

**Supplementary information**

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# Structural neural plasticity evoked by rapid-acting antidepressant interventions

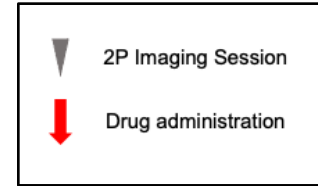
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**Title:** Structural neural plasticity evoked by rapid acting antidepressant interventions

**Authors:** Clara Liao<sup>1,2</sup>, Alisha Dua<sup>3</sup>, Cassandra Wojtasiewicz<sup>1</sup>, Conor Liston<sup>3,4</sup>, and Alex C. Kwan<sup>1,3,\*</sup>

**Supplementary Table 1: Experimental details of surveyed drug-evoked neuronal plasticity studies**



Compound	Author, year	Mouse age	Dose, treatment	Mouse strain, brain region, putative cell type imaged
Allopregnanolone	Shi et al., 2022	4-5 months	Daily dose of 10 mg/kg (s.c.) for 7 consecutive days	Thy1-GFPM, somatosensory cortex, layer V pyramidal neurons
Cocaine	Muñoz-Cuevas et al., 2013	58-112 days	Daily dose of 15 mg/kg (i.p.) for 12 consecutive days	Thy1-YFPH, dorsomedial prefrontal cortex, layer V pyramidal neurons
Diazepam	Shi et al., 2022	4-5 months	Daily dose of 5 mg/kg (i.g.) for 7 or 28 consecutive days; Daily dose of 1 mg/kg (i.g.) for 8 consecutive weeks	Thy1-GFPM, somatosensory cortex or medial prefrontal cortex (via microprism), layer V pyramidal neurons

2,5-dimethoxy-4-iodoamphetamine (DOI)	Cameron et al., 2021	n/a	1 dose of 10 mg/kg (i.p.)	Thy1-GFPM, primary sensory cortex, layer V pyramidal neurons
Fluoxetine	Shapovalov et al., 2014	n/a	100 mg/L in drinking water for 4 weeks	Thy1-GFPM, visual cortex, layer V pyramidal neurons
Haloperidol	Bowling et al., 2014	1 month	1 dose of 0.25 mg/kg (i.p.)	Thy1-YFPH, frontal association cortex, layer V pyramidal neurons
Ketamine	Phoumthippavong et al., 2016	10-21 weeks	1 dose of 10 mg/kg (i.p.)	Thy1-GFPM and Thy1-YFPH, medial frontal cortex, layer V pyramidal neurons
Ketamine	Ng et al., 2018	1 month	Daily dose of 10 mg/kg (i.p.) for 1, 2, or 7 days at various schedule relative to restraint stress	Thy1-YFPH, frontal association cortex, layer V pyramidal neurons

Ketamine	Pryazhnikov et al., 2018	4-10 weeks	Daily dose of 10 mg/kg (i.p.) for 5 consecutive days	Thy1-YFPH, somatosensory cortex, layer V pyramidal neurons
Ketamine	Moda-Sava et al., 2019	9-20 weeks	1 dose of 10 mg/kg (i.p.)	Thy1-YFPH, medial prefrontal cortex (via microprism), pyramidal cells
Ketamine-xylozine	Yang et al., 2011	1 month	2.5 or 5 mL/kg (i.p.) of 17 mg/mL ketamine and 1.7 mg/mL xylozine, then 2.5 mL/kg (s.c.) every 1.5 hr after initial injection	Thy1-YFPH, primary somatosensory cortex, layer V pyramidal neurons
5-MeO-DMT	Jefferson et al., 2023	5-8 weeks	1 dose of 20 mg/kg (i.p.)	Thy1-GFPM, medial frontal cortex, layer V pyramidal neurons

Phosphodiesterase 9 (PDE9) Inhibitor PF-04449613	Lai et al., 2018	4-5 weeks	Twice daily dose of 3.2 or 10 mg/kg (s.c.) for 1, 7, or 28 days	Thy1-YFPH, primary motor cortex, layer V pyramidal neurons
Psilocybin	Shao et al., 2021	8-10 weeks	1 dose of 1 mg/kg (i.p.)	Thy1-GFPM, medial frontal cortex, layer V pyramidal neurons
Tabernanthalog (TBG)	Cameron et al., 2021	n/a	1 dose of 50 mg/kg (i.p.)	Thy1-GFPM, primary sensory cortex, layer V pyramidal neurons
Tabernanthalog (TBG)	Lu et al., 2021	2 months	1 dose of 10 mg/kg (i.p.)	Thy1-GFPM, somatosensory cortex, layer V pyramidal neurons
$\Delta^9$ -tetrahydrocannabinol (THC)	Komorowska-Müller et al., 2023	3 or 18 months	Daily dose of 3 mg/kg for 28 days via osmotic pump (during imaging)	Thy1-GFPM, somatosensory cortex, layer V pyramidal neurons

Zolpidem	Shi et al., 2022	4-5 months	Twice daily dose of 2.5 mg/kg (i.g.) for 7 consecutive days	Thy1-GFPM, somatosensory cortex, layer V pyramidal neurons
	<p>The diagram illustrates a timeline for Zolpidem administration. The x-axis is labeled 'Day' and has markers at -14, -7, 0, 7, 14, 21, 28, 35, and 63. A break in the timeline is indicated by two parallel slashes between Day 35 and Day 63. Red arrows pointing downwards are located at Day 0, 1, 2, 3, 4, 5, and 6, representing twice-daily dosing. Grey triangles pointing downwards are located at Day -14, -7, 7, 14, 21, 28, 35, and 63, representing sampling or measurement points.</p>			

Supplementary Data: Data extraction from published studies for Figure 2

**Ketamine (Phoumthipphavong, 2016)**

	Control Datapoints			Drug Treatment Datapoints			(Scaled Drug Y) - (Scaled Cntrl Y)
	Extracted Y value	Diff from origin Y-coord	Scaled Y Coordinate	Extracted Y value	Diff from origin Y-coord	Scaled Y Coordinate	
day -3	101	0	0	107	-6	-0.991735537	-0.991735537
day -1	150	-49	-8.099173554	138	-37	-6.115702479	1.983471074
day +1	207	-106	-17.52066116	106	-5	-0.826446281	16.69421488
day +3	212	-111	-18.24710744	116	-15	-2.479338843	15.86776863
day +5	251	-150	-24.79338843	137	-36	-5.950413223	18.84297521
day +10	263	-162	-26.7768595	122	-21	-3.47107438	23.30578512
day +15	234	-133	-21.98347107	153	-52	-8.595041322	13.38842975

Final Values Plotted on Fig 4b	
X	Y
-3	-0.991736
-1	1.983471
1	16.69421
3	15.86777
5	18.84298
10	23.30579
15	13.38843

Extracted Reference Values for Scaling	Extracted Y value	Diff from origin Y-coord
Y-min (-40)	343	-242
Y = 0	101	0
Y-max (10)	40	61

**5-MeO-DMT (Jefferson, 2023)**

	Control Datapoints			Drug Treatment Datapoints			(Scaled Drug Y) - (Scaled Cntrl Y)
	Extracted Y value	Diff from origin Y-coord	Scaled Y Coordinate	Extracted Y value	Diff from origin Y-coord	Scaled Y Coordinate	
day -3	234	0	0	234	0	0	0
day -1	227	7	1.60130719	242	-8	-1.820065359	-3.431372549
day +1	218	16	3.660130719	165	69	15.78431373	12.12418301
day +3	271	-37	-8.464052288	179	55	12.58169935	21.04575163
day +5	261	-27	-6.176470588	209	25	5.718954248	11.89542484
day +7	286	-54	-12.35294118	199	35	8.006535948	20.35947712
day +34	294	-60	-13.7254902	184	50	11.4379085	25.16339869

Final Values Plotted on Fig 4b	
X	Y
-3	0
-1	-3.431373
1	12.12418
3	21.04575
5	11.89542
7	20.35948
34	25.1634

Extracted Reference Values for Scaling	Extracted Y value	Diff from origin Y-coord
Y-min (-25)	343	-109
Y = 0	234	0
Y-max (35)	81	153

**Psilocybin (Shao, 2021)**

	Control Datapoints			Drug Treatment Datapoints			(Scaled Drug Y) - (Scaled Cntrl Y)
	Extracted Y value	Diff from origin Y-coord	Scaled Y Coordinate	Extracted Y value	Diff from origin Y-coord	Scaled Y Coordinate	
day -3	134	0	0	134	0	0	0
day -1	139	-5	-1.578947368	135	-11	-0.315789474	1.263157895
day +1	145	-11	-3.473684211	112	22	6.947368421	10.42105263
day +3	144	-10	-3.157894737	102	32	10.10526316	13.26315789
day +5	141	-7	-2.210526316	100	34	10.73684211	12.94736842
day +7	140	-6	-1.894736842	95	39	12.31578947	14.21052632
day +34	167	-33	-10.42105263	113	21	6.631578947	17.05263158

Final Values Plotted on Fig 4b	
X	Y
-3	0
-1	1.263158
1	10.42105
3	13.26316
5	12.94737
7	14.21053
34	17.05263

Extracted Reference Values for Scaling	Extracted Y value	Diff from origin Y-coord
Y-min (-20)	198	-64
Y = 0	134	0
Y-max (30)	39	95

**Diazepam (Shi, 2022)**

	Control Datapoints			Drug Treatment Datapoints			(Scaled Drug Y) - (Scaled Cntrl Y)
	Extracted Y value	Diff from origin Y-coord	Scaled Y Coordinate	Extracted Y value	Diff from origin Y-coord	Scaled Y Coordinate	
day +1	89	0	0	78	-5	-1.19047619	-1.19047619
day +8	90	-1	-0.223880597	72	1	0.238095238	0.461975835
day +15	87	2	0.447761194	70	3	0.714285714	0.26652452
day +22	79	10	2.23880597	128	-55	-13.0652381	-15.33404407
day +29	90	-1	-0.223880597	123	-50	-11.9047619	-11.68088131
day +36	88	1	0.223880597	119	-46	-10.95238095	-11.17626155
day +43	77	12	2.686567164	109	-36	-8.571428571	-11.25799574
day +50	83	6	1.343283582	105	-32	-7.619047619	-8.962331201
day +78	79	10	2.23880597	79	-6	-1.428571429	-3.667377399

\*Since drug/vehicle administration began on day 15, the x-values were shifted to reflect day 1 as day -14... day 15 as day 0, etc.

Final Values Plotted on Fig 4b	
X	Y
1 -> -14	-1.190476
8 -> -7	0.461976
15 -> 0	0.266525
22 -> 7	-15.33404
29 -> 14	-11.68089
36 -> 21	-11.17626
43 -> 28	-11.25799
50 -> 35	-8.962331
78 -> 63	-3.667377

Extracted Reference Values for Scaling - Control	Extracted Y value	Diff from origin Y-coord
Y-min (70)	223	-134
Y = 100	89	0
Y-max (110)	44	45

Extracted Reference Values for Scaling - Drug	Extracted Y value	Diff from origin Y-coord
Y-min (70)	199	-126
Y = 100	73	0
Y-max (110)	31	42

**Zolpidem (Shi, 2022)**

	Control Datapoints			Drug Treatment Datapoints			(Scaled Drug Y) - (Scaled Cntrl Y)
	Extracted Y value	Diff from origin Y-coord	Scaled Y Coordinate	Extracted Y value	Diff from origin Y-coord	Scaled Y Coordinate	
day +1	89	0	0	146	-13	-1.397849462	-1.397849462
day +8	90	-1	-0.223880597	124	9	0.967741935	1.191622532
day +15	87	2	0.447761194	127	6	0.64516129	0.197400096
day +22	79	10	2.23880597	129	4	0.430107527	-1.808698443
day +29	90	-1	-0.223880597	130	3	0.322580645	0.546461242
day +36	88	1	0.223880597	125	8	0.860215054	0.636334457
day +43	77	12	2.686567164	122	11	1.182795699	-1.503771465
day +50	83	6	1.343283582	107	26	2.795698925	1.452415343
day +78	79	10	2.23880597	116	15	1.61293022	-0.625902744

\*Since drug/vehicle administration began on day 15, the x-values were shifted to reflect day 1 as day -14... day 15 as day 0, etc.

Final Values Plotted on Fig 4b	
X	Y
1 -> -14	-1.397849
8 -> -7	1.191623
15 -> 0	0.1974
22 -> 7	-1.808698
29 -> 14	0.546461
36 -> 21	0.636334
43 -> 28	-1.503771
50 -> 35	1.452415
78 -> 63	-0.625903

Extracted Reference Values for Scaling - Control	Extracted Y value	Diff from origin Y-coord
Y-min (70)	223	-134
Y = 100	89	0
Y-max (110)	44	45

Extracted Reference Values for Scaling - Drug	Extracted Y value	Diff from origin Y-coord
Y-min (70)	412	-279
Y = 100	133	0
Y-max (110)	40	93

**Allopregnenolone (Shi, 2022)**

	Control Datapoints			Drug Treatment Datapoints			(Scaled Drug Y) - (Scaled Cntrl Y)
	Extracted Y value	Diff from origin Y-coord	Scaled Y Coordinate	Extracted Y value	Diff from origin Y-coord	Scaled Y Coordinate	
day +1	89	0	0	256	3	0.280373832	0.280373832
day +8	90	-1	-0.223880597	255	4	0.373831776	0.597712373
day +15	87	2	0.447761194	265	-6	-0.560747664	-1.008508859
day +22	79	10	2.23880597	196	63	5.887850467	3.649044497
day +29	90	-1	-0.223880597	198	61	5.700834579	5.924815176
day +36	88	1	0.223880597	222	37	3.457943925	3.234063328
day +43	77	12	2.686567164	228	31	2.897196262	0.210629098
day +50	83	6	1.343283582	261	-2	-0.186915888	-1.53019947

\*Since drug/vehicle administration began on day 15, the x-values were shifted to reflect day 1 as day -14... day 15 as day 0, etc.

Final Values Plotted on Fig 4b	
X	Y
1 -> -14	0.280374
8 -> -7	0.597712
15 -> 0	-1.008509
22 -> 7	3.649044
29 -> 14	5.924815
36 -> 21	3.234063
43 -> 28	0.210629
50 -> 35	-1.530199

Extracted Reference Values for Scaling - Control	Extracted Y value	Diff from origin Y-coord
Y-min (70)	223	-134
Y = 100	89	0
Y-max (110)	44	45

Extracted Reference Values for Scaling - Drug	Extracted Y value	Diff from origin Y-coord
Y-min (80)	473	-214
Y = 100	259	0
Y-max (120)	45	214

**Cocaine (Munoz-Cuevas, 2013)**

	Control Datapoints			Drug Treatment Datapoints			(Scaled Drug Y) - (Scaled Cntrl Y)
	Extracted Y value	Diff from origin Y-coord	Scaled Y Coordinate	Extracted Y value	Diff from origin Y-coord	Scaled Y Coordinate	
day -1	121	0	0	121	0	0	0
day +1	136	-15	-2.419354839	113	8	1.290322581	3.709677419
day +3	141	-20	-3.225806452	108	13	2.096774194	5.322580645
day +5	151	-30	-4.838709677	116	5	0.806451613	5.64516129
day +7	171	-50	-8.064516129	115	6	0.967741935	9.032258065
day +9	156	-35	-5.645161293	130	-9	-1.451612903	4.193548387
day +11	160	-39	-6.290322581	132	-11	-1.774193548	4.516129032
day +13	158	-37	-5.967741935	120	1	0.161290323	6.129032258
day +15	159	-38	-6.129032258	134	-13	-2.096774194	4.032258065
day +17	187	-66	-10.64516129	130	-9	-1.451612903	9.193548387
day +19	183	-62	-10	127	-6	-0.967741935	9.032258065
day +21	190	-69	-11.12903226	135	-14	-2.258064516	8.870967742
day +23	182	-61	-9.838709677	151	-30	-4.838709677	5
day +25	194	-73	-11.77419355	147	-26	-4.193548387	7.580645161

Final Values Plotted on Fig 4b	
X	Y
-1	0
1	3.709677
3	5.322581
5	5.645161
7	9.032258
9	4.193548
11	4.516129
13	6.129032
15	4.032258
17	9.193548
19	9.032258
21	8.870968
23	5
25	7.580645

Extracted Reference Values for Scaling	Extracted Y value	Diff from origin Y-coord
Y-min (-20)	244	-123
Y = 0	121	0
Y-max (15)	28	93



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