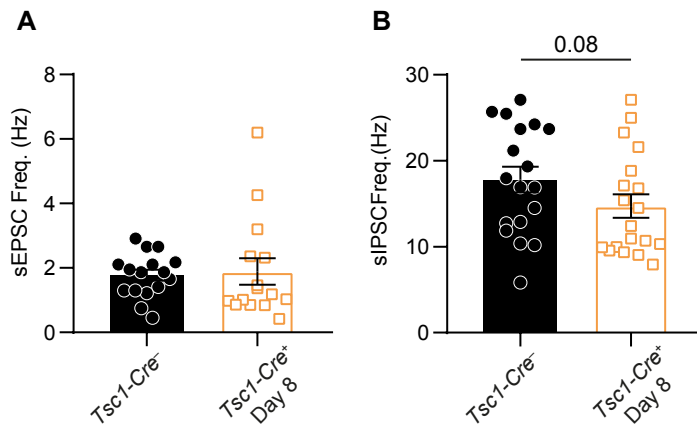
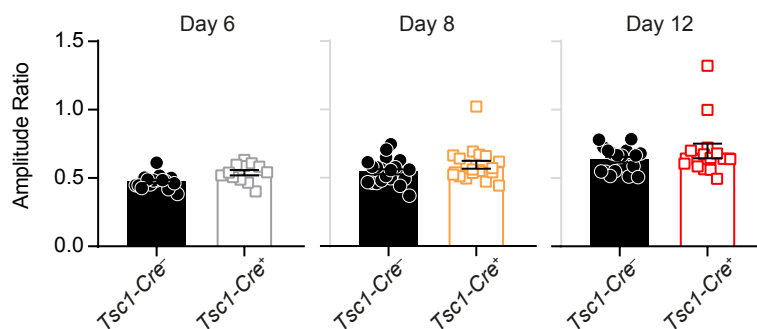


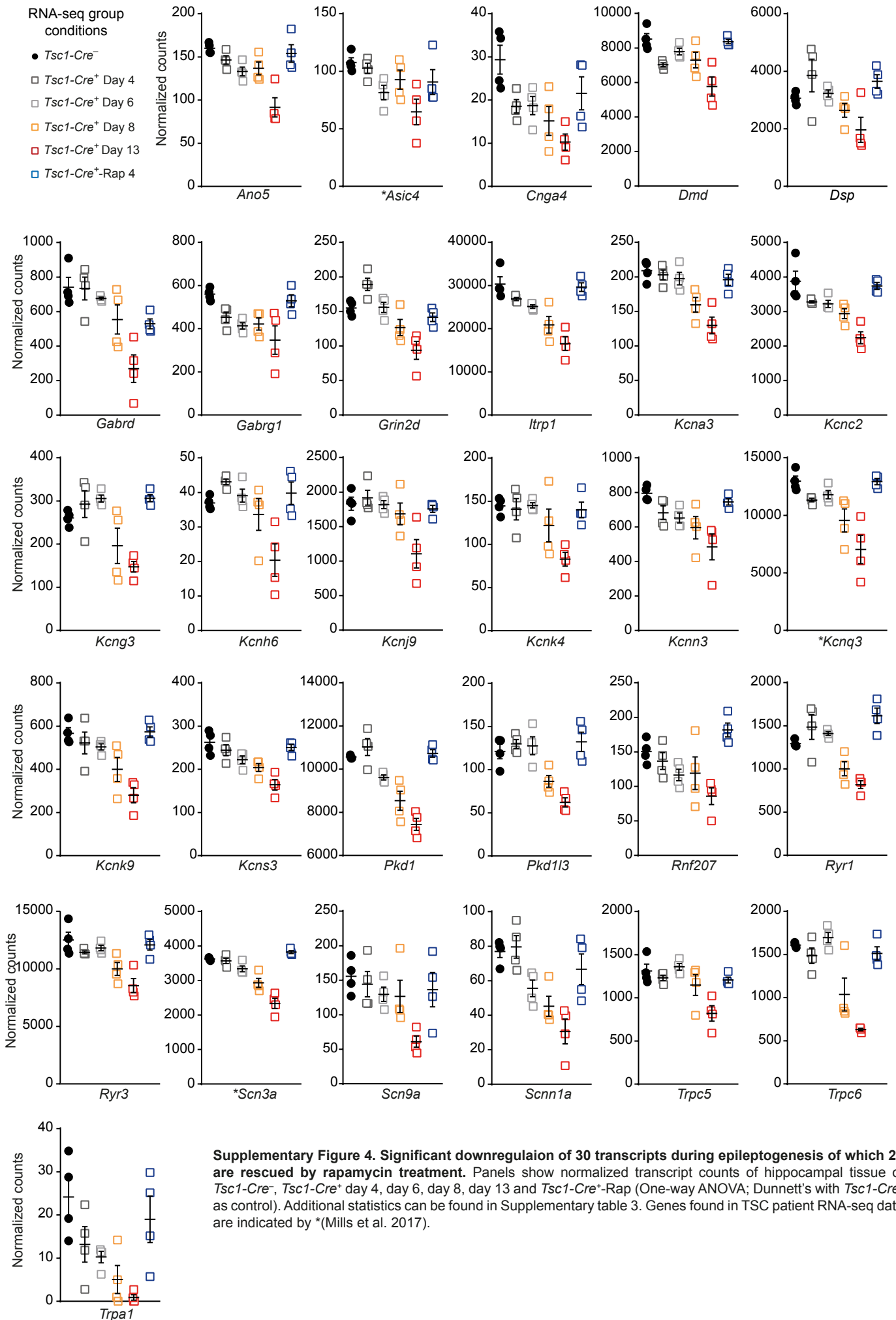
Supplementary Figure 1. Rescued cell capacitance and unaffected membrane resistance of CA1 pyramidal neurons upon early and late *in vivo* rapamycin treatment. Normalized (Cm; **A**) and membrane resistance (Rm; **B**) of CA1 pyramidal neurons of *Tsc1-Cre⁻* (black) and *Tsc1-Cre⁺* mice (red) recorded on day 12. Cm and Rm of the rapamycin-treated mice were normalized to their own *Tsc1-Cre⁻* control littermates and all measured on day 12 post gene deletion (*Tsc1-Cre⁻* n = 16, 3 mice; *Tsc1-Cre⁺* n = 15, 3 mice; Unpaired T-test; *Tsc1-Cre⁻* n = 30, 4 mice; vs *Tsc1-Cre⁺*-Rap: n = 26, 4 mice; and *Tsc1-Cre⁺*-Rap 8: n = 26, 4 mice. One-way ANOVA, Dunnett's with *Tsc1-Cre⁻* as control). Error bars indicate SEM. * P<0.05.



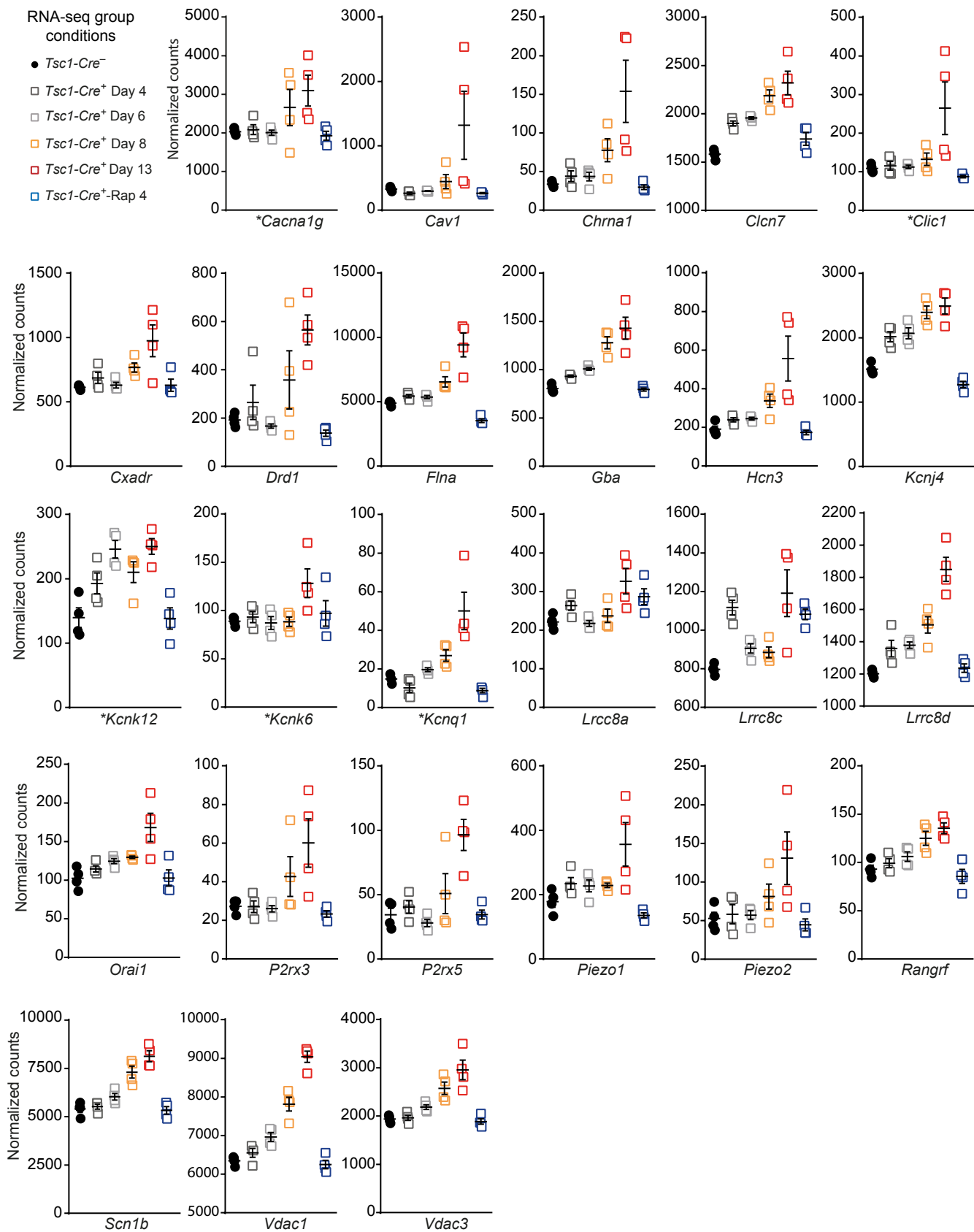
Supplementary Figure 2. Action potential dependent spontaneous excitatory and inhibitory post synaptic currents on day 8 after gene deletion. (A) Frequency of spontaneous excitatory post synaptic currents (sEPSC) and (B) spontaneous inhibitory post synaptic currents (sIPSC) measured on day 8 after *Tsc1* gene deletion. sEPSC: *Tsc1-Cre⁻* n = 16, 3 mice; *Tsc1-Cre⁺* n = 15, 3 mice; non-parametric Mann-Whitney U. sIPSC: *Tsc1-Cre⁻* n = 18, 3 mice; *Tsc1-Cre⁺* n = 19, 3 mice; non-parametric Mann-Whitney U. Error bars indicate SEM.



Supplementary Figure 3. Unaffected E/I amplitude ratio throughout epileptogenesis. The mEPSC/mIPSC amplitude ratio were recorded from the same cell (Day 6: *Tsc1-Cre⁻* n = 16, 3 mice; *Tsc1-Cre⁺* n = 12, 3 mice; independent T-test), day 8 (*Tsc1-Cre⁻* n = 26, 4 mice; *Tsc1-Cre⁺* n = 30, 6 mice; independent T-test) and day 12 (*Tsc1-Cre⁻* n = 17, 4 mice; *Tsc1-Cre⁺* n = 16, 3 mice; independent T-test). Error bars indicate SEM. v



Supplementary Figure 4. Significant downregulation of 30 transcripts during epileptogenesis of which 29 are rescued by rapamycin treatment. Panels show normalized transcript counts of hippocampal tissue of *Tsc1-Cre*⁻, *Tsc1-Cre*⁺ day 4, day 6, day 8, day 13 and *Tsc1-Cre*⁺-Rap (One-way ANOVA; Dunnett's with *Tsc1-Cre*⁻ as control). Additional statistics can be found in Supplementary table 3. Genes found in TSC patient RNA-seq data are indicated by * (Mills et al. 2017).



Supplementary Figure 5. Significant upregulation of 26 transcripts during epileptogenesis of which 25 are rescued by rapamycin treatment. Panels show normalized transcript counts of hippocampal tissue of *Tsc1-Cre*⁻, *Tsc1-Cre*⁺ day 4, day 6, day 8, day 13 and *Tsc1-Cre*⁺-Rap (One-way ANOVA; Dunnett's with *Tsc1-Cre*⁻ as control). Additional statistics can be found in Supplementary table 4. Genes found in TSC patient RNA-seq data are indicated by * (Mills et al. 2017).

Supplementary Table 1. Statistics of the passive and active membrane properties of *Tsc1-Cre*⁻ and *Tsc1-Cre*⁺ CA1 pyramidal neurons.

| | Day 6 | | | Day 8 | | | Day 12 | | |
|--|------------------------------|------------------------------|--------------------------------------|------------------------------|------------------------------|--|------------------------------|------------------------------|-----------------------------|
| | <i>Tsc1-Cre</i> ⁻ | <i>Tsc1-Cre</i> ⁺ | Statistics | <i>Tsc1-Cre</i> ⁻ | <i>Tsc1-Cre</i> ⁺ | Statistics | <i>Tsc1-Cre</i> ⁻ | <i>Tsc1-Cre</i> ⁺ | Statistics |
| V _{rest} (mV) | -48.29 ± 2.73 | -52.06 ± 2.27 | T (28) = 0.97; P = 0.34 | -47.13 ± 2.48 | -51.1 ± 2.045 | T(34) = 1.24; P = 0.22 | -50.06 ± 1.85 | -48.77 ± 1.87 | T(27) = 0.42; P = 0.68 |
| C _m (pF) | 111.37 ± 7.13 | 107.2 ± 4.25 | T (32) = 0.73; P = 0.47 | 109.5 ± 5.49 | 110.1 ± 2.96 | T(42) = 0.11; P = 0.91 | 113.9 ± 7.07 | 137.4 ± 7.17 | T(41) = 2.334; P = 0.025 |
| R _m (MΩ) | Med: 172.5 | Med: 179.5 | Mann-Whitney U = 118.5; P = 0.38 | 178.3 ± 7.62 | 189.9 ± 9.64 | T(42) = 0.95; P = 0.35 | 179.5 ± 7.48 | 179.4 ± 9.14 | T(41) = 0.0099; P = 0.99 |
| Rheobase (pA) | 91.76 ± 10.01 | 85.88 ± 5.36 | T(32) = 0.52; P = 0.61 | Med: 80 | Med: 80 | Mann-Whitney U = 205.5; P = 0.38 | 82.33 ± 4.8 | 97.93 ± 5.28 | T(40) = 1.62; P = 0.11 |
| Threshold (mV) | -46.31 ± 0.44 | -45.96 ± 0.97 | T (32) = 0.41; P = 0.68 | -44.43 ± 0.92 | -45.02 ± 0.80 | T (40) = 0.48; P = 0.63 | -45.21 ± 0.52 | -45.95 ± 0.83 | T (37) = 0.78; P = 0.44 |
| Peak Amplitude 1st AP at rheobase (mV) | Med: 97.97 | Med: 97.15 | Mann-Whitney U = 112; P = 0.28 | 98.61 ± 1.70 | 94.74 ± 1.12 | T (40) = 0.68; P = 0.51 | 98.13 ± 0.59 | 99.71 ± 1.11 | T (37) = 1.3; P = 0.19 |
| 10-90 % rise time (mV/ms) | 334.59 ± 9.23 | 341.81 ± 7.4 | T (32) = 0.61; P = 0.54 | 389.8 ± 18.66 | 383.80 ± 13.41 | T (40) = 0.266; P = 0.79 | 334.56 ± 6.8 | 345.43 ± 9.17 | T (37) = 0.96; P = 0.34 |
| 10-90 % decay time (mV/ms) | -76.89 ± 1.7 | -79.57 ± 1.73 | T (32) = 1.09; P = 0.28 | -66.68 ± 2.36 | -70.51 ± 1.82 | T (40) = 1.31; P = 0.197 | -75.702 ± 1.65 | -78.61 ± 1.61 | T (37) = 1.25; P = 0.22 |
| Half-width (ms) | 1.08 ± 0.017 | 1.08 ± 0.013 | T (32) = 0.12; P = 0.90 | 1.27 ± 0.04 | 1.243 ± 0.02 | T (40) = 0.92; P = 0.36 | 1.11 ± 0.023 | 1.18 ± 0.025 | T (37) = 2.31; P = 0.026 |
| I _h (%) | 6.68 ± 0.28 | 5.88 ± 0.4 | T (32) = 1.58; P = 0.122 | 6.10 ± 0.32 | 6.29 ± 0.31 | T (37) = 0.39; P = 0.69 | 6.58 ± 0.34 | 7.41 ± 0.51 | T (37) = 1.37; P = 0.18 |
| Latency (ms) | 22.61 ± 4.52 | 33.36 ± 3.21 | T(32) = 1.97; P = 0.06 | 51.31 ± 3.93 | 55.86 ± 3.06 | T(40) = 0.93; P = 0.36 | 30.86 ± 4.05 | 34.09 ± 3.98 | T(37) = 0.563; P = 0.58 |

Supplementary Table 2. Statistics of mEPSC and mIPSC kinetics of CA1 pyramidal neurons.

| | | Day 6 | | | Day 8 | | | Day 12 | | |
|------------------|---------------------------------|-----------------------------|-----------------------------|-------------------------------------|-----------------------------|-----------------------------|----------------------------|-----------------------------|-----------------------------|--------------------------------------|
| | | <i>Tsc1-Cre⁻</i> | <i>Tsc1-Cre⁺</i> | Statistics | <i>Tsc1-Cre⁻</i> | <i>Tsc1-Cre⁺</i> | Statistics | <i>Tsc1-Cre⁻</i> | <i>Tsc1-Cre⁺</i> | Statistics |
| mEPSC properties | Frequency (Hz) | 0.75 ± 0.077 | 0.6 ± 0.096 | T(39) = 0.21 P = .22 | 0.51 ± 0.052 | 0.82 ± 0.14 | T(54) = 1.89 P = 0.06 | 0.56 ± 0.053 | 0.46 ± 0.054 | T(34) = 1.30 P = 0.20 |
| | Amplitude (pA) | -9.65 ± 0.25 | -9.67 ± 0.29 | T(34) = 0.07; P = 0.94 | -11.21 ± 0.27 | -11.06 ± 0.43 | T(36) = 0.29; P = .78 | Med: -9.15 | Med: -8.36 | Mann-Whitney U = 84.0; P = 0.0047 |
| | Rise time (10-90% ms) | Med: 1.46 | Med: 1.67 | Mann-Whitney U = 88.0; P = 0.025 | 1.61 ± 0.41 | 1.79 ± 0.58 | T(36) = 1.15; P = 0.25 | 1.66 ± 0.09 | 1.78 ± 0.08 | T(36) = 1.02; P = 0.32 |
| | Decay time constant (10-90% ms) | 6.79 ± 0.34 | 6.95 ± 1.25 | T(34) = 0.346; P = 0.74 | 7.51 ± 0.23 | 7.6 ± 0.34 | T(36) = 0.20; P = 0.84 | 7.98 ± 0.33 | 6.71 ± 0.26 | T(36) = 2.91; P = 0.0061 |
| mIPSC properties | Frequency (Hz) | 5.69 ± 0.45 | 5.88 ± 0.46 | T(26) = 0.77 P = 0.77 | 5.47 ± 0.40 | 4.82 ± 0.29 | T(44) = 1.35 P = 0.18 | 4.52 ± 0.34 | 2.31 ± 0.31 | T(29) = 4.72 P = 0.0001 |
| | Amplitude (pA) | 20.42 ± 0.58 | 19.06 ± 0.68 | T(25) = 1.53; P = 0.14 | 19.45 ± 0.58 | 18.57 ± 0.58 | T(33) = 1.06; P = 0.29 | 15.27 ± 0.39 | 13.16 ± 0.38 | T(31) = 3.82; P = 0.0006 |
| | Rise time (10-90% ms) | 0.55 ± 0.024 | 0.61 ± 0.028 | T(25) = 1.78; P = 0.09 | 0.58 ± 0.03 | 0.66 ± 0.03 | T(33) = 1.79; P = 0.082 | 0.53 ± 0.02 | 0.75 ± 0.04 | T(31) = 4.98; P = 0.0001 |
| | Decay time constant (10-90% ms) | 11.85 ± 1.25 | 12.91 ± 1.31 | T(25) = 0.57; P = 0.57 | 14.08 ± 1.171 | 16.39 ± 1.3 | T(33) = 1.29; P = 0.2 | 13.57 ± 1.23 | 13.15 ± 1.28 | T(31) = 0.23; P = 0.81 |

Supplementary Table 3. Detailed statistics of downregulated DE ‘action potential’ genes overtime.

| | GeneID | Gene | One-way ANOVA (Dunnett's post hoc) | <i>Tsc1-Cre⁻</i> | | <i>Tsc1-Cre⁺-Day 4</i> | | | <i>Tsc1-Cre⁺-Day 6</i> | | | <i>Tsc1-Cre⁺-Day 8</i> | | | <i>Tsc1-Cre⁺-Day 13</i> | | | <i>Tsc1-Cre⁺-Rap 4</i> | | |
|----|------------------------|---------------------------|---------------------------------------|-----------------------------|---------|-----------------------------------|--------|-------|-----------------------------------|--------|-------|-----------------------------------|---------|--------|------------------------------------|---------|--------|-----------------------------------|---------|------|
| | | | | Mean | SEM | Mean | SEM | Sig | Mean | SEM | Sig | Mean | SEM | Sig | Mean | SEM | Sig | Mean | SEM | Sig |
| 1 | ENSMUSG 0000055489 | <i>Ano5</i> | F(5, 18) = 10.65 P < 0.0001 | 160.10 | 2.98 | 146.62 | 4.76 | 0.59 | 133.26 | 5.12 | 0.07 | 136.86 | 7.33 | 0.14 | 91.61 | 11.07 | 0.0001 | 154.04 | 10.14 | 0.96 |
| 2 | ENSMUSG 00000033007 | * <i>Asic4</i> | F(5, 18) = 3.68 P = 0.0180 | 107.67 | 4.09 | 102.61 | 4.40 | 0.98 | 81.50 | 6.25 | 0.12 | 92.63 | 8.37 | 0.56 | 64.68 | 11.18 | 0.0059 | 90.64 | 10.86 | 0.45 |
| 3 | ENSMUSG 00000030897 | <i>Cnga4</i> | F(5, 18) = 5.21 P = 0.0039 | 29.38 | 3.33 | 18.56 | 1.55 | 0.054 | 18.74 | 2.11 | 0.059 | 15.18 | 3.35 | 0.0091 | 10.28 | 1.87 | 0.0006 | 21.58 | 3.82 | 0.22 |
| 4 | ENSMUSG 00000045103 | <i>Dmd</i> | F(5, 18) = 8.99 P = 0.0002 | 8514.04 | 321.34 | 7027.31 | 195.35 | 0.02 | 7792.36 | 195.68 | 0.44 | 7295.8 | 453.93 | 0.07 | 5763.88 | 556.28 | 0.0001 | 8362.87 | 125.34 | 0.99 |
| 5 | ENSMUSG 00000054889 | <i>Dsp</i> | F(5, 18) = 4.41 P = 0.008 | 3063.25 | 101.93 | 3855.32 | 564.98 | 0.33 | 3227.30 | 123.76 | 0.99 | 2640.59 | 242.46 | 0.82 | 1963.39 | 434.10 | 0.1 | 3646.74 | 236.32 | 0.6 |
| 6 | ENSMUSG 00000029054 | <i>Gabrd</i> (GABAδ) | F(5, 18) = 8.63 P = 0.0003 | 741.48 | 57.51 | 733.67 | 66.17 | 0.99 | 675.78 | 7.62 | 0.90 | 554.32 | 84.23 | 0.15 | 269.23 | 80.07 | 0.0002 | 529.08 | 28.23 | 0.08 |
| 7 | ENSMUSG 00000001260 | <i>Gabrg1</i> (GABAγ1) | F(5, 18) = 5.42 P = 0.003 | 559.91 | 13.86 | 453.22 | 23.78 | 0.13 | 413.22 | 14.84 | 0.027 | 421.94 | 27.96 | 0.039 | 347.15 | 65.67 | 0.0014 | 529.34 | 28.18 | 0.94 |
| 8 | ENSMUSG 00000002771 | <i>Grin2d</i> (NMDA2D) | F(5, 18) = 12.17 P < 0.0001 | 155.13 | 5.17 | 189.14 | 9.00 | 0.06 | 155.92 | 7.43 | 0.99 | 126.71 | 11.62 | 0.15 | 93.69 | 13.04 | 0.0008 | 141.65 | 6.22 | 0.75 |
| 9 | ENSMUSG 00000030102 | <i>Itpr1</i> | F(5, 18) = 16.19 P < 0.0001 | 30329.09 | 1696.68 | 26877.54 | 374.44 | 0.26 | 25134.55 | 419.17 | 0.04 | 20907.05 | 1935.79 | 0.0004 | 16556.27 | 1593.88 | 0.0001 | 29643.23 | 1002.85 | 0.99 |
| 10 | ENSMUSG 00000047959 | <i>Kcna3</i> (Kv1.3) | F(5, 18) = 11.38 P < 0.0001 | 208.86 | 7.28 | 203.02 | 6.97 | 0.98 | 197.49 | 8.96 | 0.84 | 159.65 | 10.73 | 0.0006 | 129.67 | 12.12 | 0.0001 | 195.86 | 8.11 | 0.77 |
| 11 | ENSMUSG 00000035681 | <i>Kcnc2</i> (Kv3.2) | F(5, 18) = 13.63 P < 0.0001 | 3879.38 | 287.63 | 3276.40 | 31.48 | 0.061 | 3222.38 | 105.52 | 0.038 | 2935.95 | 143.54 | 0.002 | 2239.89 | 169.99 | 0.0001 | 3739.73 | 98.43 | 0.96 |
| 12 | ENSMUSG 00000045053 | <i>Kcng3</i> (Kv6.3) | F(5, 18) = 8.62 P = 0.0003 | 260.73 | 8.51 | 292.83 | 31.10 | 0.76 | 305.60 | 8.17 | 0.49 | 196.21 | 41.01 | 0.19 | 147.60 | 12.38 | 0.009 | 306.39 | 8.03 | 0.48 |
| 13 | ENSMUSG 00000001901 | <i>Kcnh6</i> (Kv11.2) | F(5, 18) = 6.63 P = 0.001 | 36.98 | 0.94 | 43.09 | 0.84 | 0.51 | 39.09 | 1.89 | 0.98 | 33.62 | 4.58 | 0.9 | 20.38 | 4.68 | 0.006 | 39.77 | 3.23 | 0.95 |
| 14 | ENSMUSG 00000038026 | <i>Kcnj9</i> (Kir3.3) | F(5, 18) = 5.56 P = 0.0029 | 1831.54 | 96.41 | 1917.66 | 107.19 | 0.98 | 1817.90 | 57.07 | 0.99 | 1685.28 | 157.04 | 0.87 | 1105.95 | 205.97 | 0.002 | 1756.87 | 50.24 | 0.99 |
| 15 | ENSMUSG 00000024957 | <i>Kcnk4</i> (TRAAK) | F(5, 18) = 5.10 P = 0.0044 | 144.77 | 4.81 | 140.84 | 12.32 | 0.99 | 145.24 | 3.08 | 0.99 | 121.99 | 19.00 | 0.44 | 82.91 | 8.06 | 0.003 | 139.97 | 9.09 | 0.99 |
| 16 | ENSMUSG 00000036760 | <i>Kcnk9</i> (TASK3) | F(5, 18) = 9.37 P = 0.0002 | 567.46 | 25.65 | 522.79 | 50.46 | 0.86 | 504.42 | 14.10 | 0.64 | 400.07 | 55.61 | 0.021 | 280.46 | 35.23 | 0.0002 | 573.57 | 23.93 | 0.99 |
| 17 | ENSMUSG 00000000794 | <i>Kcnn3</i> (SK3) | F(5, 18) = 5.60 P = 0.002 | 794.42 | 21.07 | 682.28 | 39.94 | 0.33 | 651.80 | 28.90 | 0.15 | 595.73 | 64.41 | 0.029 | 484.91 | 75.16 | 0.0008 | 745.06 | 17.77 | 0.91 |
| 18 | ENSMUSG 00000056258 | * <i>Kcnq3</i> (Kv7.3) | F(5, 18) = 10.70 P < 0.0001 | 12972.57 | 431.86 | 11324.96 | 152.11 | 0.35 | 11792.91 | 358.06 | 0.64 | 9553.82 | 997.13 | 0.017 | 7042.54 | 1234.75 | 0.0001 | 12938.20 | 269.68 | 0.99 |
| 19 | ENSMUSG 00000043673 | <i>Kcns3</i> (Kv9.3) | F(5, 18) = 11.33 P < 0.0001 | 262.60 | 13.25 | 244.32 | 12.42 | 0.64 | 222.33 | 9.01 | 0.064 | 204.20 | 9.23 | 0.005 | 164.23 | 12.24 | 0.0001 | 250.82 | 7.20 | 0.89 |
| 20 | ENSMUSG 00000032855 | <i>Pkd1</i> | F(5, 18) = 25.54 P < 0.0001 | 10564.87 | 36.74 | 11028.39 | 393.84 | 0.66 | 9615.08 | 115.35 | 0.1 | 8538.27 | 439.17 | 0.0003 | 7441.26 | 278.32 | 0.0001 | 10728.32 | 174.77 | 0.99 |
| 21 | ENSMUSG 00000048827 | <i>Pkd1l3</i> | F(5, 18) = 12.31 P < 0.0001 | 121.20 | 8.46 | 129.85 | 5.22 | 0.91 | 127.70 | 10.42 | 0.97 | 86.56 | 6.87 | 0.03 | 62.05 | 5.31 | 0.0004 | 132.25 | 11.15 | 0.86 |

| | | | | | | | | | | | | | | | | | | | | |
|----|------------------------|---|---|----------------|--------------|----------------|--------------|-------------|----------------|--------------|-------------|----------------|---------------|---------------|----------------|---------------|---------------|----------------|--------------|-------------|
| 22 | ENSMUSG 00000058498 | <i>*Rnf207</i> | F(5, 18) = 5.92 P = 0.002 | 150.62 | 8.58 | 136.75 | 12.07 | 0.92 | 116.48 | 23.65 | 0.29 | 119.09 | 23.65 | 0.36 | 85.71 | 12.11 | 0.013 | 181.85 | 9.94 | 0.37 |
| 23 | ENSMUSG 00000030592 | <i>Ryr1</i> | F(5, 18) = 14.70 P < 0.0001 | 1293.03 | 19.72 | 1485.25 | 142.57 | 0.32 | 1409.94 | 21.38 | 0.74 | 1001.65 | 81.12 | 0.069 | 818.23 | 44.66 | 0.002 | 1616.77 | 89.63 | 0.039 |
| 24 | ENSMUSG 00000057378 | <i>Ryr3</i> | F(5, 18) = 9.72 P = 0.0001 | 12517.11 | 667.81 | 11432.48 | 121.14 | 0.39 | 11816.40 | 225.41 | 0.75 | 9993.19 | 562.78 | 0.007 | 8552.84 | 600.93 | 0.0001 | 12092.26 | 456.70 | 0.95 |
| 25 | ENSMUSG 00000057182 | <i>*Scn3a</i> (Nav1.3 α - subunit) | F(5, 18) = 33.98 P < 0.0001 | 3620.85 | 19.05 | 3567.24 | 75.04 | 0.99 | 3339.37 | 85.39 | 0.17 | 2931.03 | 130.10 | 0.0003 | 2335.78 | 146.38 | 0.0001 | 3823.54 | 41.15 | 0.43 |
| 26 | ENSMUSG 00000075316 | <i>Scn9a</i> | F(5, 18) = 3.64 P = 0.0189 | 155.65 | 12.64 | 144.30 | 18.25 | 0.98 | 129.71 | 10.29 | 0.74 | 126.76 | 23.31 | 0.66 | 61.13 | 8.09 | 0.005 | 136.37 | 24.92 | 0.89 |
| 27 | ENSMUSG 00000030340 | <i>Scnn1a</i> | F(5, 18) = 9.04 P = 0.0002 | 76.91 | 3.43 | 79.58 | 6.54 | 0.99 | 55.58 | 4.75 | 0.10 | 45.16 | 5.82 | 0.0097 | 30.61 | 7.19 | 0.0003 | 66.64 | 8.82 | 0.67 |
| 28 | ENSMUSG 00000041710 | <i>Trpc5</i> | F(5, 18) = 6.88 P = 0.0009 | 1311.73 | 78.23 | 1231.29 | 30.47 | 0.89 | 1359.62 | 38.23 | 0.98 | 1147.94 | 120.37 | 0.39 | 819.69 | 88.93 | 0.0007 | 1207.34 | 33.77 | 0.76 |
| 29 | ENSMUSG 00000031997 | <i>Trpc6</i> | F(5, 18) = 18.71 P < 0.0001 | 1609.29 | 12.99 | 1485.21 | 89.65 | 0.82 | 1695.72 | 60.83 | 0.94 | 1036.36 | 189.68 | 0.002 | 630.99 | 13.84 | 0.0001 | 1512.63 | 77.88 | 0.92 |
| 30 | ENSMUSG 00000032769 | <i>Trpa1</i> | F(5, 18) = 5.59 P = 0.0028 | 24.21 | 4.67 | 13.20 | 4.10 | 0.16 | 10.27 | 1.34 | 0.057 | 5.06 | 3.24 | 0.0069 | 0.89 | 0.65 | 0.0012 | 18.99 | 5.37 | 0.76 |

Supplementary Table 4. Detailed statistics of upregulated DE ‘action potential’ genes overtime.

| | GeneID | Gene | One-way ANOVA (Dunnet's post hoc) | <i>Tsc1-Cre⁻</i> | | <i>Tsc1-Cre⁺-Day 4</i> | | | <i>Tsc1-Cre⁺-Day 6</i> | | | <i>Tsc1-Cre⁺-Day 8</i> | | | <i>Tsc1-Cre⁺-Day 13</i> | | | <i>Tsc1-Cre⁺-Rap 4</i> | | |
|----|------------------------|--|---|-----------------------------|--------------|-----------------------------------|---------------|-------------|-----------------------------------|----------------|---------------|-----------------------------------|---------------|--------------|------------------------------------|---------------|---------------|-----------------------------------|---------------|-------------|
| | | | | Mean | SEM | Mean | SEM | Sig | Mean | SEM | Sig | Mean | SEM | Sig | Mean | SEM | Sig | Mean | SEM | Sig |
| 1 | ENSMUSG 00000020866 | <i>*Cacna1g</i> | F(5, 18) = 3.21 P = 0.0302 | 2032.02 | 40.48 | 2085.58 | 124.97 | 0.99 | 2006.47 | 68.51 | 0.99 | 2657.52 | 467.56 | 0.34 | 3095.98 | 397.22 | 0.04 | 1930.36 | 115.20 | 0.99 |
| 2 | ENSMUSG 00000007655 | <i>Cav1</i> | F(5, 18) = 22.63 P = 0.02 | 330.3 | 15.64 | 263.4 | 17.38 | 0.99 | 287.5 | 6.22 | 0.99 | 444.7 | 107.8 | 0.99 | 1319 | 528.9 | 0.022 | 264 | 9.61 | 0.99 |
| 3 | ENSMUSG 00000027107 | <i>Chrna1</i> | F(5, 18) = 6.93 P = 0.0009 | 33.61 | 1.68 | 43.98 | 7.02 | 0.99 | 43.65 | 5.56 | 0.99 | 77.71 | 14.86 | 0.32 | 153.87 | 40.30 | 0.0008 | 29.66 | 2.89 | 0.99 |
| 4 | ENSMUSG 00000036636 | <i>Cln7</i> | F(5, 18) = 18.47 P < 0.0001 | 1582.31 | 23.93 | 1900.81 | 25.10 | 0.009 | 1958.03 | 12.02 | 0.0025 | 2187.02 | 61.79 | 0.0001 | 2320.47 | 122.01 | 0.0001 | 1740.86 | 65.59 | 0.31 |
| 5 | ENSMUSG 00000007041 | <i>*Clic1</i> | F(5, 18) = 4.89 P = 0.0053 | 108.76 | 5.01 | 115.62 | 11.44 | 0.99 | 112.41 | 4.46 | 0.99 | 132.55 | 15.82 | 0.96 | 264.65 | 67.93 | 0.006 | 87.56 | 3.04 | 0.98 |
| 6 | ENSMUSG 00000022865 | <i>Cxadr</i> | F(5, 18) = 5.46 P = 0.0031 | 613.55 | 8.41 | 686.24 | 42.45 | 0.85 | 629.46 | 21.75 | 0.99 | 766.95 | 35.3 | 0.27 | 973.92 | 123.27 | 0.0019 | 629.2 | 46.95 | 0.99 |
| 7 | ENSMUSG 00000021478 | <i>Drd1</i> | F(5, 18) = 6.45 P = 0.0013 | 192.06 | 13.44 | 265.31 | 71.29 | 0.87 | 166.99 | 8.82 | 0.99 | 358.08 | 120.38 | 0.26 | 565.06 | 62.32 | 0.002 | 137.64 | 12.91 | 0.95 |
| 8 | ENSMUSG 00000031328 | <i>Flna</i> | F5, 18) = 22.34 P < 0.0001 | 4889.15 | 88.28 | 5441.7 | 121.22 | 0.82 | 5361.06 | 124.155 | 0.89 | 6547.12 | 406.04 | 0.048 | 9417.26 | 918.61 | 0.0001 | 3532.96 | 150.75 | 0.13 |
| 9 | ENSMUSG 00000028048 | <i>Gba</i> | F(5, 18) = 22.48 P < 0.0001 | 806.10 | 20.25 | 930.54 | 9.75 | 0.38 | 1008.1 | 13.6 | 0.06 | 1280.5 | 62.72 | 0.0001 | 1429.8 | 114.61 | 0.0001 | 794.27 | 16.68 | 0.99 |
| 10 | ENSMUSG 00000028051 | <i>Hcn3</i> | F(5, 18) = 8.02 P = 0.0004 | 190.42 | 15.97 | 239.16 | 10.55 | 0.93 | 245.33 | 6.78 | 0.89 | 337.75 | 34.60 | 0.18 | 556.26 | 115.90 | 0.0003 | 173.14 | 11.16 | 0.99 |
| 11 | ENSMUSG 00000044216 | <i>Kcnj4</i> (Kir2.3) | F(5, 18) = 32.54 P < 0.0001 | 1511.66 | 42.21 | 2016.42 | 79.21 | 0.0022 | 2070.06 | 85.74 | 0.0009 | 2395.53 | 97.97 | 0.0001 | 2494.50 | 123.75 | 0.0001 | 1274.66 | 50.12 | 0.21 |
| 12 | ENSMUSG 00000050138 | *Kcnk12 (2PK channel) | F(5, 18) = 10.74 P < 0.0001 | 139.50 | 15.23 | 192.84 | 16.21 | 0.08 | 245.89 | 13.53 | 0.0004 | 210.17 | 16.17 | 0.016 | 250.23 | 12.13 | 0.0003 | 138.26 | 16.51 | 0.99 |
| 13 | ENSMUSG 00000046410 | <i>*Kcnk6</i> (TWIK2, TOSS) | F(5, 18) = 2.94 P = 0.0409 | 88.98 | 2.23 | 93.27 | 5.64 | 0.99 | 87.18 | 6.60 | 0.99 | 88.54 | 4.81 | 0.99 | 128.26 | 14.89 | 0.02 | 97.15 | 13.16 | 0.95 |
| 14 | ENSMUSG 00000009545 | <i>*Kcnq1</i> (Kv7.1) | F(5, 18) = 12.77 P < 0.0001 | 14.87 | 1.05 | 10.24 | 2.40 | 0.9 | 19.67 | 0.94 | 0.89 | 26.98 | 2.95 | 0.21 | 50.04 | 9.65 | 0.0001 | 8.80 | 1.16 | 0.77 |
| 15 | ENSMUSG 00000007476 | <i>Lrrc8a</i> | F(5, 18) = 5.18 P = 0.0041 | 221.02 | 9.07 | 263.56 | 12.18 | 0.38 | 217.43 | 7.50 | 0.99 | 237.11 | 17.28 | 0.96 | 326.72 | 32.88 | 0.0036 | 286.55 | 20.55 | 0.086 |
| 16 | ENSMUSG 00000054720 | <i>Lrrc8c</i> | F(5, 18) = 5.95 P = 0.002 | 796.38 | 13.76 | 1117.23 | 37.96 | 0.002 | 905.18 | 24.28 | 0.51 | 884.602 | 27.77 | 0.69 | 1191.66 | 120.95 | 0.0004 | 1081.92 | 26.9 | 0.007 |
| 17 | ENSMUSG 00000046079 | <i>Lrrc8d</i> (VRACs) | F(5, 18) = 27.77 P < 0.0001 | 1201.48 | 10.76 | 1357.44 | 51.09 | 0.09 | 1378.90 | 19.79 | 0.046 | 1505.41 | 50.89 | 0.0007 | 1849.74 | 75.18 | 0.0001 | 1236.02 | 26.52 | 0.97 |
| 18 | ENSMUSG 00000049686 | <i>Orai1</i> | F(5, 18) = 6.93 P = 0.0009 | 102.48 | 6.81 | 114.49 | 3.96 | 0.90 | 124.69 | 3.31 | 0.43 | 129.64 | 1.49 | 0.24 | 168.28 | 18.28 | 0.0005 | 102.84 | 10.43 | 0.99 |
| 19 | ENSMUSG 00000027071 | <i>P2rx3</i> | F(5, 18) = 4.40 P = 0.0086 | 27.28 | 1.73 | 27.04 | 3.06 | 0.99 | 26.04 | 1.65 | 0.99 | 42.66 | 10.26 | 0.39 | 60.09 | 12.51 | 0.013 | 23.33 | 1.63 | 0.99 |
| 20 | ENSMUSG 00000005950 | <i>P2rx5</i> | F(5, 18) = 8.37 P = 0.0003 | 34.48 | 5.09 | 40.48 | 4.85 | 0.98 | 28.00 | 2.80 | 0.98 | 50.90 | 15.51 | 0.55 | 96.48 | 12.06 | 0.0004 | 34.56 | 3.49 | 0.99 |
| 21 | ENSMUSG 00000014444 | <i>Piezo1</i> | F(5, 18) = 5.79 P = 0.0023 | 178.45 | 17.64 | 234.35 | 18.60 | 0.58 | 227.05 | 18.53 | 0.69 | 228.79 | 6.67 | 0.67 | 356.22 | 67.72 | 0.003 | 135.59 | 7.72 | 0.78 |

| | | | | | | | | | | | | | | | | | | | | |
|----|------------------------|--|---|----------------|---------------|----------------|---------------|-------------|----------------|---------------|-------------|----------------|---------------|---------------|----------------|---------------|---------------|----------------|---------------|-------------|
| 22 | ENSMUSG 00000041482 | <i>Piezo2</i> | F(5, 18) = 3.52 P = 0.0216 | 52.75 | 8.04 | 58.30 | 12.30 | 0.99 | 57.11 | 5.83 | 0.99 | 81.16 | 16.30 | 0.65 | 130.81 | 33.98 | 0.01 | 44.57 | 7.67 | 0.99 |
| 23 | ENSMUSG 00000032892 | <i>Rangrf</i> | F5, 18) = 11.04 P < 0.0001 | 93.01 | 4.19 | 99.26 | 4.66 | 0.90 | 106.11 | 5.0 | 0.38 | 125.07 | 7.27 | 0.0044 | 135.36 | 7.26 | 0.0003 | 85.48 | 7.26 | 0.82 |
| 24 | ENSMUSG 00000019194 | <i>Scn1b</i> (Nav1.1 β- subunit) | F(5, 18) = 28.35 P < 0.0001 | 5403.76 | 174.34 | 5522.19 | 128.05 | 0.99 | 6030.54 | 168.23 | 0.19 | 7310.30 | 306.87 | 0.0001 | 8132.58 | 281.72 | 0.0001 | 5332.62 | 197.50 | 0.99 |
| 25 | ENSMUSG 00000020402 | <i>Vdac1</i> | F(5, 18) = 74.93 P < 0.0001 | 6347.18 | 57.68 | 6553.16 | 113.92 | 0.67 | 6965.88 | 115.99 | 0.01 | 7814.14 | 177.58 | 0.0001 | 9039.30 | 145.04 | 0.0001 | 6249.80 | 106.90 | 0.97 |
| 26 | ENSMUSG 00000008892 | <i>Vdac3</i> | F(5, 18) = 16.28 P < 0.0001 | 1938.86 | 37.80 | 1962.13 | 51.54 | 0.99 | 2187.14 | 48.93 | 0.35 | 2575.43 | 128.77 | 0.002 | 2954.60 | 203.07 | 0.0001 | 1888.15 | 57.47 | 0.99 |