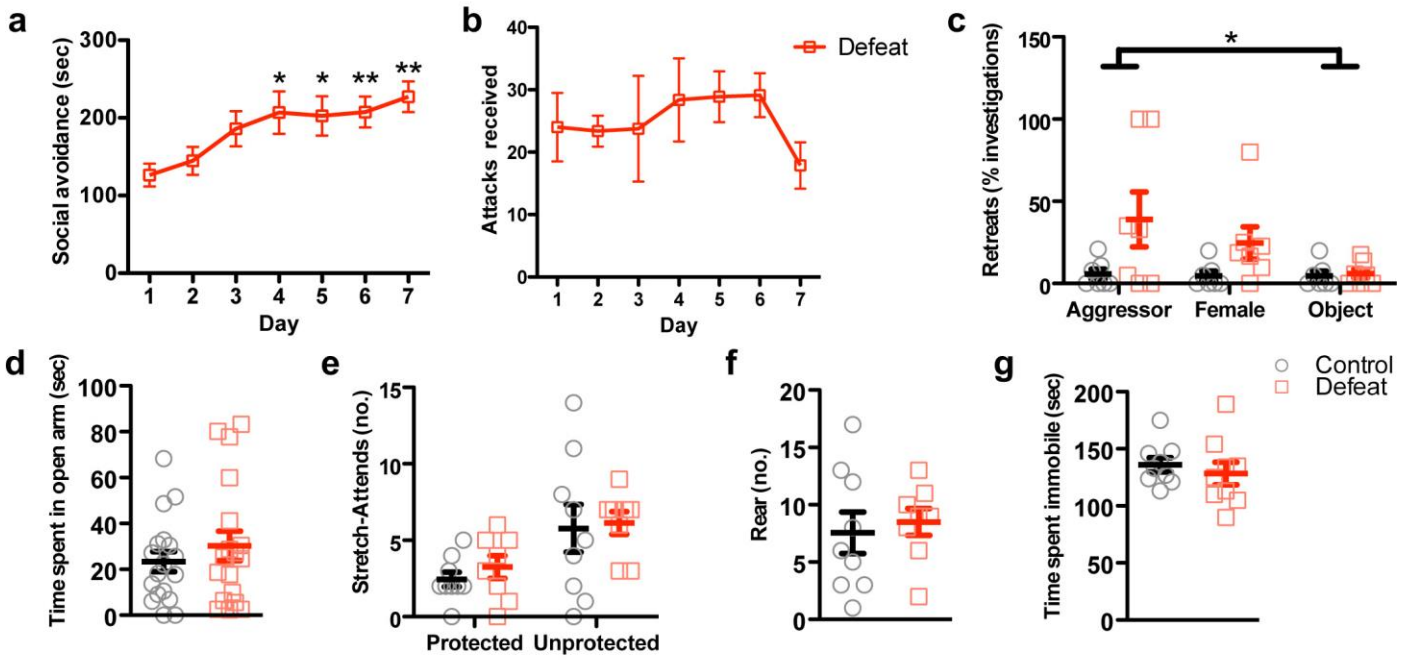
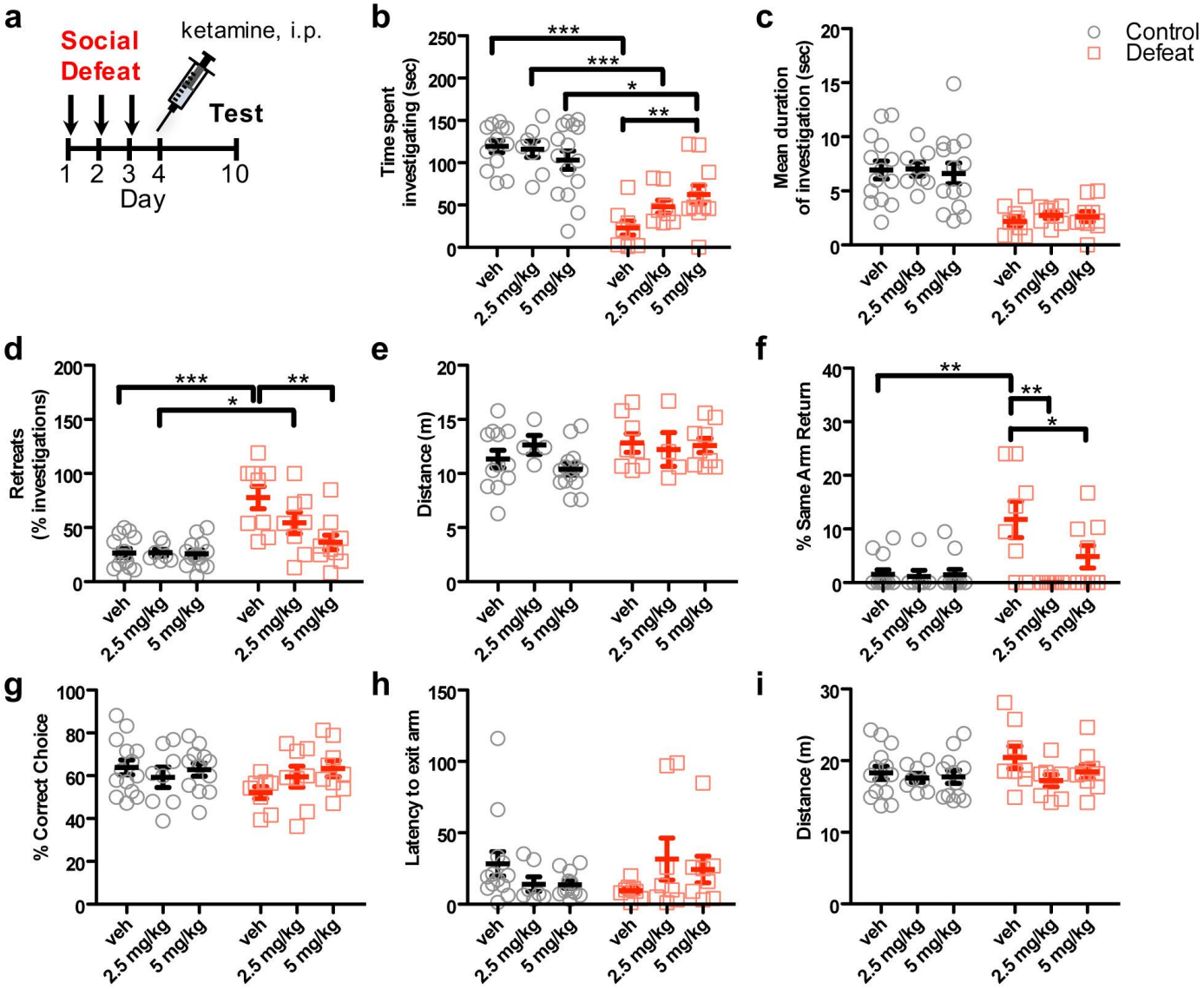



**Supplementary Figure 1**

Social, anxiety-like and depressive-like behaviors in defeated and control mice.

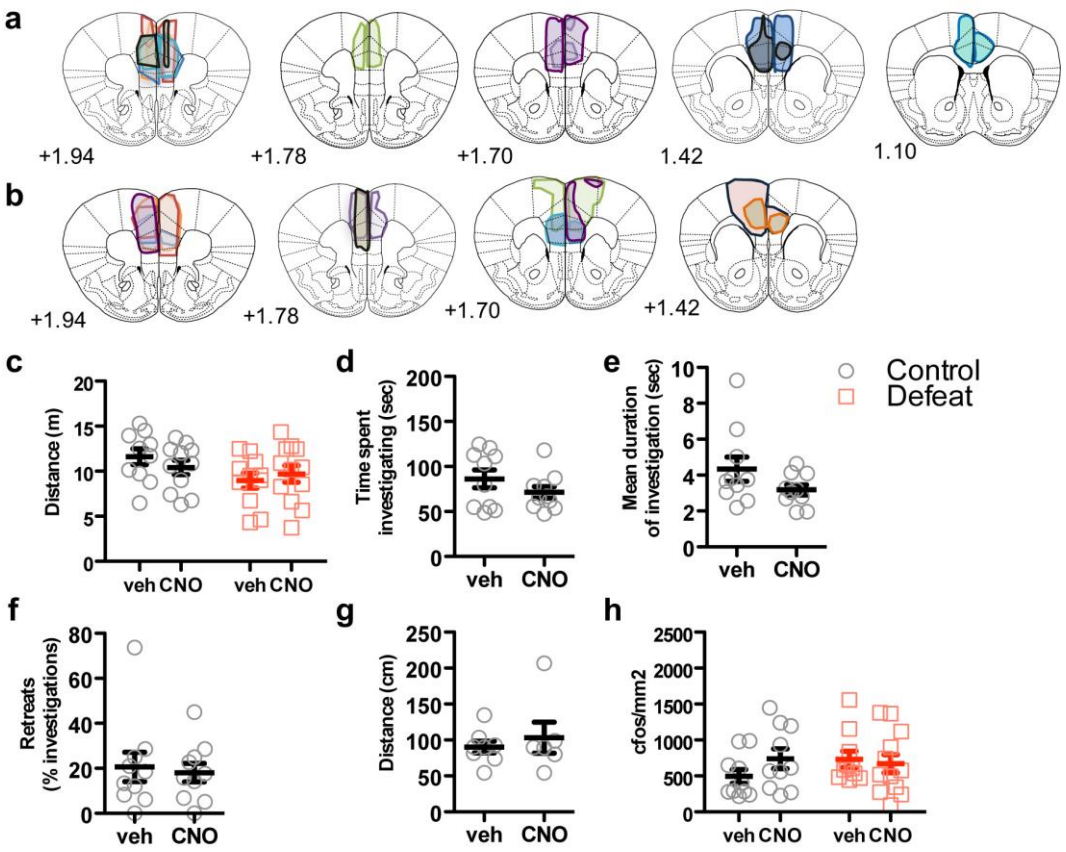
(**a**) Social avoidance (n=9; day, $F_{[6,8]} = 5.81$, p = 0.0001) and (**b**) number of attacks (n=8) across social defeat sessions during the period in which the intruder was prevented from attacking the resident by an enclosure. (**c**) Retreats made by defeated (n=7) and control (n=7) mice in response to aggressors, females or a novel object (defeat: $F_{[1,12]} = 6.5$, p = 0.026, stimulus: $F_{[2,12]}=3.48$, p=0.047). (**d**) Time spent in the open arm (control, n=18; defeat, n=18), (**e**) number of unprotected and protected stretch attends (control, n=8; defeat, n=8), and (**f**) rearing in defeated and control mice in the elevated plus maze (control, n=8; defeat, n=8). (**g**) Immobility in defeated and control mice in the tail suspension test (control, n=9; defeat, n=9). **a**, **b**, red squares represent mean of defeated mice. **c**-**g**, grey circles represent individual control mice, light red squares represent individual defeated mice, horizontal bar denotes mean. All error bars represent standard error of the mean.




**Supplementary Figure 2**

Behavioral effects of ketamine on defeated and control mice.

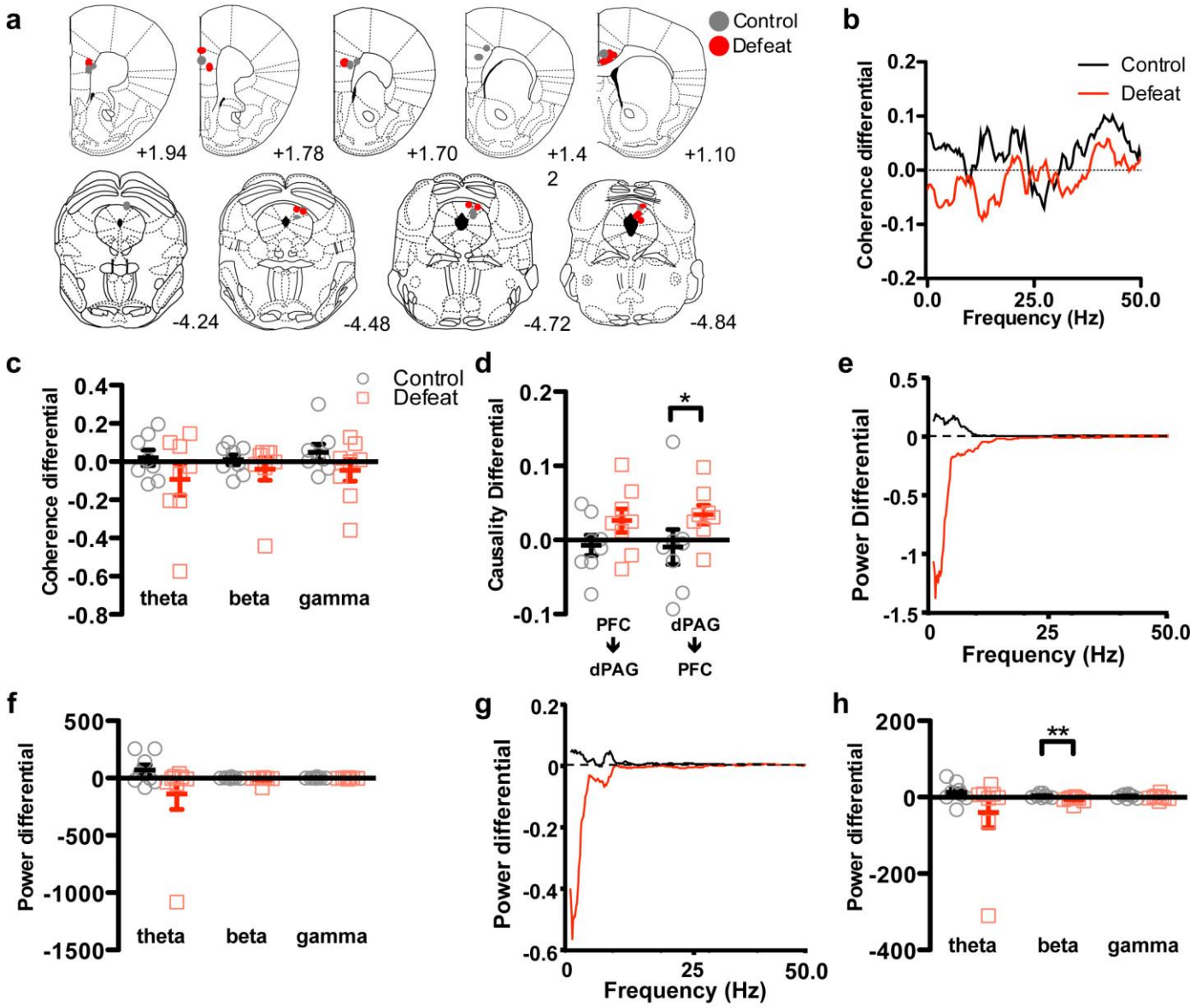
(**a**) Timeline showing behavioral testing and ketamine/vehicle administration. (**b**) Time spent investigating (defeat: $F_{[1, 57]} = 65.8$, $p < 0.0001$; defeat x ketamine: $F_{[2,57]} = 4.3$, $p = 0.018$; control/vehicle, n=13; control/2.5, n=8; control/5, n=15; defeat/vehicle, n=8; defeat/2.5, n=8; defeat/5, n=11), (**c**) duration of investigation bout (control/vehicle, n=14; control/2.5, n=8; control/5, n=14; defeat/vehicle, n=9; defeat/2.5, n=8; defeat/5, n=10), (**d**) retreats (defeat: $F_{[1,56]} = 31.9$, $p < 0.0001$; defeat x treatment: $F_{[2, 56]}= 5.9$, P=0.0048; control/vehicle, n=14; control/2.5, n=7; control/5, n=14; defeat/vehicle, n=9; defeat/2.5, n=8; defeat/5, n=10) and (**e**) baseline locomotor behavior (control/vehicle, n=12; control/2.5, n=4; control/5, n=14; defeat/vehicle, n=8; defeat/2.5, n=4; defeat/5, n=9) in control and defeated mice given vehicle or ketamine. (**f**) Same arm returns (SARs) (control/vehicle, n=13; control/2.5, n=7; control/5, n=11; defeat/vehicle, n=8; defeat/2.5, n=7; defeat/5, n=9; defeat x drug: $F_{[2, 49]} = 5.56$, P=0.0067), (**g**) spontaneous alternation (control/vehicle, n=14; control/2.5, n=8; control/5, n=12; defeat/vehicle, n=8; defeat/2.5, n=8; defeat/5, n=9), (**h**) latency to exit the start arm (control/vehicle, n=13; control/2.5, n=7; control/5, n=12; defeat/vehicle, n=8; defeat/2.5, n=8; defeat/5, n=8), and (**i**) overall distance (control/vehicle, n=14; control/2.5, n=8; control/5, n=12; defeat/vehicle, n=8; defeat/2.5, n=8; defeat/5, n=9) travelled in the Y-maze. $0.05<+p < 0.1$, $*p < 0.05$; $**p < 0.01$; $***p < 0.001$. **b-i**, grey circles represent individual control mice, light red squares represent individual defeated mice, horizontal bar denotes mean, error bars represent standard error of the mean. veh, vehicle.




**Supplementary Figure 3**

mPFC infection sites for mPFC–dPAG inhibition and behavioral effects of mPFC–SuColl inhibition in control mice.

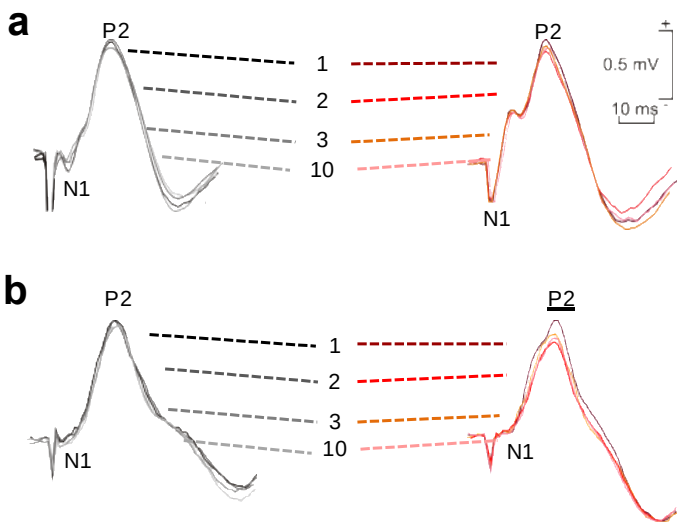
Area of viral infection (AAV-Syn::Venus-2A-HAhM4D-WPRE) visualized by endogenous Venus in mPFC of (**a**) control and (**b**) defeated mice administered CNO. (**c**) Distance travelled in the home cage in (left) control and (right) defeated mice after intra-PAG administration of CNO or vehicle (control/vehicle, n=10; control/CNO, n=10; defeat/vehicle, n=10; defeat/CNO, n=12). (d-g) Schematic describing bilateral infection of the mPFC with AAV expressing Venus fluorescent protein and HA-tagged hM4D (AAV-Syn::Venus-2A-HA-hM4D), and implantation of a guide cannula over SuColl. (**d**) Time investigating the aggressor (vehicle, n=10; CNO, n=10), (**e**) investigation bouts (vehicle, n=10; CNO, n=10), (**f**) retreats (vehicle, n=10; CNO, n=10) and (**g**) overall activity (vehicle, n=8; CNO, n=6) in control mice administered CNO or vehicle prior to testing. (**h**) Quantification of c-Fos immunopositive cells in ventrolateral (vl) PAG (control/vehicle, n=10; control/CNO, n=10; defeat/vehicle, n=10; defeat/CNO, n=12). **c**-**h**, grey circles represent individual control mice, light red squares represent individual defeated mice, horizontal bar denotes mean. All error bars represent standard error of the mean. veh, vehicle.




**Supplementary Figure 4**

Effects of social defeat on mPFC–dPAG functional connectivity when distal to the aggressor.

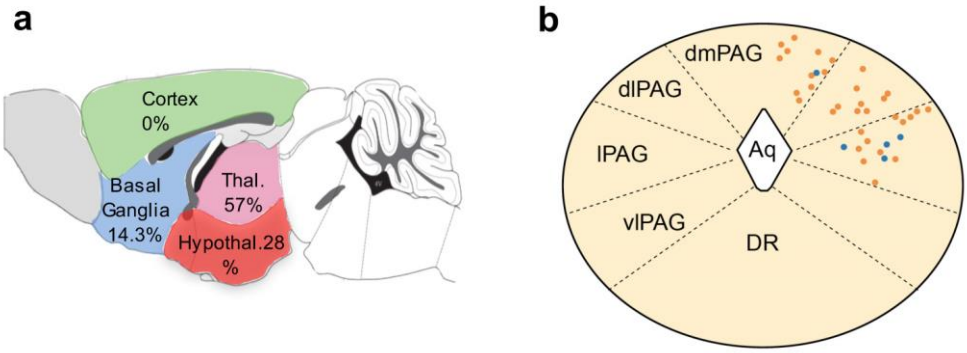
(**a**) Electrode placements for LFPs recorded in mPFC and dPAG of control (grey) and defeated (red) mice. (**b**, **c**) Relative coherence (coherence differential) in defeated (n=8) and control (n=8) mice when distal to the aggressor. (**d**) Relative causality (causality differential) in the dPAG->mPFC and mPFC-> dPAG direction in defeated (n=8) and control (n=8) mice when distal to the aggressor (U=8, p=0.038). Power spectra differential (**e**, **f**) mPFC and (**g**, **h**) PAG of defeated (n=8) and control (n=8) mice when distal to the aggressor (beta, U=6, p=0.0047). Power spectra were averaged across mice. Power in each frequency band was calculated as the sum of the power values. *P<0.05; **P<0.01. **c**, **d**, **f**, **h**, grey circles represent individual control mice, light red squares represent individual defeated mice, horizontal bar denotes mean. All error bars represent standard error of the mean.




**Supplementary Figure 5**

Extracellular synaptic field potentials in dPAG and MDT of defeated and control mice.

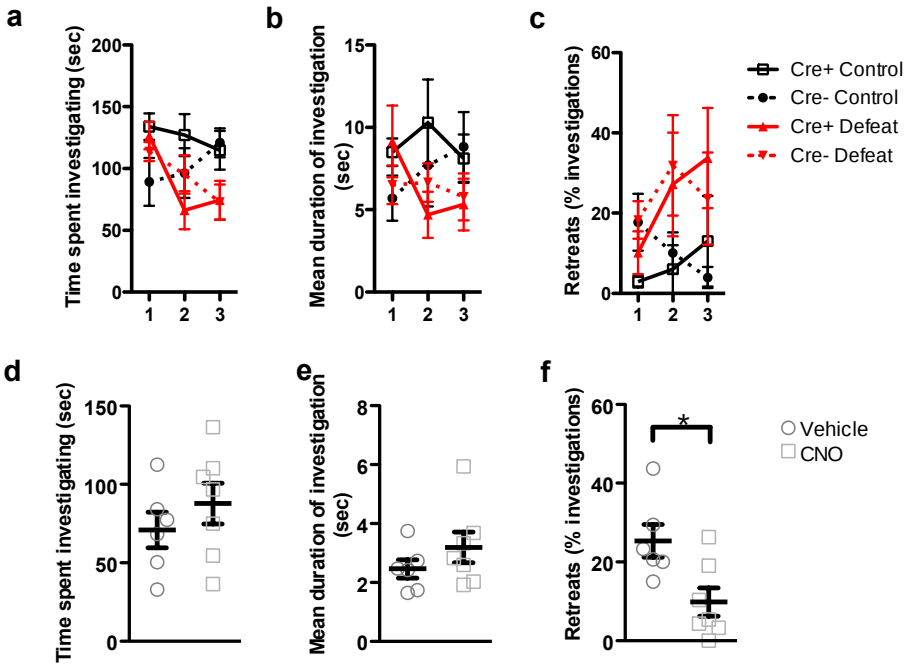
Superimposed recordings illustrating extracellular synaptic field potentials recorded at (**a**) dPAG following electrical stimulation of mPFC and at (**b**) mPFC following electrical stimulation of MDT along the different sessions. (gray scale: control group; red scale: defeated group).




**Supplementary Figure 6**

Cell-specific retrograde labeling in GAD2::Cre mice and location of Vglut2$^{+}$ neurons used for whole cell recordings.

(**a**) Summary of rabies-infected neurons (GFP+, mCherry-) in the forebrain of *VGgat*::Cre animals (percentage of the average number of retrograde neurons weighted to the number of starter cells present in each animal, n=7). No neurons were found in the olfactory bulb (grey), hippocampus (grey), or cortex. Areas not counted (midbrain and hindbrain) are indicated in white. Thal – thalamus; Hypothal – hypothalamus. (**b**) Schematic showing the location of all Vglut2+ neurons from which whole-cell recordings were made. Blue circles represent neurons with monosynaptic inputs from the PFC, and orange circles are neurons without PFC input. Aq – cerebral aqueduct; dmPAG – dorsomedial PAG; dlPAG – dorsolateral PAG; lPAG – lateral PAG; vlPAG – ventrolateral PAG; DR – dorsal raphe.




**Supplementary Figure 7**

Acquisition of social defeat in Vglut2::Cre mice and behavioral effects of inhibition of GAD2$^{+}$ cells in the dPAG.

(**a**) Time spent investigating, (**b**) mean investigation bout, and (**c**) retreats in Cre+ and Cre- defeated and control mice during the three days of acquisition. (**d**) Time spent investigating (vehicle, n=6; CNO, n=7), (**e**) mean duration of investigation (vehicle, n=6; CNO=7) and (**f**) retreats (vehicle, n=6; CNO, n=7) after systemic administration of vehicle or CNO in GAD2::Cre mice infected with AAV-*Syn*::DIO-hM4D-mCherry in the dPAG ($t(11)=2.2$, $p=0.016$). **a-c**, black circles represent mean of control mice, red squares represent mean of defeated mice. **d-f**, grey circles represent individual control mice, light red squares represent individual defeated mice, horizontal bar denotes mean. All error bars represent standard error of the mean.

Supplementary Table 1.

| | CTB647-labeled neurons | GABAergic neurons | GABAergic CTB647-labeled neurons |
|---|---|---|---|
| Anterior cingulate | 130 | 1442 | 0 |
| Prelimbic | 259 | 1108 | 0 |
| Infralimbic | 194 | 976 | 0 |
| **Total** | **583** | **3526** | **0** |

Supplementary Table 2.

| | Mouse | | | | | | | | Average weighted to no. of starter cells | Total no. of cells |
|---|---|---|---|---|---|---|---|---|---|---|
| | #1 | #2 | #3 | #4 | #5 | #6 | #7 | #8 | | |
| **Cortex** | **2** | **0** | **7** | **0** | **76** | **27** | **7** | **63** | **28.0** | **182** |
| FrA | | | | | | | | 1 | 0.2 | 1 |
| M2 | | | 1 | | | | | 1 | 0.3 | 2 |
| S1 | | | 1 | | 20 | 10 | | 4 | 4.2 | 35 |
| S2 | | | | | 3 | | 1 | 1 | 0.8 | 5 |
| Au | | | | | 6 | 1 | | 9 | 3.0 | 16 |
| V1 | | | | | 1 | | | 10 | 2.5 | 11 |
| V2 | | | | | 17 | 6 | | 9 | 4.7 | 32 |
| mPFC | 2 | | | | 8 | 5 | 3 | 2 | 2.4 | 20 |
| VO | | | | | | | 2 | 1 | 0.6 | 3 |
| LO | | | | | 2 | | | 2 | 0.7 | 4 |
| Ai | | | 1 | | 2 | | | | 0.3 | 3 |
| Ect | | | | | | | | 1 | 0.2 | 1 |
| RSA | | | | | 7 | 2 | 1 | 19 | 5.7 | 29 |
| RSG | | | | | 6 | | | 3 | 1.5 | 9 |
| LPtA | | | 4 | | 4 | 3 | | | 1.0 | 11 |
| **Striatal-like Structures** | **1** | **0** | **0** | **0** | **9** | **40** | **1** | **5** | **5.3** | **56** |
| LS | 1 | | | | 4 | 2 | 1 | | 0.8 | 8 |
| MeA | | | | | 1 | | | 1 | 0.4 | 2 |
| BMA | | | | | 1 | | | | 0.1 | 1 |
| CeA | | | | | 3 | 38 | | 4 | 4.0 | 45 |
| **Pallidum-like Structures** | **0** | **0** | **0** | **0** | **1** | **39** | **0** | **6** | **4.2** | **46** |
| BSTS | | | | | 1 | 36 | | 2 | 3.1 | 39 |
| VP | | | | | | 1 | | | 0.1 | 1 |
| SI | | | | | | 2 | | 4 | 1.1 | 6 |
| **Thalamus** | **13** | **3** | **17** | **14** | **749** | **186** | **0** | **446** | **218.8** | **1428** |
| LGN | 13 | 2 | 10 | 11 | 494 | 55 | | 332 | 149.0 | 917 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| AAD | | | | | 1 | | | | 0.1 | 1 |
| Re | | | | 1 | 1 | 3 | | 14 | 3.9 | 19 |
| LDVL | | | | | 1 | | | | 0.1 | 1 |
| RT | | | | | 5 | 4 | | 9 | 3.0 | 18 |
| LPRM | | | | | 2 | | | | 0.3 | 2 |
| SPF | | | | | 83 | | | 33 | 18.3 | 116 |
| APTD | | | | | 33 | 6 | | | 4.6 | 39 |
| PSTh | | | | | 7 | 59 | | 11 | 7.6 | 77 |
| PoT | | | | | 68 | 31 | | | 10.8 | 99 |
| LPL | | | | | | | | 39 | 9.2 | 39 |
| Undefined thalamus | | 1 | 7 | 2 | 54 | 28 | | 8 | 11.8 | 100 |
| **Hypothalamus** | **7** | **3** | **34** | **19** | **500** | **426** | **8** | **522** | **225.4** | **1519** |
| Pe | | | | | | 1 | | | 0.1 | 1 |
| LPO | | | 1 | | | 2 | | | 0.2 | 3 |
| DM | | | 2 | | 11 | 12 | 1 | 27 | 8.9 | 53 |
| AH | | | | | 37 | 15 | | 37 | 14.5 | 89 |
| MPA | | | 4 | 1 | 7 | 28 | | 3 | 4.1 | 43 |
| MPO | | | 2 | | 5 | 25 | 2 | 18 | 7.1 | 52 |
| PMD | 1 | | | 1 | 36 | 11 | | | 5.7 | 49 |
| PaP | | | | | | 1 | | 8 | 2.0 | 9 |
| PVN | | | 1 | | 4 | | | | 0.6 | 5 |
| VMHa | | | | | 14 | 7 | 2 | 9 | 4.7 | 32 |
| VMHdm | 1 | 1 | 9 | 2 | 42 | 19 | 2 | 52 | 20.5 | 128 |
| VMHvl | | 1 | | | 5 | 15 | | 12 | 4.5 | 33 |
| PH | | | | | 24 | 34 | | | 5.4 | 58 |
| PeF | | | | | 4 | 31 | | | 2.7 | 35 |
| LH | 1 | | | 6 | 36 | 98 | | 86 | 33.4 | 227 |
| LPO | | | 1 | | | 2 | | | 0.2 | 3 |
| Tu | | | | | 2 | | | | 0.3 | 2 |
| TC | | | | | | 11 | | | 0.8 | 11 |
| ZI | 4 | 1 | 14 | 9 | 273 | 114 | 1 | 270 | 110.0 | 686 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **density of starter cells in dPAG (n/mm$^2$)** | 21.6 | 38.6 | 106.4 | 468.8 | 203.6 | 110.3 | 276.8 | 375.5 | | |

dPAG, dorsal periaqueductal grey. **Cortex**: Au, auditory cortex; Ect, ectorhinal cortex; FrA, frontal association cortex; LO, lateral orbital cortex; LPtA, lateral parietal association cortex; M2, secondary motor cortex; mPFC, medial prefrontal cortex; RSA, retrosplenial agranular cortex; RSG, retrosplenial granula cortex; S1, primary somatosensory cortex; S2, secondary somatosensory cortex; V1, primary visual cortex; V2, secondary visual cortex; Vo, ventral orbital cortex. **Striatal-like structures**: BMA, basomedial amygdala; CeA, central amygdala; LS, lateral septum; MeA, medial amygdala. **Pallidum-like structures**: BSTS, bed nucleus of the stria terminalis; SI, substantia innominata; VP, ventral pallidum. **Thalamus**: AAD, anterior amygdaloid area (dorsal); APTD, anterior posterior thalamic nucleus; LDVL, laterodorsal thalamus; LGN, lateral geniculate nucleus; LPRM, lateral posterior thalamic nucleus; LPL, lateral posterior thalamic nucleus; PoT, posterior thalamus; PSTh, parasubthalamic nucleus; Re, nucleus reuniens; RT, reticular thalamic nucleus; SPF, subparafascicular thalamic nucleus. **Hypothalamus**: AH, anterior hypothalamus; DM, dorsomedial hypothalamus; LH, lateral hypothalamus; LPO, lateral preoptic nucleus; PaP, paraventricular posterior nucleus; Pe, periventricular hypothalamic nucleus; PeF, perifornical region; PH, posterior hypothalamus; PMD, premamillary nucleus (dorsal); PVN, paraventricular nucleus; MPA, median preoptic area; MPO, medial preoptic nucleus; Tc, tuber cinereum; Tu, tuberal nucleus; VMHa, anterior VMH; VMHdm, dorsomedial VMH; VMHvl, ventrolateral VMH; ZI, zona incerta.

Supplementary Table 3.

| | Mouse | | | | | | | Average weighted to no. of starter cells | Total no. of cells |
|---|---|---|---|---|---|---|---|---|---|
| | #1 | #2 | #3 | #4 | #5 | #6 | #7 | | |
| **Cortex** | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0.0 | 0 |
| **Striatal-like Structures** | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 0.5 | 2 |
| LS | | | | | | 1 | | 0.3 | 1 |
| CeA | | | | | | | 1 | 0.2 | 1 |
| **Pallidum-like Structures** | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0.0 | 0 |
| **Thalamus** | 3 | 1 | 0 | 2 | 2 | 0 | 0 | 1.0 | 8 |
| LGN | 3 | 1 | | 1 | 2 | | | 0.9 | 7 |
| Undefined thalamus | | | | 1 | | | | 0.1 | 1 |
| **Hypothalamus** | 0 | 0 | 0 | 2 | 2 | 0 | 0 | 0.6 | 4 |
| MPA | | | | | 1 | | | 0.2 | 1 |
| PH | | | | 1 | | | | 0.1 | 1 |
| ZI | | | | 1 | 1 | | | 0.3 | 2 |
| **density of starter cells in dPAG (n/mm$^2$)** | 70.2 | 59.8 | 21.5 | 82.1 | 94.9 | 172.0 | 103.7 | | |

dPAG, dorsal periaqueductal grey. **Striatal-like structures**: CeA, central amygdala; Ls, lateral septum. **Thalamus**: LGN, lateral geniculate nucleus. **Hypothalamus**: MPA, median preoptic area; PH, posterior hypothalamus; ZI, zona incerta.