

Support information

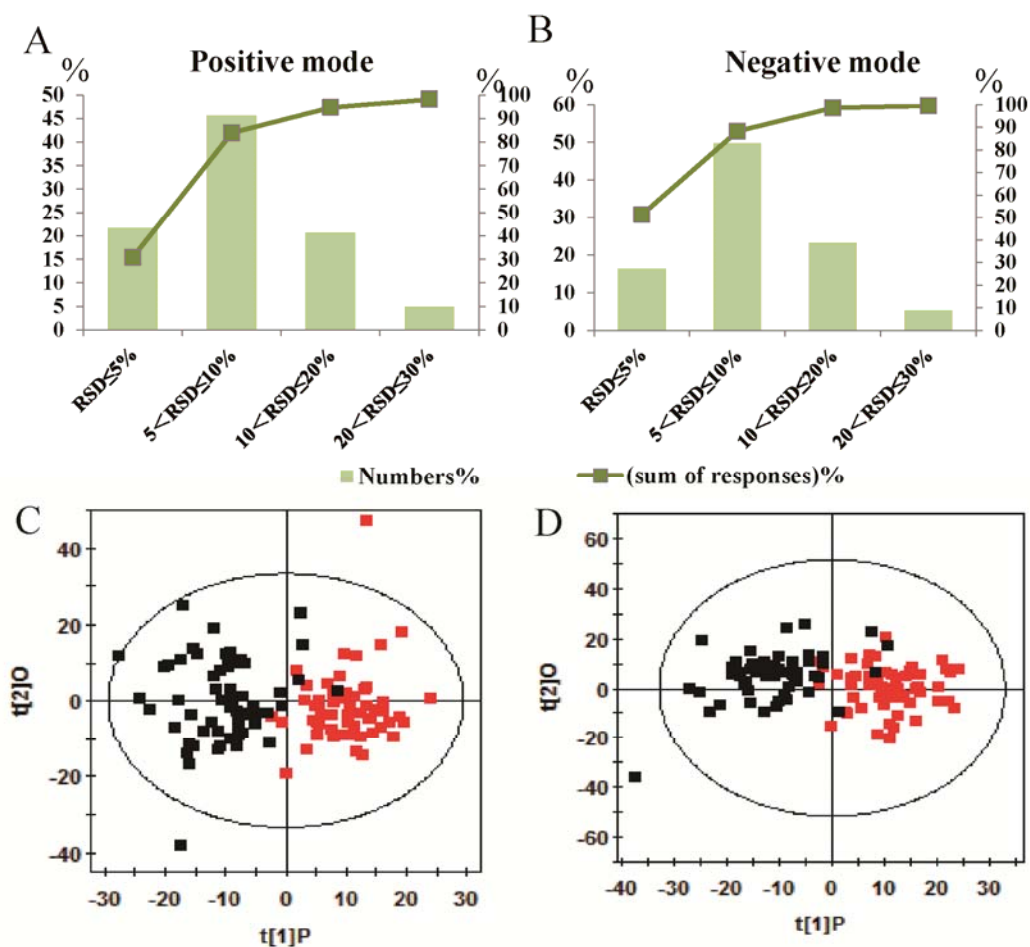


Figure S1. A-B: RSD distribution of quality control samples for evaluating method reproducibility in discovery phase (A) positive mode (B) negative mode. C-D: Scores plots of OPLS model based on UV scaling for MDD subjects (black box) and healthy control (red box) separation (C) $R^2Y=0.735$ & $Q^2=0.575$ in positive mode, (D) $R^2Y=0.676$ & $Q^2=0.518$ in negative mode

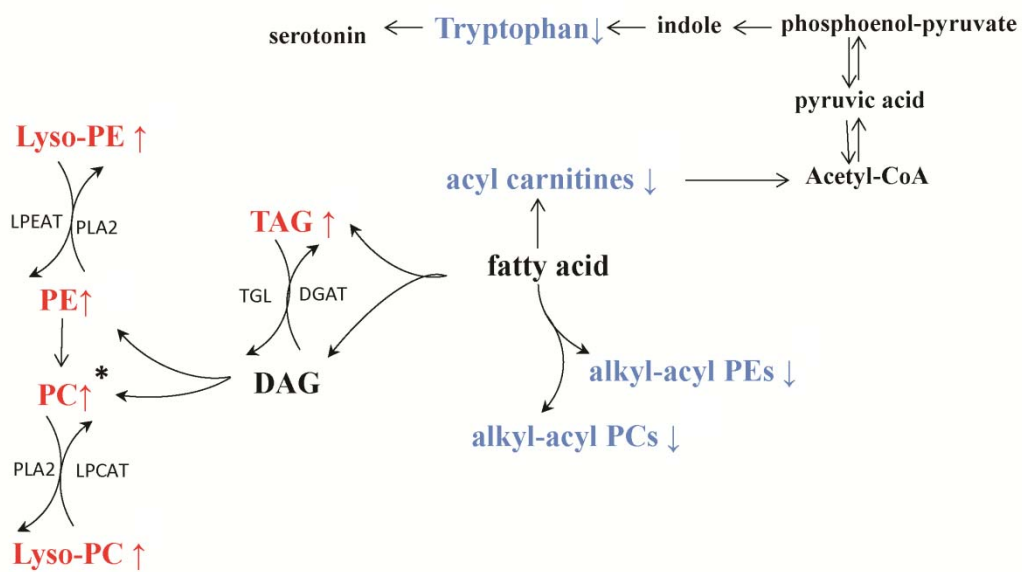


Figure S2. The pronounced changed pathways in major depressive disorder. The arrows ($\uparrow$ and $\downarrow$) means significantly up-regulated (red) and down-regulated (blue) metabolites in MDD subjects). Black: non-significant and not detected metabolites.

Table S1 Differential metabolites between M-/S-MDD and HC in discovery phase

Differential metabolites	Discovery phase			
	M-MDD/HC ratio	adj.p (M-MDD vs HC)	S-MDD/HC ratio	adj.p (S-MDD vs HC)
carnitine C10:1	0.61	0.002	0.48	<0.001
carnitine C10:2	0.71	0.004	0.63	<0.001
carnitine C8:0	0.74	0.048	0.58	<0.001
carnitine C14:2	0.74	0.036	0.73	0.019
carnitine C6:0	0.74	0.036	0.72	0.009
carnitine C14:3	0.82	0.036	0.77	0.012
carnitine C10:0	—	—	0.62	0.001
carnitine C12:0	—	—	0.75	0.019
carnitine C12:1	—	—	0.86	0.045
carnitine C3:0	—	—	0.80	0.041
FFA 16:2	0.73	0.041	—	—
methionine	0.87	0.009	0.88	0.006
PC O 36:2	0.83	0.009	0.83	0.009
PE O 34:3	0.74	0.015	0.64	<0.001
PE O 36:5	0.76	0.009	0.66	<0.001
PE O 38:7	0.80	0.020	0.73	0.001
PE O 36:6	—	—	0.67	0.011
stearic amide	0.82	0.036	—	—
tryptophan	0.90	0.036	0.84	0.002
deoxycholic acid	—	—	0.27	<0.001
lithocholic acid	—	—	0.45	0.002
LPC 16:1 sn-1	1.27	0.036	1.22	0.010
LPC 16:1 sn-2	1.35	0.009	1.27	0.004
LPC 16:0 sn-2	—	—	1.07	0.036
LPC 18:1 sn-1	—	—	1.14	0.009
LPC 18:1 sn-2	—	—	1.23	0.006
LPC 20:1 sn-1	—	—	1.24	0.022
LPC 20:1 sn-2	—	—	1.28	0.017
LPC 22:4 sn-1	—	—	1.28	0.041
LPC 22:4 sn-2	—	—	1.21	0.023
LPC P-16:0	—	—	1.32	0.012
LPE 16:0 sn-1	1.23	0.036	1.33	0.004
LPE 16:0 sn-2	1.23	0.008	1.28	0.002
LPE 18:1 sn-2	1.34	0.036	1.59	0.004

LPE 22:5 sn-1	1.35	0.024	1.33	0.009
LPE 16:1 sn-1	1.44	0.024	1.42	0.003
LPE 18:0 sn-1	—	—	1.24	0.039
LPE 18:0 sn-2	—	—	1.26	0.023
LPE 18:2 sn-1	—	—	1.28	0.031
LPE 18:2 sn-2	—	—	1.39	0.004
LPE 20:3 sn-1	—	—	1.24	0.047
PC 32:1	1.35	0.036	1.32	0.010
PC 32:0	—	—	1.18	0.019
PE 34:2	1.28	0.036	1.24	0.010
PE 36:4	1.24	0.009	1.20	0.024
glycodesoxycholic acid	1.57	0.036	1.75	0.019
glycoursodeoxycholic acid	—	—	1.70	0.049
taurochenodeoxycholic acid	—	—	1.51	0.028

p values were obtained from nonparametric test with FDR limit <0.05.

Table S2 Differential metabolites between M-/S-MDD and HC in validation phase

Differential metabolites	Validation phase			
	M-MDD/HC ratio	adj.p (M-MDD vs HC)	S-MDD/HC ratio	adj.p (S-MDD vs HC)
carnitine C10:1	0.59	<0.001	0.63	<0.001
carnitine C10:2	0.63	<0.001	0.68	<0.001
carnitine C8:0	0.57	<0.001	0.73	0.002
carnitine C6:0	0.60	<0.001	0.83	0.045
carnitine C14:2	0.64	<0.001	0.73	0.012
carnitine C14:3	0.65	<0.001	0.69	0.002
carnitine C10:0	—	—	0.72	0.004
carnitine C12:0	—	—	0.77	0.020
carnitine C12:1	—	—	0.77	0.036
FFA 16:2	0.63	<0.001	0.75	0.037
PE O 38:7	0.73	0.041	0.67	0.010
PE O 36:5	0.73	0.024	0.60	<0.001
PC O 36:2	0.77	0.049	—	—
PE O 34:3	—	—	0.52	<0.001
PE O 36:6	—	—	0.45	<0.001
tryptophan	0.85	0.006	0.81	0.002
LPC 16:1 sn-1	1.35	0.007	1.43	<0.001
LPC 16:1 sn-2	1.36	0.008	1.44	<0.001
LPC 16:0 sn-2	—	—	1.26	<0.001
LPC 18:1 sn-1	—	—	1.23	<0.001
LPC 18:1 sn-2	—	—	1.20	<0.001
LPC 20:1 sn-2	—	—	1.17	0.026
LPC 22:4 sn-1	—	—	1.06	0.036
LPE 16:0 sn-1	1.23	0.002	1.47	<0.001
LPE 16:0 sn-2	1.23	0.018	1.59	<0.001
LPE 22:5 sn-1	1.30	0.008	1.45	<0.001
LPE 18:1 sn-2	1.54	<0.001	1.70	<0.001
LPE 16:1 sn-1	1.76	0.002	1.91	<0.001
LPE 18:0 sn-1	—	—	1.35	<0.001
LPE 18:0 sn-2	—	—	1.40	<0.001
LPE 18:2 sn-1	—	—	1.40	<0.001
LPE 18:2 sn-2	—	—	1.43	<0.001
LPE 20:3 sn-1	—	—	1.49	<0.001
PC 32:1	1.32	0.038	1.36	0.006

PE 36:4	2.03	<0.001	1.97	0.014
PE 34:2	1.38	0.040	1.66	<0.001

p values were obtained from nonparametric test with FDR limit <0.05.