Entorhinal cortex lesion induces homeostatic synaptic plasticity of CA3 pyramidal neurons

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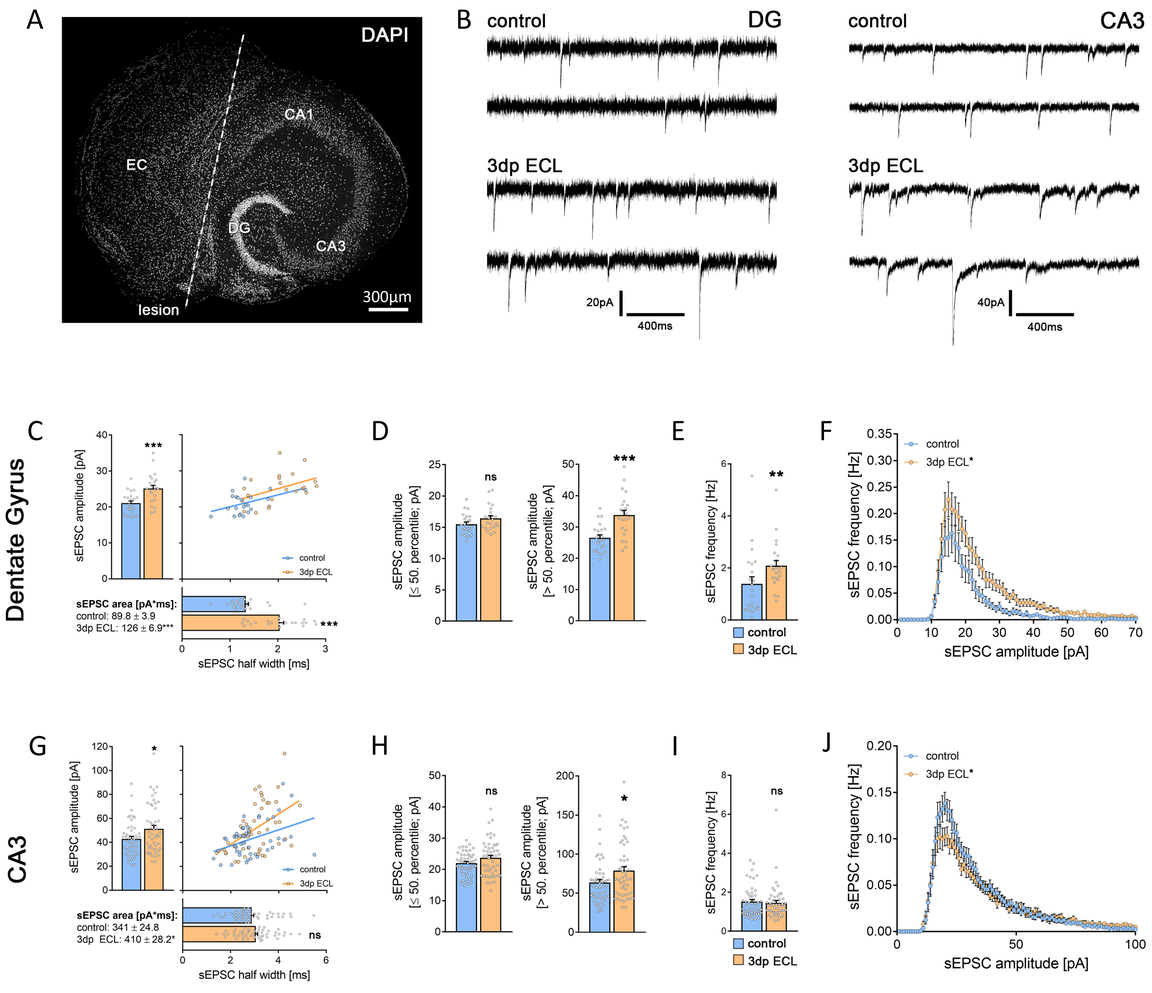
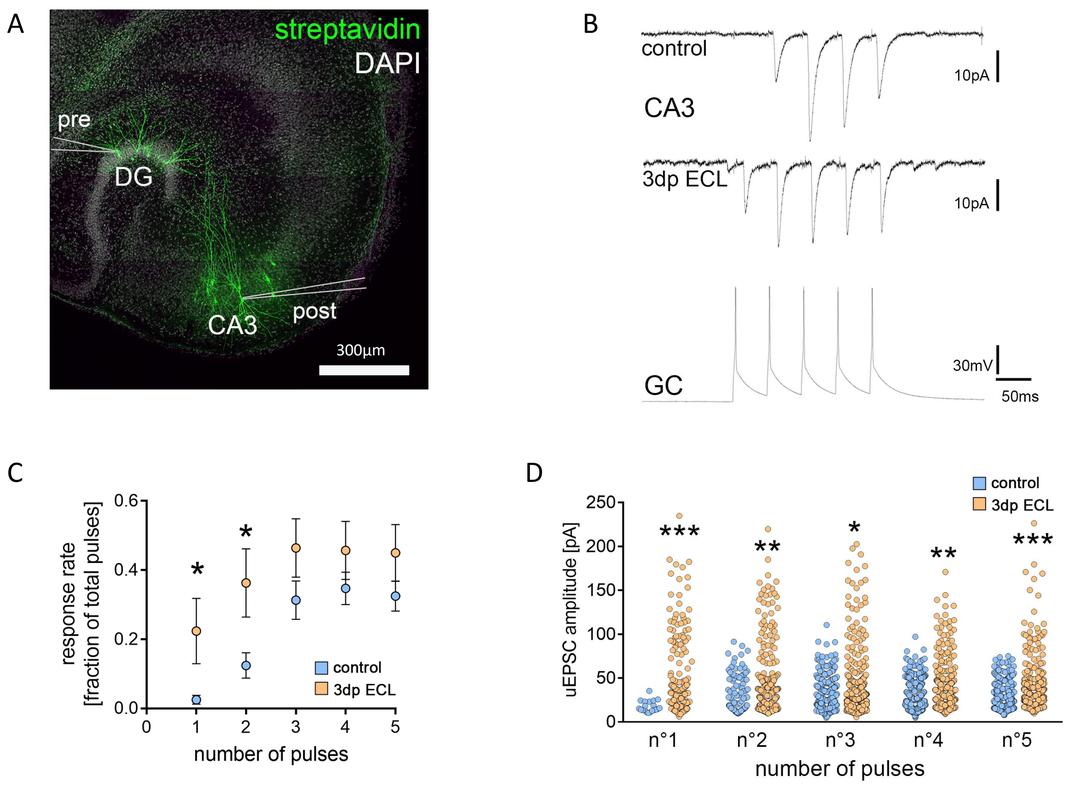
Introduction: A common aspect of many neurological diseases is the denervation of brain regions due to demyelination or cell death. Nonetheless, the underlying mechanisms involved in lesion-induced reorganization of neural networks warrant further investigation. In this study, we assessed the effects of a partial denervation on excitatory synaptic transmission of hippocampal neurons.

1) Entorhinal cortex lesion (ECL) induces homeostastic synaptic plasticity in both dentate granule cells and CA3 pyramidal cells



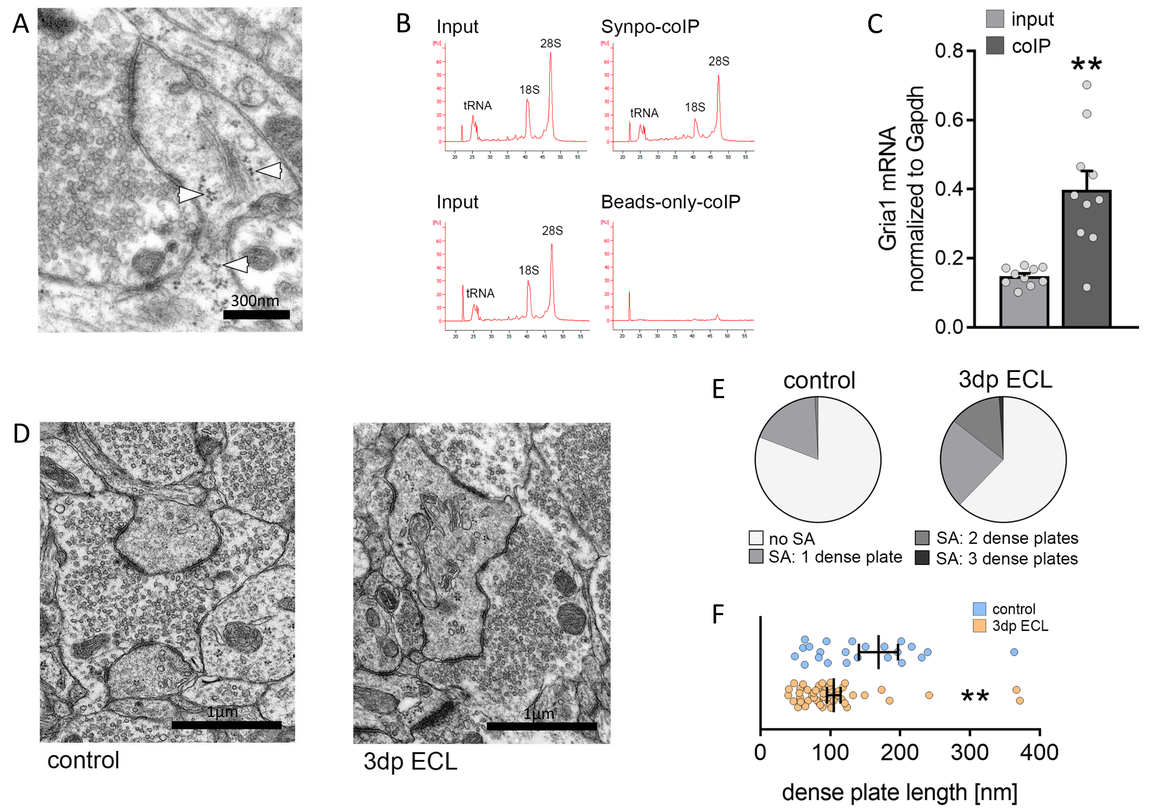
Statistics: (C-E) $n_{control}$ = 22 cells, n_{ECL} = 22 cells, Mann-Whitney test. For sEPSC recordings cells were held at -70 mV. Percentile analysis was performed for each cell respectively. (F) $n_{control}$ = 22 cells, n_{ECL} = 22 cells, RM two-way ANOVA. (G-I) $n_{control}$ = 48 cells, n_{ECL} = 49 cells, Mann-Whitney test. (J) $n_{control}$ = 48 cells, n_{ECL} = 49 cells, RM two-way ANOVA. (K) $n_{control}$ = 22 cells, n_{ECL} = 22 cells, Mann-Whitney test. (L) $n_{control}$ = 22 cells, n_{ECL} = 22 cells, RM two-way ANOVA. (M) $n_{control}$ = 48 cells, n_{ECL} = 49 cells, Mann-Whitney test. (N) $n_{control}$ = 48 cells, n_{ECL} = 49 cells, RM two-way ANOVA. Values represent mean±s.e.m (Mann-Whitney test: *p < 0.05; **p < 0.01; ***p < 0.001; ns, not significant differences. XY-plots were analyzed by RM two-way ANOVA: significant differences were indicated by * irrespective of their level of significance).

2) Paired whole cell recordings demonstrate changes in the dynamics of hippocampal mossy fiber/CA3 synapses after ECL



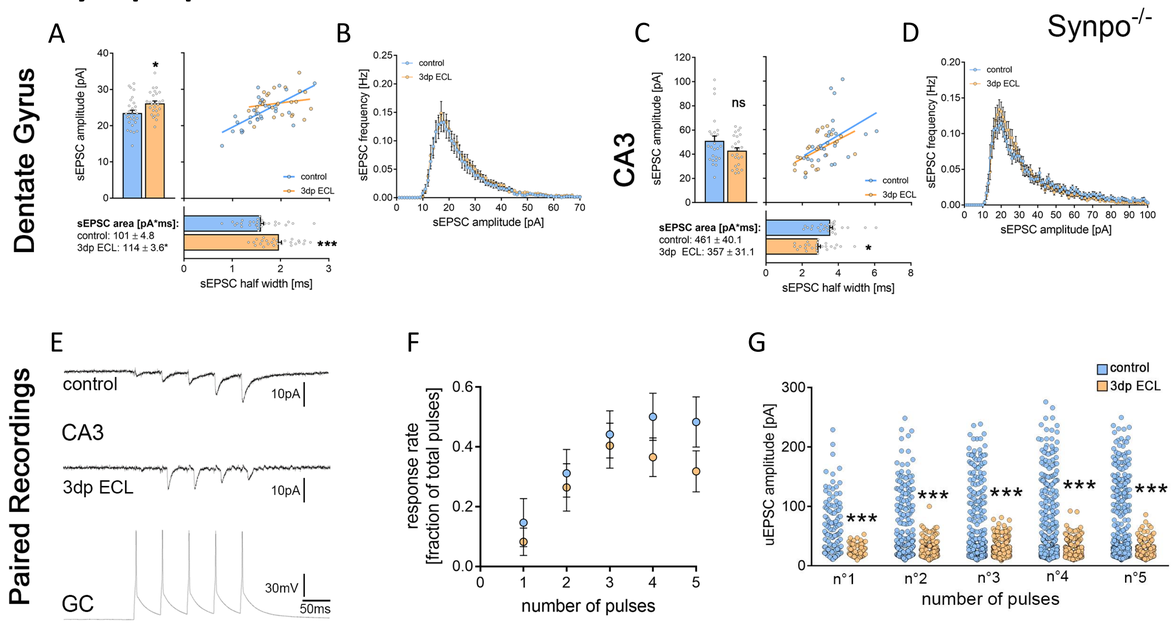
Statistics: (C) $n_{control}$ = 10 cells, n_{ECL} = 10 cells, Mann-Whitney test for the respective pulse numbers. (D) $n°1_{control}$ = 20 events, $n°1_{ECL}$ = 187 events; $n°2_{control}$ = 115 events, $n°2_{ECL}$ = 304 events; $n°3_{control}$ = 292 events, $n°3_{ECL}$ = 394 events; $n°4_{control}$ = 326 events, $n°4_{ECL}$ = 385 events; $n°5_{control}$ = 307 events, $n°5_{ECL}$ = 384 events, Mann-Whitney test for the respective pulse numbers. Values represent mean±s.e.m (Mann-Whitney test: *p < 0.05; **p < 0.01; ***p < 0.001).

3) The spine apparatus organelle is a plastic hub for ribosomes and excitatory synapse related mRNAs



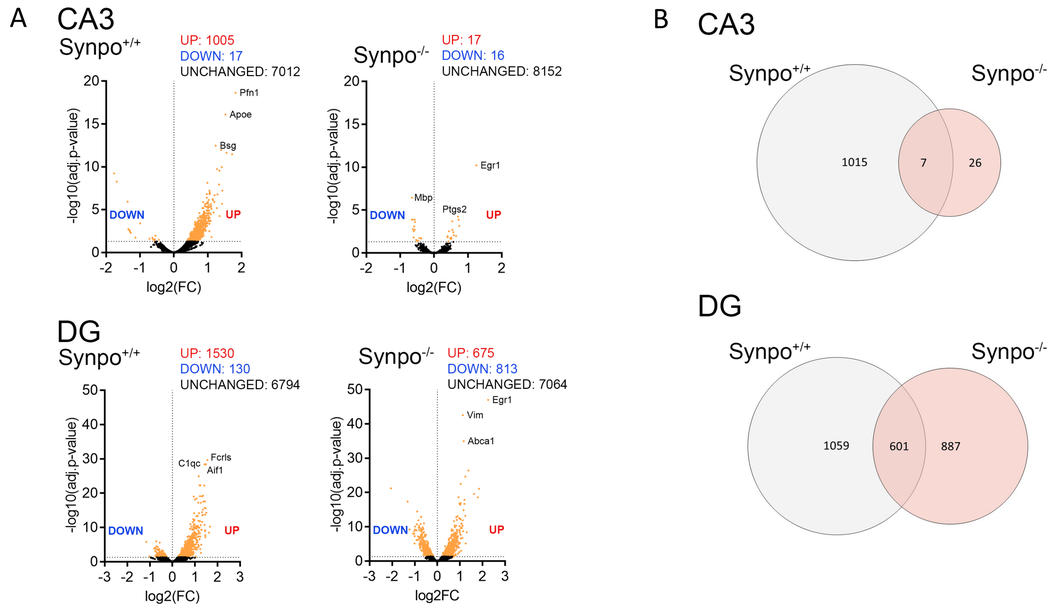
Statistics: (C) n_{input} = 10; n_{coIP} = 10, Mann-Whitney test. (E) $n_{control}$ = 120; n_{ECL} = 90. (F) $n_{control}$ = 24; n_{ECL} = 48, Mann-Whitney test. Values represent mean±s.e.m (Mann-Whitney test: **p < 0.01).

4) ECL-induced homeostatic plasticity of CA3 pyramidal neurons depends on synaptopodin



Statistics: (A) $n_{control}$ = 29 cells, n_{ECL} = 26 cells, Mann-Whitney test. (B) $n_{control}$ = 29 cells, n_{ECL} = 26 cells, RM two-way ANOVA. (C) $n_{control}$ = 25, n_{ECL} = 25, Mann-Whitney test. (D) $n_{control}$ = 25 cells, n_{ECL} = 25 cells, RM two-way ANOVA. (F) $n_{control}$ = 12 cells, n_{ECL} = 10 cells, Mann-Whitney test for the respective pulse numbers. (G) $n°1_{control}$ = 144 events, $n°1_{ECL}$ = 82 events; $n°2_{control}$ = 300 events, $n°2_{ECL}$ = 263 events; $n°3_{control}$ = 426 events, $n°3_{ECL}$ = 402 events; $n°4_{control}$ = 486 events, $n°4_{ECL}$ = 364 events; $n°5_{control}$ = 472 events, $n°5_{ECL}$ = 317 events; Mann-Whitney test for the respective pulse numbers. Values represent mean±s.e.m (Mann-Whitney test: *p < 0.05; ***p < 0.001; ns, not significant differences).

5) ECL leads to synaptopodin-dependent transcriptomic changes in organotypic tissue cultures



Statistics: Synpo+/+ CA3: $n_{control}$ = 2, n_{ECL} = 3; GC: $n_{control}$ = 4, n_{ECL} = 7; Synpo-/- CA3: $n_{control}$ = 6, n_{ECL} = 6; GC: $n_{control}$ = 7, n_{ECL} = 4. DESeq2-analysis, Galaxy server. Genes are labeled as significant when adj. P-value < 0.05.

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Conclusion: Lesion-induced homeostatic synaptic plasticity of granule cells and CA3 pyramidal neurons depends on the spine apparatus organelle which might act as a hub for local protein synthesis.