



Supplementary files

Principal component analysis

Hippocampus

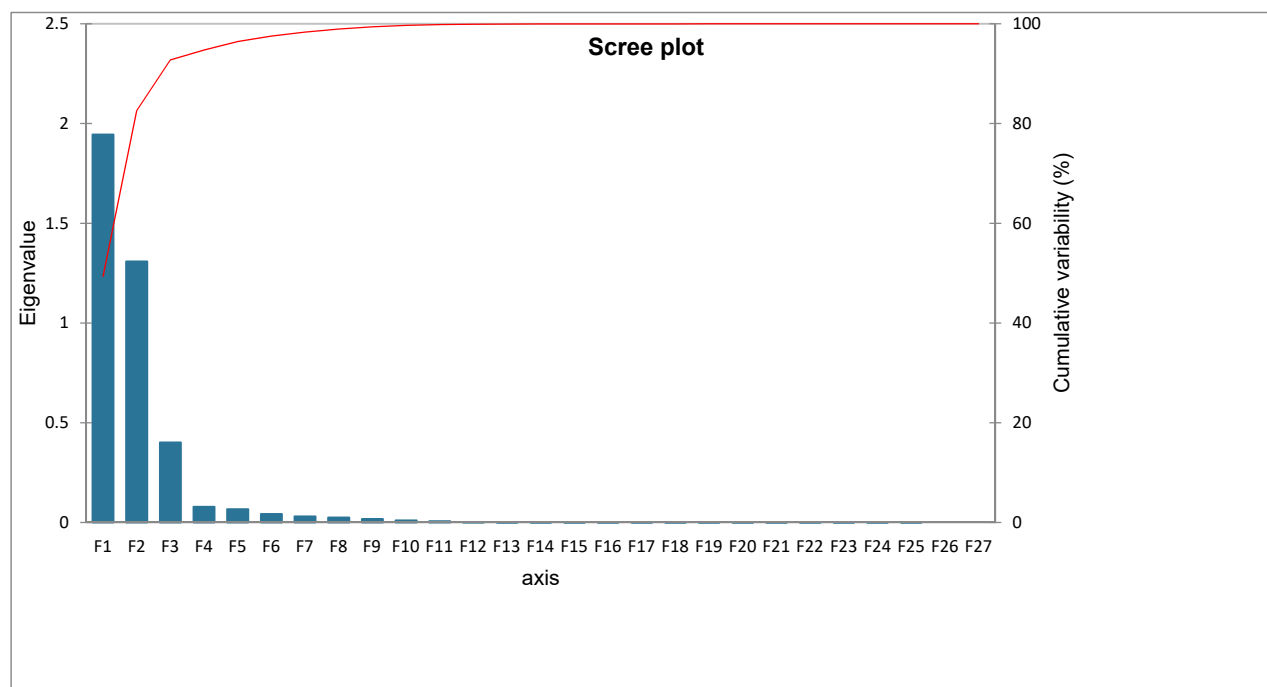


Figure S1. Scree-plot of PCA of number factors

Frontal cortex

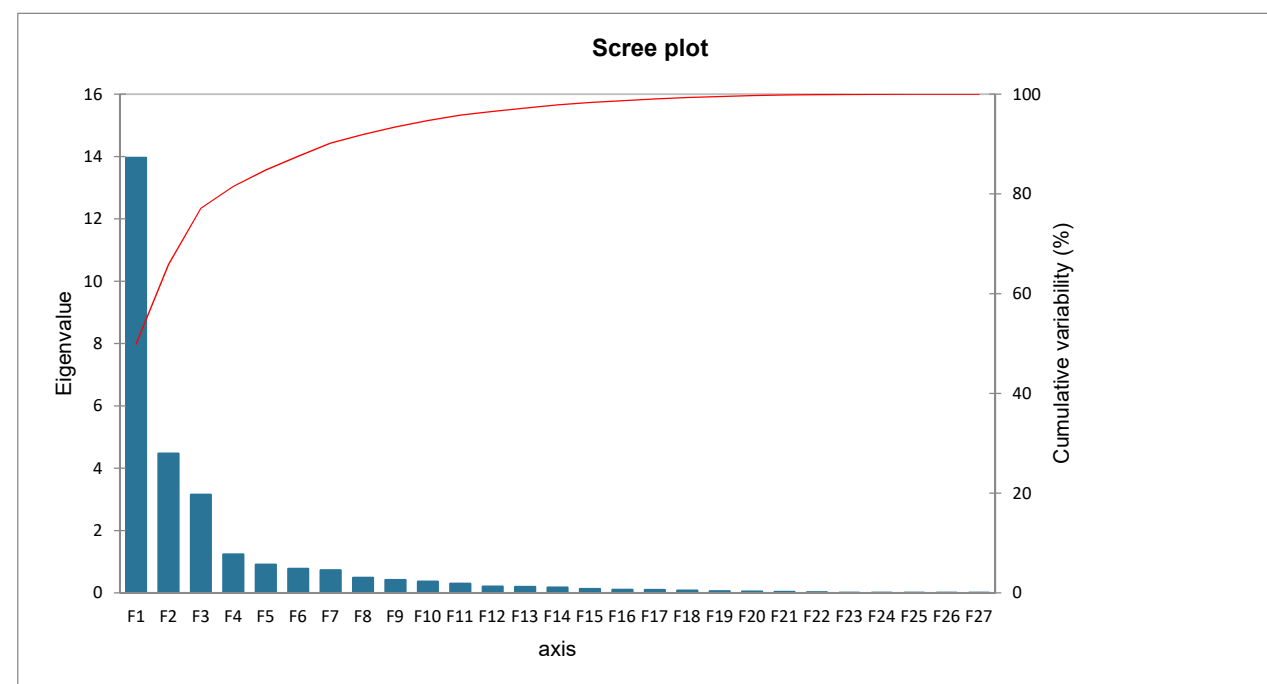


Figure S2. Scree-plot of PCA number factors in frontal cortex

Heatmaps

Frontal cortex

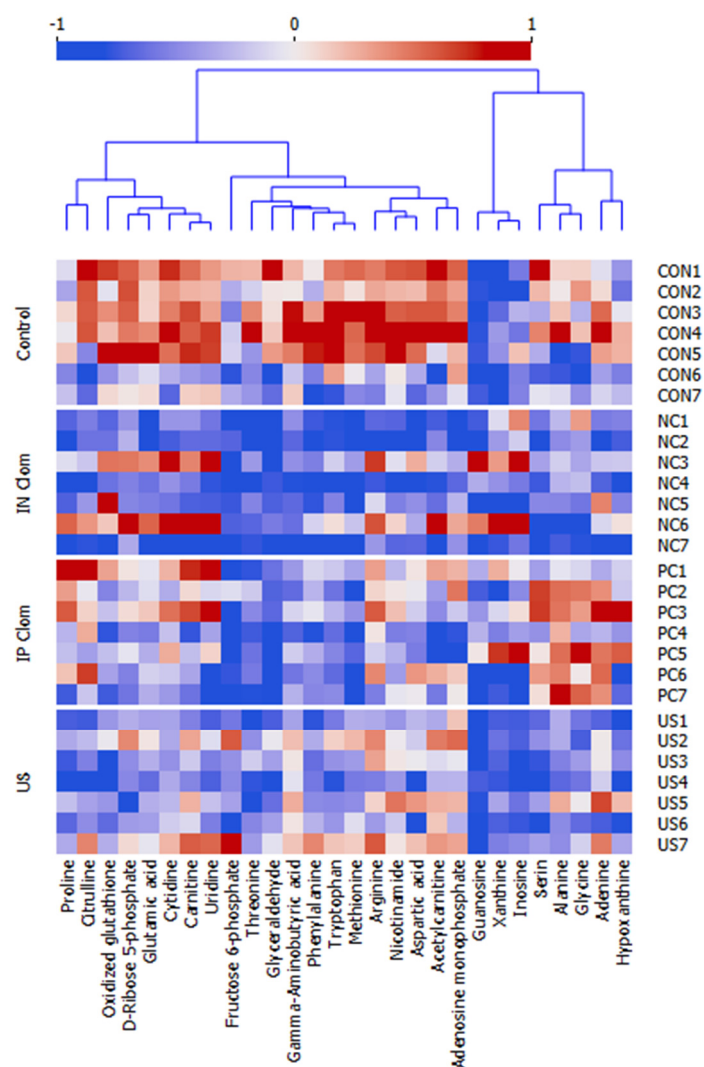


Figure S3. Clustered heatmap of metabolites in the frontal cortex of individual rat

Metabolites in the frontal cortex		Control	IN Clom	IP Clom	US	Mann-Whitney pairwise comparison <i>p</i> -value					
						Control - US	Control - IN Clom	Control - IP Clom	IN Clom - US	IP Clom - US	IN Clom - IP Clom
	Citrulline	0.44	0.33	0.45	0.33						
	Serin	0.31	0.23	0.32	0.24		0.020				
	Hypoxanthine	0.13	0.11	0.13	0.10		0.003	0.024	0.026	0.038	
	Adenine	0.09	0.07	0.09	0.08	0.038	0.002	0.011			
	Alanine	0.11	0.08	0.14	0.09					0.002	0.002
	Proline	0.85	0.70	0.95	0.69						
	Glycine	0.00	0.00	0.00	0.00	0.026	0.004	0.007			
	Guanosine	0.00	0.00	0.00	0.00					0.004	0.012
	Xanthine	0.02	0.04	0.04	0.02						
	Inosine	0.01	0.03	0.02	0.01					0.026	0.026
	D-Ribose 5-phosphate	0.03	0.02	0.01	0.01						
	Oxidized glutathione	0.11	0.08	0.07	0.06						
	Uridine	0.03	0.02	0.02	0.02				0.026		
	Cytidine	1.17	0.92	1.01	0.89						
	Aspartic acid	0.39	0.26	0.33	0.31	0.007	0.004			0.003	0.002
	Phenylalanine	0.31	0.17	0.23	0.23		0.002		0.020		
	Arginine	0.20	0.15	0.18	0.17		0.038				0.038
	Carnitine	1.12	0.83	0.92	0.94		0.017	0.017			
	Nicotinamide	4.13	2.81	3.26	3.42	0.017	0.004	0.026			
	Tryptophan	0.58	0.31	0.33	0.37		0.002	0.002	0.026	0.011	
	Threonine	1.39	0.90	0.98	0.97	0.002		0.017			
	Glutamic acid	4.76	3.40	3.83	3.63	0.026					
	Adenosine monophosphate	2.84	1.61	2.06	2.40		0.017				0.038
	Gamma-Aminobutyric acid	1.71	0.74	0.98	1.41	0.011		0.026			
	Methionine	0.09	0.04	0.04	0.06		0.001	0.002	0.001	0.004	
	Glyceraldehyde	0.02	0.00	0.00	0.01	0.007		0.011			
	Fructose 6-phosphate	0.00	0.00	0.00	0.00						
	Acetylcarnitine	0.53	0.40	0.39	0.50	0.017				0.017	

Figure S4. Clustered mean frontal cortex concentration of metabolites in animal groups with pairwise comparison between groups

Hippocampus

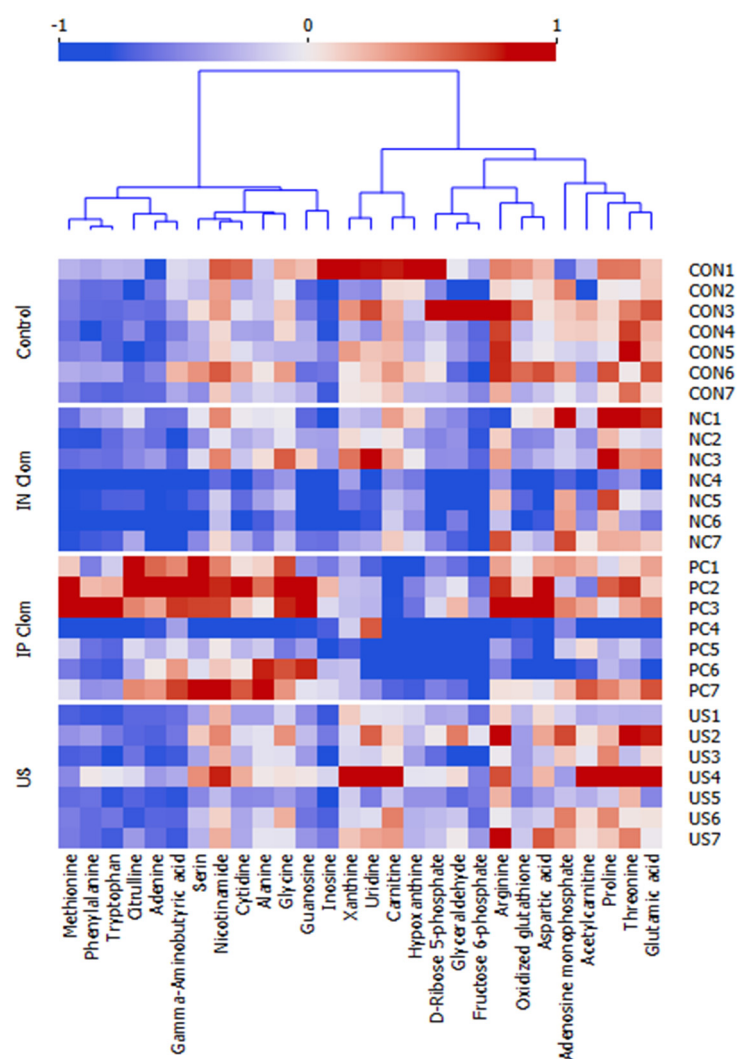


Figure S5. Clustered heatmap of metabolites in the frontal cortex of individual rat

Metabolites in the hippocampus		Control	IN Clom	IP Clom	US	Mann-Whitney pairwise comparison <i>p</i> -value					
						Control - US	Control - IN Clom	Control - IP Clom	IN Clom - US	IP Clom - US	IN Clom - IP Clom
Aspartic acid		0.38	0.35	0.35	0.21		0.007		0.011		
Nicotinamide		4.13	3.97	3.88	3.11						
Oxidized glutathione		0.20	0.14	0.17	0.08	0.011	0.017				
Glutamic acid		5.00	4.79	4.12	3.41						
Uridine		0.05	0.05	0.04	0.03						
Threonine		1.14	1.19	0.95	0.82						
Xanthine		0.13	0.14	0.10	0.07					0.001	
Arginine		0.21	0.20	0.16	0.14		0.026				
D-Ribose 5-phosphate		0.06	0.05	0.03	0.02		0.002	0.011	0.011		
Hypoxanthine		0.16	0.13	0.07	0.11			0.001		0.001	0.001
Carnitine		2.15	2.20	0.64	1.56			0.001		0.001	0.001
Adenosine monophosphate		1.95	1.95	1.41	1.42						
Fructose 6-phosphate		0.01	0.01	0.00	0.00				0.011		
Proline		1.05	1.05	0.79	0.85						
Acetylcarnitine		0.89	1.14	0.89	0.70				0.029		
Glyceraldehyde		0.02	0.03	0.02	0.02						
Guanosine		0.00	0.01	0.01	0.00						
Glycine		0.00	0.00	0.00	0.00						
Cytidine		1.85	1.60	1.88	1.10						0.049
Alanine		0.15	0.14	0.16	0.11						
Serin		0.37	0.35	0.44	0.23						
Phenylalanine		0.34	0.34	0.45	0.20						
Methionine		0.11	0.09	0.18	0.05		0.001		0.017		0.017
Tryptophan		0.54	0.49	0.78	0.33						
Gamma-Aminobutyric acid		2.72	1.50	3.69	0.95	0.007	0.001	0.017		0.001	0.001
Inosine		0.04	0.05	0.07	0.04						0.038
Citrulline		0.59	0.66	1.11	0.54			0.017			0.038
Adenine		0.11	0.10	0.19	0.09			0.017		0.017	0.004

Figure S6. Clustered mean hippocampus concentration of metabolites in animal groups with pairwise comparison between groups

Table S1. Results from the pathway analysis; Total - the total number of compounds in the pathway; Hits - the actually matched number from the user uploaded data; The *p* - the original *p*-value calculated from the enrichment analysis; Holm *p* - the *p*-value adjusted by Holm-Bonferroni method; FDR - the *p*-value adjusted using False Discovery Rate; Impact - the pathway impact value calculated from pathway topology analysis.

Pathway Name	Total	Hits	<i>p</i>	-log(<i>p</i>)	Holm <i>p</i>	FDR	Impact
A. Metabolic pathways in frontal cortex related to depression-like behaviors induced by US stress.							
Tryptophan metabolism	41	1	4.4473E-5	4.3519	0.0012	0.0012	0.1431

Aminoacyl-tRNA biosynthesis	<u>48</u>	10	9.3534E-4	3.029	0.0243	0.0026	0.1667
Alanine, aspartate and glutamate metabolism	<u>28</u>	4	0.0011	2.9426	0.0285	0.0026	0.5072
Arginine and proline metabolism	<u>38</u>	4	0.0011	2.9414	0.0285	0.0026	0.2455
Arginine biosynthesis	<u>14</u>	4	0.0012	2.9381	0.0285	0.0026	0.4213
D-Glutamine and D-glutamate metabolism	<u>6</u>	1	0.0012	2.9331	0.0285	0.0026	0.5
Pentose phosphate pathway	<u>21</u>	1	0.0052	2.2855	0.0777	0.0108	0.185
Nicotinate and nicotinamide metabolism	<u>15</u>	2	0.0061	2.2133	0.0857	0.0118	0.1943
Glycine, serine and threonine metabolism	<u>34</u>	2	0.0344	1.4635	0.432	0.058	0.2307
B. Metabolic pathways in hippocampus related to antidepressant effect of intraperitoneal clomipramine							
Purine metabolism	<u>66</u>	7	0.0216	1.665	0.6056	0.4853	0.1305