comparison between CA1 and CA3 1 hour after transient global cerebral ischemia (tGCI). Significant differences are evident between both sub-regions 1 hour after tGCI, much earlier than any cellular changes.



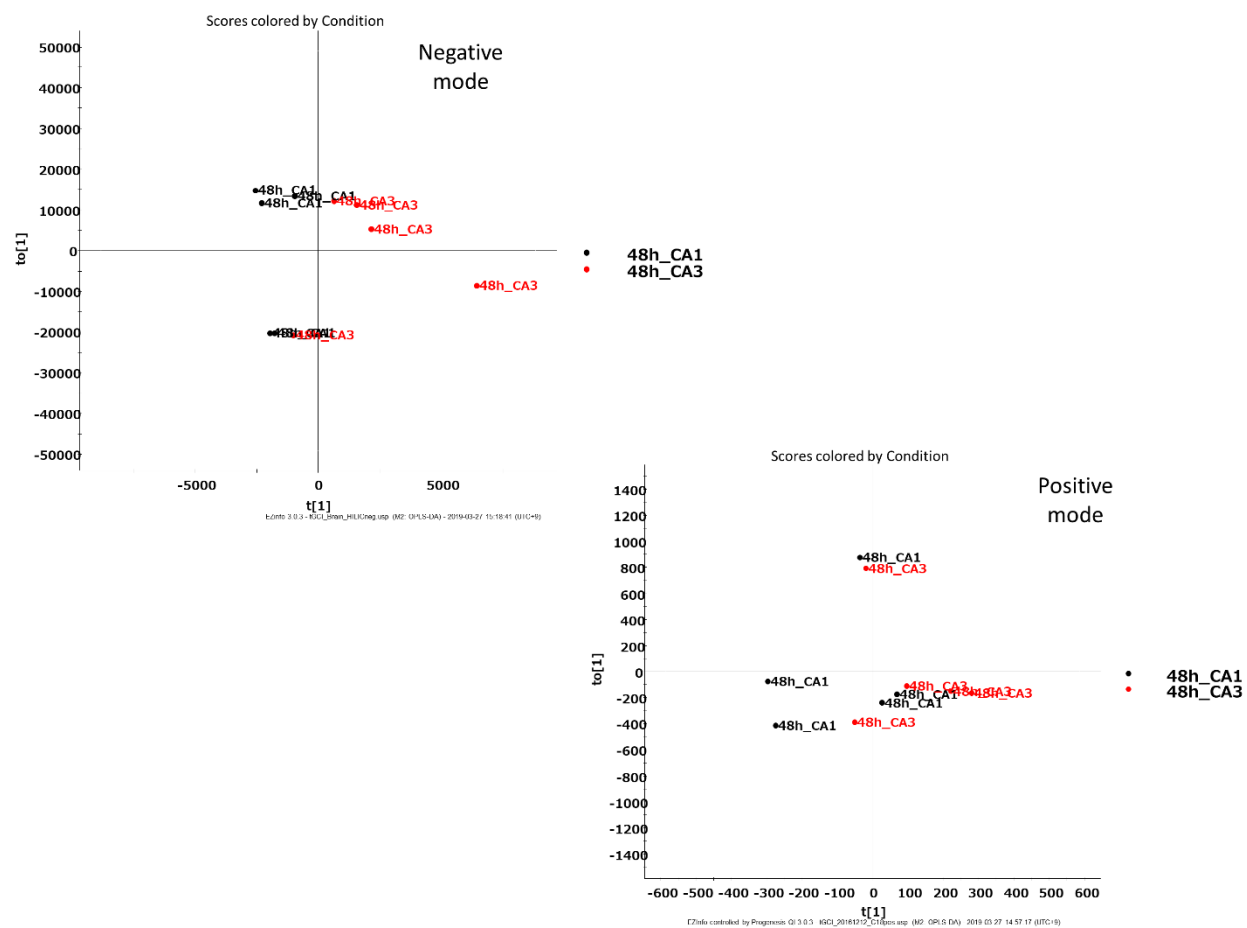
Supplementary Figure 2: Principle component analysis comparison between CA1 and CA3 6 hours after tGCI. Significant differences still exist between both sub-regions 6 hours after tGCI.



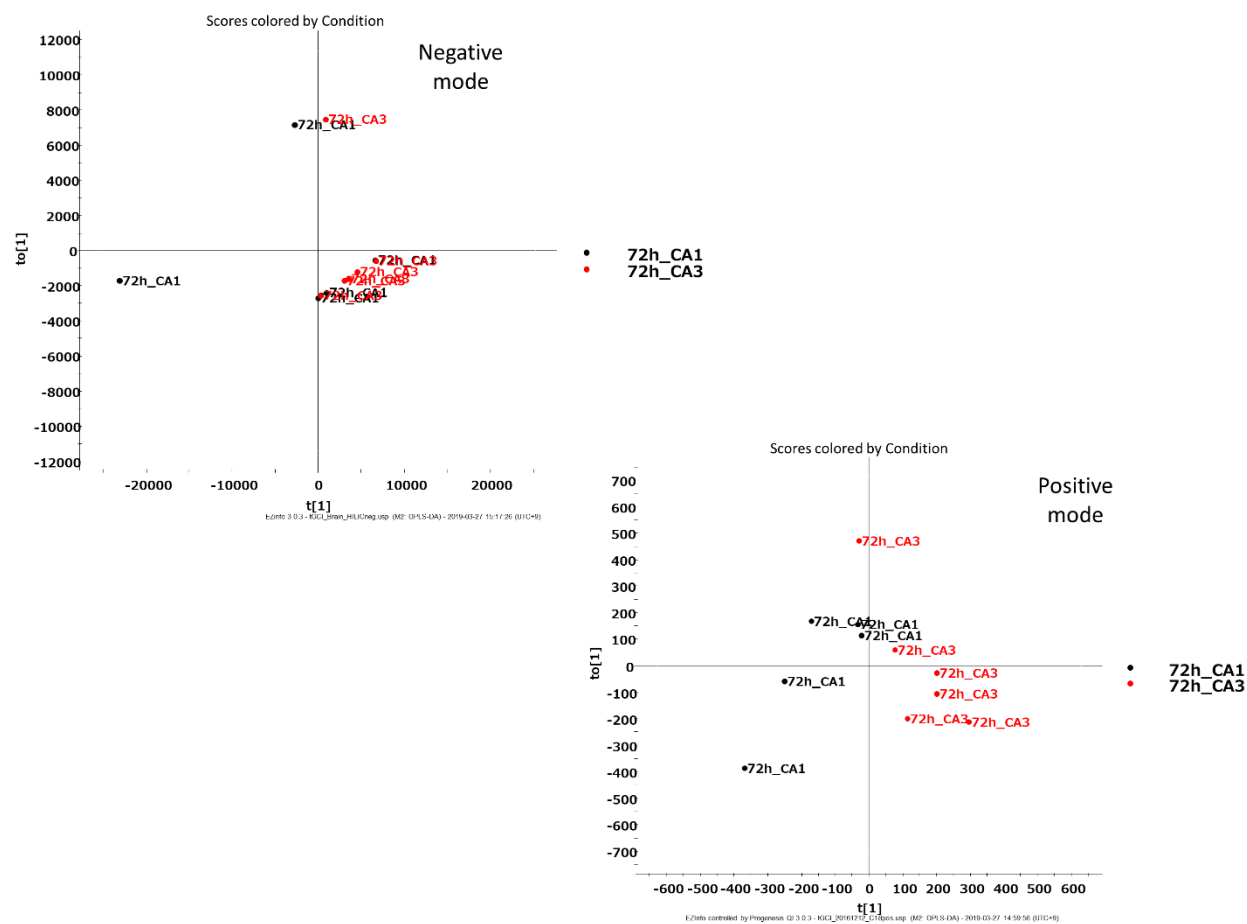
Supplementary Figure 3: Principle component analysis comparison between CA1 and CA3 24 hours after tGCI. 24 hours after tGCI, the pattern of metabolome regulation converges in both subregions, evident as less separation on PCA analysis.



Supplementary Figure 4: Principle component analysis comparison between CA1 and CA3 48 hours after tGCI. As with the 24 hours mark, no significant differences exist between both regions at this time point.



Supplementary Figure 5: Principle component analysis comparison between CA1 and CA3 72 hours after tGCI. At this time-point apoptosis is consistently observed in CA1. There appears to be some differences between both regions, but less sharp than at earlier time points.



Supplementary Table 1: Significant and successfully annotated compounds in CA1 after ANOVA and Levene test.

Compound name	<i>tR</i> _m/z	Detect ed	Formula	Neutr al	Addu ct	Theoriti cal m/z	Delt a ppm	Stat us	Mode	Pubchem ID	f.val ue	p.value	FDR
Guanosine	4.17_282.083 6m/z	282.08 36	C10H13N5O 5	283.09 17	M-H	282.084 4	2.8	C	Negati ve	6802	21.2 78	4.15E- 08	3.65E -05
N-omega-(ADP-D- ribosyl)-L-arginine (ADP- Ribosyl-L-arginine)	3.98_698.179 7m/z	698.17 97	C21H35N9O 15P2	715.17 28	M+H -H2O	698.170 1	-13.8	P	Positiv e	46173712	15.3 67	8.26E- 07	9.93E -05
gamma-Glutamylglutamic acid	5.36_275.087 9m/z	275.08 79	C10H16N2O 7	276.09 58	M-H	275.088 5	2.2	P	Negati ve	92865	14.7 27	1.20E- 06	0.000 16
Xanthine	3.50_151.025 7m/z	151.02 57	C5H4N4O2	152.03 34	M-H	151.026 1	2.6	P	Negati ve	1188	14.5 92	1.30E- 06	0.000 16
5-Aminoimidazole-4- carboxamide	4.12_109.051 0m/z	109.05 10	C4H6N4O	126.05 42	M+H -H2O	109.051 5	4.6	P	Positiv e	9679	14.4 95	1.38E- 06	0.000 15
Adenine	3.19_134.046 8m/z	134.04 68	C5H5N5	135.05 45	M-H	134.047 2	3.0	C	Negati ve	190	13.7 97	2.11E- 06	0.000 17
Adenosine	3.20_266.088 8m/z	266.08 88	C10H13N5O 4	267.09 68	M-H	266.089 5	2.6	C	Negati ve	60961	13.6 71	2.28E- 06	0.000 17
Uracil	2.53_111.019 6m/z	111.01 96	C4H4N2O2	112.02 73	M-H	111.020 0	3.6	C	Negati ve	1174	13.3 83	2.73E- 06	0.000 17
Cysteine	4.81_120.012 1m/z	120.01 21	C3H7NO2S	121.01 97	M-H	120.012 5	3.3	C	Negati ve	5862	13.3 09	2.86E- 06	0.000 17
Stachyose	3.99_705.191 3m/z	705.19 13	C24H42O21	666.22 19	M+K	705.185 0	-8.9	P	Positiv e	439531	13.0 9	3.29E- 06	0.000 32
Acetyl-L-methionine	3.12_190.053 9m/z	190.05 39	C7H13NO3S	191.06 16	M-H	190.054 3	2.1	P	Negati ve	448580	13.0 81	3.31E- 06	0.000 17
S-formylglutathione	3.20_334.076 2m/z	334.07 62	C11H17N3O 7S	335.07 87	M-H	334.071 4	-14.4	P	Negati ve	189122	12.4 27	5.08E- 06	0.000 22
gamma-Glutamylglutamine	5.08_274.103 9m/z	274.10 39	C10H17N3O 6	275.11 17	M-H	274.104 5	2.2	P	Negati ve	150914	11.6 1	8.88E- 06	0.000 29
Inosine	3.74_267.072 8m/z	267.07 28	C10H12N4O 5	268.08 08	M-H	267.073 5	2.6	C	Negati ve	6021	10.8 21	1.56E- 05	0.000 43
hypoxanthine	3.34_135.030 9m/z	135.03 09	C5H4N4O	136.03 85	M-H	135.031 2	2.2	C	Negati ve	790	10.7 35	1.66E- 05	0.000 44
D-Ribose 5-phosphate	5.16_229.011 2m/z	229.01 12	C5H11O8P	230.01 92	M-H	229.011 9	3.1	P	Negati ve	439236	10.6 31	1.79E- 05	0.000 45
Cytosine	3.97_94.0399 m/z	94.039 9	C4H5N3O	111.04 33	M+H -H2O	94.0406	7.4	C	Positiv e	597	10.0 76	2.72E- 05	0.001 51
Glutathione	3.19_288.070 7m/z	288.07 07	C10H17N3O 6S	307.08 38	M- H2O- H	288.065 4	-18.4	C	Negati ve	124886	9.77 83	3.42E- 05	0.000 73

Uridine diphosphate-N-acetylgalactosamine	5.43_646.049 9m/z	646.04 99	C17H27N3O 17P2	607.08 16	M+K	646.044 7	-8.0	P	Positive	445675	9.29 86	5.00E- 05	0.001 93
4-phosphopantothenoylecysteine	3.33_401.081 7m/z	401.08 17	C12H23N2O 9PS	402.08 62	M-H	401.078 9	-7.0	P	Negative	440304	9.03 27	6.20E- 05	0.001 12
L-histidine	4.89_154.061 7m/z	154.06 17	C6H9N3O2	155.06 95	M-H	154.062 2	3.2	C	Negative	6274	9.02 53	6.23E- 05	0.001 12
4-Aminobutanol	0.98_70.0650 m/z	70.065 0	C4H9NO	87.068 4	M+H -H2O	70.0657	10.0	P	Positive	118	8.72 95	7.96E- 05	0.002 64
UDP-N-Acetyl-D-hexosamine	3.97_590.079 8m/z	590.07 98	C17H27N3O 17P2	607.08 16	M+H -H2O	590.078 9	-1.5	P	Positive	445675	8.28 75	0.00011 56	0.003 21
Glutamylglutamic acid	1.44_277.103 2m/z	277.10 32	C10H16N2O 7	276.09 58	M+H	277.103 0	-0.7	P	Positive	439500	8.28 38	0.00011 6	0.003 21
Cytidine	4.01_242.077 7m/z	242.07 77	C9H13N3O5	243.08 55	M-H	242.078 2	2.1	C	Negative	6175	8.06 55	0.00014 01	0.002 09
Cytidine-5'-monophosphate-5-N-acetylneuraminic acid	3.99_597.142 8m/z	597.14 28	C20H31N4O 16P	614.14 73	M+H -H2O	597.144 6	3.0	P	Positive	448209	7.67 42	0.00019 8	0.004 43
Nicotinamide adenine dinucleotide (NAD ⁺)	2.95_664.114 4m/z	664.11 44	C21H28N7O 14P2	664.11 69	M+H	664.116 9	3.8	C	Positive	5892	7.51 54	0.00022 85	0.004 99
Aconitic acid (cis)	5.48_173.008 6m/z	173.00 86	C6H6O6	174.01 64	M-H	173.009 2	3.5	C	Negative	643757	7.47 15	0.00023 77	0.002 97
Arginine	7.23_173.103 9m/z	173.10 39	C6H14N4O2	174.11 17	M-H	173.104 4	2.9	C	Negative	232	7.43 25	0.00024 63	0.002 97
Gluconic acid	3.75_195.050 5m/z	195.05 05	C6H12O7	196.05 83	M-H	195.051 0	2.6	C	Negative	10690	7.28 99	0.00028 07	0.003 22
Uracil	3.31_111.019 7m/z	111.01 97	C4H4N2O2	112.02 73	M-H	111.020 0	2.7	C	Negative	1174	6.73 72	0.00047 2	0.004 77
Dopamine 4-O-sulfate	3.50_214.021 3m/z	214.02 13	C8H11NO5S	233.03 58	M- H2O- H	214.017 4	-18.2	P	Negative	123932	6.71 58	0.00048 18	0.004 81
6-Hydroxyhexanoic acid	2.62_131.070 9m/z	131.07 09	C6H12O3	132.07 86	M-H	131.071 4	3.8	P	Negative	14490	6.45 48	0.00062 06	0.005 87
5-hydroxypentanoic acid	2.83_117.055 4m/z	117.05 54	C5H10O3	118.06 30	M-H	117.055 7	2.6	P	Negative	25945	6.33 31	0.00069 96	0.006 34
Uridine	3.31_243.061 6m/z	243.06 16	C9H12N2O6	244.06 95	M-H	243.062 3	2.9	C	Negative	6029	6.28 19	0.00073 6	0.006 4
Phosphohydroxypyruvic Acid	5.26_164.956 5m/z	164.95 65	C3H5O7P	183.97 73	M- H2O- H	164.958 9	14.5	P	Negative	105	5.67 41	0.00136 54	0.009 49
N-acetyl-L-phenylalanine	2.77_206.081 7m/z	206.08 17	C11H13NO3	207.08 95	M-H	206.082 3	2.9	P	Negative	74839	5.66 96	0.00137 18	0.009 49
D-mannitol	4.56_181.071 3m/z	181.07 13	C6H14O6	182.07 90	M-H	181.071 8	2.8	P	Negative	6251	5.63 68	0.00141 95	0.009 67

Acetyl Glutamic Acid	3.06_188.055 9m/z	188.05 59	C7H11NO5	189.06 37	M-H	188.056 4	2.7	P	Negative	70914	5.58 83	0.00149 33	0.010 02
Methylcitric acid	5.55_205.034 8m/z	205.03 48	C7H10O7	206.04 27	M-H	205.035 4	2.9	P	Negative	515	5.57 05	0.00152 15	0.010 06
N-Formyl-L-glutamic acid	3.06_156.029 8m/z	156.02 98	C6H9NO5	175.04 81	M-H2O-H	156.029 7	-0.6	P	Negative	439376	5.47 21	0.00168 78	0.010 67
L-tryptophan	4.06_203.082 1m/z	203.08 21	C11H12N2O 2	204.08 99	M-H	203.082 6	2.5	C	Negative	6305	5.44 05	0.00174 51	0.010 88
N-Acetyl-S-(N-methylcarbamoyl)cysteine	4.56_219.044 9m/z	219.04 49	C7H12N2O4 S	220.05 18	M-H	219.044 5	-1.8	P	Negative	108218	5.40 2	0.00181 81	0.011 18
1-(beta-D-Ribofuranosyl)-1,4-dihydronicotinamide (reduced nicotinamide riboside)	1.26_295.066 2m/z	295.06 62	C11H16N2O 5	256.10 59	M+K	295.069 1	9.8	P	Positive	11507134	5.22 73	0.00219 22	0.022 95
Guanosine Diphosphate Mannose	3.97_588.083 1m/z	588.08 31	C16H25N5O 16P2	605.07 72	M+H-H2O	588.074 5	-14.6	P	Positive	18396	5.21 52	0.00222 09	0.022 95
Lipoyl-amp	4.98_534.088 1m/z	534.08 81	C18H26N5O 8PS2	535.09 60	M-H	534.088 8	1.3	P	Negative	23724672	5.21 44	0.00222 29	0.013 11
Cytidine-5'-diphosphate	3.97_386.015 6m/z	386.01 56	C9H15N3O1 1P2	403.01 82	M+H-H2O	386.015 5	-0.3	P	Positive	6132	5.15 58	0.00236 84	0.024 21
N-acetyl-L-leucine	2.81_172.097 5m/z	172.09 75	C8H15NO3	173.10 52	M-H	172.097 9	2.3	P	Negative	70912	5.15 03	0.00238 27	0.013 63
P1,P4-Bis(5'-xanthosyl) tetraphosphate	6.12_892.987 5m/z	892.98 75	C20H26N8O 23P4	870.00 61	M+N a	892.995 3	8.7	P	Positive	440322	5.02 3	0.00273 78	0.026 31
N-acetylneuraminic acid	4.65_290.087 4m/z	290.08 74	C11H19NO9	309.10 60	M-H2O-H	290.087 6	0.7	P	Negative	445063	4.92 49	0.00304 99	0.015 96
Biotinyl-5-AMP	3.97_556.141 0m/z	556.14 10	C20H28N7O 9PS	573.14 07	M+H-H2O	556.138 0	-5.4	P	Positive	440839	4.84 55	0.00333 08	0.029 92
Nicotinic acid	1.41_121.040 3m/z	121.04 03	C6H8N2O2	140.05 86	M-H2O-H	121.040 2	-0.8	P	Negative	938	4.65 09	0.00414 3	0.019 47
isocitric acid or citric acid	5.64_191.019 3m/z	191.01 93	C6H8O7	192.02 70	M-H	191.019 7	2.1	C	Negative	1198 or 311	4.61 27	0.00432 59	0.019 7
L-phenylalanine	3.84_164.071 3m/z	164.07 13	C9H11NO2	165.07 90	M-H	164.071 7	2.4	C	Negative	6140	4.41 96	0.00539 46	0.022 69
Cytidine Diphosphate Ethanolamine	5.26_445.052 1m/z	445.05 21	C11H20N4O 11P2	446.06 04	M-H	445.053 1	2.2	P	Negative	123727	4.22 65	0.00674 98	0.026 68
Aspartic Acid	4.98_114.019 3m/z	114.01 93	C4H7NO4	133.03 75	M-H2O-H	114.019 1	-1.8	C	Negative	5960	4.22 04	0.00679 85	0.026 68

N-acetyl-l-aspartic aid	3.40_156.029 8m/z	156.02 98	C6H9NO5	175.04 81	M- H2O- H	156.029 7	-0.6	P	Negati ve	65065	4.16 83	0.00722 67	0.027 74
Glycerol 3-phosphate	5.04_171.006 0m/z	171.00 60	C3H9O6P	172.01 37	M-H	171.006 4	2.3	P	Negati ve	754	4.15 63	0.00732 97	0.027 89
N-acetyl-l-glutamic acid	3.40_188.055 9m/z	188.05 59	C7H11NO5	189.06 37	M-H	188.056 4	2.7	P	Negati ve	70914	4.06 76	0.00813 91	0.030 57
Leucine	3.90_130.086 9m/z	130.08 69	C6H13NO2	131.09 46	M-H	130.087 4	3.8	C	Negati ve	6106	3.83 06	0.01080 7	0.039 42
5-amino-6-(5-phospho-D- ribitylamino)uracil	5.15_355.066 9m/z	355.06 69	C9H17N4O9 P	356.07 33	M-H	355.066 0	-2.5	P	Negati ve	18666812	3.71 37	0.01245 6	0.044 69
N-Acetylornithine or Theanine	4.65_173.092 7m/z	173.09 27	C7H14N2O3	174.10 04	M-H	173.093 2	2.9	P	Negati ve	439232 or 439378	3.68 27	0.01293 6	0.045 38
phosphoethanolamine	5.17_140.011 4m/z	140.01 14	C2H8NO4P	141.01 91	M-H	140.011 8	2.9	P	Negati ve	1015	3.63 49	0.01371 6	0.047 28
Phosphodimethylethanolamine	5.04_168.042 7m/z	168.04 27	C4H12NO4P	169.05 04	M-H	168.043 1	2.4	P	Negati ve	151438	3.58 42	0.01459 9	0.049 74

Abbreviations: C: confirmed by chemical standard. P: Putative annotation

Supplementary Table 2: Significant and successfully annotated compounds in CA3 after ANOVA.

Compound name	<i>t</i> R _{m/z}	Detect ed	Formula	Neutra l	Addu ct	Theoriti cal m/z	Delt a pp m	Stat us	Mode	PubChem ID	f.val ue	p.valu e	FDR
gamma-Glutamylglutamic acid	5.36_275.0879 m/z	275.08 79	C10H16N2O7	276.09 58	M-H	275.0885	2.2	P	Negati ve	92865	24.07	8.22E- 09	2.42E -06
Glutathione	3.19_288.0707 m/z	288.07 07	C10H17N3O6 S	307.08 38	M- H2O- H	288.0654	- 18.4	C	Negati ve	124886	20.43 3	4.19E- 08	5.89E -06
Hypoxanthine	3.34_135.0309 m/z	135.03 09	C5H4N4O	136.03 85	M-H	135.0312	2.2	C	Negati ve	790	19.36 7	7.05E- 08	6.94E -06
S-formylglutathione	3.20_334.0762 m/z	334.07 62	C11H17N3O7 S	335.07 87	M-H	334.0714	- 14.4	P	Negati ve	189122	18.00 7	1.42E- 07	9.62E -06
Adenosine	3.20_266.0888 m/z	266.08 88	C10H13N5O4	267.09 68	M-H	266.0895	2.6	C	Negati ve	60961	15.87 5	4.59E- 07	1.93E -05
Cytidine	4.01_242.0777 m/z	242.07 77	C9H13N3O5	243.08 55	M-H	242.0782	2.1	C	Negati ve	6175	15.18 5	6.89E- 07	2.34E -05
gamma-Glutamylglutamine	5.08_274.1039 m/z	274.10 39	C10H17N3O6	275.11 17	M-H	274.1045	2.2	P	Negati ve	150914	15.12	7.16E- 07	2.34E -05
N-acetylhexosamine 6-phosphate	5.06_300.0483 m/z	300.04 83	C8H16NO9P	301.05 63	M-H	300.0490	2.3	P	Negati ve	439219	13.85 5	1.57E- 06	4.32E -05
N-Carbamoylsarcosine	5.01_131.0458 m/z	131.04 58	C4H8N2O3	132.05 35	M-H	131.0462	3.1	P	Negati ve	439375	12.87 5	2.97E- 06	7.28E -05
Arginine	7.23_173.1039 m/z	173.10 39	C6H14N4O2	174.11 17	M-H	173.1044	2.9	C	Negati ve	232	12.69 2	3.36E- 06	7.41E -05
D-hexose-1-phosphate	5.16_229.0112 m/z	229.01 12	C5H11O8P	230.01 92	M-H	229.0119	3.1	P	Negati ve	439236	12.53 6	3.73E- 06	7.92E -05
N-Acetylornithine or Theanine	4.65_173.0927 m/z	173.09 27	C7H14N2O3	174.10 04	M-H	173.0932	2.9	P	Negati ve	439232 or 439378	11.35 2	8.60E- 06	0.000 14
L-(-)-Threonine	4.82_118.0506 m/z	118.05 06	C4H9NO3	119.05 82	M-H	118.0510	3.4	C	Negati ve	6288	10.87 1	1.23E- 05	0.000 17
N-Formyl-L-glutamic acid	3.06_156.0298 m/z	156.02 98	C6H9NO5	175.04 81	M- H2O- H	156.0297	-0.6	P	Negati ve	439376	10.66 7	1.43E- 05	0.000 19
Acetyl Glutamic Acid	3.06_188.0559 m/z	188.05 59	C7H11NO5	189.06 37	M-H	188.0564	2.7	P	Negati ve	70914	10.55 4	1.56E- 05	0.000 2
Glutamylglutamic acid	1.44_277.1032 m/z	277.10 32	C10H16N2O7	276.09 58	M+H	277.1030	-0.7	P	Positiv e	439500	10.52 3	1.60E- 05	0.001 91

Cystathionine	5.44_221.0596 m/z	221.05 96	C7H14N2O4S	222.06 74	M-H	221.0602	2.7	C	Negati ve	834	10.45 4	1.68E- 05	0.000 2
Citrulline	5.10_174.0877 m/z	174.08 77	C6H13N3O3	175.09 57	M-H	174.0884	4.0	C	Negati ve	9750	10.43 7	1.70E- 05	0.000 2
Aspartic Acid	4.98_114.0193 m/z	114.01 93	C4H7NO4	133.03 75	M- H2O- H	114.0191	-1.8	C	Negati ve	5960	10.42 3	1.72E- 05	0.000 2
Serine	5.06_104.0354 m/z	104.03 54	C3H7NO3	105.04 26	M-H	104.0353	-1.0	C	Negati ve	5951	10.24	1.98E- 05	0.000 21
5-hydroxypentanoic acid	2.83_117.0554 m/z	117.05 54	C5H10O3	118.06 30	M-H	117.0557	2.6	P	Negati ve	25945	10.04 5	2.31E- 05	0.000 22
Inosine	3.74_267.0728 m/z	267.07 28	C10H12N4O5	268.08 08	M-H	267.0735	2.6	C	Negati ve	6021	10.04 2	2.32E- 05	0.000 22
Xanthine	3.50_151.0257 m/z	151.02 57	C5H4N4O2	152.03 34	M-H	151.0261	2.6	P	Negati ve	1188	9.907 8	2.58E- 05	0.000 24
Pantothenol	2.76_186.1131 m/z	186.11 31	C9H19NO4	205.13 14	M- H2O- H	186.1130	-0.5	P	Negati ve	4678	9.156 8	4.74E- 05	0.000 34
Uracil	3.31_111.0197 m/z	111.01 97	C4H4N2O2	112.02 73	M-H	111.0200	2.7	C	Negati ve	1174	9.015 5	5.34E- 05	0.000 37
Fumaric acid or Maleic acid	5.17_115.0033 m/z	115.00 33	C4H4O4	116.01 10	M-H	115.0037	3.5	P	Negati ve	444972 or 444266	8.920 3	5.78E- 05	0.000 4
L-Pyroglutamic acid	4.36_128.0349 m/z	128.03 49	C5H7NO3	129.04 26	M-H	128.0353	3.1	P	Negati ve	7405	8.861	6.08E- 05	0.000 4
L-Glutamic acid 5-phosphate	5.17_207.9987 m/z	207.99 87	C5H10NO7P	227.01 95	M- H2O- H	208.0011	11.5	P	Negati ve	440099	8.589 4	7.67E- 05	0.000 46
N-acetyl-l-glutamic acid	3.40_188.0559 m/z	188.05 59	C7H11NO5	189.06 37	M-H	188.0564	2.7	P	Negati ve	70914	8.521 2	8.13E- 05	0.000 48
Homovanillic acid or Phenylpyruvic acid	2.62_163.0396 m/z	163.03 96	C9H10O4	182.05 79	M- H2O- H	163.0395	-0.6	P	Negati ve	1738 or 997	8.466 8	8.53E- 05	0.000 48
Cysteine	4.81_120.0121 m/z	120.01 21	C3H7NO2S	121.01 97	M-H	120.0125	3.3	C	Negati ve	5862	8.453 8	8.62E- 05	0.000 48
Betalamic acid	3.57_192.0331 m/z	192.03 31	C9H9NO5	211.04 81	M- H2O- H	192.0297	- 17.7	P	Negati ve	5281176	8.291 9	9.94E- 05	0.000 52
Phosphodimethylethanolamine	5.04_168.0427 m/z	168.04 27	C4H12NO4P	169.05 04	M-H	168.0431	2.4	P	Negati ve	151438	8.290 7	9.95E- 05	0.000 52
N-acetyl-l-aspartic acid	3.40_156.0298 m/z	156.02 98	C6H9NO5	175.04 81	M- H2O- H	156.0297	-0.6	P	Negati ve	65065	8.208	0.0001 07	0.000 54
Homocarnosine	5.21_239.1143 m/z	239.11 43	C10H16N4O3	240.12 22	M-H	239.1150	2.9	P	Negati ve	10243361	8.202	0.0001 08	0.000 54

Alanine	4.75_88.0401 m/z	88.0401	C3H7NO2	89.0477	M-H	88.0404	3.4	C	Negative	5950	8.0873	0.000119	0.00057
Guanosine	4.17_282.0836 m/z	282.0836	C10H13N5O5	283.0917	M-H	282.0844	2.8	C	Negative	6802	8.0805	0.00012	0.00057
D-Galactose	5.25_179.0556 m/z	179.0556	C6H12O6	180.0634	M-H	179.0561	2.8	P	Negative	6036	7.9003	0.000141	0.00063
2,5-Dichloro-4-oxohex-2-enedioate	7.78_206.9284 m/z	206.9284	C6H4Cl2O5	225.9436	M-H2O-H	206.9252	-15.5	P	Negative	5282172	7.8883	0.000142	0.00063
phosphoethanolamine	5.17_140.0114 m/z	140.0114	C2H8NO4P	141.0191	M-H	140.0118	2.9	P	Negative	1015	7.881	0.000143	0.00063
Taurine	4.85_124.0070 m/z	124.0070	C2H7NO3S	125.0147	M-H	124.0074	3.2	C	Negative	1123	7.8734	0.000144	0.00063
Malic acid	5.20_133.0138 m/z	133.0138	C4H6O5	134.0215	M-H	133.0142	3.0	C	Negative	525	7.7747	0.000158	0.00067
2-methylpropanedioic acid	7.71_116.9592 m/z	116.9592	C4H8Se	135.9791	M-H2O-H	116.9607	12.8	P	Negative	487	7.7372	0.000163	0.00068
Dopachrome	3.27_174.0225 m/z	174.0225	C9H7NO4	193.0375	M-H2O-H	174.0191	-19.5	P	Negative	5459802	7.6416	0.000178	0.00072
N-acetylneuraminic acid	4.80_308.0980 m/z	308.0980	C11H19NO9	309.1060	M-H	308.0987	2.3	P	Negative	439197	7.5554	0.000193	0.00076
PE(40:6)	2.48_790.5376 m/z	790.5376	C45H78NO8P	791.5465	M-H	790.5392	2.0	P	Negative	9546798	7.3997	0.000223	0.00081
Ascorbic acid or Glucuronic acid	4.73_175.0243 m/z	175.0243	C6H10O7	194.0427	M-H2O-H	175.0243	0.0	P	Negative	54670067 or 94715	7.2985	0.000246	0.00087
Neuraminic acid	4.37_266.0874 m/z	266.0874	C9H17NO8	267.0954	M-H	266.0881	2.6	P	Negative	441037	7.2355	0.000261	0.00091
N-acetylneuraminic acid	4.65_290.0874 m/z	290.0874	C11H19NO9	309.1060	M-H2O-H	290.0876	0.7	P	Negative	445063	7.1517	0.000282	0.00094
N-acetyl-D-glucosamine 6 phosphate	4.82_300.0387 m/z	300.0387	C8H15NO9S	301.0468	M-H	300.0395	2.7	P	Negative	440996	6.9086	0.000357	0.00111
N-acetyl-L-glutamic acid	4.89_188.0559 m/z	188.0559	C7H11NO5	189.0637	M-H	188.0564	2.7	P	Negative	70914	6.7077	0.000434	0.00129
Phenylacetaldehyde	4.21_103.0546 m/z	103.0546	C8H8O	120.0575	M+H-H2O	103.0548	1.9	P	Positive	998	6.4278	0.000573	0.01328
L-Xylonic acid	4.73_165.0399 m/z	165.0399	C5H10O6	166.0477	M-H	165.0405	3.6	P	Negative	6971043	6.2114	0.000714	0.00184
Lipoyl-amp	4.98_534.0881 m/z	534.0881	C18H26N5O8PS2	535.0960	M-H	534.0888	1.3	P	Negative	23724672	6.2065	0.000717	0.00184

Xanthylic acid	5.25_345.0196 m/z	345.01 96	C10H13N4O9 P	364.04 20	M- H2O- H	345.0236	11.6	P	Negati ve	73323	6.061 9	0.0008 32	0.002 03
4-Phosphopantothenoylcysteine	3.33_401.0817 m/z	401.08 17	C12H23N2O9 PS	402.08 62	M-H	401.0789	-7.0	P	Negati ve	440304	6.053 8	0.0008 39	0.002 04
Aspartic acid	5.01_132.0298 m/z	132.02 98	C4H7NO4	133.03 75	M-H	132.0302	3.0	C	Negati ve	5960	6.030 3	0.0008 6	0.002 06
L-threonic acid	4.52_135.0295 m/z	135.02 95	C4H8O5	136.03 72	M-H	135.0299	3.0	C	Negati ve	5460407	5.988 2	0.0008 98	0.002 12
N-Acetyl-L-phenylalanine	2.77_206.0817 m/z	206.08 17	C11H13NO3	207.08 95	M-H	206.0823	2.9	P	Negati ve	74839	5.962 7	0.0009 22	0.002 15
UDP-GlcNAc	5.43_646.0499 m/z	646.04 99	C17H27N3O1 7P2	607.08 16	M+K	646.0447	-8.0	P	Positiv e	445675	5.962 5	0.0009 22	0.018 75
Creatinine	3.29_112.0513 m/z	112.05 13	C4H9N3O2	131.06 95	M- H2O- H	112.0511	-1.8	C	Negati ve	588	5.869 6	0.0010 16	0.002 33
2-hydroxyglutaric acid	5.07_147.0295 m/z	147.02 95	C5H8O5	148.03 72	M-H	147.0299	2.7	P	Negati ve	43	5.784 4	0.0011 12	0.002 5
Hexose 1-phosphate	5.36_259.0217 m/z	259.02 17	C6H13O9P	260.02 97	M-H	259.0224	2.7	P	Negati ve	123912	5.754 8	0.0011 47	0.002 57
Cytidine-5'-monophosphate-5-N-acetylneuraminic acid	3.99_597.1428 m/z	597.14 28	C20H31N4O1 6P	614.14 73	M+H- H2O	597.1446	3.0	P	Positiv e	448209	5.633	0.0013 05	0.023 22
Glycerol 3-phosphate	5.04_171.0060 m/z	171.00 60	C3H9O6P	172.01 37	M-H	171.0064	2.3	P	Negati ve	754	5.620 9	0.0013 22	0.002 84
D-4-Hydroxy-2-oxoglutarate	3.73_142.9981 m/z	142.99 81	C5H6O6	162.01 64	M- H2O- H	142.9980	-0.7	P	Negati ve	440853	5.452 9	0.0015 84	0.003 23
Glutathione	4.91_306.0758 m/z	306.07 58	C10H17N3O6 S	307.08 38	M-H	306.0765	2.3	C	Negati ve	124886	5.423 3	0.0016 36	0.003 32
PE(38:6)	2.51_762.5060 m/z	762.50 60	C43H74NO8P	763.51 52	M-H	762.5079	2.5	P	Negati ve	9546799	5.362	0.0017 48	0.003 52
succinic acid	3.73_99.0090 m/z	99.009 0	C4H6O4	118.02 66	M- H2O- H	99.0082	-8.1	C	Negati ve	1110	5.313 9	0.0018 43	0.003 67
N-Acetyl-D-hexosamine-6-phosphate	5.12_282.0353 m/z	282.03 53	C8H16NO9P	301.05 63	M- H2O- H	282.0379	9.2	P	Negati ve	440996	5.176 6	0.0021 43	0.004 19
5-Aminoimidazole ribonucleotide	3.86_276.0353 m/z	276.03 53	C8H14N3O7P	295.05 69	M- H2O- H	276.0385	11.6	P	Negati ve	161500	5.072 4	0.0024 06	0.004 54
Glycerophosphatidylethanolamine	5.12_214.0481 m/z	214.04 81	C5H14NO6P	215.05 59	M-H	214.0486	2.3	P	Negati ve	123874	4.857 3	0.0030 64	0.005 43

Dopamine 4-O-sulfate	3.50_214.0213 m/z	214.02 13	C8H11NO5S	233.03 58	M- H20- H	214.0174	- 18.2	P	Negati ve	123932	4.732 3	0.0035 33	0.006 06
D-Ribose 5-phosphate	4.66_211.0009 m/z	211.00 09	C5H11O8P	230.01 92	M- H20- H	211.0008	-0.5	P	Negati ve	439236	4.021 5	0.0081 62	0.012 07

Abbreviations: C: confirmed by chemical standard. P: Putative annotation

Supplementary table 3: Pathway analysis in CA1 using MetaboAnalyst

Pathway	Total	Expected	Hits	Raw p	-logP	Holm adjust	FDR	Impact
Purine metabolism	66	2.0994	9	0.000146	8.835	0.012227	0.012227	0.05958
Pantothenate and CoA biosynthesis	19	0.60437	4	0.00246	6.0074	0.20422	0.093769	0.17857
Aminoacyl-tRNA biosynthesis	48	1.5268	6	0.003349	5.6991	0.27461	0.093769	0
beta-Alanine metabolism	21	0.66799	3	0.026865	3.6169	1	0.5499	0
Pyrimidine metabolism	39	1.2406	4	0.032732	3.4194	1	0.5499	0.1142
Arginine biosynthesis	14	0.44533	2	0.070701	2.6493	1	0.94058	0
Nicotinate and nicotinamide metabolism	15	0.47714	2	0.079962	2.5262	1	0.94058	0
Histidine metabolism	16	0.50895	2	0.089579	2.4126	1	0.94058	0.22131
Amino sugar and nucleotide sugar metabolism	37	1.1769	3	0.11039	2.2038	1	0.99381	0.07042
Phenylalanine, tyrosine and tryptophan biosynthesis	4	0.12724	1	0.12141	2.1086	1	0.99381	0.5
Citrate cycle (TCA cycle)	20	0.63618	2	0.13101	2.0325	1	0.99381	0.09501
Pentose phosphate pathway	21	0.66799	2	0.14197	1.9521	1	0.99381	0.05183
Thiamine metabolism	7	0.22266	1	0.20287	1.5952	1	1	0
Glutathione metabolism	28	0.89066	2	0.22291	1.501	1	1	0.25939
Alanine, aspartate and glutamate metabolism	28	0.89066	2	0.22291	1.501	1	1	0.3101
Valine, leucine and isoleucine biosynthesis	8	0.25447	1	0.22835	1.4769	1	1	0

Taurine and hypotaurine metabolism	8	0.25447	1	0.22835	1.4769	1	1	0
Glyoxylate and dicarboxylate metabolism	32	1.0179	2	0.27083	1.3063	1	1	0.02381
Biotin metabolism	10	0.31809	1	0.27693	1.284	1	1	0.15
Cysteine and methionine metabolism	33	1.0497	2	0.28285	1.2629	1	1	0.09687
Glycine, serine and threonine metabolism	34	1.0815	2	0.29485	1.2213	1	1	0.02247
Glycerophospholipid metabolism	36	1.1451	2	0.31879	1.1432	1	1	0.0514
Phenylalanine metabolism	12	0.38171	1	0.32251	1.1316	1	1	0.35714
Fructose and mannose metabolism	18	0.57256	1	0.44302	0.81414	1	1	0.10766
Sphingolipid metabolism	21	0.66799	1	0.49513	0.70293	1	1	0.0142
Galactose metabolism	27	0.85885	1	0.58544	0.53539	1	1	0.05832
Arginine and proline metabolism	38	1.2087	1	0.71176	0.34002	1	1	0.03401
Valine, leucine and isoleucine degradation	40	1.2724	1	0.73027	0.31434	1	1	0
N-Glycan biosynthesis	41	1.3042	1	0.73908	0.30235	1	1	0
Tryptophan metabolism	41	1.3042	1	0.73908	0.30235	1	1	0.14305

Supplementary table 4: Pathway analysis in CA3 using MetaboAnalyst

Column1	Total	Expected	Hits	Raw p	-logP	Holm adjust	FDR	Impact
Arginine biosynthesis	14	0.44533	4	0.000715	7.2436	0.060039	0.034261	0.22843
Purine metabolism	66	2.0994	8	0.000816	7.1114	0.067706	0.034261	0.13571
Alanine, aspartate and glutamate metabolism	28	0.89066	5	0.001494	6.5066	0.12248	0.041821	0.3125
Pantothenate and CoA biosynthesis	19	0.60437	4	0.00246	6.0074	0.1993	0.051669	0.17857
Aminoacyl-tRNA biosynthesis	48	1.5268	5	0.016121	4.1276	1	0.27083	0.16667
Taurine and hypotaurine metabolism	8	0.25447	2	0.024554	3.7069	1	0.33038	0.42857
Amino sugar and nucleotide sugar metabolism	37	1.1769	4	0.027531	3.5924	1	0.33038	0.07631
Phenylalanine metabolism	12	0.38171	2	0.05338	2.9303	1	0.52898	0.40476
Glutathione metabolism	28	0.89066	3	0.056676	2.8704	1	0.52898	0.26648
Glycine, serine and threonine metabolism	34	1.0815	3	0.090758	2.3996	1	0.76237	0.23069
Phenylalanine, tyrosine and tryptophan biosynthesis	4	0.12724	1	0.12141	2.1086	1	0.85184	0
Citrate cycle (TCA cycle)	20	0.63618	2	0.13101	2.0325	1	0.85184	0.06254
beta-Alanine metabolism	21	0.66799	2	0.14197	1.9521	1	0.85184	0
Sphingolipid metabolism	21	0.66799	2	0.14197	1.9521	1	0.85184	0.0142
Thiamine metabolism	7	0.22266	1	0.20287	1.5952	1	1	0
Valine, leucine and isoleucine biosynthesis	8	0.25447	1	0.22835	1.4769	1	1	0

Ascorbate and aldarate metabolism	10	0.31809	1	0.27693	1.284	1	1	0
Cysteine and methionine metabolism	33	1.0497	2	0.28285	1.2629	1	1	0.11776
Glycerophospholipid metabolism	36	1.1451	2	0.31879	1.1432	1	1	0.12872
Pyrimidine metabolism	39	1.2406	2	0.35435	1.0375	1	1	0.0811
Glycosylphosphatidylinositol (GPI)-anchor biosynthesis	14	0.44533	1	0.36527	1.0071	1	1	0.00399
Butanoate metabolism	15	0.47714	1	0.38565	0.95282	1	1	0
Nicotinate and nicotinamide metabolism	15	0.47714	1	0.38565	0.95282	1	1	0
Tyrosine metabolism	42	1.336	2	0.3893	0.94341	1	1	0.0254
Histidine metabolism	16	0.50895	1	0.40539	0.90291	1	1	0
Selenocompound metabolism	20	0.63618	1	0.47832	0.73748	1	1	0
Pentose phosphate pathway	21	0.66799	1	0.49513	0.70293	1	1	0
Pyruvate metabolism	22	0.6998	1	0.51142	0.67056	1	1	0
Propanoate metabolism	23	0.73161	1	0.52719	0.64019	1	1	0
Galactose metabolism	27	0.85885	1	0.58544	0.53539	1	1	0.0338
Glyoxylate and dicarboxylate metabolism	32	1.0179	1	0.64844	0.43318	1	1	0.04233
Arginine and proline metabolism	38	1.2087	1	0.71176	0.34002	1	1	0
Valine, leucine and isoleucine degradation	40	1.2724	1	0.73027	0.31434	1	1	0.02264
Primary bile acid biosynthesis	46	1.4632	1	0.77909	0.24963	1	1	0.02239

Supplementary table 5: Pathway analysis comparison between CA1 and CA3 for the top enriched pathways

Purine metabolism								
Compound	Fold change CA1/CA3 at 1h	<i>p</i> value at 1h	Fold change CA1/CA3 at 6h	<i>p</i> value at 6h	Fold change CA1/CA3 at 24h	<i>p</i> value at 24h	Fold change CA1/CA3 at 48h	<i>p</i> value at 48h
Xanthine	1.7588	0.0010891*	1.4582	0.29148	1.2818	0.21123	0.96751	0.95765
Adenosine	1.9538	0.0011372*	1.6099	0.18632	1.0913	0.69475	1.0978	0.87087
Hypoxanthine	1.2007	0.12287	0.94336	0.82242	1.0833	0.49377	1.0593	0.92024
Inosine	1.3733	0.16827	0.95208	0.86442	1.1782	0.42174	1.0969	0.88289
Guanosine	3.1701	0.014953*	1.5817	0.29517	1.387	0.4335	1.0583	0.95733
P1,P4-Bis(5'-xanthosyl) tetraphosphate	0.51471	0.012739*	0.5637	0.03795 *	0.66243	0.12286	0.58191	0.20417

Adenine	1.7042	0.0026681*	1.4266	0.27022	1.0774	0.68995	1.0837	0.87641
Xanthylic acid	1.1021	0.16955	0.92621	0.78003	0.91277	0.38845	0.90798	0.87198
5-Aminoimidazole ribonucleotide	0.73986	0.1403	0.65573	0.14012	1.0474	0.79435	0.75144	0.6688
Deoxyadenosine	2.29	0.0438*	2.4508	0.12075	0.69645	0.47698	1.6237	0.27851
D-ribulose-5-phosphate	1.3824	0.16744	1.0421	0.88944	0.99669	0.98669	1.0749	0.90482
Pantothenate and CoA biosynthesis								
Compound	Fold change CA1/CA3 at 1h	p value at 1h	Fold change CA1/CA3 at 6h	p value at 6h	Fold change CA1/CA3 at 24h	p value at 24h	Fold change CA1/CA3 at 48h	p value at 48h
4- Phosphopantothenoylc ysteine	1.6829	0.06404 9	1.643	0.2662 2	0.99152	0.98036	1.2038	0.7434

Cysteine	1.4951	0.11354	1.1476	0.6344 6	1.0804	0.60779	0.98479	0.97766
Aspartic acid	1.2117	0.17311	0.95263	0.85261	1.0316	0.81506	0.96321	0.94597
Uracil	1.4419	0.13372	0.92985	0.7757 7	0.88862	0.71559	0.83425	0.70403

Alanine, aspartate and glutamate metabolism

Compound	Fold change CA1/CA3 at 1h	<i>p</i> value at 1h	Fold change CA1/CA3 at 6h	<i>p</i> value at 6h	Fold change CA1/CA3 at 24h	<i>p</i> value at 24h	Fold change CA1/CA3 at 48h	<i>p</i> value at 48h
Succinic acid	0.62752	0.01464*	0.64719	0.05190 4	1.0038	0.96565	0.76293	0.56864
Fumaric acid	1.2355	0.0083438 *	0.91613	0.72676	1.0114	0.80613	1	1.0
Aspartic acid	1.2117	0.17311	0.95263	0.85261	1.0316	0.81506	0.96321	0.94597
Alanine	1.0263	0.3037	0.84792	0.49557	0.96783	0.44661	0.92894	0.89177
N-acetyl-L-aspartic acid	1.0206	0.73904	0.94738	0.83424	1.0058	0.96128	1.1	0.87343

Amino sugar and nucleotide sugar metabolism

Compound	Fold change CA1/CA3 at 1h	<i>p</i> value at 1h	Fold change CA1/CA3 at 6h	<i>p</i> value at 6h	Fold change CA1/CA3 at 24h	<i>p</i> value at 24h	Fold change CA1/CA3 at 48h	<i>p</i> value at 48h
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UDP-N-acetylhexosamine	2.014	0.039048 *	1.3797	0.56825	0.69802	0.58776	0.88629	0.85069
Cytidine-5'-monophosphate-5-N-acetylneuraminic acid	1.2751	0.19647	1.0594	0.47213	1.2953	0.29737	1.3966	0.49665
N-acetylhexosamine 6-phosphate	1.1604	0.51195	0.6991	0.1415	0.92597	0.59162	0.84709	0.78809
Hexose 1-phosphate	1.2324	0.66317	0.57718	0.10502	0.93001	0.88252	0.96336	0.95602
Arginine Biosynthesis								
Compound	Fold change CA1/CA3 at 1h	p value at 1h	Fold change CA1/CA3 at 6h	p value at 6h	Fold change CA1/CA3 at 24h	p value at 24h	Fold change CA1/CA3 at 48h	p value at 48h
Fumaric acid	1.2355	0.0083438 *	0.91613	0.72676	1.0114	0.80613	1	1
Aspartic acid	1.2117	0.17311	0.95263	0.85261	1.0316	0.81506	0.96321	0.94597
N-acetylornithine	1.1319	0.10318	0.87532	0.58444	0.99968	0.9983	1.1535	0.80676
Citrulline	0.95223	0.57081	0.66935	0.09351 2	0.89638	0.27443	1.0666	0.90996
Arginine	1.1262	0.36643	0.73376	0.21789	1.0314	0.75544	0.83497	0.72117
Aminoacyl tRNA biosynthesis								
Compound	Fold change CA1/CA3 at 1h	p value at 1h	Fold change CA1/CA3 at 6h	p value at 6h	Fold change CA1/CA3 at 24h	p value at 24h	Fold change CA1/CA3 at 48h	p value at 48h
Cysteine	1.4951	0.11354	1.126	0.70198	1.126	0.70198	0.98297	0.98046

L-phenylalanine	1.2398	0.30231	0.91307	0.77351	0.91307	0.77351	1.2577	0.71714
Tryptophan	1.1845	0.45237	0.92792	0.78877	0.92792	0.78877	1.2041	0.76089
Aspartic acid	1.1466	0.0020419	0.93421	0.77241	0.93421	0.77241	0.9491	0.91734
Arginine	1.1262	0.36643	0.73411	0.21776	0.73411	0.21776	0.83498	0.72114
Serine	1.0999	0.17174	0.84517	0.49276	0.84517	0.49276	0.93258	0.89637
Leucine	1.0979	0.58169	0.98114	0.93911	0.98114	0.93911	1.1442	0.79511
L-Threonine	1.0546	0.5682	0.83023	0.45916	0.83023	0.45916	1.0187	0.97277
L-histidine	1.0426	0.84052	0.74632	0.27004	0.74632	0.27004	0.95434	0.92202
Pyrimidine metabolism								
Compound	Fold change CA1/CA3 at 1h	<i>p</i> value at 1h	Fold change CA1/CA3 at 6h	<i>p</i> value at 6h	Fold change CA1/CA3 at 24h	<i>p</i> value at 24h	Fold change CA1/CA3 at 48h	<i>p</i> value at 48h
Cytidine	1.4302	1.5202E-6*	1.014	0.9578 1	0.94387	0.59865	1.2009	0.76026
Cytidine-5'- diphosphate (CDP)	1.0789	0.47721	1.0338	0.5048 4	1.175	0.15044	1.1046	0.79249
dCMP	1.315	0.25596	1.3745	0.5860 6	1.1696	0.63434	0.80876	0.76938
Uracil	1.4419	0.13372	0.92985	0.7757 7	0.88862	0.71559	0.83425	0.70403

Uridine	1.3193	0.019158*	0.97654	0.9324 3	1.0135	0.91674	1.0344	0.95344
Beta-Alanine metabolism								
Compound	Fold change CA1/CA3 at 1h	<i>p</i> value at 1h	Fold change CA1/CA3 at 6h	<i>p</i> value at 6h	Fold change CA1/CA3 at 24h	<i>p</i> value at 24h	Fold change CA1/CA3 at 48h	<i>p</i> value at 48h
Uracil	1.4419	0.13372	0.92985	0.7757 7	0.88862	0.71559	0.83425	0.70403
Aspartic acid	1.1466	0.0020419	0.93421	0.77241	0.93421	0.77241	0.9491	0.91734
L-histidine	1.0426	0.84052	0.74632	0.27004	0.74632	0.27004	0.95434	0.92202
Taurine and hypotaurine metabolism								
Compound	Fold change CA1/CA3 at 1h	<i>p</i> value at 1h	Fold change CA1/CA3 at 6h	<i>p</i> value at 6h	Fold change CA1/CA3 at 24h	<i>p</i> value at 24h	Fold change CA1/CA3 at 48h	<i>p</i> value at 48h
Cysteine	1.4951	0.11354	1.126	0.70198	1.126	0.70198	0.98297	0.98046
Taurine	1.1	0.007*	0.909	0.704	1.005	0.899	1.136	0.797

Legend: Asterisk: statistically significant