Supplementary Table 1 Closed components

Ligands (n)	E_1		E_2		E_3		E_4		E_5	
	τ (ms)	a (%)	τ (ms)	a (%)	τ (ms)	a (%)	τ (ms)	a (%)	τ (ms)	a (%)
Glu/Gly (5)	**0.22 ± 0.01**	**42 ± 4**	**1.74 ± 0.08**	**43 ± 4**	**4.6 ± 0.2**	**14 ± 1**	**27 ± 3**	**0.7 ± 0.1**	**2,572 ± 451**	**0.17 ± 0.03**
Glu/DCS (5)	**0.27 ± 0.01**	23 ± 7	**2.7 ± 0.2**	45 ± 5	**7.2 ± 0.4**	27 ± 6	32 ± 5	1.5 ± 0.5	2,448 ± 407	0.31 ± 0.1
p	0.005	0.03	0.001	0.7	0.001	0.06	0.4	0.2	0.8	0.2
Glu/Ala (6)	**0.27 ± 0.01**	24 ± 3	**3.5 ± 0.4**	29 ± 2	**9.4 ± 0.1**	**45 ± 4**	37 ± 5	2.3 ± 0.7	3,070 ± 302	**0.28 ± 0.03**
p	0.01	0.003	0.003	0.005	0.002	0.001	0.1	0.08	0.3	0.03
Glu/ACPC (9)	0.25 ± 0.01	40 ± 5	**3.0 ± 0.2**	36 ± 3	**10 ± 1**	**23 ± 3**	82 ± 20	1.4 ± 0.2	3,114 ± 280	0.27 ± 0.05
p	0.06	0.530	0.001	0.1	0.006	0.044	0.1	0.05	0.3	0.1
Glu/ACBC (5)	0.23 ± 0.06	19 ± 4	**4.5 ± 0.8**	18 ± 4	**26 ± 6**	**42 ± 6**	**88 ± 18**	**20 ± 3**	1,562 ± 349	0.90 ± 0.36
p	0.6	0.003	0.009	0.001	0.007	0.001	0.01	0.001	0.1	0.08
HCA/Gly (7)	**0.26 ± 0.01**	24 ± 5	**2.3 ± 0.2**	35 ± 5	**7.7 ± 0.5**	**39 ± 7**	36 ± 3	1.9 ± 0.7	2,569 ± 311	0.31 ± 0.05
p	0.02	0.018	0.001	0.2	0.001	0.013	0.08	0.2	0.9	0.06
SYM/Gly (5)	0.25 ± 0.02	26 ± 4	**3.2 ± 0.3**	33 ± 5	**9.1 ± 0.6**	**37 ± 5**	37 ± 3	3.5 ± 1.8	1,745 ± 551	0.35 ± 0.09
p	0.1	0.014	0.002	0.1	0.001	0.001	0.05	0.1	0.1	0.2
Gly/HQA (5)	0.22 ± 0.01	37 ± 3	**2.0 ± 0.1**	20 ± 3	**11 ± 1**	**44 ± 2**	34 ± 5	**8 ± 2**	2,950 ± 355	0.36 ± 0.09
p	0.8	0.010	0.03	0.001	0.003	0.001	0.3	**0.006**	0.5	0.08
Gly/QA (8)	0.34 ± 0.06	29 ± 3	2.4 ± 0.3	27 ± 6	60 ± 19	15 ± 3	**372± 89**	**28 ± 8**	2,392 ± 94	4.03 ± 2.09
p	0.1	0.028	0.104	0.08	0.050	0.826	0.01	0.02	0.6	0.1

Closed components of NMDA receptors activated with GluN1 or GluN2A partial agonists. Kinetic models having five closed states were fit to individual single-channel files; time constants (ms) and relative areas (%) of individual components are given as means ± sem, n patches in each condition. Statistical significance of differences relative to the Glu/Gly agonist pair were evaluated for each condition with Student's t-test ($p < 0.05$). Colors highlight statistically significant increases (blue) or decreases (red). With exception of QA for which we observed high variability, all partial agonists regardless of the subunit which they activate increased τ_{E2} and τ_{E3}. In addition, agonist-specific changes were also observed.

Supplementary Table 2 Open components

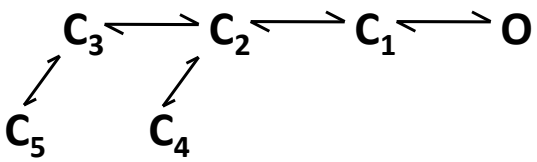
Ligands	MOT	E_{fast}		E_{low}		E_{medium}		E_{high}	
		τ_{fast} (ms)	a_{fast} (%)	τ_{low} (ms)	a_{low} (%)	τ_{med} (ms)	a_{med} (%)	τ_{high} (ms)	a_{high} (%)
Glu/Gly	**11 ± 1**	**0.38 ± 0.05**	**2.0 ± 0.2**	**4.9 ± 0.6**	**29 ± 5**	**12 ± 1**	**58 ± 5**	**25 ± 2**	**14 ± 5**
n	5	5		5		5		4	
Glu/DCS	8.4 ± 1.5	0.31 ± 0.04	3 ± 1	3.9 ± 0.6	42 ± 13	9.6 ± 1.8	64 ± 3	**16.4 ± 1.7**	16 ± 5
p	0.1	0.2	0.01	0.2	0.3	0.2	0.4	0.01	0.7
n	5	5		4		4		4	
Glu/Ala	**5.3 ± 0.7**	0.37 ± 0.05	4 ± 1	**3.0 ± 0.2**	75 ± 9	**5.9 ± 1.0**	51 ± 13	**16.0 ± 2.6**	19 ± 8
p	0.001	0.8	0.04	0.04	0.004	0.003	0.6	0.02	0.8
n	6	6		3		5		6	
SYM/Gly	**5.8 ± 1.0**	0.43 ± 0.11	5 ± 1	**2.6 ± 0.2**	44 ± 11	**5.8 ± 0.5**	62 ± 12	**12.5 ± 0.9**	28 ± 12
p	0.006	0.7	0.07	0.02	0.2	0.003	0.7	0.0001	0.5
n	5	5		3		4		4	
HCA/Gly	**5.0 ± 0.9**	0.58 ± 0.20	10 ± 4	**2.8 ± 0.3**	53 ± 11	**6.6 ± 0.5**	38 ± 11	**12.5 ± 1.0**	16 ± 10
p	0.002	0.3	0.09	0.006	0.1	0.001	0.1	0.0001	0.8
n	7	7		6		6		6	

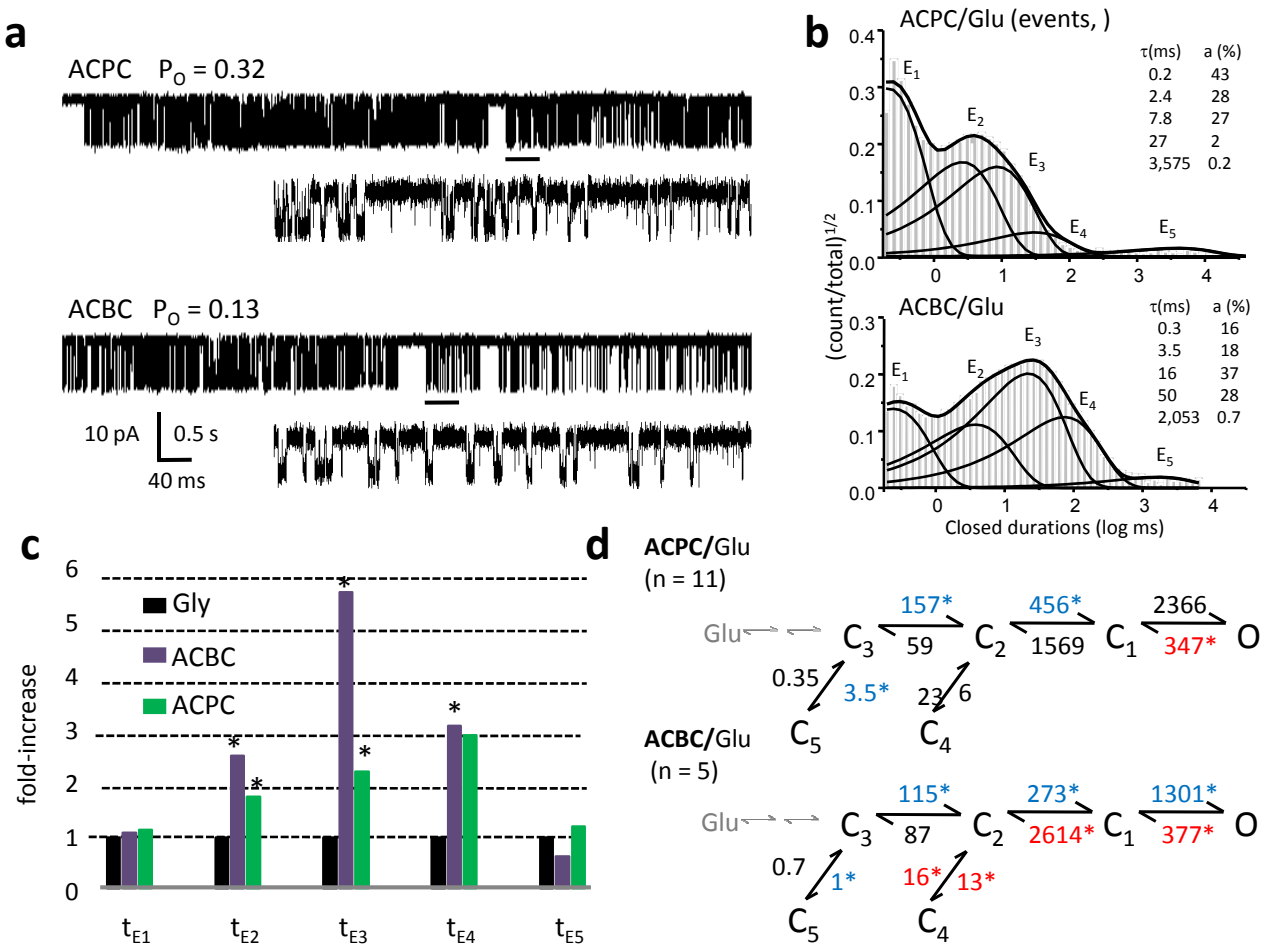
Open components of NMDA receptors activated with GluN1 or GluN2A partial agonists. Kinetic models having 3 or four 4 open states were fit to individual single-channel files; All files had a fast open component (E_{fast}), and at least two of the E_{low}, E_{medium} and E_{high}. For each component, time constants (ms) and relative areas (%) are given as means ± sem, for the patches analyzed. Statistical significance of differences relative to the full agonists pair Glu/Gly were evaluated for each condition with Student's t-test. Colors highlight statistically significant decreases (blue) or increases (red). As a general trend, partial agonists at either subunit decrease the duration of individual components. In a few instances, the relative area of the shorter open components was also increased.

Supplementary Table 3 Rate constants

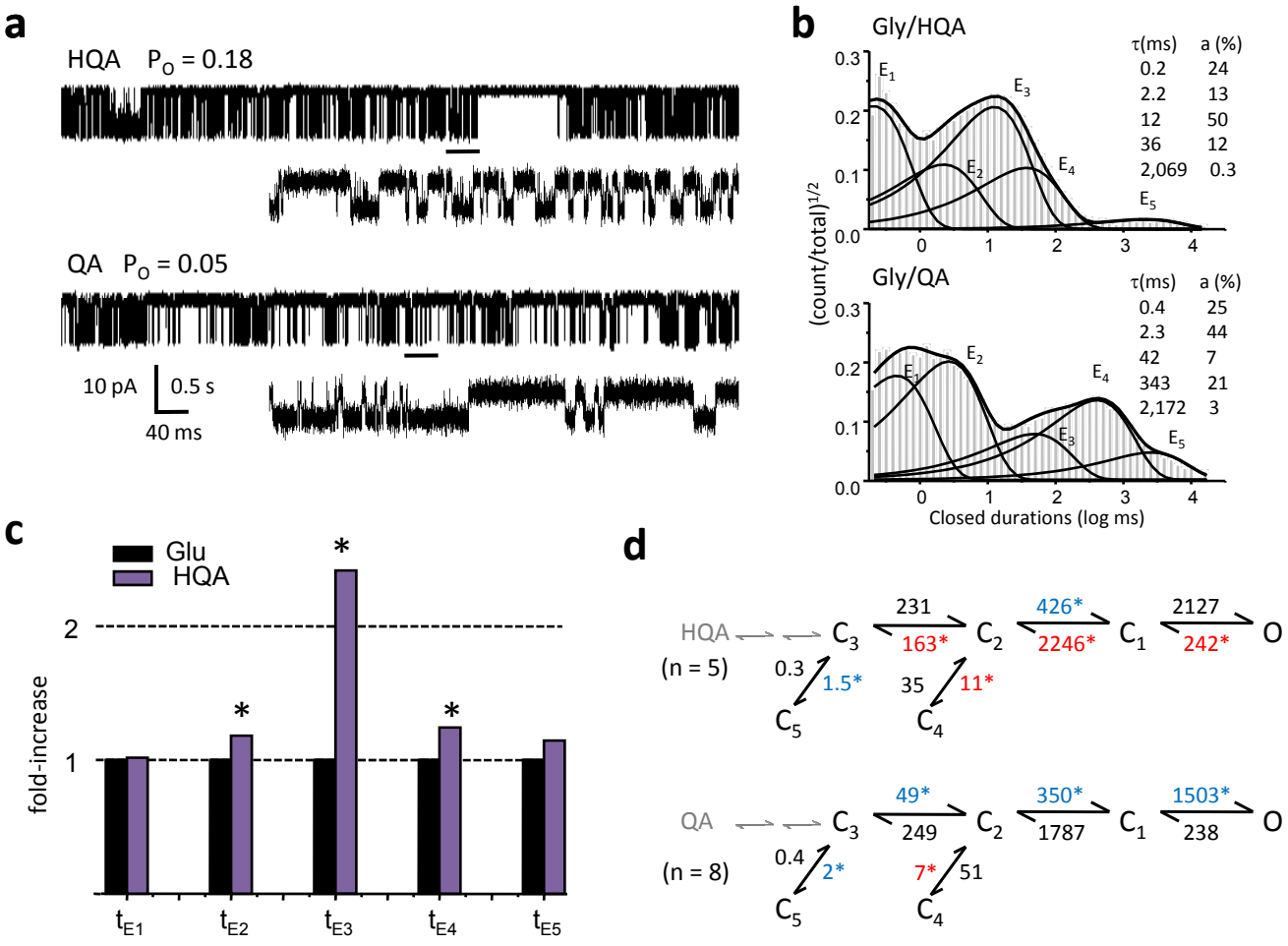
Ligands (n)	$C_3 \rightarrow C_2$	$C_3 \leftarrow C_2$	$C_2 \rightarrow C_1$	$C_2 \leftarrow C_1$	$C_1 \rightarrow O$	$C_1 \leftarrow O$	$C_3 \rightarrow C_5$	$C_3 \leftarrow C_5$	$C_2 \rightarrow C_4$	$C_2 \leftarrow C_4$
Glu/Gly (5)	**257 ± 9**	**60 ± 3**	**775 ± 65**	**1434 ± 88**	**2959 ± 313**	**142 ± 18**	**7.5 ± 1.0**	**0.5 ± 0.1**	**6.0 ± 0.6**	**38.4 ± 3.9**
Glu/DCS (5)	**177 ± 9**	45 ± 6	654 ± 37	**1736 ± 69**	**1639 ± 225**	175 ± 39	5.3 ± 1.0	0.5 ± 0.1	4.3 ± 1.4	34.6 ± 6.1
p	0.001	0.06	0.1	0.02	0.009	0.4	0.2	0.9	0.2	0.6
Glu/Ala (6)	**182 ± 17**	52 ± 8	**478 ± 16**	**2015 ± 82**	**1483 ± 245**	**245 ± 29**	**2.8 ± 0.4**	0.4 ± 0.03	3.5 ± 0.9	30.4 ± 4.4
p	0.005	0.4	0.001	0.001	0.004	0.01	0.001	0.2	0.06	0.2
HCA/Gly (7)	**177 ± 16**	44 ± 6	628 ± 81	**1903 ± 114**	**1581 ± 334**	**282 ± 35**	**4.2 ± 0.6**	0.5 ± 0.04	**3.2 ± 0.9**	**24.7 ± 3.5**
p	0.003	0.06	0.2	0.01	0.016	0.01	0.01	0.8	0.04	0.02
SYM/Gly (5)	**177 ± 18**	57 ± 12	**479 ± 39**	**2034 ± 96**	**1790 ± 305**	**236 ± 23**	**3.0 ± 0.4**	0.6 ± 0.1	5.3 ± 1.8	29.7 ± 4.2
p	0.003	0.8	0.005	0.002	0.028	0.01	0.003	0.2	0.6	0.1

Rate constants of NMDA receptors activation with GluN1 or GluN2A partial agonists. Kinetic models with five closed and one open states (see model below) were fit to individual single-channel files; and rate constants are given for each condition as means ± sem, for the patches analyzed. Statistical significance of differences relative to the full agonists pair Glu/Gly were evaluated for each condition with Student's t-test. Colors highlight statistically significant ($p<0.05$) decreases (blue) or increases (red). With two exceptions ($C_2 \rightarrow C_1$ for DCS and HCA) partial agonists at either subunit decreased all the activation rate constants ($C_3 \rightarrow C_2$, $C_2 \rightarrow C_1$ and $C_1 \rightarrow O$) and increased with one exception ($O \rightarrow C_1$ for DCS) all deactivation rate constants ($O \rightarrow C_1$, $C_1 \rightarrow C_2$, $C_2 \rightarrow C_3$). Microscopic desensitization rates were also significantly decreased (C_3-C_5, except for DCS).

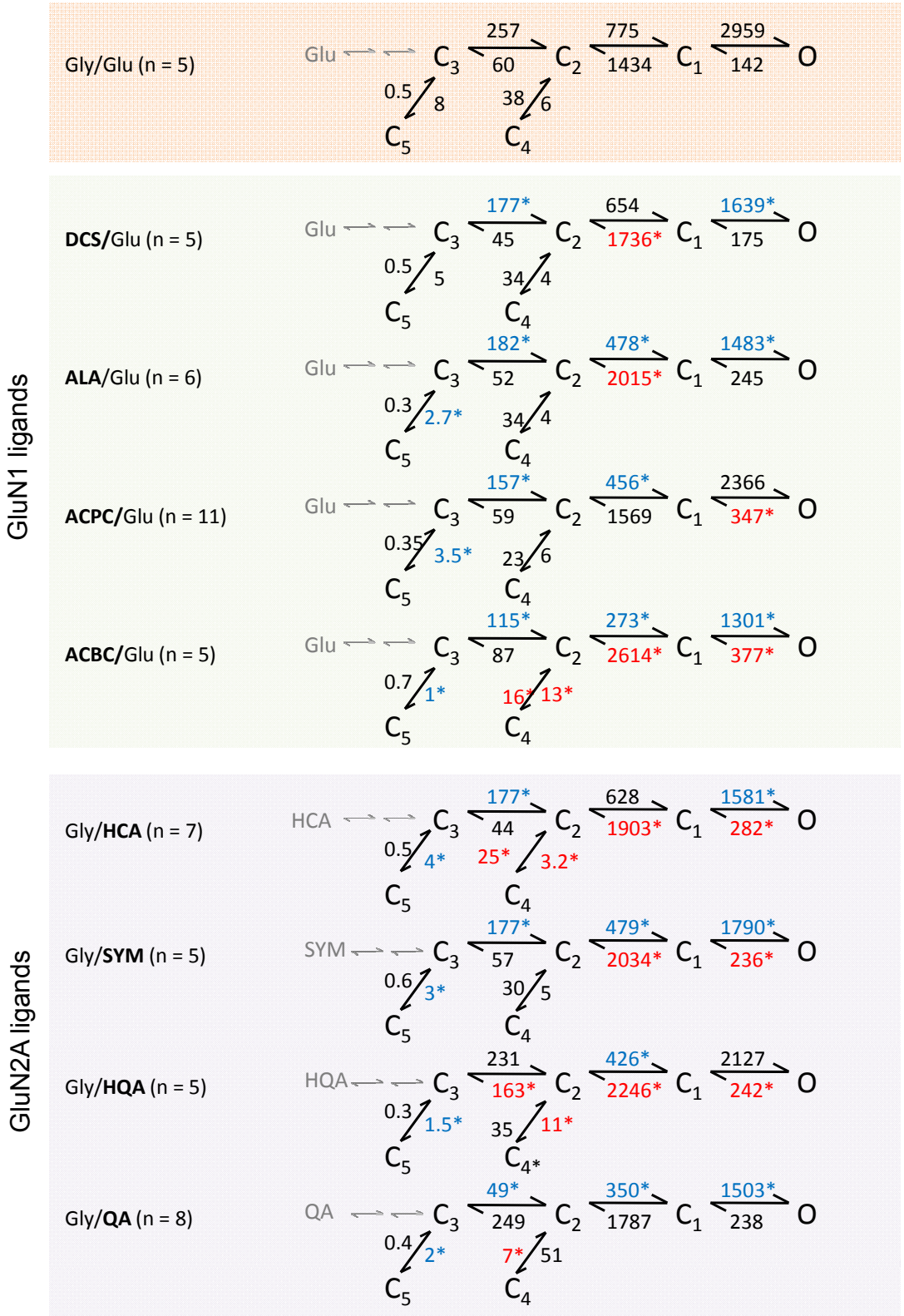




Supplementary Figure 1 NMDA receptor activities with the GluN1 partial agonists ACPC and ACBC
a, Representative single-channel trace (10 s, filtered for display at 1 kHz, openings are down). Glutamate (1 mM) was included in all recordings alongside saturating concentrations of the indicated co-agonist. Underlined portion (500 ms) of each record is expanded below filtered at 12 kHz. **b**, Histograms of closed interval distributions for a record in each condition (events: ACPC, 268,957; ACBC, 11,256) are overlaid with probability distributions (thick lines) and exponential components E_1 - E_5 (thin lines) calculated from fits of a 5C3O state model to the entire sequence of events in the respective file. *Insets* show time constants and areas for the corresponding exponential components. **c,** Bar graph represents increase in time constants for ACBC (purple, n = 5) and ACPC (green, n = 11) relative to glycine (black). **d**, State models with rate constants represented the means of results from fits to n patches in each condition. Open states are represented as an aggregate O, for simplicity. Two sequential binding steps are represented in grey. Asterisks denote rates which were significantly decreased (blue) or increased (red) from Glu/Gly ($p < 0.05$).

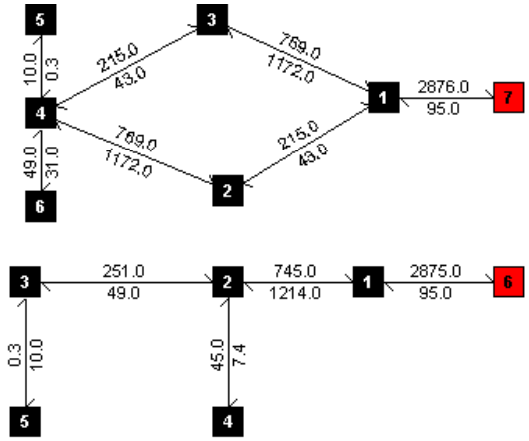


Supplementary Figure 2 NMDA receptor activities with the GluN2A partial agonists HQA and QA
a, Representative single-channel trace (10 s, filtered for display at 1 kHz, openings are down). Glycine (0.1 mM) was included in all recordings alongside saturating concentrations of the indicated agonist. Underlined portion (500 ms) of each record is expanded below filtered at 12 kHz. **b**, Histograms of closed interval distributions for a record in each condition (events: HQA, 107,523; QA, 28,525) are overlaid with probability distributions (thick lines) and exponential components E_1 - E_5 (thin lines) calculated from fits of a 5C3O state model to the entire sequence of events in the respective file. *Insets* show time constants and areas for the corresponding exponential components. **c**, State models with rate constants represented as averages of results from fits to individual records in each condition. Open states are represented as an aggregate O, for simplicity. Two sequential binding steps are represented in grey. Asterisks denote rates which were significantly decreased (blue) or increased (red) from Glu/Gly ($p < 0.05$).



Supplementary Figure 3 Summary of GluN1/GluN2A activation reactions of receptors with partial agonists Single-channel files recorded from cell-attached patches exposed to saturation concentrations of the agonists indicated were fit individually with the 5C1O state-models illustrated (black states and arrows). Rate constants (means) for the n files considered for each condition, are indicated above the arrow representing the respective transition. Statistical significance of differences (*, $p < 0.05$) were evaluated for each condition with Student's t-test relative to the full agonists pair Glu/Gly. Colors, emphasize statistically significant decreases (blue) or increases (red). As a general trend, partial agonists at either subunit decrease the rate constants of transitions that lead to opening and increase the rate constants of transitions that lead away from the open state. Kinetic changes observed are similar for both partial agonist classes and are spread across the entire activation reaction, affecting the majority of the transitions considered.

Glu/Gly– (CTR4) Events: 331,680



Cyclic model results:
LL: 1,486,470.**15**
LL/event: 4.4816**39**

Closed: mean, 6.2 ms

tau (ms)	amp (%)
0.23	47
0.46	0.29
1.73	41
4.49	10
22.7	0.76
2,929	0.16

Open, mean: 15.4 ms

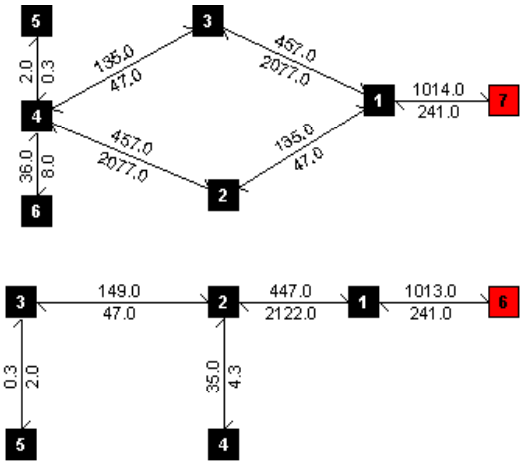
Linear model results:
LL: 1,486,470.**92**
LL/event: 4.4816**41**

Closed: mean, 6.2 ms

tau (ms)	a (%)
0.23	47
-	-
1.7	41
4.4	10
22	0.78
2,926	0.16

Open: mean, 5.4

Glu/Ala (ALA5) Events: 317,143



Cyclic model results:
LL: 1,303,901.**26**
LL/event: 4.1113985

Closed: mean, 19 ms

tau (ms)	a (%)
0.29	17
0.37	0.27
4.1	26
12	50
30	5.2
2,861	0.36

Open: mean, 4.7 ms

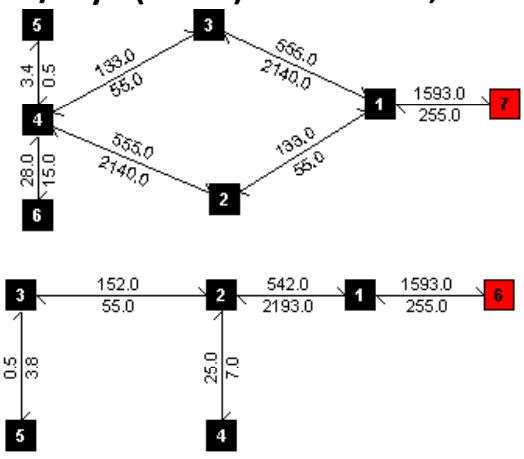
Linear model results:
LL: 1,303,901.**41**
LL/event: 4.1113989

Closed: mean: 19 ms

tau (ms)	a (%)
0.29	17
-	-
4.1	26
12	50
30	5.2
2,860	0.36

Open: mean, 4.7

SYM /Gly– (SYM4) Events: 226,578



Cyclic model results:
LL: 987,816.5**1**
LL/event: 4.359719**4**

Closed: mean, 15 ms

tau (ms)	a (%)
0.24	22
0.35	0.19
3.2	40
9.3	34
41	3.2
2,090	0.4 4

Open, mean 4.8 ms

Linear model results:
LL: 987,816.5**5**
LL/event: 4.359719**6**

Closed: mean, 15 ms

tau (ms)	a (%)
0.24	22
--	--
3.2	40
9.3	34
41	3.2
2,090	0.44

Open, mean 4.8 ms

Modeling For each of the conditions illustrated (Glu/Gly, Glu/Ala and SYM/Gly), one single-channel file was fit separately with the two models illustrated. In each panel: *top*, cyclic model representing independent activation of two subunits: a slow transition (C_4-C_3 and C_2-C_1, were fixed to be identical with each other) or a fast transition (C_3-C_1 and C_4-C_2, were constrained to remain equal to each other during fitting); *below*, a sequential model where the slow transition (C_3-C_2) occurs before a faster transition (C_2-C_1).

Rate constants were estimated for each file with either model; the calculated time constant are illustrated in side panels at right, rate constants are indicated above the respective transition (arrow). LL and LL/event are given for each file, along with the calculated time constants (ms) and relative areas (%) for the closed exponential components. Although the linear model has fewer variables it returned marginally higher LL values, in each of the conditions tested. For this reason, and because the calculated values for exponential components (times and amplitudes) as well as rate constants were similar, we chose the simpler model for our analyses.