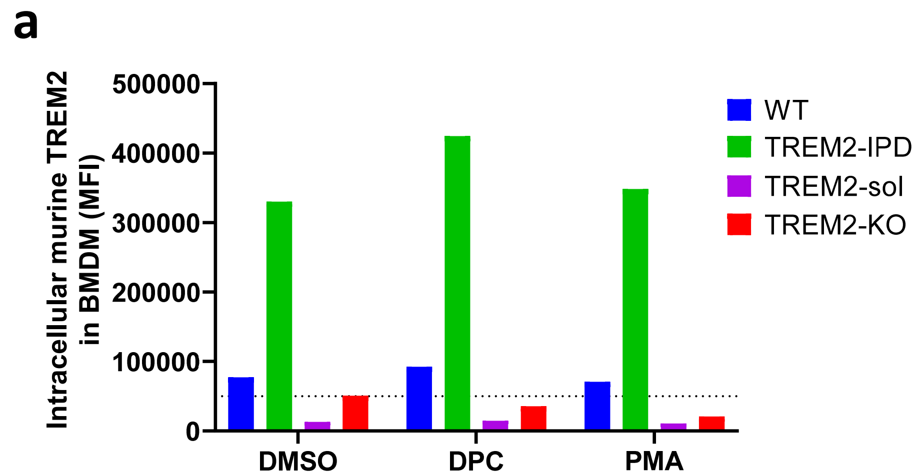

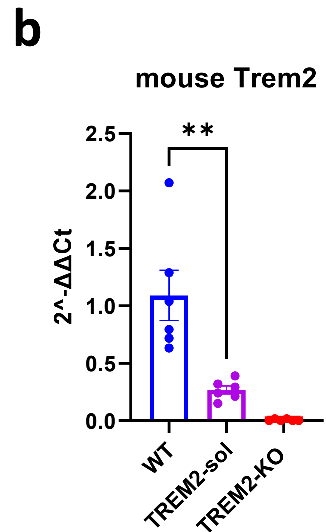

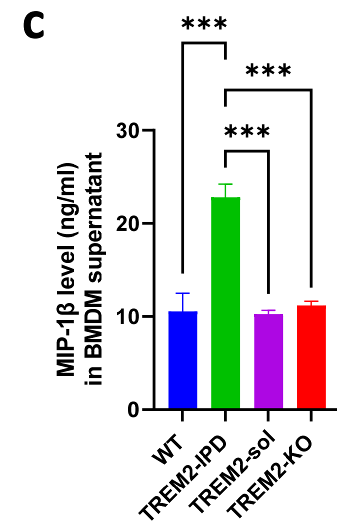

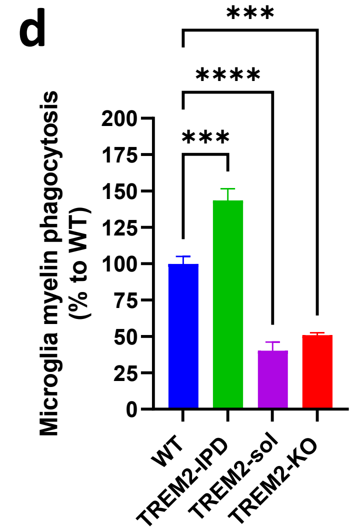

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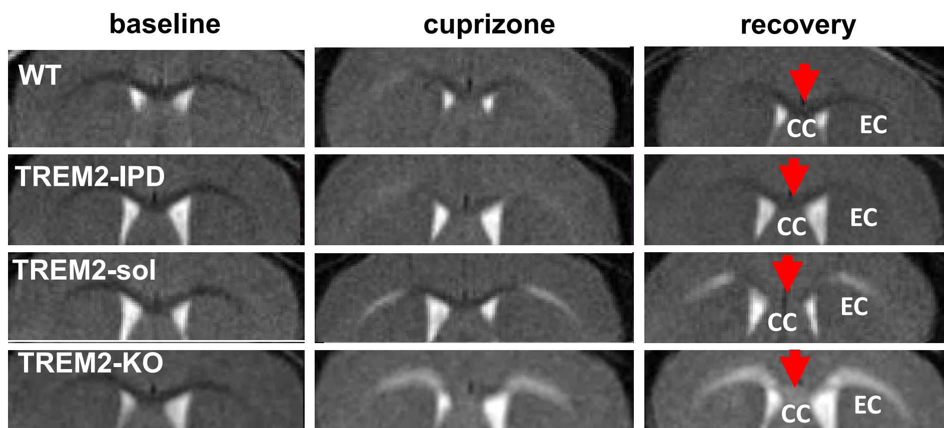

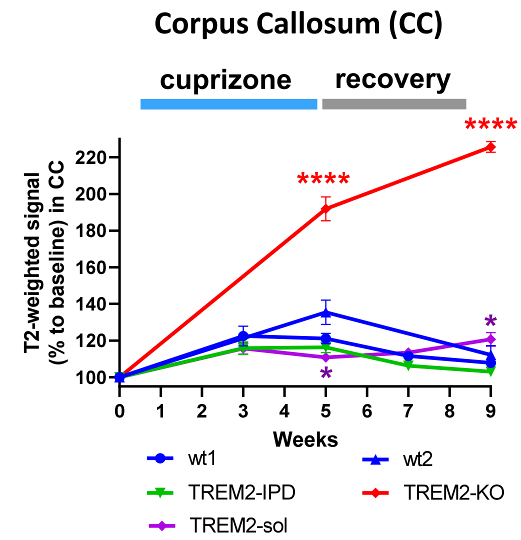

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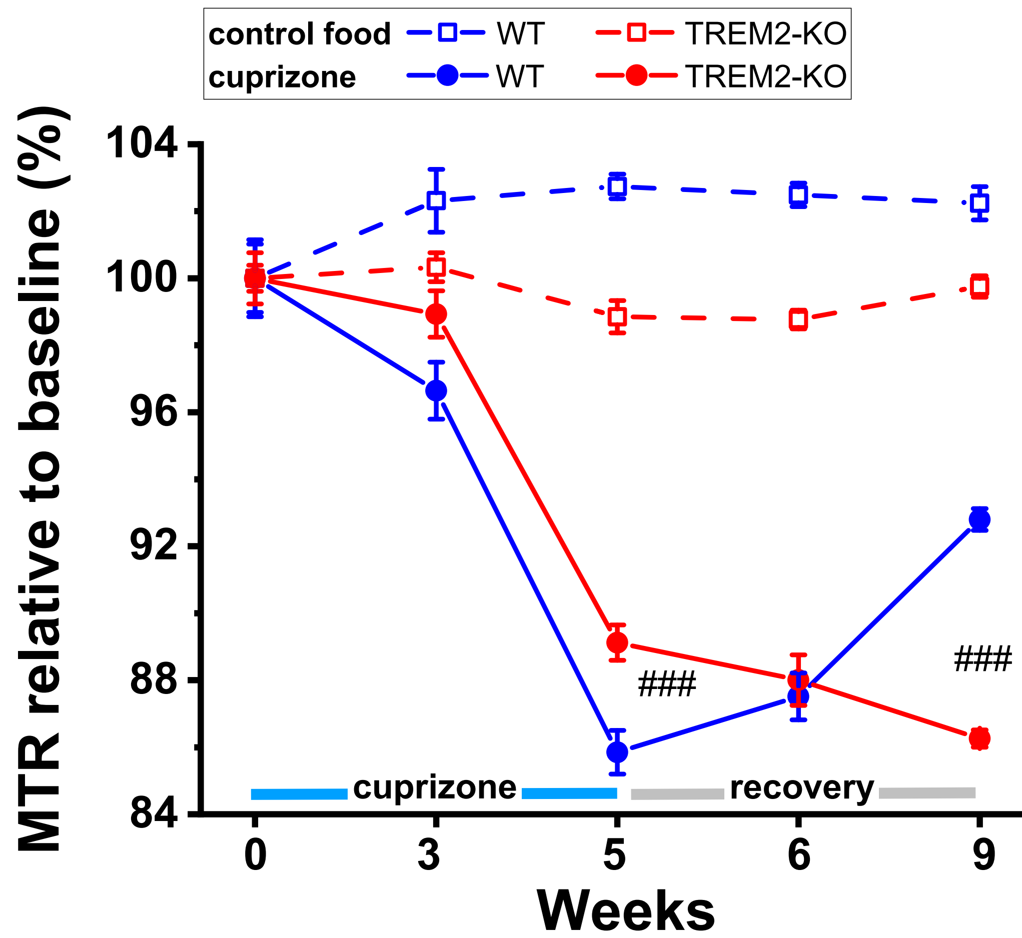

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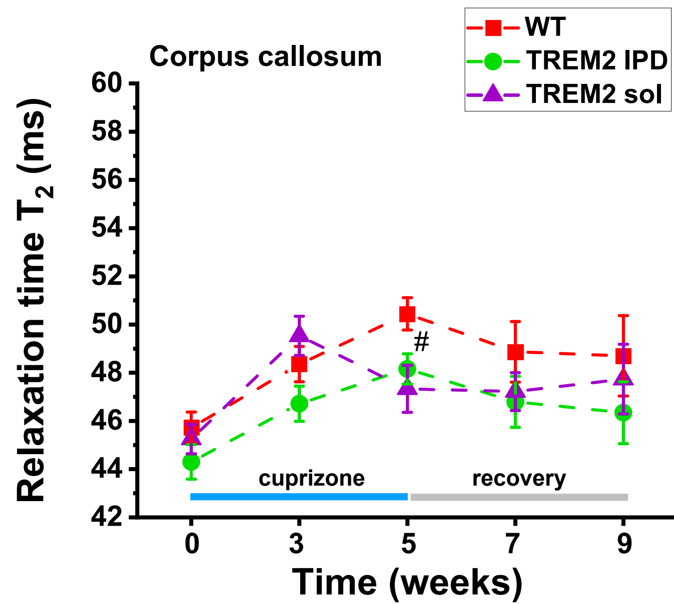

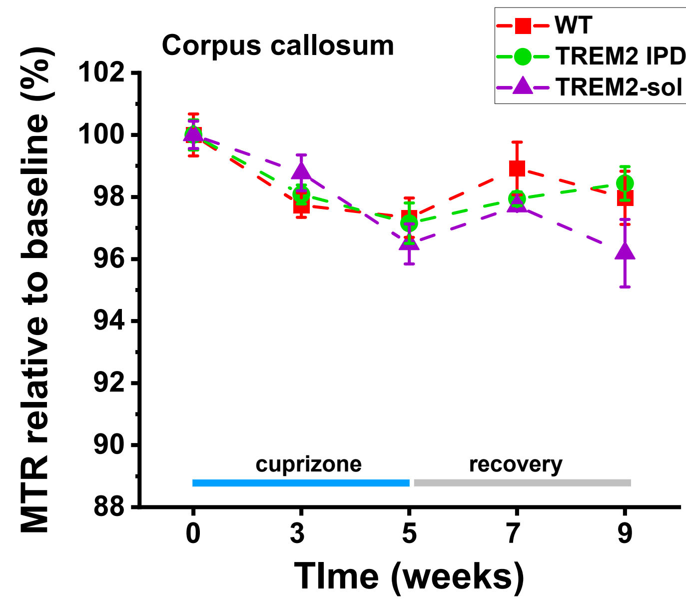

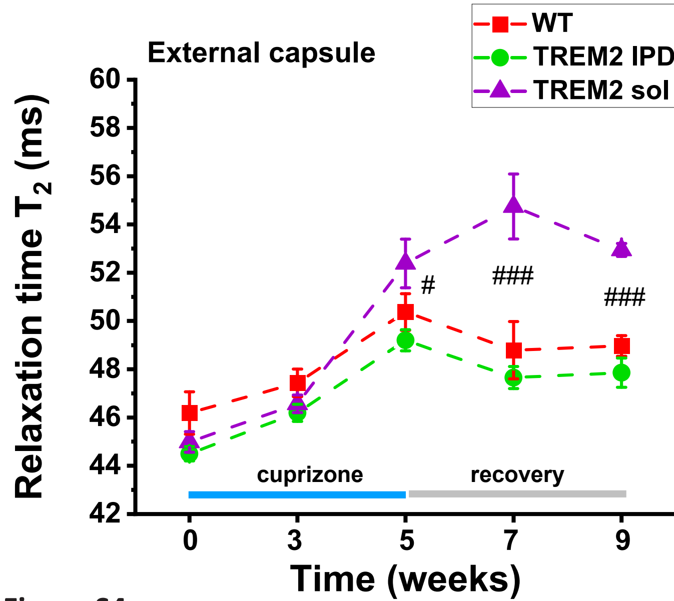

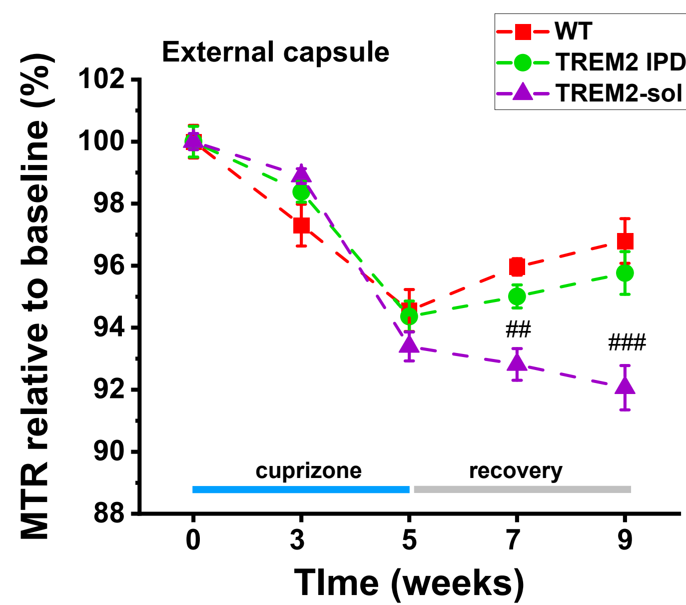

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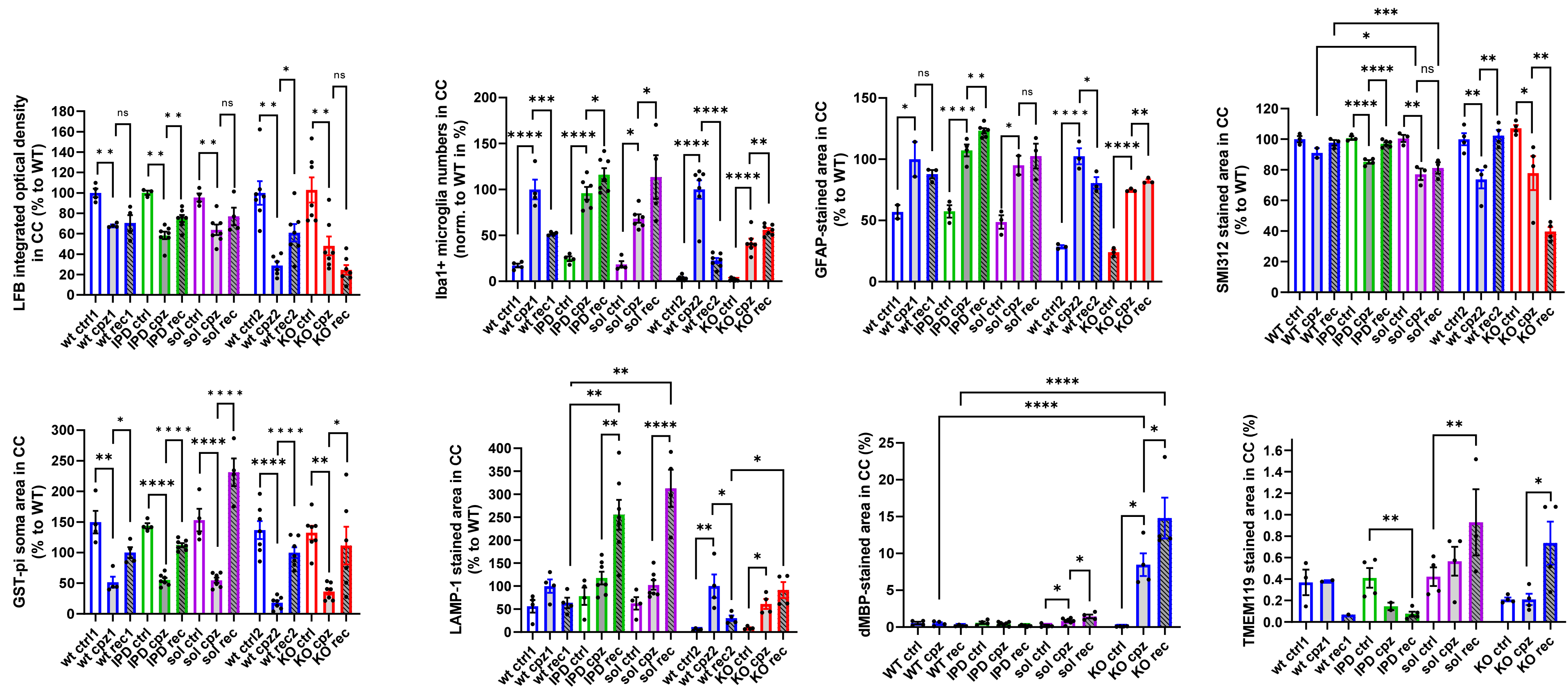

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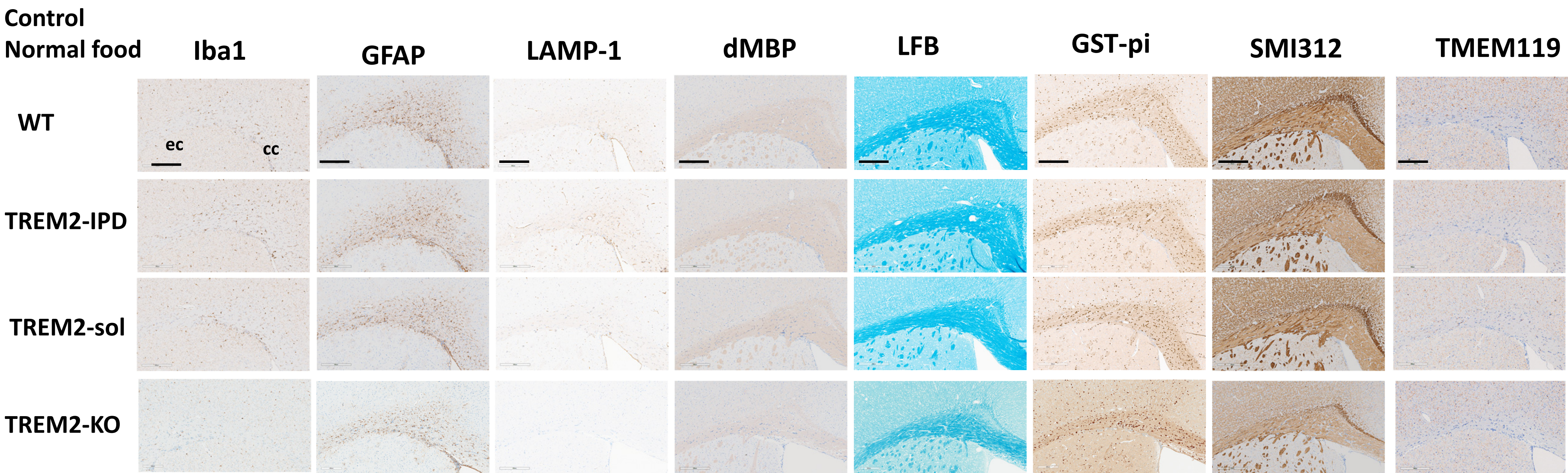

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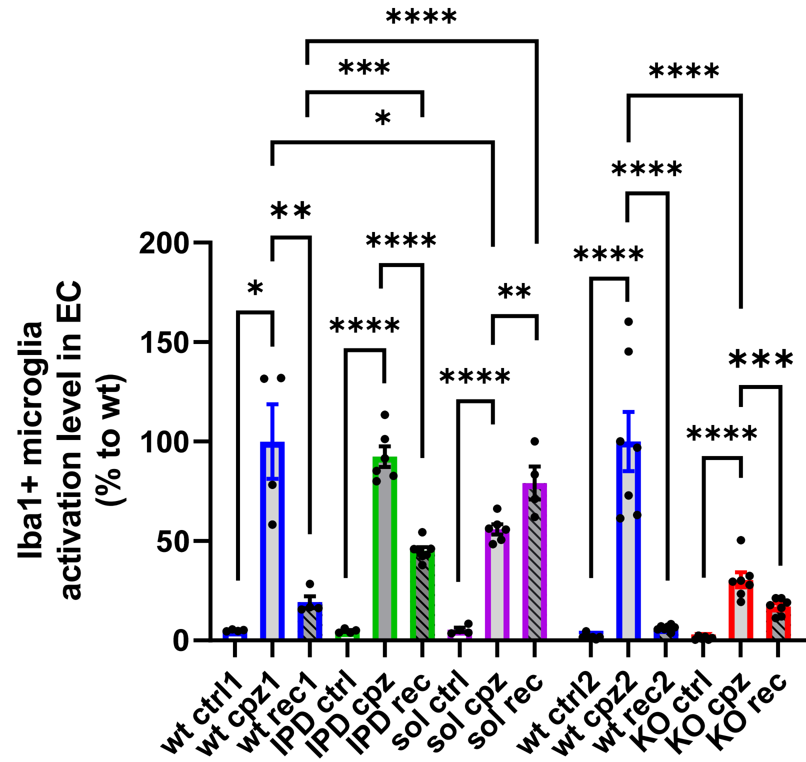

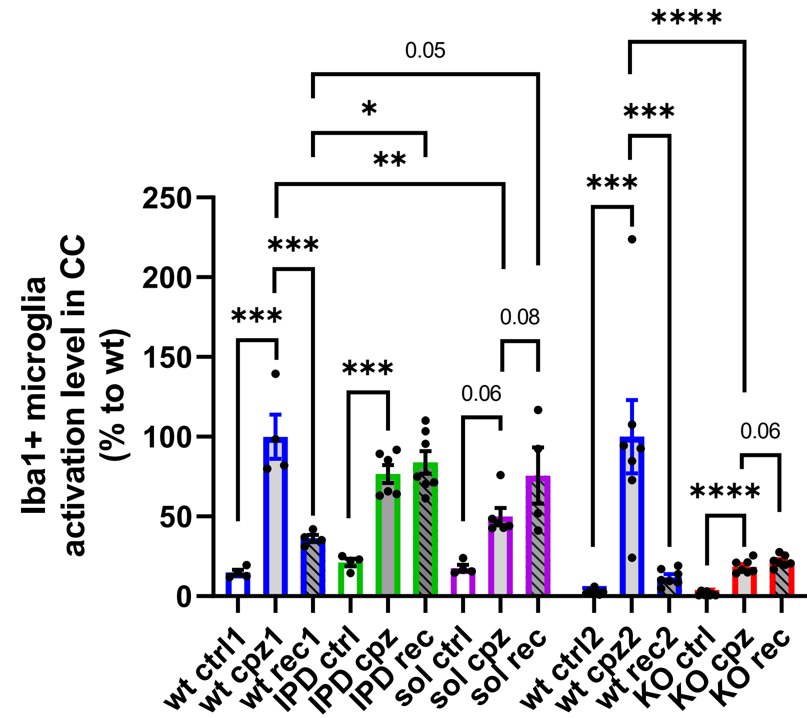

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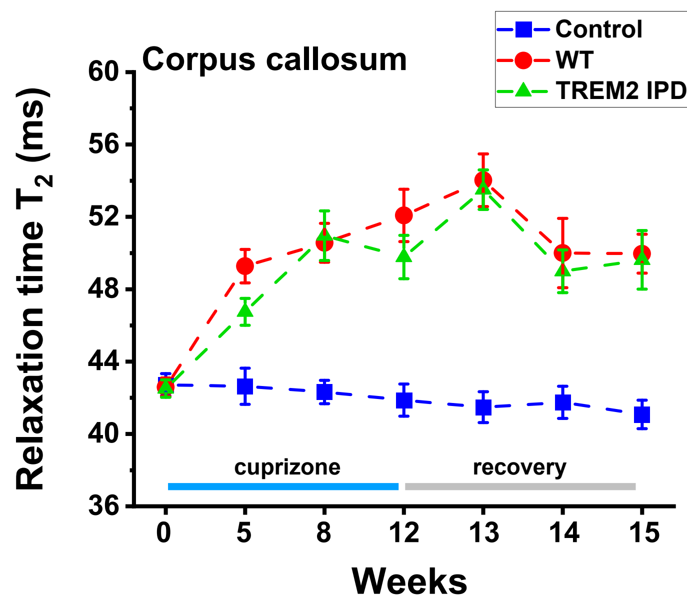
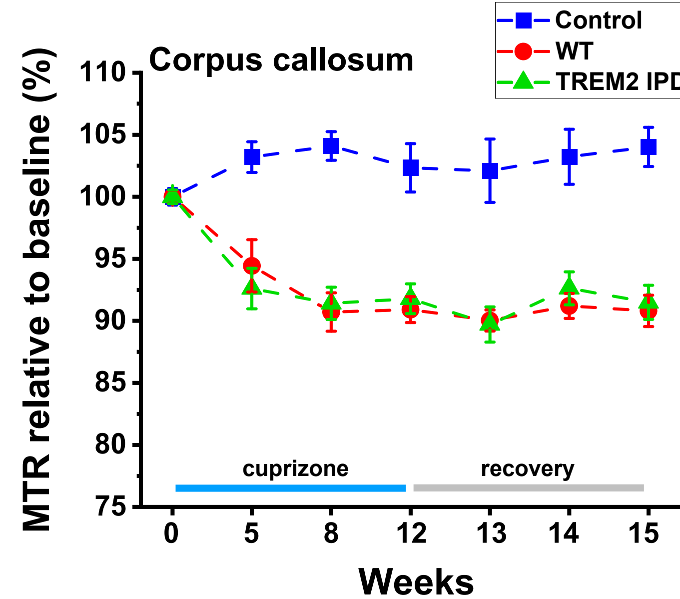
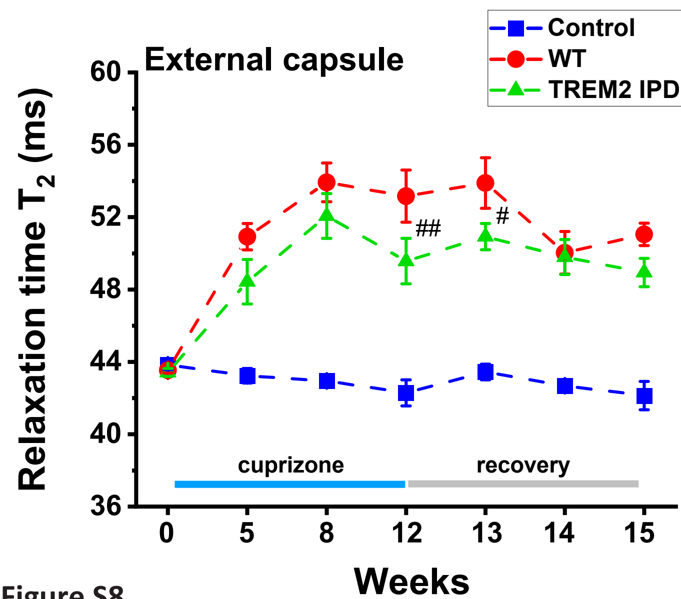






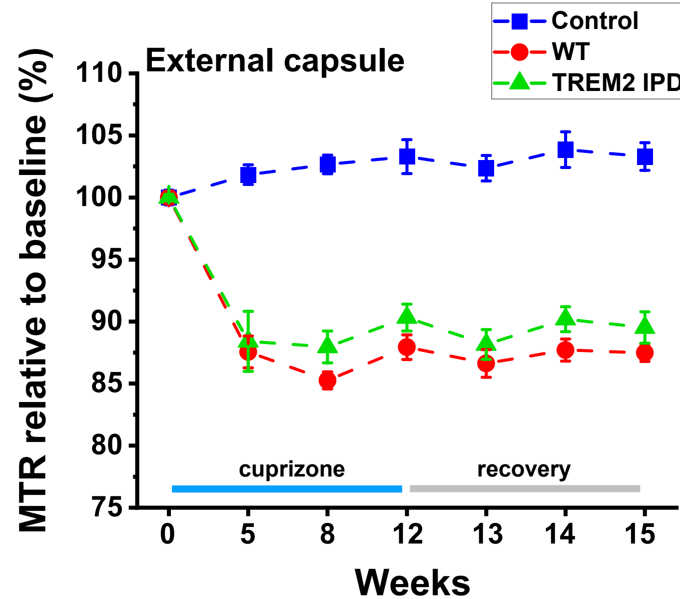
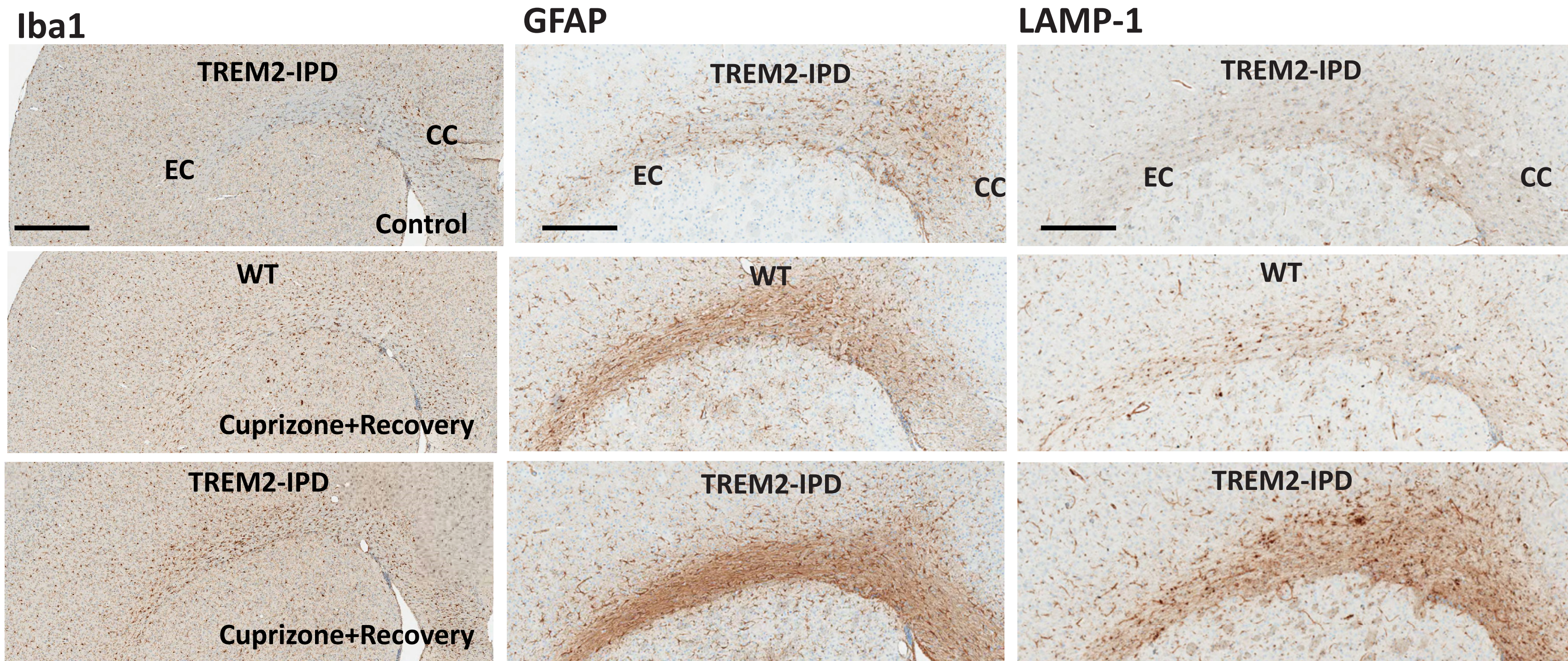


Figure S8



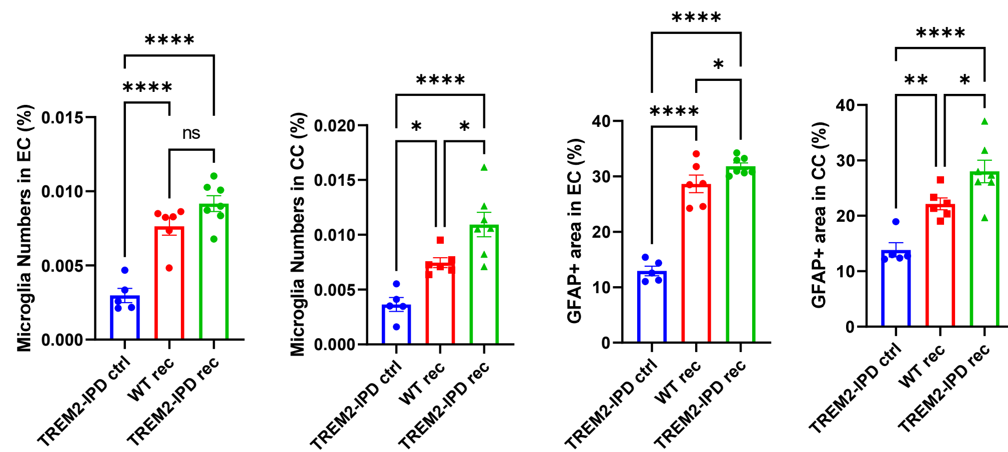


Figure S9

Additional figure legends

Figure S1. Characterization of TREM2-sol in bone-marrow derived macrophages, brain and primary microglia. a Flow cytometry analysis of murine intracellular TREM2 in BMDM. MFI: median fluorescence intensity. Cells were either untreated or treated with the sheddase inhibitor DCP333 (5µM overnight, DPC) or the sheddase activator PMA (50ng/ml for 30min). The gate for TREM2 positive cells was set based on the isotype control (threshold 0.2% positive cells in the isotype control). The dotted line marks the background signal which is observed in TREM2-KO. **b** Mouse Trem2 qRT-PCR of total RNA from WT and TREM2-sol brains (age 12 months old). Normalized to Gapdh, 2^-ΔΔCt= 2^-(ΔCtTrem2-AvgΔCtControl/). n=6 per group. Statistics: Unpaired t-test two-tailed. **: p<0.01. **c** MIP1-β analysis in supernatants from BMDM for each genotype data in triplicates (n=3) at days in vitro (DIV) 7. **d** *In vitro* phagocytosis of primary microglia over 24h with 10µg pHrodo-myelin per well. The WT AUC of the integrated fluorescence intensities was set to 100%. All genotypes were compared to the other three, and all significant differences are displayed. In both experiments, data for each genotype data was generated in triplicates (n=3). Fluorescence measurements in wells without prey were used as controls (data not shown). Statistics: One-way ANOVA test with Tukey`s multiple comparisons test (***: p <.001, ****: p <0.0001).

Figure S2. T_2-weighted MRI signal analysis in the CC region for the 5-week cuprizone model in WT, TREK2-KO, TREM2-sol and TREM2-IPD mice. Groups consisted of mice treated for 5 weeks with control food (normal food) or 0.2% cuprizone in food and then switched back to control food (normal food) for the 4-week recovery. MRI measurements were performed at week 0 (baseline), week 3 and week 5 of cuprizone intoxication, at week 7 (2 weeks of recovery on control food) and at week 9 (4 weeks of recovery on control food). Mice were culled at week 9 immediately after the last MRI measurement. EC: external capsule, CC: corpus callosum. Group sizes: n=7-9 for all genotypes and at all time-point. Statistics: ANOVA with random effects comparisons indicated significant differences with respect to WT mice: *: p<0.05, ****: p<0.0001. For each group examined, T_2-weighted signals were significantly increased with respect to baseline values (significances not shown). Data are shown as means±SEM. wt1 is the respective wildtype group for the study with TREM2-IPD and TREM2-sol, wt2 is the wildtype group for the TREM2-KO study.

Figure S3. MTR analyses in the combined external capsule (EC) and corpus callosum (CC) region for the 5-week cuprizone and 4-week recovery model. Data (means±SEM) presented as relative to baseline values for each genotype. Group sizes: n=14 until week 5, n=7 until week 9 for all genotypes. Statistics: Anova with random effects. The levels of significance ###: p<0.001 correspond to comparisons betweenTREM2-KO and WT animals at the specified time points. WT: wildtype, TREM2-KO: TREM2 knockout

Figure S4. MRI analyses in external capsule (EC) and corpus callosum (CC) of TREM2-IPD and TREM2-sol mice for the 5-week cuprizone and 4-week recovery model. Data presented as means±SEM. Group sizes: n=7 for each genotype. Statistics: ANOVA with random effects. The levels of significance #: p<0.05, ##: p<0.01, ###: p<0.001 correspond to comparisons betweenTREM2-sol and WT animals at the specified time points. WT: wildtype, TREM2-IPD: TREM2 cleavage-reduced, TREM2-sol: TREM2 soluble-only.

Figure S5. Quantitative image analysis of histological stainings in CC. Luxol fast blue (LFB) optical density (OD) analysis of LFB (normalized to WT at control food), mature oligodendrocytes (GST-π soma area in %), myelin basic protein debris (dMBP-stained area in %), neurofilament (SMI312-stained area in %). Iba1-positive soma numbers (normalized to WT at week 5 cuprizone), LAMP-1 (lysosomal-associated membrane protein 1)-stained area in %, TMEM119 (homeostatic marker, TMEM119-stained area in %), astrocytes (GFAP-stained area in %). Group sizes: n=7 for all genotypes and time-points. Data shown as means±SEM. WT: wildtype, TREM2-IPD: TREM2 cleavage-reduced, TREM2-sol: TREM2 soluble-only, TREM2-KO: TREM2 knockout. Ctrl: control food, cpz: cuprizone food for 5 weeks, rec: recovery on control food for 4 weeks. CC: corpus callosum. Scale bars: 300µm (overview), 50 µm (close-up). Statistics: Holm-Sidak`s multiple comparison test one-way ANOVA (*: p<0.05, **: p<0.01, ***: p<0.001, ****: p<0.0001). Comparisons not indicated are non-significant. Wt ctrl1, wt cpz1 and wt rec1 are the respective wildtype groups for the study with TREM2-IPD and TREM2-sol, wt ctrl2, wt cpz2 and wt rec2 are the wildtype groups for the TREM2-KO study. Only statistical analysis within a study was performed. The analyses of dMBP and TMEM119 for the respective wt groups for TREM2-KO were omitted as no obvious signals were observed.

Figure S6. Brain histological analysis for WT, TREM2-IPD, TREM2-sol and TREM2-KO mice receiving control normal food showed no difference between groups. Quantitative image analysis is shown in Fig. 3 and 5. Luxol Fast Blue (LFB), mature oligodendrocytes (GST-π), myelin basic protein debris (dMBP), neurofilament (SMI312), Iba1, LAMP-1 (lysosomal-associated membrane protein 1), TMEM119 (homeostatic marker), astrocytes (GFAP). WT: wildtype, TREM2-IPD: TREM2 cleavage-reduced, TREM2-sol: TREM2 soluble-only, TREM2-KO: TREM2 knockout. ec: external capsule, cc: corpus callosum. Scale bars: 300µm.

Figure S7. Image analysis of Iba1-positive microglia activation in the EC and CC (normalized to WT in %) from the staining shown in Fig. 5. Microglia activation is calculated as microglia and proximal processes area normalized to non soma-associated processes area. Data are shown as means±SEM. WT: wildtype, TREM2-IPD: TREM2 cleavage-reduced, TREM2-sol: TREM2 soluble-only, TREM2-KO: TREM2 knockout. Ctrl: control food, cpz: cuprizone food for 5 weeks, rec: recovery on control food for 4 weeks. ec: external capsule, cc: corpus callosum. Statistics: Holm-Sidak`s multiple comparison test one-way ANOVA (*: $p<0.05$, **: $p<0.01$, ***: $p<0.001$, ****: $p<0.0001$). Comparisons not indicated are non-significant. wt ctrl1, wt cpz1 and wt rec1 are the respective wildtype groups for the study with TREM2-IPD and TREM2-sol, wt ctrl2, wt cpz2 and wt rec2 are the wildtype groups for the TREM2-KO study. Only statistical analysis within a study was performed.

Figure S8. MRI analyses of TREM2-IPD mice in the chronic cuprizone model. Data presented as means±SEM. Group sizes: n=7 for each genotype. Statistics: ANOVA with random effects. The levels of significance #$0.01<p<0.05$, ##$0.001<p<0.01$ correspond to comparisons between TREM2-IPD and WT animals at the specified time points. WT: wildtype, TREM2-IPD: TREM2 cleavage-reduced. Control refers to TREM2-IPD mice receiving normal food throughout the study.

Figure S9. Microglia (Iba1), astrocytes (GFAP) and lysosomal marker LAMP-1 were quantified in WT and TREM2-IPD in the chronic cuprizone model (12-week cuprizone treatment and 3-week recovery). Group sizes: n=5-7. Data are shown as means±SEM. WT: wildtype, TREM2-IPD: TREM2 cleavage-reduced. Ctrl: control food, rec: recovery on control food for 3 weeks. EC: external capsule, CC: corpus callosum. Scale bars: 500µm. Statistics: Holm-Sidak`s multiple comparison test one-way ANOVA (*: $p<0.05$, **: $p<0.01$, ****: $p<0.0001$, n.s.: not significant).