

## Supplementary Information

### Construction and Analysis of Protein-Protein Interaction Network of

### Heroin Use Disorder

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## **Legend of Tables**

Table S1. The seed proteins associated with HUD

Table S2. The proteins in PPI network extracted from STRING database associated with HUD

Table S3. The topological measurements of PPI network

Table S4. The proteins in the PPI network (with co-expression) extracted from STRING database associated with HUD

Table S5. The topological measurements of PPI network (with co-expression)

Table S6. Top 25 nodes with high degree and their respective BC and CC

Table S7. Top 25 nodes with high BC and their respective  $k$  and CC

Table S8. The proteins in the backbone network (with co-expression)

Table S9. The proteins in the 2<sup>nd</sup> extended PPI network (with co-expression) involved in the KEGG pathways of alcoholism, amphetamine addiction, and cocaine addition

Table S10. The miRNA targeting genes by stress-induced

Table S11. The miRNA-disease associations in HMDD v3.0

## Legend of Figures

Figure S1. The PPI network (with co-expression)

Figure S2. The backbone network (with co-expression)

Figure S3. The 13-protein-subnetwork of the two backbones

Figure S4. The 2<sup>nd</sup> extended PPI network (with co-expression)

\*The red ones are nodes in amphetamine addiction pathway

+The blue ones are nodes in cocaine addiction pathway

#The green ones are nodes in alcoholism pathway

Figure S5. The KEGG pathways of alcoholism

Figure S6. The KEGG pathways of amphetamine addiction

Figure S7. The KEGG pathways of cocaine addiction

Table S1. The seed proteins associated with HUD

Label	Name	Description
1	AUTS2	autism susceptibility candidate 2
2	CD74	CD74 molecule, major histocompatibility complex, class II invariant chain
3	CEBPB	CCAAT/enhancer binding protein (C/EBP), beta
4	CEBPG	CCAAT/enhancer binding protein (C/EBP), gamma
5	ENO2	enolase 2 (gamma, neuronal)
6	HAT1	histone acetyltransferase 1
7	IMPDH2	IMP (inosine 5'-monophosphate) dehydrogenase 2
8	JUN	jun proto-oncogene
9	MBD1	methyl-CpG binding domain protein 1
10	PDK1	pyruvate dehydrogenase kinase, isozyme 1
11	PRKCB	protein kinase C, beta
12	RASA1	RAS p21 protein activator
13	RGS3	regulator of G-protein signaling 3

Table S2. The proteins in the PPI network extracted from STRING database associated with HUD

Label	Names	Description
1	ARHGAP35	Rho GTPase activating protein 35
2	ATF1	Activating transcription factor 1
3	ATF2	Activating transcription factor 2
4	ATF3	Activating transcription factor 3
5	ATIC	5-aminoimidazole-4-carboxamide ribonucleotide formyltransferase/IMP cyclohydrolase
6	AURKB	Aurora kinase B
7	BATF3	Basic leucine zipper transcription factor, ATF-like 3; AP-1 family transcription factor that controls the
8	BPGM	2,3-bisphosphoglycerate mutase
9	CD74	CD74 molecule, major histocompatibility complex, class II invariant chain
10	CEBPA	CCAAT/enhancer binding protein (C/EBP), alpha
11	CEBPB	CCAAT/enhancer binding protein (C/EBP), betaplays essential and redundant functions with CE [...]
12	CEBPD	CCAAT/enhancer binding protein (C/EBP), delta heterodimer with CEBPB (PubMed:1741402)
13	CEBPG	CCAAT/enhancer binding protein (C/EBP), gamma promoter
14	CHUK	Conserved helix-loop-helix ubiquitous kinase
15	COPS5	COP9 constitutive photomorphogenic homolog subunit 5 (Arabidopsis)
16	CREB1	cAMP responsive element binding protein 1
17	CREBBP	CREB binding protein
18	CSK	C-src tyrosine kinase
19	CTSL1	Cathepsin L1; Important for the overall degradation of proteins in lysosomes
20	DLAT	Dihydrolipoamide S-acetyltransferase
21	DOK1	Docking protein 1, 62kDa (downstream of tyrosine kinase 1)
22	DOK2	Docking protein 2, 56kDa
23	DUSP1	Dual specificity phosphatase 1
24	DVL2	Dishevelled, dsh homolog 2
25	EGFR	Epidermal growth factor receptor
26	EGR1	Early growth response 1
27	ENO2	Enolase 2 (gamma, neuronal)
28	ENO3	Enolase 3 (beta, muscle)
29	ENSG00000250741	NT5C1B-RDH14 readthroug
30	EP300	E1A binding protein p300
31	EPHB2	EPH receptor B2
32	EPHB3	EPH receptor B3
33	ESR1	Estrogen receptor 1

34	ETS1	V-ets erythroblastosis virus E26 oncogene homolog 1 (avian);
35	ETS2	V-ets erythroblastosis virus E26 oncogene homolog 2 (avian)
36	FOS	FBJ murine osteosarcoma viral oncogene homolog
37	FOSB	FBJ murine osteosarcoma viral oncogene homolog B
38	FOSL1	FOS-like antigen 1
39	FOSL2	FOS-like antigen 2
40	GATA2	GATA binding protein 2
41	GMPR	Guanosine monophosphate reductase
42	GMPR2	Guanosine monophosphate reductase 2
43	GMPS	Guanine monphosphate synthetase;
44	GNA11	Guanine nucleotide binding protein (G protein), alpha 11 (Gq class)
45	GNA14	Guanine nucleotide binding protein (G protein), alpha 14
46	GNA15	Guanine nucleotide binding protein (G protein), alpha 15 (Gq class)
47	GNAQ	Guanine nucleotide binding protein (G protein), q polypeptide
48	GNB2L1	Guanine nucleotide binding protein (G protein), beta polypeptide 2-like 1
49	GSK3B	Glycogen synthase kinase 3 beta
50	GTF2B	General transcription factor IIB
51	HAT1	Histone acetyltransferase 1
52	HCK	Hemopoietic cell kinase
53	HLA-DMB	Major histocompatibility complex, class II, DM beta
54	HLA-DPA1	Major histocompatibility complex, class II, DP alpha 1
55	HLA-DRA	Major histocompatibility complex, class II, DR alpha
56	HLA-DRB1	Major histocompatibility complex, class II, DR beta 1
57	HLA-DRB5	Major histocompatibility complex, class II, DR beta 5
58	HPRT1	Hypoxanthine phosphoribosyltransferase 1
59	HRAS	v-Ha-ras Harvey rat sarcoma viral oncogene homolog
60	IKBKB	Inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase beta
61	IMPDH1	IMP (inosine 5'-monophosphate) dehydrogenase 1
62	IMPDH2	IMP (inosine 5'-monophosphate) dehydrogenase 2
63	ITPA	Inosine triphosphatase (nucleoside triphosphate pyrophosphatase)
64	JDP2	Jun dimerization protein 2
65	JUN	Jun proto-oncogene
66	KAT2B	K(lysine) acetyltransferase 2
67	LCK	Lymphocyte-specific protein tyrosine kinase
68	MAFB	V-maf musculoaponeurotic fibrosarcoma oncogene homolog B (avian)
69	MAPK1	Mitogen-activated protein kinase 1

70	MAPK10	Mitogen-activated protein kinase 10
71	MAPK11	Mitogen-activated protein kinase 11
72	MAPK14	Mitogen-activated protein kinase 14
73	MAPK3	Mitogen-activated protein kinase 3
74	MAPK8	Mitogen-activated protein kinase 8
75	MAPK9	Mitogen-activated protein kinase 9
76	MYB	V-myb myeloblastosis viral oncogene homolog (avian)
77	NFATC2	Nuclear factor of activated T-cells, cytoplasmic, calcineurin-dependent 2
78	NFE2L2	Nuclear factor (erythroid-derived 2)-like 2
79	NR3C1	Nuclear receptor subfamily 3, group C, member 1 (glucocorticoid receptor)
80	NT5C1A	5'-nucleotidase, cytosolic IA
81	NT5C2	5'-nucleotidase, cytosolic II
82	NT5E	5'-nucleotidase, ecto (CD73)
83	PCK1	Phosphoenolpyruvate carboxykinase 1 (soluble)
84	PDGFRB	Platelet-derived growth factor receptor, beta polypeptide
85	PDHA1	Pyruvate dehydrogenase (lipoamide) alpha 1
86	PDHB	Pyruvate dehydrogenase (lipoamide) beta
87	PDHX	Pyruvate dehydrogenase complex, component X
88	PDK1	Pyruvate dehydrogenase kinase, isozyme 1
89	PDPK1	3-phosphoinositide dependent protein kinase-1
90	PGAM1	Phosphoglycerate mutase 1 (brain)
91	PGAM2	Phosphoglycerate mutase 2 (muscle)
92	PGAM4	Phosphoglycerate mutase family member 4
93	PKLR	Pyruvate kinase, liver and RBC;
94	PKM	Pyruvate kinase, muscle
95	PRKCB	Protein kinase C, beta
96	PRKCD	Protein kinase C, delta
97	RASA1	RAS p21 protein activator (GTPase activating protein) 1
98	RBBP4	Retinoblastoma binding protein 4
99	RBBP7	Retinoblastoma binding protein 7
100	RELA	V-rel reticuloendotheliosis viral oncogene homolog A (avian)
101	RGS3	Regulator of G-protein signaling 3
102	RPS6KA1	Ribosomal protein S6 kinase, 90kDa, polypeptide 1
103	SHC1	SHC (Src homology 2 domain containing) transforming protein 1
104	SMAD3	SMAD family member 3
105	SMARCA4	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a, member 4
106	SMARCB1	SWI/SNF related, matrix associated, actin dependent regulator of

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		chromatin, subfamily b, member 1
107	SMARCD1	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily d, member 1
108	SP1	Sp1 transcription factor
109	SRC	V-src sarcoma (Schmidt-Ruppin A-2) viral oncogene homolog (avian)
110	STAT4	Signal transducer and activator of transcription 4
111	YES1	V-yes-1 Yamaguchi sarcoma viral oncogene homolog 1

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seed	AUTS2	Autism susceptibility candidate 2
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seed	MBD1	methyl-CpG binding domain protein 1
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Table S4. The proteins in the PPI network (with co-expression) extracted from STRING database associated with HUD

Label	Names	Description
1	ARHGAP35	Rho GTPase activating protein 35
2	ATF2	Activating transcription factor 2
3	ATF3	Activating transcription factor 3
4	ATIC	5-aminoimidazole-4-carboxamide ribonucleotide formyltransferase/IMP cyclohydrolase
5	BATF3	Basic leucine zipper transcription factor, ATF-like 3
6	BPGM	2,3-bisphosphoglycerate mutase
7	CAD	Carbamoyl-phosphate synthetase 2, aspartate transcarbamylase, and dihydroorotase
8	CD74	CD74 molecule, major histocompatibility complex, class II invariant chain
9	CEBPA	CCAAT/enhancer binding protein (C/EBP), alpha
10	CEBPB	CCAAT/enhancer binding protein (C/EBP), betaplays essential and redundant functions with CE [...]
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13	CHUK	Conserved helix-loop-helix ubiquitous kinase
14	COPS5	COP9 constitutive photomorphogenic homolog subunit 5 (Arabidopsis)
15	CPS1	Carbamoyl-phosphate synthase 1
16	CREB1	cAMP responsive element binding protein 1
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33	ESR1	Estrogen receptor 1
34	ETS1	V-ets erythroblastosis virus E26 oncogene homolog 1 (avian);
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36	FOS	FBJ murine osteosarcoma viral oncogene homolog
37	FOSB	FBJ murine osteosarcoma viral oncogene homolog B
38	FOSL1	FOS-like antigen 1
39	FOSL2	FOS-like antigen 2
40	GAPDH	Glyceraldehyde-3-phosphate dehydrogenase
41	GAPDHS	Glyceraldehyde-3-phosphate dehydrogenase, spermatogenic
42	GMPR	Guanosine monophosphate reductase
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44	GMPS	Guanine monphosphate synthetase;
45	GNA11	Guanine nucleotide binding protein (G protein), alpha 11 (Gq class)
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55	HLA-DPB1	Major histocompatibility complex, class II, DR alpha
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57	HLA-DRA	Major histocompatibility complex, class II, DR beta 5
58	HLA-DRB1	Major histocompatibility complex, class II, DR beta 1
59	HLA-DRB5	Major histocompatibility complex, class II, DR beta 5
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84	PDHA1	Pyruvate dehydrogenase (lipoamide) alpha 1
85	PDHB	Pyruvate dehydrogenase (lipoamide) beta
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88	PDPK1	3-phosphoinositide dependent protein kinase-1
89	PGAM1	Phosphoglycerate mutase 1 (brain)
90	PGAM2	Phosphoglycerate mutase 2 (muscle)
91	PGAM4	Phosphoglycerate mutase family member 4
92	PGK1	Phosphoglycerate kinase 1
93	PGK2	Phosphoglycerate kinase 2
94	PKLR	Pyruvate kinase, liver and RBC
95	PKM	Pyruvate kinase, muscle
96	PNMAL2	Paraneoplastic Ma antigen family-like 2
97	PRKCB	Protein kinase C, beta
98	PRKCD	Protein kinase C, delta
99	RASA1	RAS p21 protein activator (GTPase activating protein) 1
100	RBBP4	Retinoblastoma binding protein 4
101	RBBP7	Retinoblastoma binding protein 7
102	RELA	V-rel reticuloendotheliosis viral oncogene homolog A (avian)
103	RGS3	Regulator of G-protein signaling 3
104	SMARCA4	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a, member 4
105	SMARCB1	SWI/SNF related, matrix associated, actin dependent regulator of

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		chromatin, subfamily b, member 1
106	SMARCD1	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily d, member 1
107	SP1	Sp1 transcription factor
108	SRC	V-src sarcoma (Schmidt-Ruppin A-2) viral oncogene homolog (avian)
109	STAT4	Signal transducer and activator of transcription 4
110	TPI1	Triosephosphate isomerase 1
111	YES1	V-yes-1 Yamaguchi sarcoma viral oncogene homolog 1

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seed	AUTS2	Autism susceptibility candidate 2
seed	MBD1	methyl-CpG binding domain protein 1

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Table S6. Top 25 nodes with high degree and their respective BC and CC

Label	Name	Degree	Betweenness centrality	Closeness centrality
1*	<b>JUN</b>	<b>43</b>	<b>0.138335165</b>	<b>0.436507937</b>
2	<b>MAPK14</b>	<b>32</b>	<b>0.083166142</b>	<b>0.433070866</b>
3	FOS	26	0.059760577	0.415094340
4	LCK	26	0.058523406	0.371621622
5	<b>RELA</b>	<b>25</b>	<b>0.069572515</b>	<b>0.421455939</b>
6	MAPK1	25	0.046624799	0.423076923
7	<b>CREBBP</b>	<b>24</b>	<b>0.163843625</b>	<b>0.452674897</b>
8	ATF2	24	0.022118131	0.402930403
9	EP300	23	0.129821489	0.443548387
10	MAPK8	22	0.044774657	0.418250951
11	HRAS	22	0.027715087	0.358306189
12*	RASA1	21	0.037173088	0.351437700
13	SRC	21	0.023429190	0.360655738
14	MAPK3	19	0.019268371	0.408921933
15	SHC1	18	0.030403520	0.390070922
16	CREB1	17	0.128192989	0.433070866
17	YES1	17	0.015116120	0.350318471
18	MAPK11	17	0.014441917	0.400000000
19	SP1	17	0.007943959	0.392857143
20	CSK	16	0.056993119	0.385964912
21	ESR1	16	0.023134181	0.395683453
22*	CEBPB	15	0.023990476	0.384615385
23	SMAD3	15	0.012296350	0.384615385
24	NR3C1	14	0.002076446	0.381944444
25	ITPA	13	0.181820962	0.250000000

Note: The bold ones have both large degree and high BC

The asterisk ones are the seed proteins (3 nodes: JUN, RASA1, CEBPB)

Table S7. Top 25 nodes with high BC and their respective  $k$  and CC

Label	Name	Degree	Betweenness centrality	Closeness centrality
1	PCK1	7	0.354489853	0.384615385
2	ITPA	13	0.181820962	0.250000000
3	<b>CREBBP</b>	<b>24</b>	<b>0.163843625</b>	<b>0.452674897</b>
4*	<b>JUN</b>	<b>43</b>	<b>0.138335165</b>	<b>0.436507937</b>
5	PKLR	6	0.135446205	0.309859155
6	PKM	6	0.135446205	0.309859155
7	EP300	23	0.129821489	0.443548387
8	CREB1	17	0.128192989	0.433070866
9	<b>MAPK14</b>	<b>32</b>	<b>0.083166142</b>	<b>0.433070866</b>
10	<b>RELA</b>	<b>25</b>	<b>0.069572515</b>	<b>0.421455939</b>
11	FOS	26	0.059760577	0.415094340
12	LCK	26	0.058523406	0.371621622
13	CSK	16	0.056993119	0.385964912
14	MAPK1	25	0.046624799	0.423076923
15	MAPK8	22	0.044774657	0.418250951
16*	RASA1	21	0.037173088	0.351437700
17	HLA-DRB1	10	0.036399507	0.332326284
18*	ENO2	8	0.035223798	0.299727520
19	ENO3	8	0.035223798	0.299727520
20	SHC1	18	0.030403520	0.390070922
21	HRAS	22	0.027715087	0.358306189
22	PDHA1	6	0.026549903	0.241758242
23	PDHB	6	0.026549903	0.241758242
24*	CEBPB	15	0.023990476	0.384615385
25	SRC	21	0.023429190	0.360655738

Note: The bold ones have both large degree and high BC

The asterisk ones are the seed proteins (4 nodes: JUN, RASA1, ENO2, CEBPB)

Table S8. The proteins in the backbone network (with co-expression)

Label	Name	Description	Degree	Betweenness centrality
1	<b>JUN</b>	Jun proto-oncogene	38	.120966583
2	<b>MAPK14</b>	Mitogen-activated protein kinase 14	27	.059088263
3	<b>FOS</b>	FBJ murine osteosarcoma viral oncogene homolog	24	.194660537
4	<b>EP300</b>	E1A binding protein p300	23	.169481630
5	<b>RELA</b>	V-rel reticuloendotheliosis viral oncogene homolog A (avian)	22	.084060558
6	<b>ATF2</b>	Activating transcription factor 2	22	.025940031
7	<b>CREBBP</b>	CREB binding protein	22	.119716044
8	<b>MAPK8</b>	Mitogen-activated protein kinase 8	21	.049177394
9	<b>MAPK1</b>	Mitogen-activated protein kinase 1	18	.040309594
10	SP1	Sp1 transcription factor	17	.009311159
11	ESR1	Estrogen receptor 1	16	.136690750
12	<b>ITPA</b>	Inosine triphosphatase (nucleoside triphosphate pyrophosphatase)	15	.238968585
13	<b>PKM</b>	Pyruvate kinase, muscle	10	.163451120
14	<b>PKLR</b>	Pyruvate kinase, liver and RBC	10	.163451120
15	HLA-DRB1	Major histocompatibility complex, class II, DR beta 1	10	.151674014
16	<b>PCK1</b>	Phosphoenolpyruvate carboxykinase 1 (soluble)	7	.322721318
Average			18.88±7.80	0.128104±0.083565

Note: The bold ones are both in the backbone networks with and without co-expression setting in the STRING

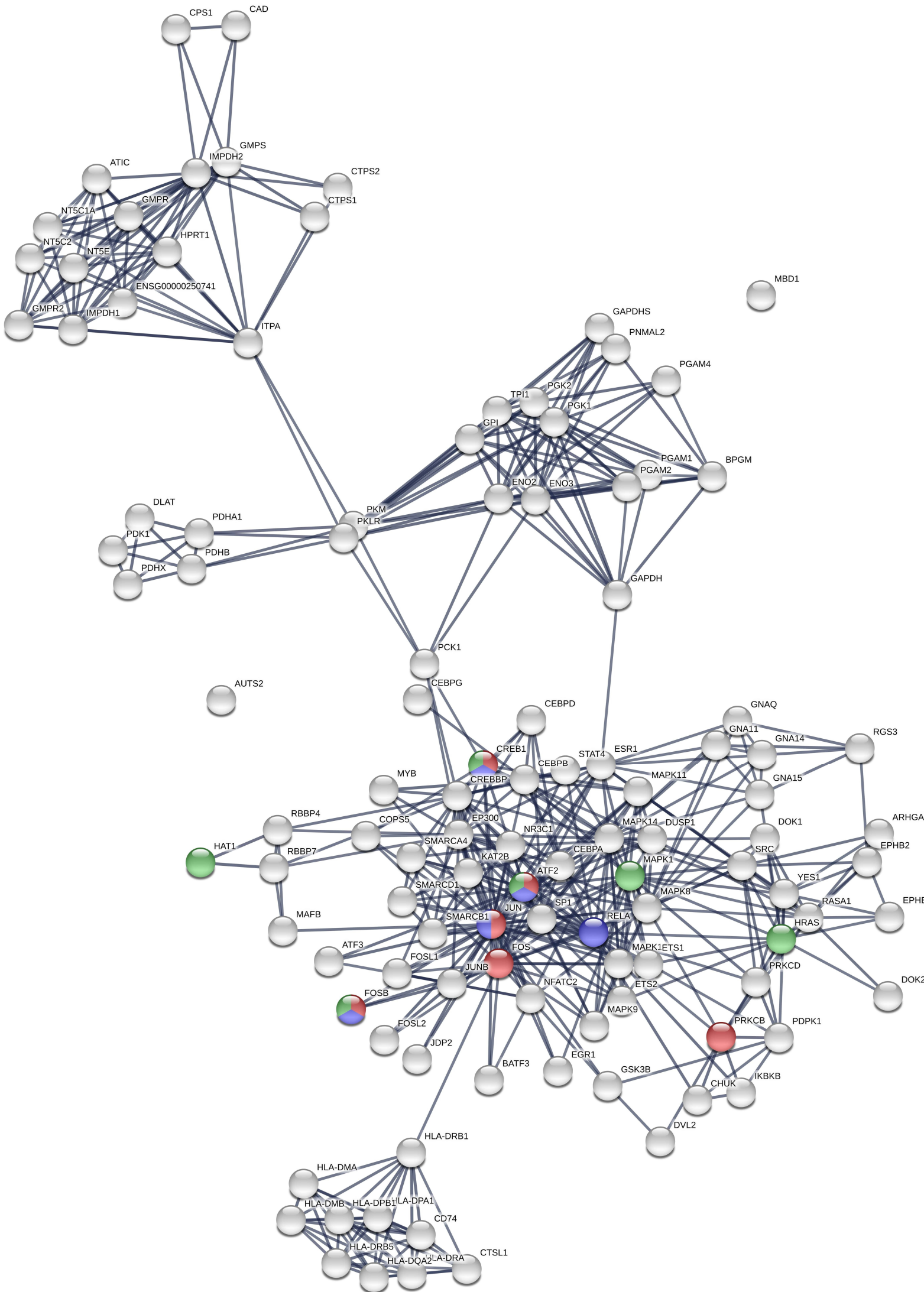
Table S9. The proteins in the 2<sup>nd</sup> extended PPI network (with co-expression) involved in the KEGG pathways of alcoholism, amphetamine addiction, and cocaine addiction

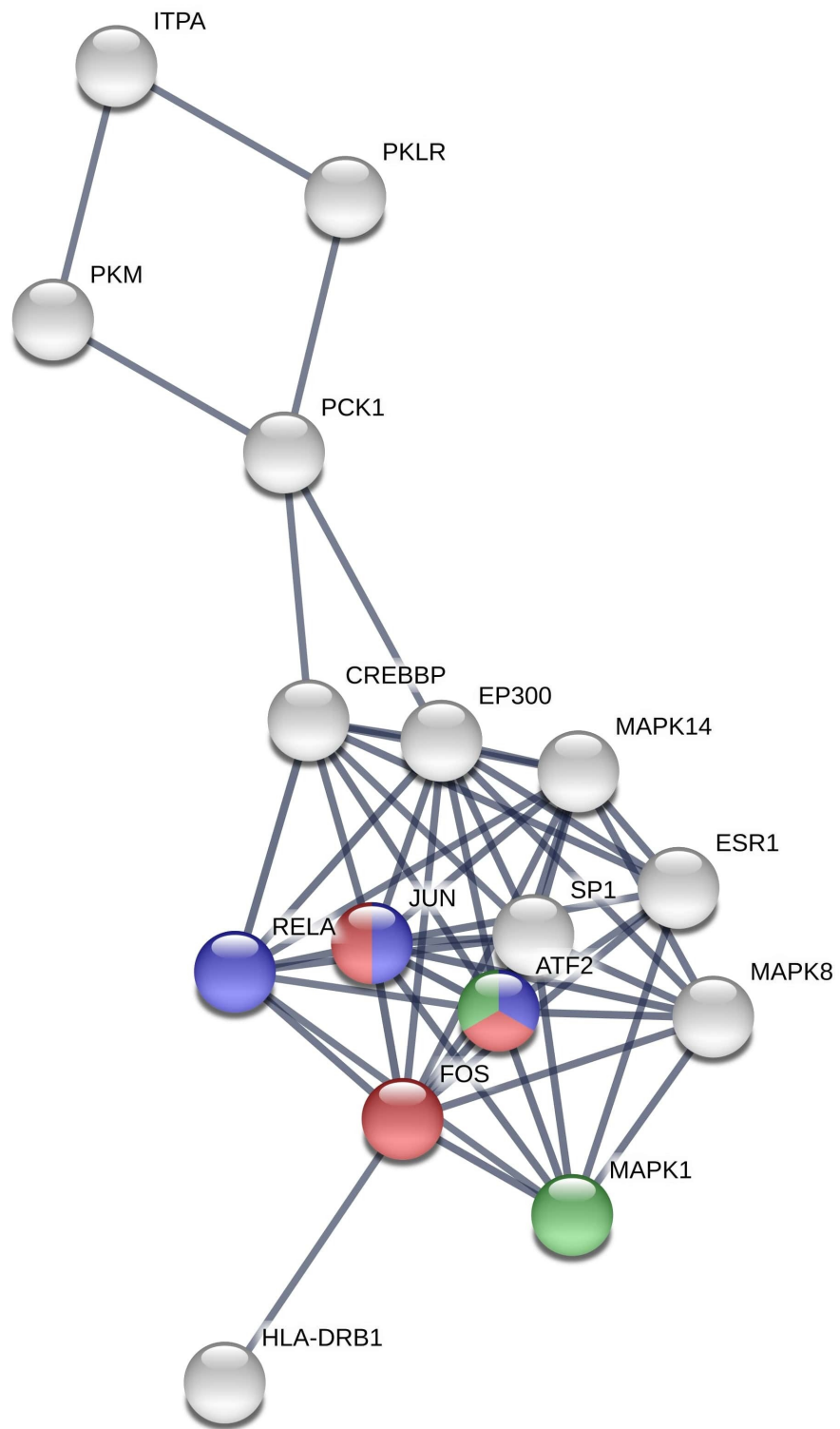
KEGG pathway	Name	Description
Alcoholism	ATF2	Activating transcription factor 2
Alcoholism	BRAF	V-raf murine sarcoma viral oncogene homolog B1
Alcoholism	CREB5	cAMP responsive element binding protein 5
Alcoholism	FOSB	cAMP responsive element binding protein 1
Alcoholism	HDAC2	Histone deacetylase 2
Alcoholism	HDAC6	Histone deacetylase 6
Alcoholism	MAP2K1	Mitogen-activated protein kinase kinase 1
Alcoholism	MAPK1	Mitogen-activated protein kinase 1
Alcoholism	MAPK3	Mitogen-activated protein kinase 3
Alcoholism	RAF1	V-raf-1 murine leukemia viral oncogene homolog 1
Amphetamine	ATF2	Activating transcription factor 2
Amphetamine	CREB5	cAMP responsive element binding protein 5
Amphetamine	FOS	FBJ murine osteosarcoma viral oncogene homolog
Amphetamine	FOSB	FBJ murine osteosarcoma viral oncogene homolog B
Amphetamine	JUN	Jun proto-oncogene
Cocaine	ATF2	Activating transcription factor 2
Cocaine	CREB5	cAMP responsive element binding protein 5
Cocaine	FOSB	FBJ murine osteosarcoma viral oncogene homolog B
Cocaine	JUN	Jun proto-oncogene
Cocaine	NFKB1	Nuclear factor of kappa light polypeptide gene enhancer in B-cells 1
Cocaine	RELA	V-rel reticuloendotheliosis viral oncogene homolog A (avian)

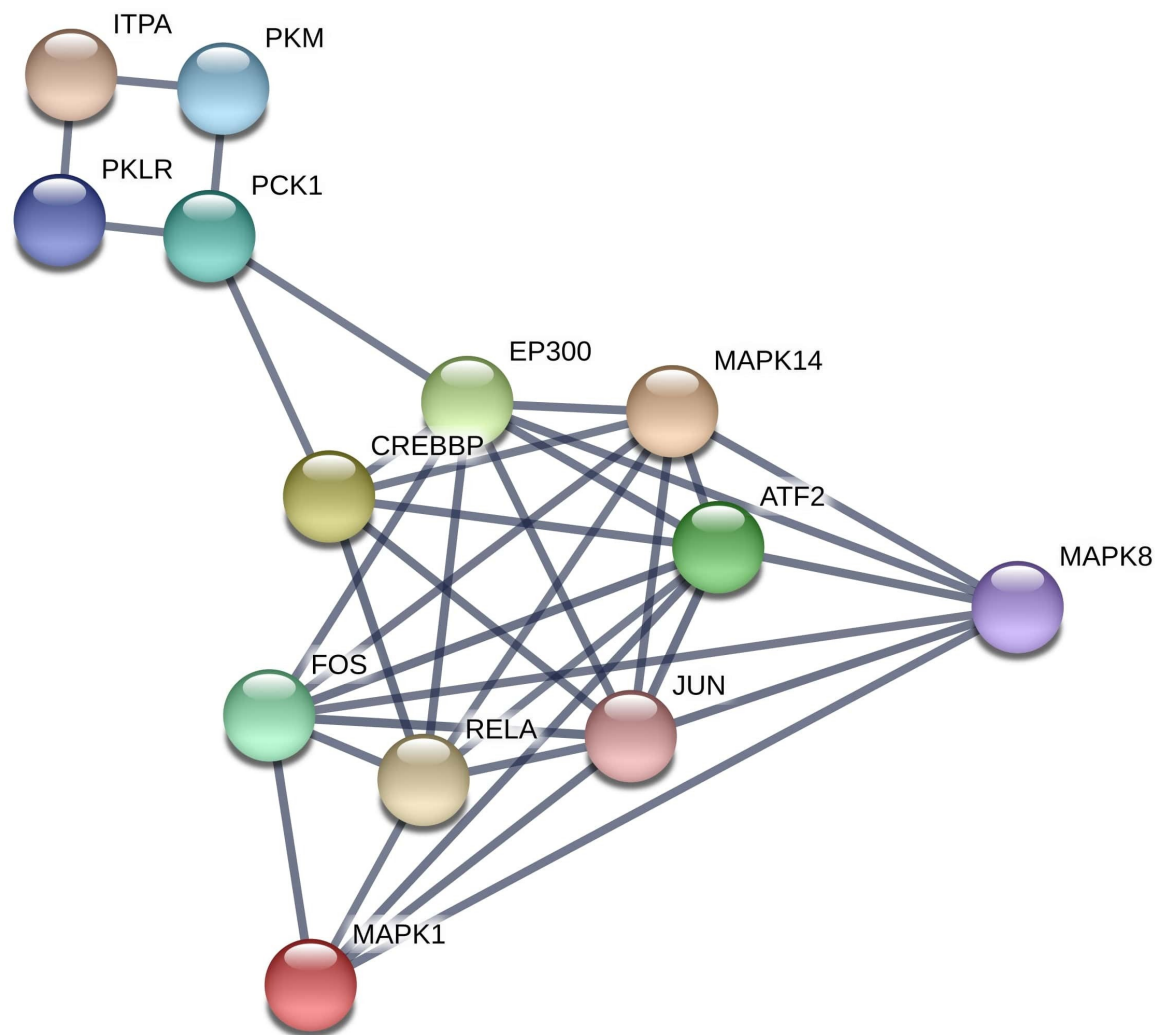


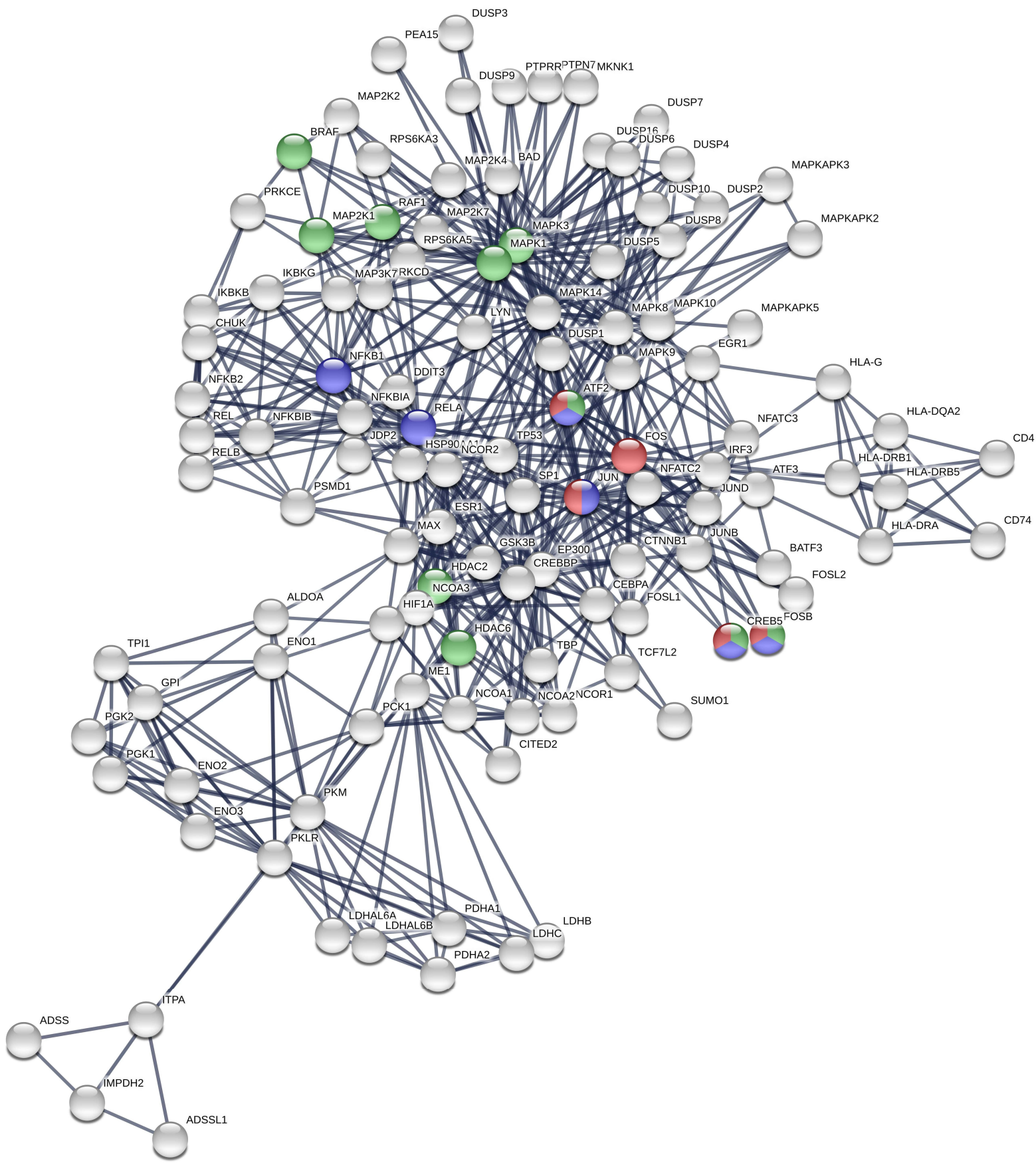
Table S10. The miRNA targeting genes by stress-induced

Gene Name	Description	Stress-induced differentially expressed miRNA
FOS	FBJ murine osteosarcoma viral oncogene homolog	miR-221, miR-29a
JUN	jun proto-oncogene	miR-15b, miR-30a
MAPK1	mitogen-activated protein kinase 1	miR-124, miR-132, miR-15b, miR-106b, miR-186, miR-19a, miR-204, miR-26a, miR-410, miR-32
MAPK14	mitogen-activated protein kinase 14	miR-124, miR-351, miR-19a, miR-22
RELA	v-rel avian reticuloendotheliosis viral oncogene homolog A	miR-124





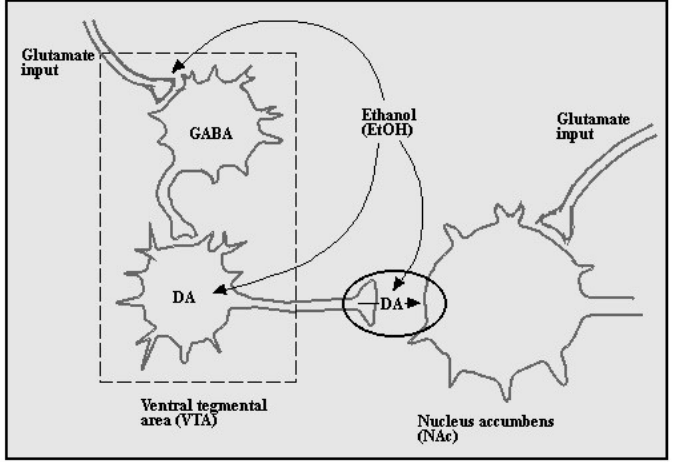
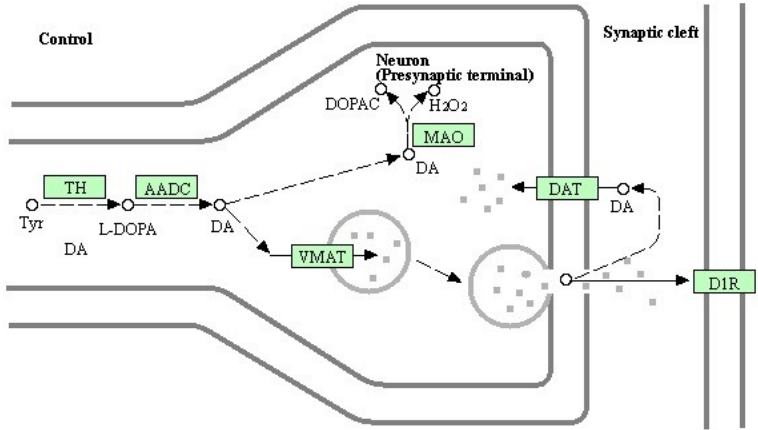




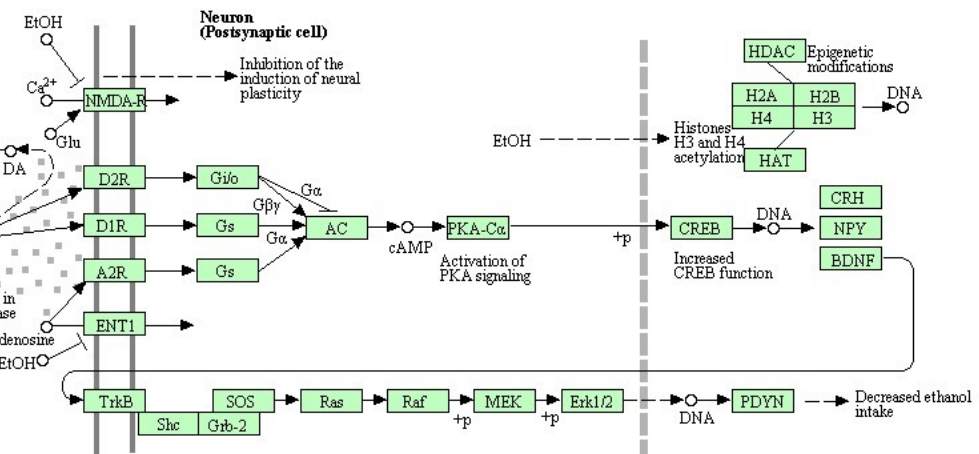
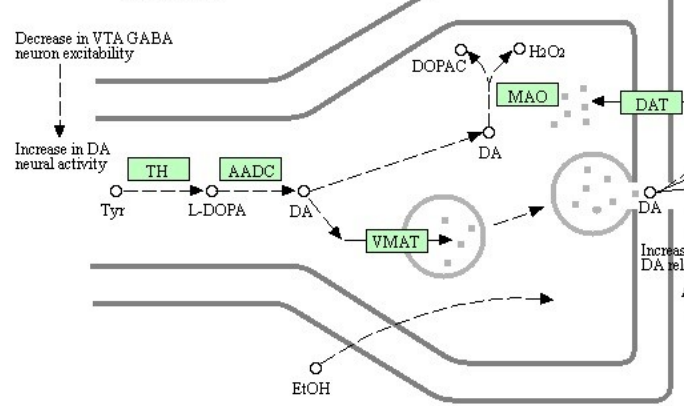


**ALCOHOLISM**

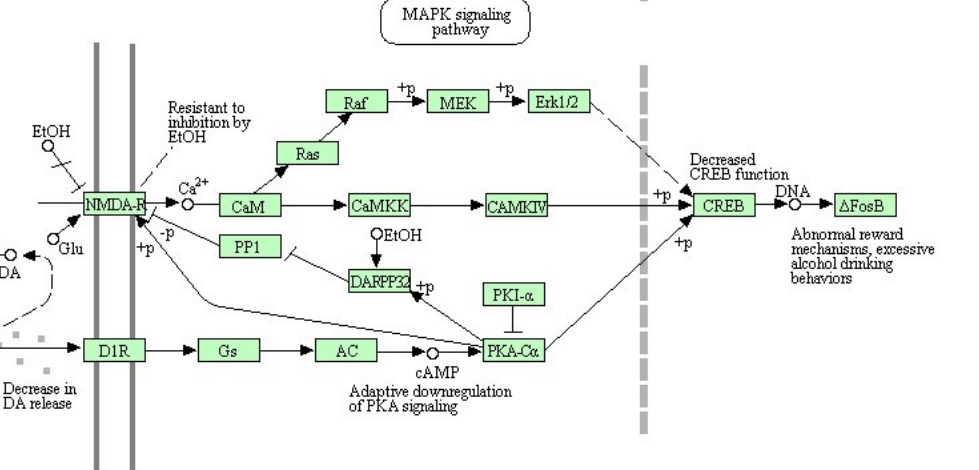
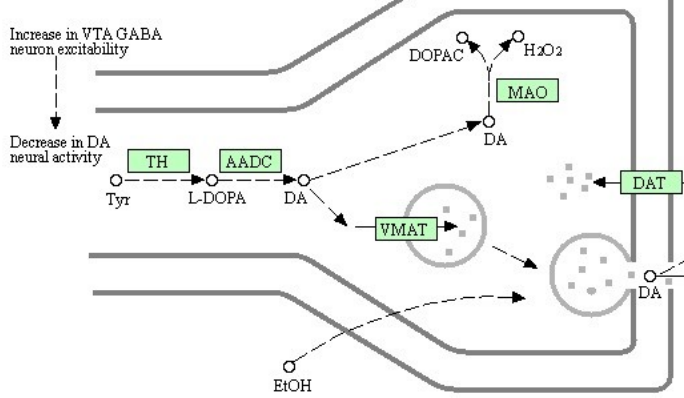
**Dopaminergic synapse**



**Acute ethanol**

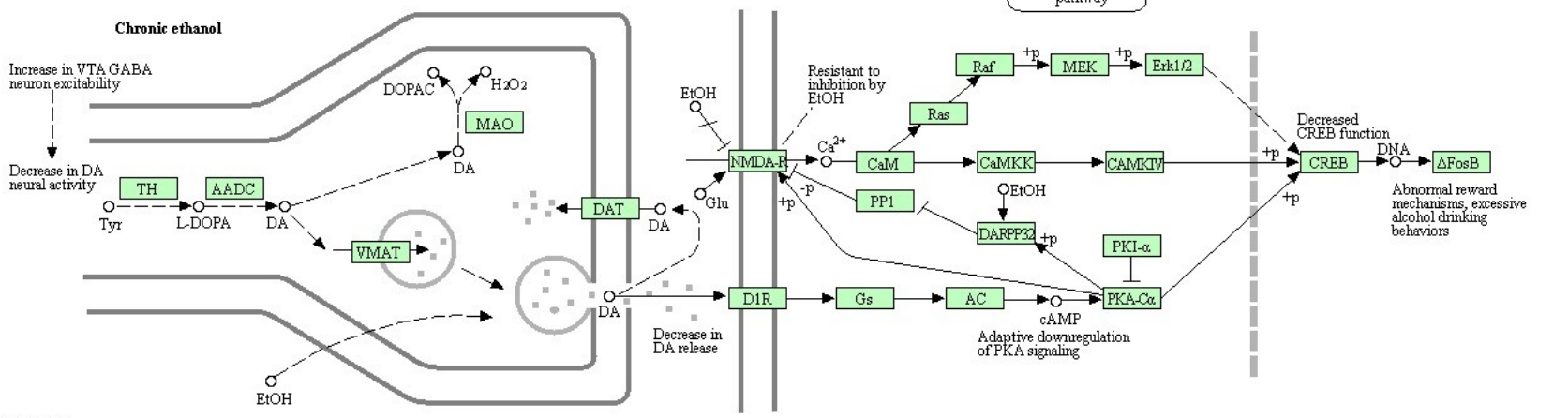
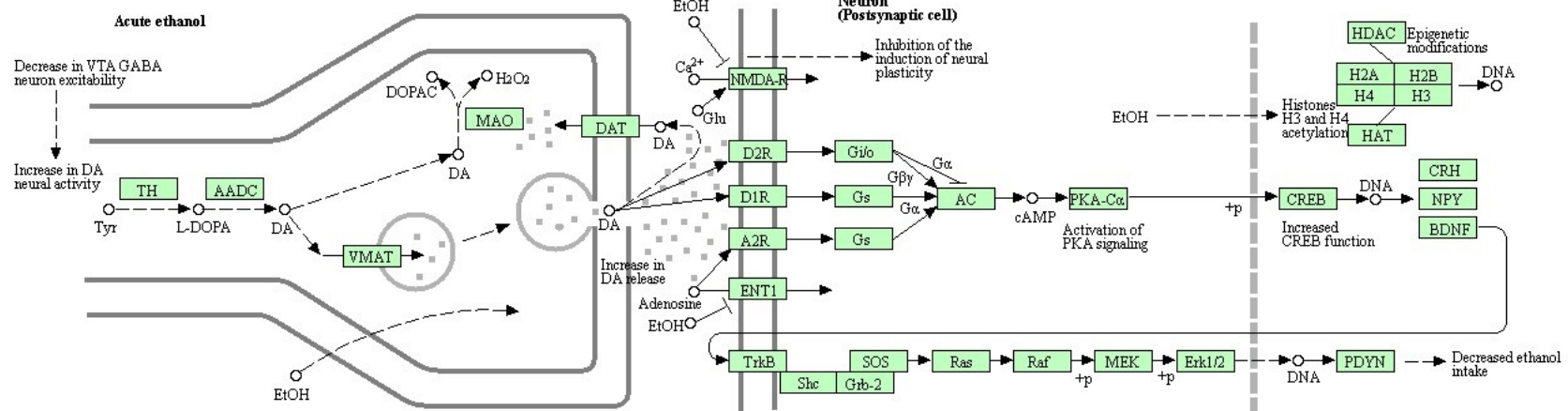
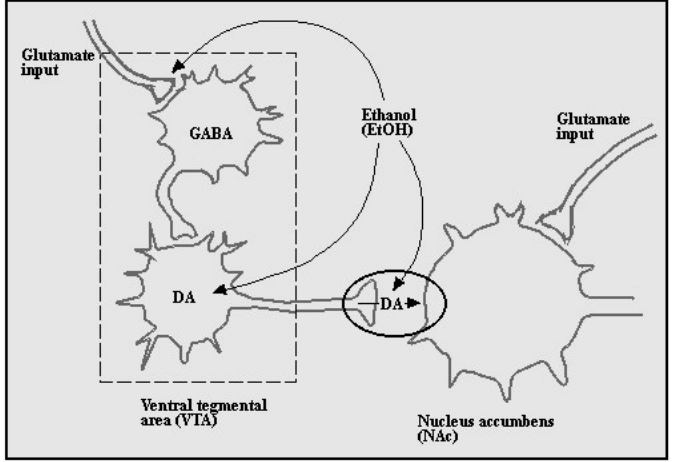
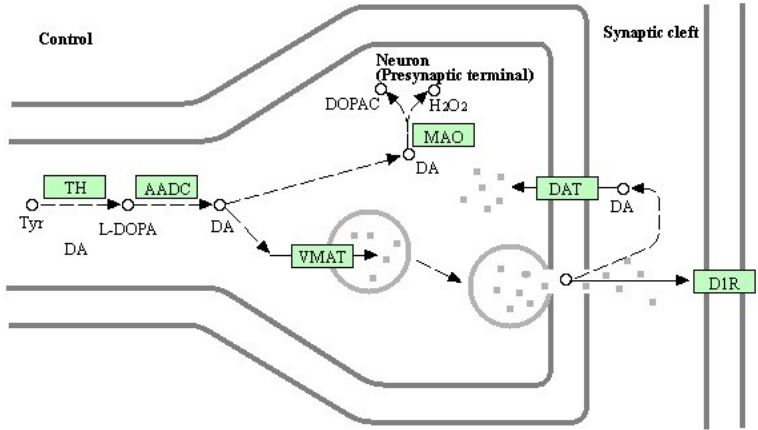


**Chronic ethanol**



**ALCOHOLISM**

**Dopaminergic synapse**



AMPHETAMINE ADDICTION

