Table S2: Rate parameters and total amounts

The rate parameters and total amounts were taken from the literature whenever possible, but in most cases they resulted from the manual fitting of the model to phenotypic data. Thus, most of the references in the last column of the following tables are a guide to the edges but not their weight. The reactions were color coded as a function of the sub-network they belong to.

	D1R and G-protein activation cycle. Compartmental distribution.
	Generation, hydrolysis and effectors of cAMP.
	D32 sub-network.
	Activation and inactivation of most Ca^{2+} binding proteins.
	PKA substrates phosphorylation and dephosphorylation, except NMDAR.
	Activation cycle of Fyn.
	Tyrosine phosphorylation, dephosphorylation and traffic of NMDAR (NR2B).
	Phosphorylation and dephosphorylation of NMDAR (NR1) by PKA.
	MAPK cascade and DUSP negative feedback.

Enzymatic reactions

ID	Reaction	kf (nM-1s-1)	kr (s-1)	kcat (s-1)	References
enz:79	AC5GaolfGTP + ATP <-> AC5GaolfGTP*ATP -> AC5GaolfGTP + cAMP	0.006	96	24	[1–5]
enz:80	AC5 + ATP <-> AC5*ATP -> AC5 + cAMP	0.00025	4	1	[1–5]
enz:81	AC5CaGaolfGTP + ATP <-> AC5CaGaolfGTP*ATP -> AC5CaGaolfGTP + cAMP	0.003	48	12	[1–5]
enz:82	AC5Ca + ATP <-> AC5Ca*ATP -> AC5Ca + cAMP	0.000125	2	0.5	[1–5]
enz:1	PDE1c + cAMP <-> PDE1c*cAMP -> PDE1c + AMP	0.0046	44	11	[1]
enz:2	PDE4p + cAMP <-> PDE4p*cAMP -> PDE4p + AMP	0.25	40	10	[1]
enz:31	PDE4 + cAMP <-> PDE4*cAMP -> PDE4 + AMP	0.083	8	2	[6]
enz:30	PKAc + PDE4 <-> PKAc*PDE4 -> PKAc + PDE4p	0.014	40	10	[6]
enz:58	PDE4PPase + PDE4p <-> PDE4PPase*PDE4p -> PDE4PPase + PDE4	0.033	8	2	[6]
enz:56	PDE10 + cAMP <-> PDE10*cAMP -> PDE10 + AMP	0.083	8	2	[7–9]
enz:57	PDE10c + cAMP <-> PDE10c*cAMP -> PDE10c + AMP	0.5	40	10	[7–9]
enz:3	PKAc + D32 <-> PKAc*D32 -> PKAc + D32p34	0.0047	28	7	[1]
enz:9	PP2Bc + D32p34 <-> PP2Bc*D32p34 -> PP2Bc + D32	0.021	6	1.5	[1]
enz:10	PP2Bc + PP1D32p34 <-> PP2Bc*PP1D32p34 -> PP2Bc + PP1 + D32	0.017	4	1	[1]
enz:11	B72PP2A + D32p34 <-> B72PP2A*D32p34 -> B72PP2A + D32	0.0024	0.4	0.1	[1]
enz:12	B72PP2A + PP1D32p34 <-> B72PP2A*PP1D32p34 -> B72PP2A + PP1 + D32	0.000062	0.4	0.1	[1]
enz:24	B72PP2ACa + D32p34 <-> B72PP2ACa*D32p34 -> B72PP2ACa + D32	0.0024	0.4	0.1	[1]
enz:25	B72PP2ACa + PP1D32p34 <-> B72PP2ACa*PP1D32p34 -> B72PP2ACa + PP1 + D32	0.000062	0.4	0.1	[1]
enz:5	CDK5 + D32 <-> CDK5*D32 -> CDK5 + D32p75	0.0011	8	2	[1]
enz:23	B56PP2A + D32p75 <-> B56PP2A*D32p75 -> B56PP2A + D32	0.00047	6	1.5	[1,10]
enz:6	B56PP2Ap + D32p75 <-> B56PP2Ap*D32p75 -> B56PP2Ap + D32	0.002	32	8	[1,10]
enz:7	B72PP2A + D32p75 <-> B72PP2A*D32p75 -> B72PP2A + D32	0.000068	4	1	[11,12]
enz:8	B72PP2ACa + D32p75 <-> B72PP2ACa*D32p75 -> B72PP2ACa + D32	0.0017	24	6	[11,12]
enz:77	PP1 + CaMKIIc <-> PP1*CaMKIIc -> PP1 + CaMCa4CaMKII	0.000039	0.34	0.086	[12]
enz:78	PP1 + CaMKIIp <-> PP1*CaMKIIp -> PP1 + CaMKII	0.000039	0.34	0.086	[12]
enz:14	PKAc + STEP <-> PKAc*STEP -> PKAc + STEPp	0.014	40	10	[13]
enz:13	PP1 + STEPp <-> PP1*STEPp -> PP1 + STEP	0.0029	32	8	[14]
enz:83	PKAc + STEP2 <-> PKAc*STEP2 -> PKAc + STEP2p	0.014	40	10	[13]
enz:84	PP1 + STEP2p <-> PP1*STEP2p -> PP1 + STEP2	0.0029	32	8	[14]
enz:54	PKAc + GluR1 <-> PKAc*GluR1 -> PKAc + GluR1p	0.08	40	10	[12]
enz:55	PP1 + GluR1p <-> PP1*GluR1p -> PP1 + GluR1	0.035	9.6	2.4	[12]
enz:4	PKAc + B56PP2A <-> PKAc*B56PP2A -> PKAc + B56PP2Ap	0.0013	0.4	0.1	[1,10]
enz:47	STEP + Fynpa <-> STEP*Fynpa -> STEP + Fyn	0.0042	4	1	[15]
enz:51	**STEPp + Fynpa <-> STEPp*Fynpa -> STEPp + Fyn**	0.0042	4	1	[15]
enz:39	FynpiGolf + FynpiGolf <-> FynpiGolf*FynpiGolf -> FynpapiGolf + FynpiGolf	0.083	0.8	0.2	[16–19]
enz:36	STEP + Fynpapi <-> STEP*Fynpapi -> STEP + Fynpi	0.0042	4	1	[15]

enz:50	**STEPp + Fynpapi <-> STEPp*Fynpapi -> STEPp + Fynpi**	0.0042	4	1	[15]
enz:40	Csk + Fyn <-> Csk*Fyn -> Csk + Fynpi	0.13	20	5	[16–18]
enz:48	PTPa + Fynpi <-> PTPa*Fynpi -> PTPa + Fyn	0.00096	0.8	0.2	[16–18]
enz:41	Csk + Fynpa <-> Csk*Fynpa -> Csk + Fynpapi	0.13	20	5	[16–18]
enz:49	PTPa + Fynpapi <-> PTPa*Fynpapi -> PTPa + Fynpa	0.00096	0.8	0.2	[16–18]
enz:43	Fyn + NMDARi <-> Fyn*NMDARi -> Fyn + NMDARipY	0.017	40	10	[16,20,21]
enz:45	Fynpa + NMDARi <-> Fynpa*NMDARi -> Fynpa + NMDARipY	0.017	40	10	[16,20,21]
enz:34	Fynpapi + NMDARi <-> Fynpapi*NMDARi -> Fynpapi + NMDARipY	0.017	40	10	[16,20,21]
enz:38	STEP + NMDARipY <-> STEP*NMDARipY -> STEP + NMDARi	0.0094	12	3	[22,23]
enz:52	**STEPp + NMDARipY <-> STEPp*NMDARipY -> STEPp + NMDARi**	0.0094	12	3	[22,23]
enz:44	Fyn + NMDARm <-> Fyn*NMDARm -> Fyn + NMDARmpY	0.017	40	10	[16,20,21]
enz:46	Fynpa + NMDARm <-> Fynpa*NMDARm -> Fynpa + NMDARmpY	0.017	40	10	[16,20,21]
enz:35	Fynpapi + NMDARm <-> Fynpapi*NMDARm -> Fynpapi + NMDARmpY	0.017	40	10	[16,20,21]
enz:37	STEP + NMDARmpY <-> STEP*NMDARmpY -> STEP + NMDARm	0.0094	12	3	[22,23]
enz:53	**STEPp + NMDARmpY <-> STEPp*NMDARmpY -> STEPp + NMDARm**	0.0094	12	3	[22,23]
enz:69	Fyn + NMDARipS <-> Fyn*NMDARipS -> Fyn + NMDARipYpS	0.017	40	10	[16,20,21]
enz:70	Fynpa + NMDARipS <-> Fynpa*NMDARipS -> Fynpa + NMDARipYpS	0.017	40	10	[16,20,21]
enz:71	Fynpapi + NMDARipS <-> Fynpapi*NMDARipS -> Fynpapi + NMDARipYpS	0.017	40	10	[16,20,21]
enz:67	STEP + NMDARipYpS <-> STEP*NMDARipYpS -> STEP + NMDARipS	0.0094	12	3	[22,23]
enz:68	**STEPp + NMDARipYpS <-> STEPp*NMDARipYpS -> STEPp + NMDARipS**	0.0094	12	3	[22,23]
enz:74	Fyn + NMDARmpS <-> Fyn*NMDARmpS -> Fyn + NMDARmpYpS	0.017	40	10	[16,20,21]
enz:73	Fynpa + NMDARmpS <-> Fynpa*NMDARmpS -> Fynpa + NMDARmpYpS	0.017	40	10	[16,20,21]
enz:72	Fynpapi + NMDARmpS <-> Fynpapi*NMDARmpS -> Fynpapi + NMDARmpYpS	0.017	40	10	[16,20,21]
enz:75	STEP + NMDARmpYpS <-> STEP*NMDARmpYpS -> STEP + NMDARmpS	0.0094	12	3	[22,23]
enz:76	**STEPp + NMDARmpYpS <-> STEPp*NMDARmpYpS -> STEPp + NMDARmpS**	0.0094	12	3	[22,23]
enz:59	PKAc + NMDARm <-> PKAc*NMDARm -> PKAc + NMDARmpS	0.017	8	2	[24]
enz:60	PP1 + NMDARmpS <-> PP1*NMDARmpS -> PP1 + NMDARm	0.017	8	2	[25]
enz:61	PKAc + NMDARmpY <-> PKAc*NMDARmpY -> PKAc + NMDARmpYpS	0.017	8	2	[24]
enz:62	PP1 + NMDARmpYpS <-> PP1*NMDARmpYpS -> PP1 + NMDARmpY	0.017	8	2	[25]
enz:64	PKAc + NMDARi <-> PKAc*NMDARi -> PKAc + NMDARipS	0.017	8	2	[24]
enz:63	PP1 + NMDARipS <-> PP1*NMDARipS -> PP1 + NMDARi	0.017	8	2	[25]
enz:66	PKAc + NMDARipY <-> PKAc*NMDARipY -> PKAc + NMDARipYpS	0.017	8	2	[24]
enz:65	PP1 + NMDARipYpS <-> PP1*NMDARipYpS -> PP1 + NMDARipY	0.017	8	2	[25]
enz:22	RASGTP + GAPRAS <-> GAPRAS*RASGTP -> GAPRAS + RASGDP	0.00089	0.36	0.09	[26–28]
enz:29	RAFc + GAPRAS <-> GAPRAS*RAFc -> GAPRAS + RAF + RASGDP	0.00089	0.36	0.09	[26–28]
enz:19	RAFc + MEKp <-> RAFc*MEKp -> RAFc + MEKc	0.0094	1.2	0.3	[29,30]
enz:18	MKKP + MEKp <-> MKKP*MEKp -> MKKP + MEK	0.0019	24	6	[29,30]
enz:20	RAFc + MEK <-> RAFc*MEK -> RAFc + MEKp	0.0094	1.2	0.3	[29,30]
enz:17	MKKP + MEKc <-> MKKP*MEKc -> MKKP + MEKp	0.0019	24	6	[29,30]
enz:21	MEKc + ERK <-> MEKc*ERK -> MEKc + ERKpT	0.032	1.2	0.3	[29,30]
enz:28	DUSP1 + ERKpT <-> DUSP1*ERKpT -> DUSP1 + ERK	0.0011	4	1	[29,30]
enz:32	B56PP2A + ERKpT <-> B56PP2A*ERKpT -> B56PP2A + ERK	0.000005	0.04	0.01	[31,32]
enz:33	B56PP2Ap + ERKpT <-> B56PP2Ap*ERKpT -> B56PP2Ap + ERK	0.000005	0.04	0.01	[31,32]
enz:15	MEKc + ERKpT <-> MEKc*ERKpT -> MEKc + ERKpp	0.032	1.2	0.3	[29,30]
enz:27	DUSP1 + ERKpp <-> DUSP1*ERKpp -> DUSP1 + ERKpT	0.0011	4	1	[29,30]
enz:16	STEP + ERKpp <-> STEP*ERKpp -> STEP + ERKpT	0.01	2.4	0.6	[13,32]
enz:87	**STEPp + ERKpp <-> STEPp*ERKpp -> STEPp + ERKpT**	0	2.4	0.6	[13,32]
enz:85	**STEP2 + ERKpp <-> STEP2*ERKpp -> ERKpT + STEP2**	0	2.4	0.6	[13,32]
enz:86	**STEP2p + ERKpp <-> STEP2p*ERKpp -> STEP2p + ERKpT**	0	2.4	0.6	[13,32]
enz:26	TF + ERKpp <-> ERKc*TF -> TFc + ERKpp	0.000021	0.1	0.025	[33]

Reactions in bold are run depending of the crosstalking scheme. Table SI defines which reactions are activated in each crosstalking scheme. They are matched via the name of the Michaelis-Menten complex where Fynp and NMDARp in Table S1 represent any phosphorylated forms of active Fyn and NMDAR in SM2. The scheme 010 is the default one where none of these reactions in bold is active (kf = 0).

Reversible reactions

ID	Reaction	kf (nM-1s-1)	kr (s-1)	References
rev:4	D1R + DA <-> D1RDA	0.00025	10	[34,35]
rev:1	D1RG + DA <-> D1RDAGolf	0.005	2	[34,35]
rev:3	D1R + Golf <-> D1RG	0.0005	1	[34,35]
rev:2	D1RDA + Golf <-> D1RDAGolf	0.05	1	[34,35]
rev:31	D1Rm + DA <-> D1RmDa	0.00025	10	[34,35]
rev:33	D1RmGolf + DA <-> D1RmDaGolf	0.005	2	[34,35]
rev:32	D1Rm + Golfm <-> D1RmGolf	0.0005	1	[34,35]
rev:34	D1RmDa + Golfm <-> D1RmDaGolf	0.05	1	[34,35]
rev:28	AD1R + D1Rpool <-> D1R	0.1	0.1	-
rev:36	AD1Rm + D1Rpool <-> D1Rm	0.000002	0.01	-
rev:29	AGolf + Golfpool <-> Golf	0.000006	0.1	-
rev:35	AGolfm + Golfpool <-> Golfm	0.0005	0.1	-
rev:21	AC5 + Ca <-> AC5Ca	0.001	0.9	[1]
rev:41	AC5*ATP + Ca <-> AC5Ca*ATP	0.001	0.9	[1]
rev:5	AC5 + GaolfGTP <-> AC5GaolfGTP	0.00033	0.01	[1,36]
rev:22	AC5Ca + GaolfGTP <-> AC5CaGaolfGTP	0.00033	0.01	[1,36]
rev:39	AC5*ATP + GaolfGTP <-> AC5GaolfGTP*ATP	0.00033	0.01	[1,36]
rev:40	AC5Ca*ATP + GaolfGTP <-> AC5CaGaolfGTP*ATP	0.00033	0.01	[1,36]
rev:7	PDE1 + CaMCa4 <-> PDE1c	0.1	1	[1]
rev:37	PDE10 + 2 cAMP <-> PDE10c	0.000001 (*)	9	[7–9]
rev:25	PKA + cAMP <-> PKAcAMP2	0.00026	0.06	[1]
rev:26	PKAcAMP2 + cAMP <-> PKAcAMP4	0.00035	0.6	[1]
rev:27	PKAcAMP4 <-> PKAc + PKAreg	0.001	0.096	[1]
rev:12	D32p75 + PKAc <-> PKAcD32p75	0.00037	1	[1]
rev:11	D32p34 + PP1 <-> PP1D32p34	0.4	0.58	[1]
rev:13	B72PP2A + Ca <-> B72PPA2Ca	0.0001	0.1	[11,12]
rev:6	CaM + Ca <-> CaMCa2	0.006	9.1	[1]
rev:14	CaMCa2 + Ca <-> CaMCa4	0.1	1000	[1]
rev:8	PP2B + CaM <-> PP2BCaM	1	3	[1]
rev:9	PP2B + CaMCa4 <-> PP2Bc	1	0.3	[1]
rev:15	PP2BCaM + Ca <-> PP2BCaMCa2	0.006	0.91	[1]
rev:16	PP2BCaMCa2 + Ca <-> PP2Bc	0.1	10	[1]
rev:17	PP2B + CaMCa2 <-> PP2BCaMCa2	1	0.3	[1]
rev:10	CaMKII + CaMCa4 <-> CaMCa4CaMKII	0.00075	0.1	[1]
rev:38	CaMKIIc <-> CaMCa4 + CaMKIIp	0.013	0.0008	[1]
rev:30	Gbgolfm + Fynpi <-> FynpiGolf	0.05	5	-
rev:23	RASGRF1 + 4 Ca <-> GRFRASc	0.0000001 (**)	1000000	[26–28]
rev:18	RASGTP + RASGRF1c <-> RASGRF1cRASGTP	0.1	17	[37–39]
rev:20	RASGDP + RASGRF1c <-> RASGRF1cRASGDP	0.1	17	[37–39]
rev:19	RASGTP + RAF <-> RAFc	0.09	5	[26–28]
rev:24	2 TFc + DNA <-> TFDNA	0.01(2)	1	[33]

* $nM^{-2}s^{-1}$, ** $nM^{-4}s^{-1}$

Irreversible reactions

ID	Reaction	k (s-1)	References
irr:1	GaolfGTP -> GaolfGDP	1	[40]
irr:17	GaolfmGTP -> GaolfmGDP	1	[40]
irr:2	D1RDAGolf -> Gbgolf + D1RDA + GaolfGTP	2	[41]
irr:16	D1RmDaGolf -> D1RmDa + GaolfmGTP + Gbgolfm	2	[41]
irr:18	Gbgolfm + GaolfmGDP -> Golfm	100	[1]
irr:26	GaolfGDP + Gbgolf -> Golf	100	[1]
irr:27	cAMP + AC5GaolfGTP -> AC5GaolfGTP*ATP	0.006	[1]
irr:28	cAMP + AC5 -> AC5*ATP	0.000125	[1]
irr:29	cAMP + AC5Ca -> AC5Ca*ATP	0.00025	[1]
irr:30	cAMP + AC5CaGaolfGTP -> AC5CaGaolfGTP*ATP	0.003	[1]
irr:3	CaMCa4CaMKII -> CaMKIIc	0.005	[12]
irr:10	B56PP2Ap -> B56PP2A	0.004	[1,10]
irr:21	NMDARm -> NMDARi	0.002	[42–46]
irr:22	NMDARi -> NMDARm	0.00001	[42–46]
irr:23	NMDARipS -> NMDARmpS	0.00001	[42–46]
irr:24	NMDARmpS -> NMDARipS	0.002	[42–46]
irr:25	NMDARipYpS -> NMDARmpYpS	0.002	[42–46]
irr:19	FynpapiGolf -> Fynpapi + Gbgolfm	50	-
irr:4	RASGRF1cRAS -> RASGRF1cRASGDP	4	[37–39]
irr:5	RASGRF1cRAS -> RASGRF1cRASGTP	20	[37–39]
irr:8	RASGRF1cRASGTP -> RASGRF1cRAS	5	[37–39]
irr:9	RASGRF1cRASGDP -> RASGRF1cRAS	5	[37–39]
irr:6	RAFc -> RAF + RASGDP	0.00045	[47]
irr:7	RASGTP -> RASGDP	0.00045	[47]
irr:11	TFc -> TF	0.05	[33]
irr:12	TFDNA + Nucleotides -> TFDNA + DUSP1mRNA	0.03	[33]
irr:13	DUSP1mRNA + aa -> DUSP1 + DUSP1mRNA	0.06	[33]
irr:15	DUSP1mRNA -> Nucleotides	0.0003	[33]
irr:14	DUSP1 -> aa	0.00037	[33]

Total amounts

N	Species	Total amount
1	Ca	60
2	DA	10
3	D1Rpool	7000
4	Golfpool	5000
5	AD1R	700
6	AD1Rm	900
7	AGolf	2000
8	AGolfm	500
9	ATP	5000000
10	AC5	400
11	PDE1	3000
12	PDE4	1000
13	PDE4PPase	50
14	PDE10	1000
15	PKA	1200
16	CDK5	1800
17	DARPP32	50000
18	PP1	1000
19	B56PP2A	2000
20	B72PP2A	2000
21	PP2B	4000
22	CaM	10000
23	CaMKII	20000
24	Fyn	300
25	PTPa	300
26	Csk	50
27	STEP	300
28	STEP2	300
29	NMDAR	1000
30	GluR1	3000
31	RasGRF1	800
32	GAPRAS	300
33	RAS	500
34	RAF	400
35	MEK	500
36	MKKP	1000
37	ERK	3600
38	TF	50
39	DNA	1
40	Nucleotides	1
41	aa	1

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