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***SYNGAP1* heterozygosity disrupts sensory processing by reducing touch-related activity within somatosensory cortex circuits**

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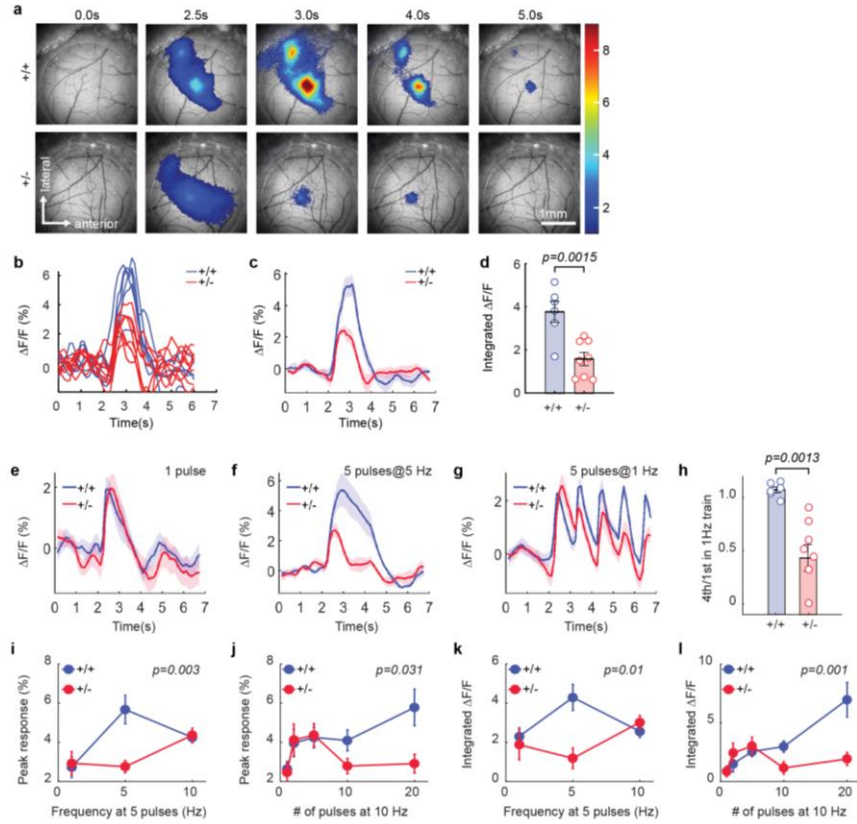
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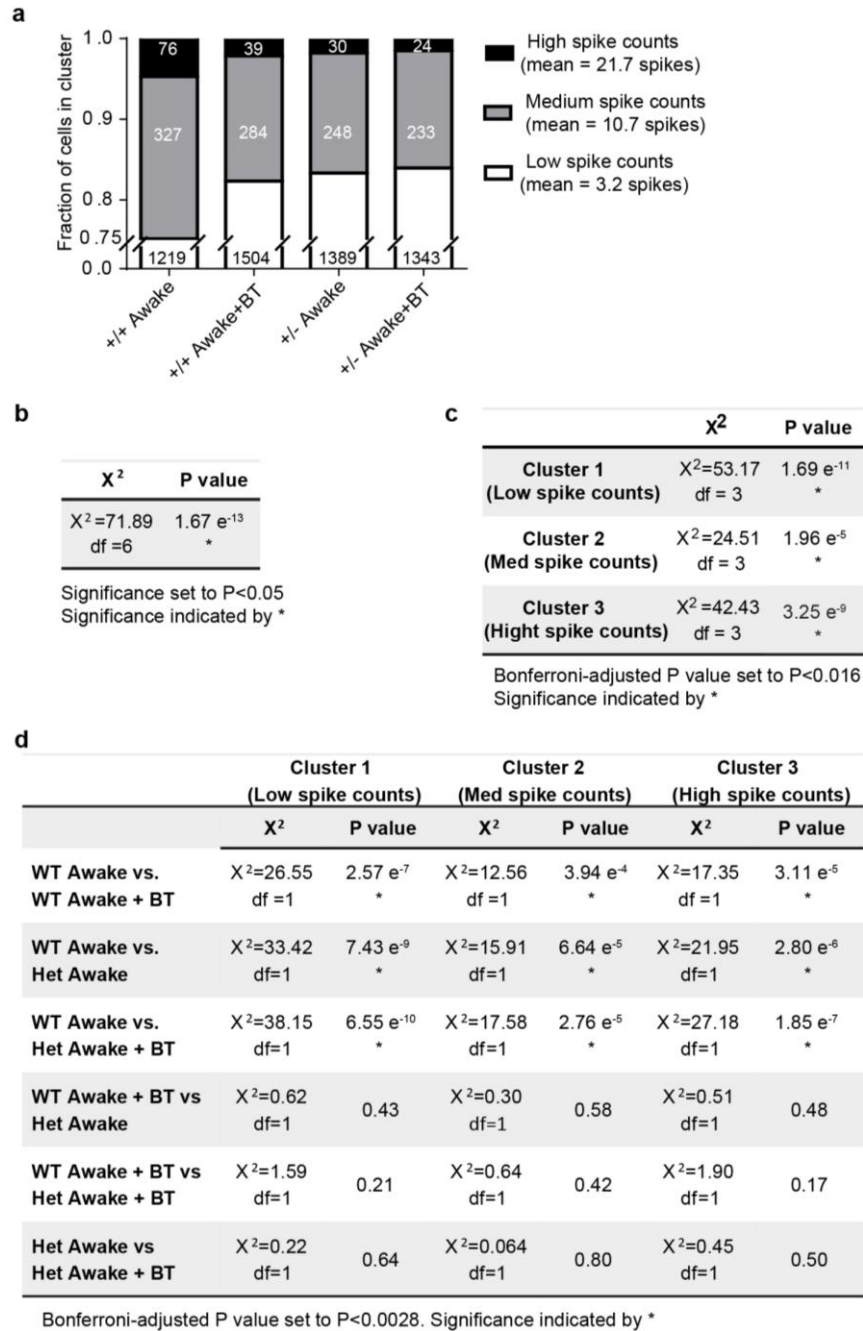
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Supplementary Figure 1

Impaired sensory-evoked GCaMP6s dynamics in SSC of *Syngap1* mice

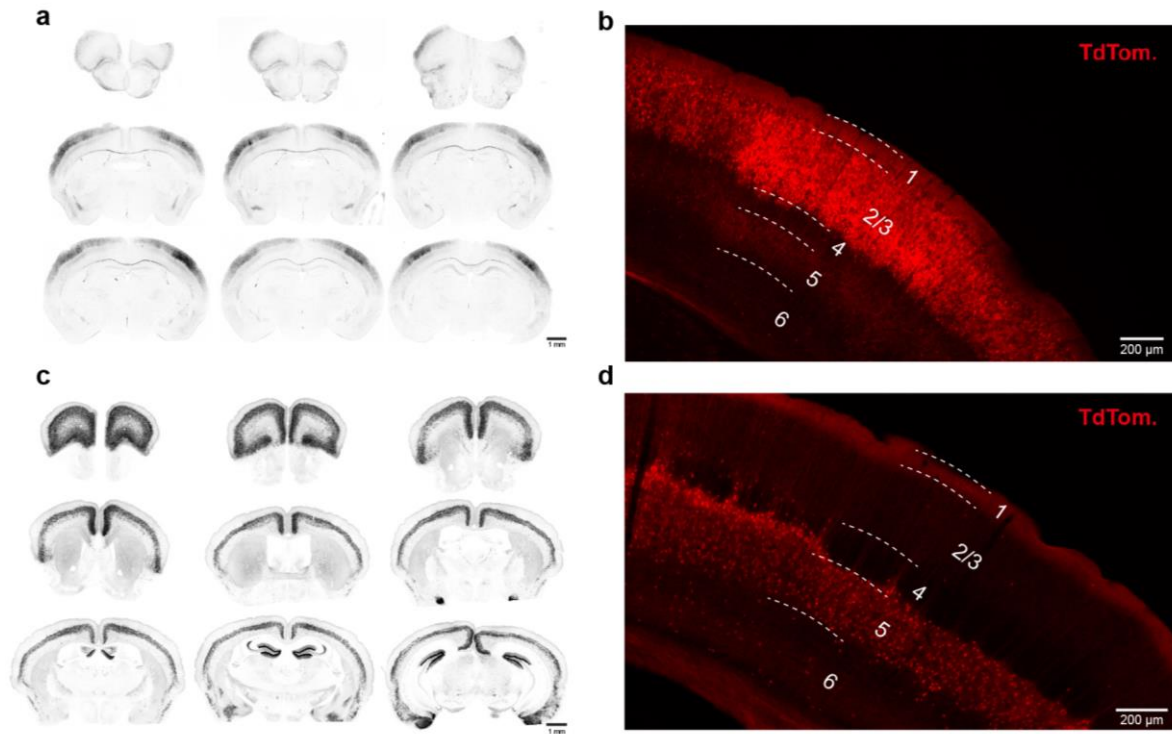
(a) Example wide-field $\Delta F/F$ images superimposed over craniotomy pictures of WT and Het mice. (b-d) Traces of individual (b) and averaged (c) GCaMP6s responses, as well as a scatter plot showing the integrated $\Delta F/F$ signal amplitude (d) in response to 5 pulses at 5 Hz (Student's t-test $t(12)=4.09$ $p=0.0015$). (e-g) Average time courses of GCaMP6s dynamics in response to a single whisker stimulation (e), 5 pulses at 5 Hz (f) and 5 pulses at 1 Hz (g) stimulation protocols. (h) Scatter plot showing ratio of fourth pulse to first pulse in 5 pulse at 1 Hz paradigm (Student's t-test $t(12)=4.16$ $p=0.0013$). Peak (i, j) and integrated (k, l) $\Delta F/F$ responses for increasing number of pulses at 10 Hz (j, l) and increasing frequency of pulses at 5 pulses (i, k) (2-way RM-ANOVA : (i) $F(1,12)=3.90$ $p=0.07$ for genotype and $F(2,24)=7.44$ $p=0.003$ for genotype and frequency interaction; (j) $F(1,12)=2.27$ $p=0.16$ for genotype and $F(4,48)=2.92$ $p=0.031$ for genotype and frequency interaction; (k) $F(1,12)=7.11$ $p=0.02$ for genotype and $F(2,24)=4.92$ $p=0.01$ for genotype and frequency interaction; (l) $F(1,12)=4.22$ $p=0.06$ for genotype and $F(4,48)=5.96$ $p=0.001$ for genotype and frequency interaction). Open circles represent animal means, black lines or closed circles indicate population means and error bars or shaded areas indicate SEMs. Data were obtained $n=6$ WT and $n=8$ Het mice from two cohorts of animals. All statistical tests were two-sided.



Supplementary Figure 2

Cluster analysis of ongoing and whisker-generated spike counts in SSC L2/3 neurons from awake *Syngap1* mice

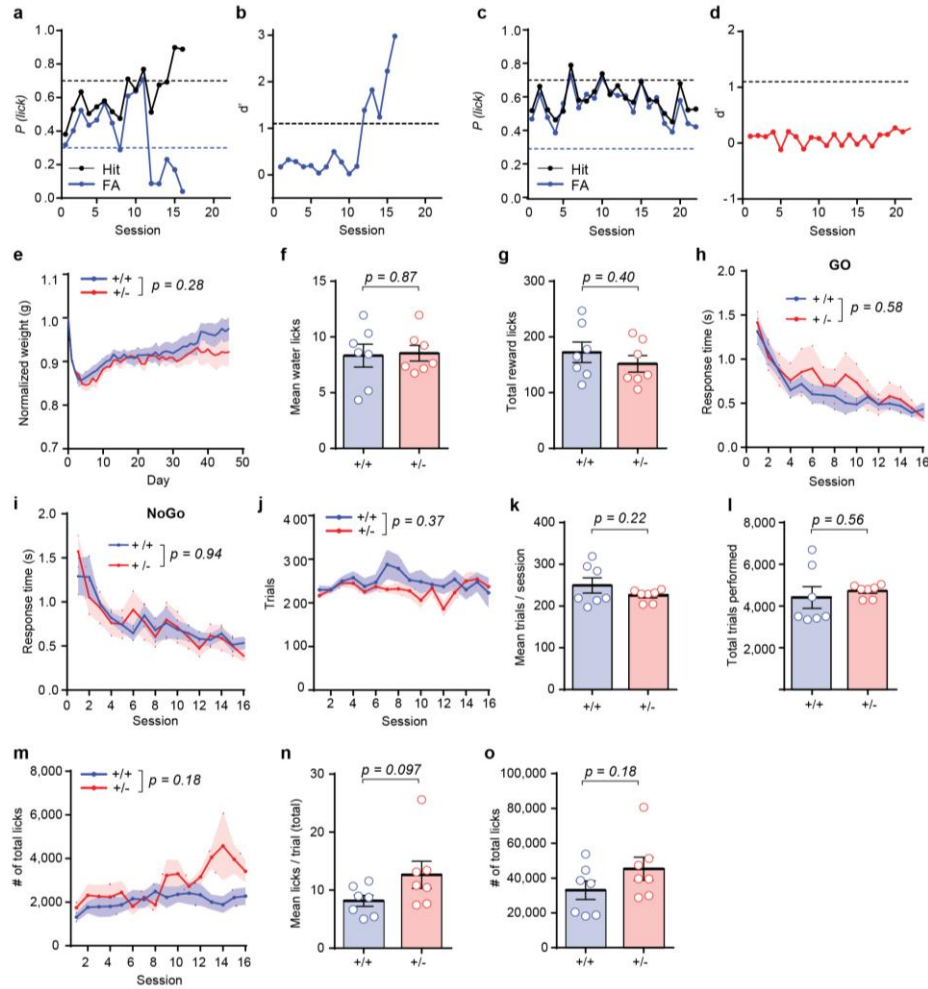
(a) Relating to Fig. 2, graph showing the fraction of neurons clustered into low- (white), medium- (gray), and high-spiking (black) activity clusters. Mean spike count for each cluster is noted in the graph legend. Number of neurons in each cluster is denoted on the bar graph for each group. (b) Results of Chi-square analysis showing overall effect on how the neurons clustered across the four groups. (c) Results of Chi-square analyses demonstrating differences in each of the three activity clusters when comparing the four experimental groups. (d) Results of Chi-square analyses comparing the four groups to each other for all three activity clusters.



Supplementary Figure 3

Cell-type-specific recombination in Cux2-Cre^{ERT2} and Rbp4-Cre lines

(a) Representative coronal brain sections of a Cux2-Cre^{ERT2}+/+;Ai9+/- mouse, where Cre activity is reported by red fluorescence (black) from the TdTomato expression at PND60 (TMX injection at PND2). **(b)** Representative coronal brain section from a Cux2-Cre^{ERT2}+/+;Ai9+/- mouse, where Cre activity is reported by TdTomato expression in the somatosensory cortex (red) at PND60 (TMX injection at PND2). **(c)** Representative coronal brain sections of a Rbp4Cre+/+;Ai6+/- mouse, where Cre activity is reported by green fluorescence (black) from the zsGreen expression at PND60. **(d)** Representative coronal brain section from a Rbp4Cre+/+;Ai9+/- mouse where Cre activity is reported by TdTomato expression in the somatosensory cortex (red) at PND60. Validation of the Cre driver lines were repeated in 2-3 mice per genotype.



Supplementary Figure 4

Additional performance metrics of *Syngap1* mice in the go-no-go task

Representative learning curves during Step 2 training for a WT (**a, b**) and a Het (**c, d**) mouse depicting probability of licking on Go (black) and NoGo (blue) trials (**a, c**) and discrimination index (**b, d**). Learning curves were similar for 6/7 WT and 7/7 Het mice. (**e**) Normalized bodyweights of mice from one day before water restriction to the completion of the experiment (2-way RM-ANOVA with Bonferroni's multiple comparison, Genotype: $F_{(1,12)}=1.29$, $p=0.28$; Day: $F_{(45,540)}=6.64$, $p=1.19E-29$; Genotype*Day interaction: $F_{(45,540)}=0.49$, $p=0.99$). (**f, g**) Scatter plots of licking behavior during lick-port training depicting mean number of water licks (**f**, Unpaired t-test: $t(12)=0.17$, $p=0.87$) and total reward licks (**g**, Unpaired t-test $t(12)=0.88$, $p=0.40$). (**h, i**) Averaged response times across sessions during Go (**h**, 2-way RM-ANOVA with Bonferroni's multiple comparison, Genotype: $F_{(1,12)}=0.33$, $p=0.58$; Session: $F_{(15,180)}=16.84$, $p=5.965E-27$; Genotype*Session interaction: $F_{(15,180)}=0.89$, $p=0.57$) and NoGo (**i**, 2-way RM-ANOVA with Bonferroni's multiple comparison, Genotype: $F_{(1,12)}=0.0059$, $p=0.94$; Session: $F_{(15,180)}=13.94$, $p=4.88E-23$; Genotype*Session interaction: $F_{(15,180)}=0.95$, $p=0.51$) trials. (**j-l**) For Step 2 training, mean number of trials plotted against session (**j**, 2-way RM-ANOVA with Bonferroni's multiple comparison, Genotype: $F_{(1,12)}=0.88$, $p=0.37$; Session: $F_{(15,180)}=1.88$, $p=0.028$; Genotype*Session interaction: $F_{(15,180)}=1.56$, $p=0.088$), scatter plots of mean trials per session (**k**: Unpaired t-test $t(12)=1.29$, $p=0.22$) and total trials performed (**l**: Unpaired t-test $t(12)=0.59$, $p=0.56$). (**m**) Mean number of total licks for each session in Step 2 training (2-way RM-ANOVA with Bonferroni's multiple comparison, Genotype: $F_{(1,12)}=2.08$, $p=0.18$; Session: $F_{(15,180)}=3.51$, $p=2.73E-5$; Genotype*Session interaction: $F_{(15,180)}=2.58$, $p=0.0016$). (**n**) Scatter plot of mean licks per trial in Step 2 training (Mann-Whitney test, $U=11$, $p=0.097$). (**o**) Scatter plot of total number of licks in Step 2 training (Unpaired t-test $t(12)=1.44$, $p=0.18$). (**e-o**) Open circles represent individual animals, closed circles or solid black lines indicate population means and error bars or shaded area represent the SEMs. (**a,c**) Solid black and blue dashed lines indicate performance criteria for hits and FAs, respectively. (**b,d**) Solid black line indicates performance criteria for d'. All data obtained from $n=7$ WT and $n=7$ Het mice, from two cohorts of animals. All statistical tests were two-sided.