

Online Resource 1. Mean water intake for vehicle and fluoxetine treated mice.

Strain	Mean Water Intake Per Cage (mL)#	SEM	Mean Water Intake Per Cage (mL)*	SEM	Water Intake between Treatment Groups (mL)
129S1/SvlmJ	5.2	0.2	3.7	0.3	1.43
A/J	5.3	0.2	4.7	0.2	0.63
AKR/J	7.4	0.2	5.4	0.2	1.98
BALB/cJ	5.7	0.3	5.1	0.3	0.61
BTBR T+ tf/J	7.1	0.2	6.4	0.2	0.71
BUB/BnJ	7.3	0.4	5.8	0.2	1.53
C3H/HeJ	5.0	0.2	4.7	0.2	0.27
C57BL/6J	6.0	0.2	4.5	0.2	1.51
C57BLKS/J	6.1	0.2	4.7	0.2	1.39
C57BR/cdJ	8.9	0.3	8.0	0.3	0.92
C58/J	5.7	0.2	4.6	0.2	1.08
CBA/J	6.1	0.2	4.9	0.2	1.14
DBA/2J	6.4	0.2	6.0	0.2	0.37
FVB/NJ	5.4	0.3	5.2	0.2	0.25
I/LnJ	6.4	0.2	4.8	0.2	1.57
LG/J	8.9	0.4	5.8	0.2	3.10
LP/J	3.7	0.2	3.6	0.2	0.14
MA/MyJ	6.7	0.2	5.0	0.2	1.69
MRL/MpJ	13.2	0.4	8.2	0.2	4.98
NOD/LtJ	7.1	0.2	5.1	0.2	2.04
NOR/LtJ	5.8	0.1	6.6	0.2	0.84
NZB/BINJ	6.0	0.2	4.9	0.2	1.16
NZW/LacJ	9.7	0.2	11.2	0.5	1.53
P/J	5.2	0.2	4.9	0.2	0.25
PL/J	5.7	0.2	3.9	0.2	1.82
RIIS/J	4.2	0.2	4.1	0.2	0.12
SJL/J	7.2	0.3	5.4	0.3	1.76
SM/J	5.4	0.2	5.9	0.3	0.53
SWR/J	6.9	0.3	5.0	0.1	1.92

SEM = standard error of the mean; # Denotes behavioral mean water intake for control mice (water); * Denotes mean water intake for fluoxetine-treated mice

Online Resource 2. Behavioral responses in the open field and tail suspension tests between control and fluoxetine treatment groups

Strain	Total number of animals tested per strain	Number of animals excluded from the TST analysis	Mean TST Immobility Scores (secs)#	SEM	Mean TST Immobility Scores (secs)*	SEM	Mean OF Center Time (secs)#	SEM	Mean OF Center Time (secs)*	SEM	Mean Total Distance Traveled in the OF(cm)#	SEM	Mean Total Distance Traveled in the OF (cm)*	SEM
129S1/SvImJ	28	2	122.5	11.9	115.3	10.8	23.0	17.7	2.3	1.6	450.2	98.5	360.2	87.5
A/J	30	3	106.9	11.7	115.4	5.4	1.2	1.1	6.6	5.9	257.5	59.2	293.4	76.4
AKR/J	18	2	192.6	10.3	171.2	15.6	70.9	10.8	71.0	15.5	1905.1	173.3	1824.1	119.5
BALB/cJ	39	4	107.2	10.6	56.6	7.9	46.9	23.3	30.8	10.5	968.8	268.5	1018.5	211.6
BTBR T+ tf/J	21	4	15.7	8.8	7.3	4.3	56.2	11.1	48.3	9.3	1909.7	192.6	2131.0	237.4
BUB/BnJ	18	1	142.3	10.2	97.3	10.5	111.9	14.0	147.8	14.6	1607.0	145.3	2392.9	272.7
C3H/HeJ	30	2	97.3	8.8	112.3	12.3	65.0	6.8	63.7	5.9	1104.1	60.7	1079.8	42.8
C57BL/6J	21	5	175.7	18.6	103.5	11.7	77.2	10.8	65.8	9.0	1128.4	74.6	1174.7	105.6
C57BLKS/J	24	3	101.3	13.6	72.6	14.8	38.8	6.1	37.3	6.7	775.1	77.8	1004.9	190.8
C57BR/cdJ	27	5	97.5	19.6	33.3	10.4	193.0	15.8	156.0	15.2	2134.3	109.9	2712.5	206.6
C58/J	18	0	80.9	13.1	83.2	7.2	124.3	15.9	105.6	16.0	1998.1	240.0	2972.8	583.8
CBA/J	30	2	135.0	8.8	44.9	8.5	70.5	11.5	56.4	12.3	1051.1	106.4	1506.6	103.9
CE/J	24	3	108.8	16.5	76.9	9.9	79.2	12.0	89.5	7.6	1546.2	118.3	1518.4	140.5
DBA/2J	36	9	44.3	10.0	19.1	4.7	33.8	5.8	15.6	3.4	1085.5	84.4	1824.3	255.4
FVB/NJ	18	2	53.3	13.6	70.4	11.5	136.0	6.8	112.8	7.3	2209.3	148.3	1869.8	107.3
I/LnJ	24	8	79.2	28.6	77.2	18.4	60.8	8.5	40.5	12.2	2065.3	124.4	2040.5	284.6
LG/J	21	3	27.2	13.4	4.5	1.4	85.9	16.0	44.4	22.0	1677.1	97.9	1271.0	63.3
LP/J	28	9	196.7	13.5	177.7	19.5	56.1	27.3	28.7	8.2	1011.0	195.4	611.7	90.8
MA/MyJ	18	0	79.1	18.0	33.9	10.5	131.6	12.5	76.8	15.0	2349.2	182.9	3511.8	395.2
MRL/MpJ	21	4	16.0	5.1	14.7	5.4	107.9	11.4	85.8	18.3	1471.8	67.6	1395.7	137.1
NOD/LtJ	24	3	165.4	8.6	141.2	7.4	164.5	18.7	146.6	12.5	2669.3	229.6	2555.1	173.0
NOR/LtJ	24	7	105.0	9.9	84.6	18.9	145.1	12.1	157.2	15.0	2410.6	180.6	2282.1	94.6
NZB/BINJ	24	6	161.3	31.0	201.3	8.5	33.5	7.0	13.5	4.1	1070.3	63.0	942.2	123.1
NZW/LacJ	21	4	124.7	19.7	161.9	17.1	76.3	7.6	80.6	16.7	1078.5	54.6	1350.7	162.1
P/J	23	3	130.3	17.5	40.7	10.1	114.7	20.3	59.8	13.1	1807.3	56.4	2445.8	300.5
PL/J	24	2	170.0	11.9	137.6	11.0	71.3	4.7	57.2	4.5	1840.4	106.8	1770.2	113.8
RIIS/J	21	0	18.6	4.6	32.8	11.0	69.2	4.1	79.9	6.6	2050.6	100.4	1825.0	84.8
SJL/J	24	4	143.7	13.1	145.7	15.4	109.2	37.2	27.0	17.7	945.1	106.2	853.5	78.7
SM/J	18	4	229.5	6.4	137.2	13.3	70.6	5.9	38.4	7.7	1999.5	71.8	3180.8	641.0
SWR/J	24	0	50.3	9.9	69.6	12.4	91.3	5.4	105.2	11.0	1393.5	83.0	1499.3	67.6

TST = tail suspension test; OF = open field; SEM = standard error of the mean; # Denotes behavioral scores for control mice (water); * Denotes behavioral scores for fluoxetine-treated mice

Online Resource 3. Serum Levels of Fluoxetine and its Metabolite Norfluoxetine Following Chronic Antidepressant Treatment

Strain	Number of Animals (N)	Fluoxetine (ng/ml)	SEM	Norfluoxetine (ng/ml)	SEM
129S1/SvlmJ	13	1152.9	58.0	1079.8	45.2
A/J	15	937.9	47.7	1222.6	48.0
AKR/J	9	988.1	53.4	1119.2	49.3
BALB/cJ	12	800.2	40.5	930.8	49.9
BTBR T+ tf/J	12	912.1	51.4	1238.5	79.2
BUB/BnJ	9	1396.9	143.4	1391.7	148.1
C3H/HeJ	15	763.1	66.4	949.5	65.1
C57BL/6J	7	1327.6	220.9	1509.0	186.3
C57BLKS/J	12	1243.5	96.1	1195.0	47.6
C57BR/J	10	988.9	151.0	1260.4	153.7
C58/J	9	987.2	116.5	1335.6	105.9
CBA/J	11	1103.9	108.3	1093.3	108.9
CE/J	12	1084.4	73.2	1401.2	74.0
DBA/2J	16	956.5	95.7	1026.7	56.4
FVB/NJ	9	595.2	81.4	798.3	120.0
I/LnJ	8	1606.5	318.3	1438.3	130.9
LG/J	9	1540.0	117.0	1612.2	134.9
LP/J	19	719.6	67.3	783.4	73.7
MA/MyJ	9	1905.6	223.9	1314.3	120.0
MRL/MpJ	9	1066.7	183.5	1047.4	143.1
NOD/LtJ	12	775.5	81.9	912.0	80.6
NOR/LtJ	15	483.3	48.4	746.9	65.2
NZB/B1NJ	12	1311.1	142.6	1156.3	81.2
NZW/LacJ	9	591.4	66.6	762.9	48.0
P/J	11	1885.5	407.3	1267.5	246.7
PL/J	12	757.4	97.2	825.9	111.9
RHIS/J	12	470.3	36.5	578.6	25.8
SJL/J	11	1274.8	107.9	1124.5	64.8
SM/J	8	1187.0	320.2	1160.2	256.4
SWR/J	12	749.3	110.7	643.8	108.6

SEM = standard error of the mean

Online Resource 4. Mean relative fluorescence intensity (RFI) values for thirty-one neurobiochemical analytes measured in the cortex of thirty mouse inbred strains

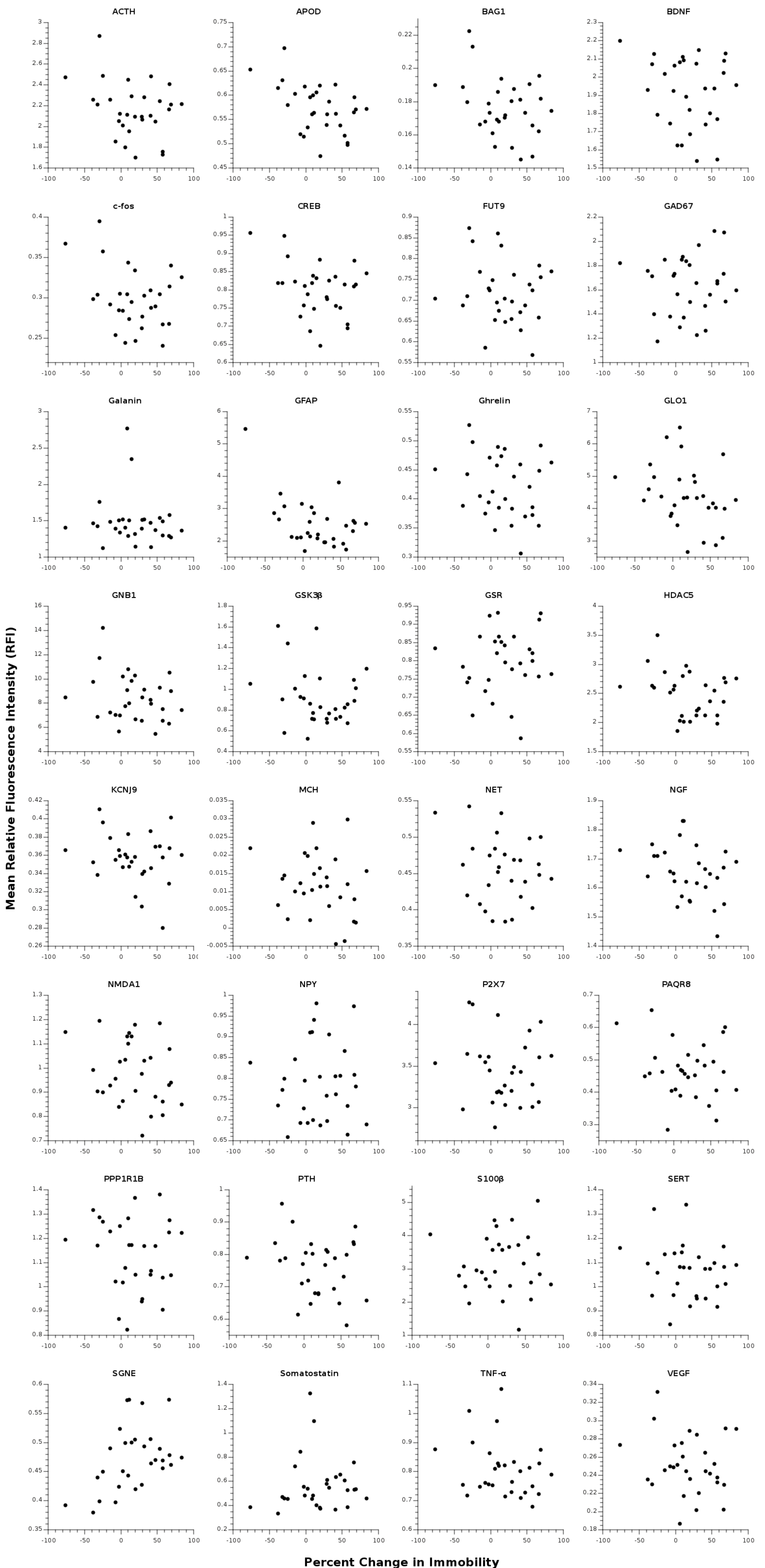
Strains	ACTH*	STD	ACTH*	STD	FUT9*	STD	FUT9*	STD	APOD*	STD	APOD*	STD	BAG1*	STD	BAG1*	STD	BDNF*	STD	BDNF*	STD	c-fos*	STD	c-fos*	STD	CREB*	STD	CREB*	STD	PPP1R1B*	STD	PPP1R1B*	STD	GAD67*	STD	GAD67*	STD	Galanin*	STD	Galanin*	STD	GFAP*	STD	GFAP*	STD	Ghrelin*	STD	Ghrelin*	STD	KCNJ9*	STD	KCNJ9*	STD	GSR*	STD	GSR*	STD	GLO1*	STD	GLO1*	STD	GNB1*	STD	GNB1*	STD	GSK3β*	STD	GSK3β*	STD	HDAC5*	STD	HDAC5*	STD	MCH*	STD	MCH*	STD	NGF*	STD	NGF*	STD	NPY*	STD	NPY*	STD	NMDA1*	STD	NMDA1*	STD	NET*	STD	NET*	STD	P2X7*	STD	P2X7*	STD	PTH*	STD	PTH*	STD	PAQR8*	STD	PAQR8*	STD	S100β*	STD	S100β*	STD	SGNE*	STD	SGNE*	STD	SERT*	STD	SERT*	STD	Somatostatin*	STD	Somatostatin*	STD	TNF-α*	STD	TNF-α*	STD	VEGF*	STD	VEGF*	STD
129Sv/SvJm	1.80	0.066	1.62	0.105	0.65	0.019	0.50	0.017	0.60	0.013	0.56	0.009	0.15	0.006	0.12	0.007	2.08	0.024	1.74	0.058	0.24	0.009	0.28	0.008	0.69	0.030	0.62	0.017	1.08	0.034	0.76	0.030	1.29	0.093	1.13	0.056	1.41	0.031	0.98	0.019	2.25	0.029	1.51	0.025	0.35	0.026	0.53	0.038	3.49	0.176	1.77	0.263	7.79	0.775	8.43	0.654	0.86	0.052	0.67	0.042	2.04	0.089	1.63	0.102	0.00	0.008	0.01	0.006	1.78	0.034	1.66	0.036	0.91	0.024	0.47	0.024	1.04	0.061	0.73	0.045	0.48	0.016	0.40	0.013	2.76	0.055	2.22	0.107	0.72	0.065	0.78	0.079	0.48	0.040	0.32	0.032	3.58	0.306	1.85	0.153	0.50	0.008	0.35	0.010	1.08	0.019	0.84	0.031	1.33	0.128	1.01	0.118	0.81	0.021	0.39	0.016	0.19	0.010	0.19	0.007	0.20	0.009						

Denotes RFI values for control mice (water); * Denotes RFI values for fluoxetine-treated mice. STD stands for standard deviation. ACTH = Adrenocorticotropic releasing hormone; APOD = Apolipoprotein D; BAG1 = BCL2-associated atgane 1; BDNF = Brain-derived neurotrophic factor; CREB = CAMP response element-binding; PPP1R1B = Protein phosphatase 1 subunit 1B; DAT = Dopamine transporter; GAD67 = Glutamic acid decarboxylase-67; GAL = Galanin; GFAP = Glial fibrillary acidic protein; GLO1 = Glyoxalase 1; GNB1 = Guanine nucleotide-binding protein subunit beta 1; GSK3β = Glycogen synthase kinase 3 beta; GSR = Glutathione reductase; HDAC5 = Histone deacetylase 5; KCN9 = Potassium inwardly-rectifying channel, subfamily J, member 9; MCH = Melanin concentrating hormone; NET = Norepinephrine transporter; NGF = Nerve growth factor; NMDA1 = Glutamate receptor; NPY = Neuropeptide Y; P2X7 = Purinergic receptor ligand-gated ion channel 7; PAQR8 = Progesterin and adipoQ receptor 8; PTH = Parathyroid hormone; S100β = S100 beta protein; SERT = Serotonin transporter; SGNE = Secretogranin V; TNF-α = Tumor necrosis factor-alpha; VEGF = Vascular endothelial growth factor

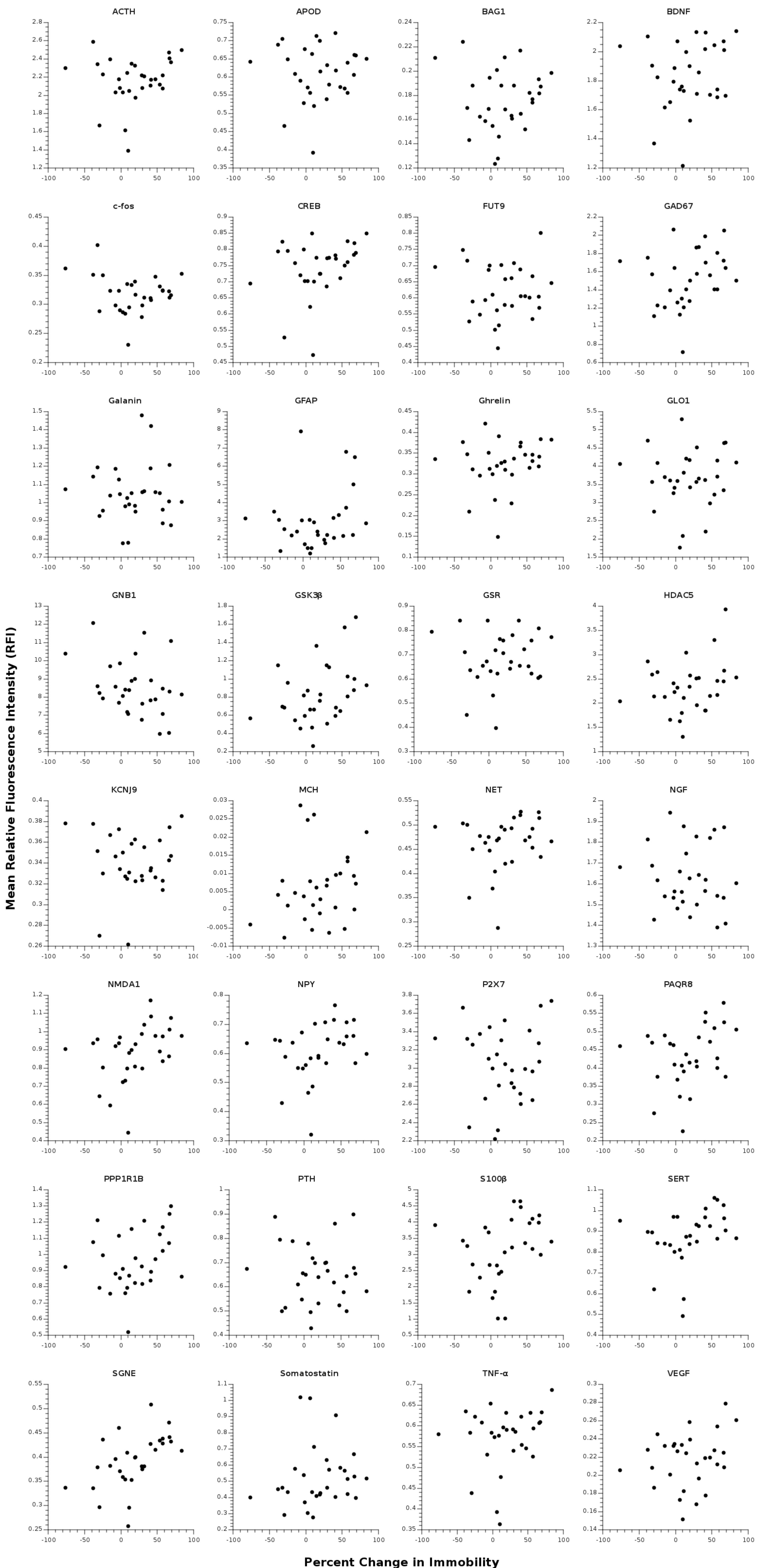
Online Resource 5. Pairwise comparisons of behavioral scores between treatment groups.

Strain	U-Statistic for Percent Time Spent Immobile in the TST	Adjusted <i>p</i>-values***	U-Statistic for Percent Time Spent in the Center of the OF	Adjusted <i>p</i>-values***
129S1/SvlmJ	96	0.537	111.5	0.294
A/J	114	0.264	115.0	0.917
AKR/J	41	0.345	40.0	0.965
BALB/cJ	249.5	0.001**	47.5	0.879
BTBR T+ tf/J	45	0.386	61.0	0.619
BUB/BnJ	62	0.012*	51.5	0.136
C3H/HeJ	121	0.291	117.5	0.836
C57BL/6J	57	0.007**	63.5	0.500
C57BLKS/J	71	0.260	63.0	0.843
C57BR/cdJ	95	0.023*	124.0	0.097
C58/J	42	0.895	53.0	0.270
CBA/J	190.5	0.00002**	117.0	0.369
CE/J	69	0.286	70.0	0.256
DBA/2J	131.5	0.094^	262.5	0.014*
FVB/NJ	43	0.248	64.0	0.038
I/LnJ	24	0.427	66.5	0.063
LG/J	61	0.070^	77.0	0.037
LP/J	41.5	0.826	115.0	0.147
MA/MyJ	63	0.047*	68.0	0.015*
MRL/MpJ	37	0.923	57.5	0.265
NOD/LtJ	81	0.067^	61.0	0.974
NOR/LtJ	48	0.205	55.5	0.973
NZB/BINJ	46	0.594	95.5	0.022
NZW/LacJ	50	0.178	39.0	0.895
P/J	90	0.001**	79.0	0.025
PL/J	94	0.025*	102.5	0.078
RIIS/J	66	0.394	73.0	0.177
SJL/J	50	0.970	100.5	0.009**
SM/J	49	0.002**	64.0	0.007**
SWR/J	93	0.225	83.0	0.525

*** Following Mann-Whitney U test for post-hoc pairwise comparisons of behavioral scores between treatment groups, *p*-values were adjusted for multiple comparisons using the Benjamini-Hochberg correction for multiple testing; ** denotes *p*-values $p < 0.01$; * denotes *p*-values $p < 0.05$; ^denotes *p*-values $p < 0.10$



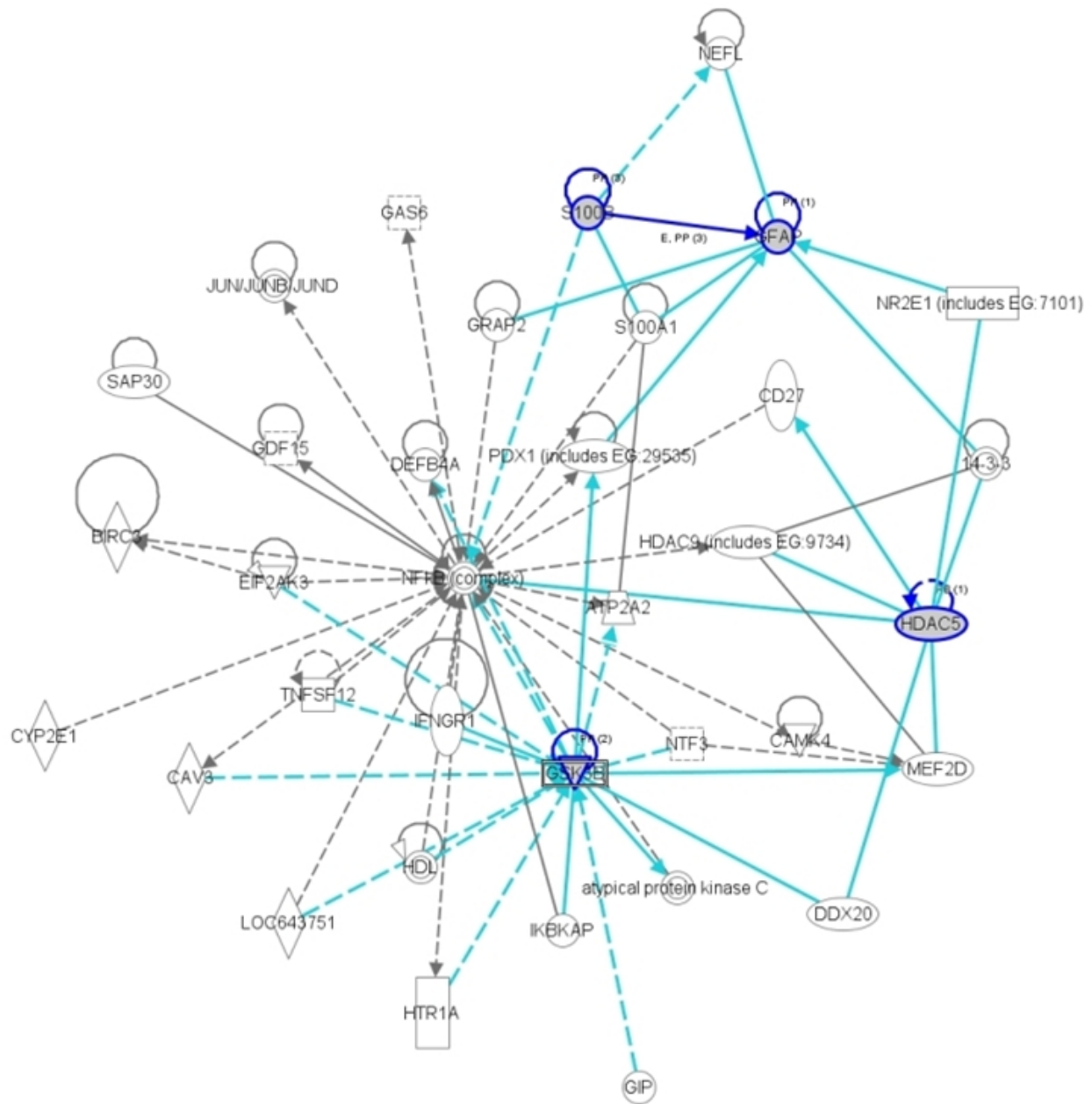
Online Resource 6a. Scatter plots of depressive-like and neurobiochemical measures in the control group



Online Resource 6b. Scatter plots of depressive-like and neurobiochemical measures in the fluoxetine group

Online Resource 7. Covariance of behavior and neurobiochemical levels explained by partial least squares (PLS) latent vectors

	Percent covariance explained for behavior and biochemical levels	Cumulative percent covariance explained for behavior and biochemical levels
<i>Vehicle</i>		
Vector 1	59	59
Vector 2	29	88
Vector 3	12	100
<i>Fluoxetine</i>		
Vector 1	56	56
Vector 2	33	89
Vector 3	11	100



Online Resource 8. Cellular adhesion and proliferation pathway links candidate antidepressant biochemical markers S100 β , GFAP, GSK3 β , and HDAC5

Online Resource 9a. Informative genes used to predict treatment groups in the kNN leave-one-out cross-validation test

Genes	Description
Gm129	gene model 129
Lgi2	leucine-rich repeat LGI family, member 2
Erf	Ets2 repressor factor
Gnb4	guanine nucleotide binding protein (G protein), beta 4
Cdc42ep3	CDC42 effector protein (Rho GTPase binding) 3
Anp32a	acidic (leucine-rich) nuclear phosphoprotein 32 family, member A
2400009B08Rik	RIKEN cDNA 2400009B08 gene, sema domain, immunoglobulin domain (Ig), transmembrane domain (TM) and short cytoplasmic domain, (semaphorin) 4A,
Sema4a	
Gpc1	glypican 1
Inhba	inhibin beta-A
C030003D03Rik	RIKEN cDNA C030003D03 gene
Sgsm1	small G protein signaling modulator 1

Online Resource 9b. Informative genes used to predict response groups in the kNN leave-one-out cross-validation test

Genes	Description
Copg2as2	coatamer protein complex, subunit gamma 2, antisense 2
Prcp	prolylcarboxypeptidase (angiotensinase C)
Gpr115	G protein-coupled receptor 115
Gxylt2	glycosyltransferase 8 domain containing 4
Plb1	phospholipase B1
Txndc9	thioredoxin domain containing 9
Mum11l	melanoma associated antigen (mutated) 1-like 1
EG545391	predicted gene

Online Resource 10. List of candidate baseline genetic markers that account for variable antidepressant response

Gene	Gene Name	p -value	R ²	Adjusted R ²
9230108115Rik	RIKEN cDNA 9230108115 gene	0.00014	0.61	0.58
Gm16432	Predicted gene 16432	0.00057	0.53	0.51
C78760	Expressed sequence C78760	0.00069	0.52	0.49
Smurf2	SMAD specific E3 ubiquitin protein ligase 2	0.00086	0.51	0.48
2610005L07Rik	Cadherin 11 pseudogene	0.00113	0.49	0.46
Lmo3	LIM domain only 3	0.00156	0.47	0.44
Tcrb-J	T-cell receptor beta, joining region	0.00206	0.46	0.42
LOC665506	T-cell receptor beta, joining region	0.00278	0.44	0.40
Pabpc1	Poly(A) binding protein, cytoplasmic 1	0.00431	0.41	0.37
Ern1	Endoplasmic reticulum (ER) to nucleus signalling 1	0.00461	0.40	0.37
LOC627901	Similar to zinc finger protein 14	0.00533	0.39	0.36