Supplementary Fig 1

A

B

C

NTg-PR/NTg Control Diet

beta-Alanine metabolism
Lysine degradation
Biotin metabolism
D-glutamine and D-glutamate metabolism
Aminoacyl-tRNA synthesis
Citrate cycle (TCA cycle)
Glycine, serine and threonine metabolism
Cysteine and methionine metabolism
Arginine biosynthesis
Arginine and proline metabolism
Alanine, aspartate and glutamate metabolism
Glyoxylate and dicarboxylate metabolism
Valine, leucine and isoleucine degradation
Valine, leucine and isoleucine biosynthesis
Phenylalanine, tyrosine and tryptophan metabolism
Histidine metabolism
Phenylalanine metabolism
Nitrogen metabolism
Ubiquinone and other terpenoid, quinone biosynthesis
Tryptophan metabolism
Riboflavin metabolism
Glycolysis/gluconeogenesis
Purine metabolism
Folate biosynthesis
Pyrimidine metabolism
Pyruvate metabolism

- Down
- Up
- NS

D

Supplementary Figure 1: Distinct metabolic signatures in male and female NTg mice following long term PR. (A) Principal Component Analysis (PCA) of NTg males and females. (B) Heat map representation of the top 25 altered serum metabolites in both NTg-PR fed females and males, represented as $\log_2$ fold change from NTg mice on a control diet. (C) Significantly up and down regulated pathways for each sex and diet were determined using KEGG enrichment. (D) Methionine cycle and its intermediates are summarized in (D). n=5-6 biologically independent mice per group; statistics for the overall effects of diet, sex, and the interaction represent the p value from a 2-way ANOVA, *$p < 0.05$, from a Sidak's post-test examining the effect of parameters identified as significant in the 2-way ANOVA. Data represented as mean ± SEM.

Supplementary Figure 2
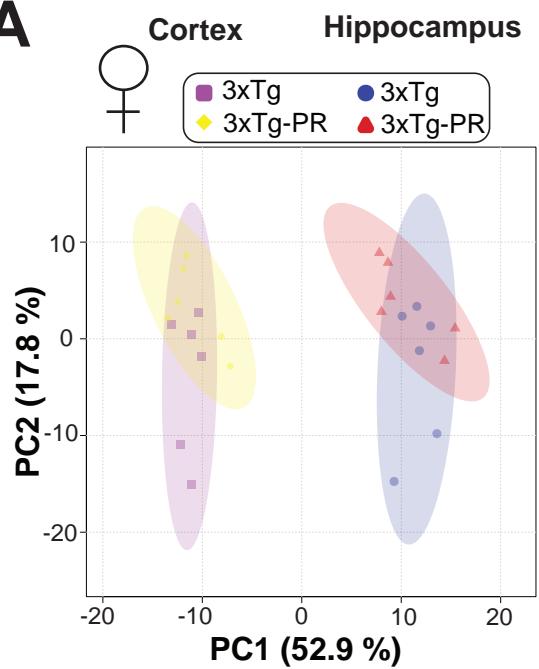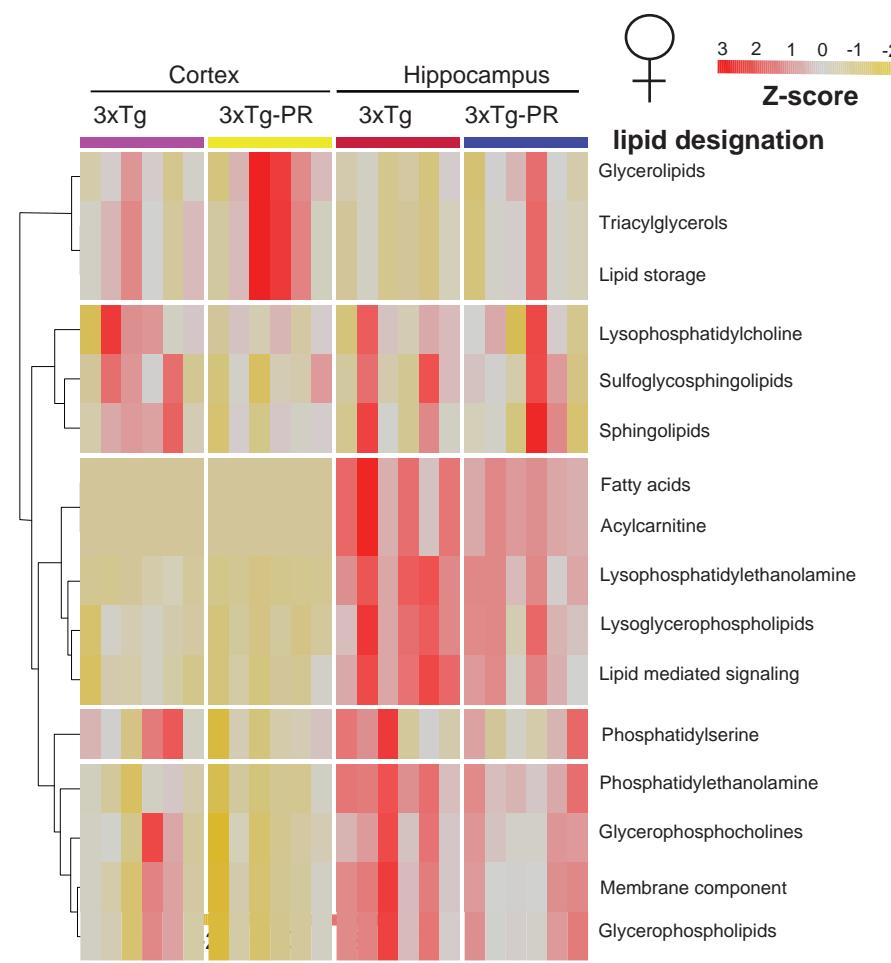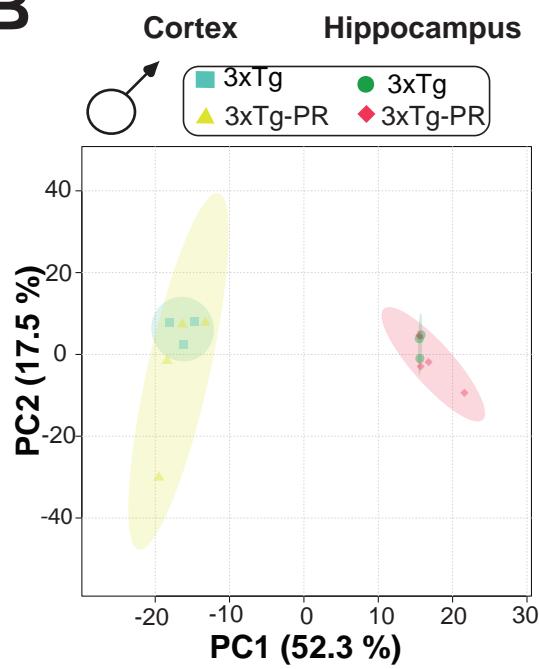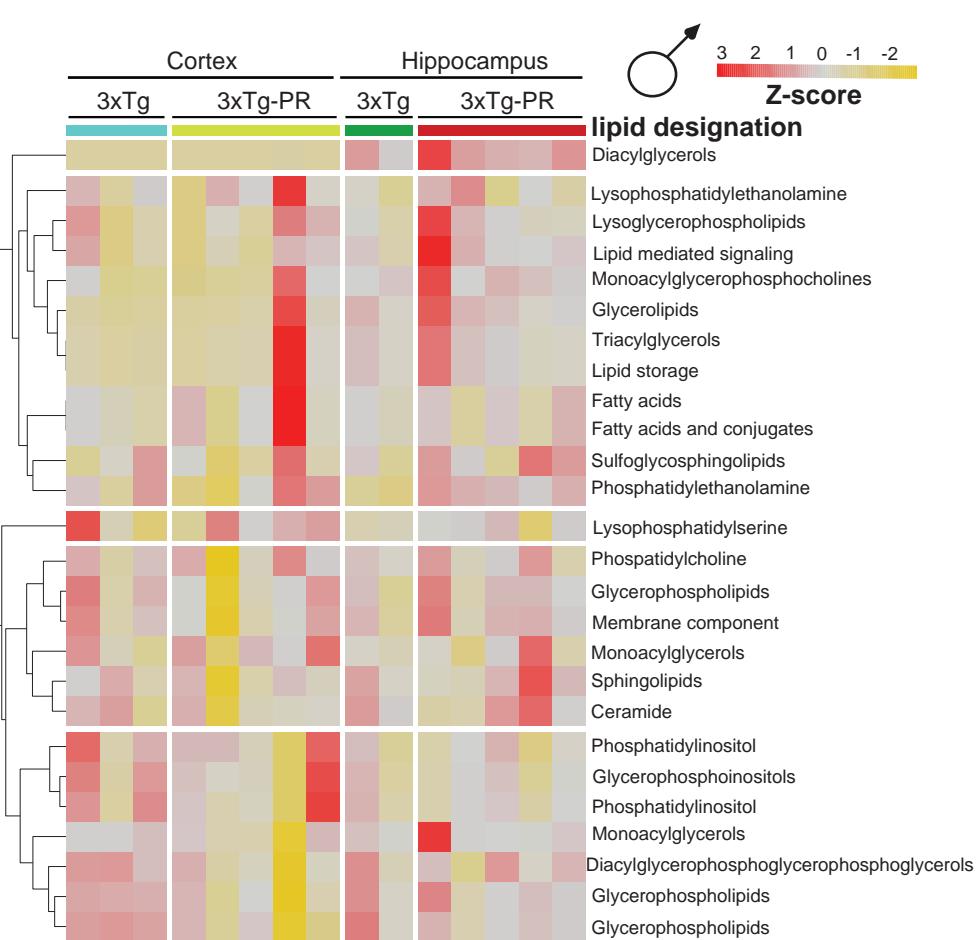
Supplementary Figure 2: Region specific lipidome changes in the brains of 3xTg mice.

(A-D) PCA of the variations in lipid classes in the hippocampus and cortex of female (A) and male (C) 3xTg mice. Heat maps of altered lipid classes in cortex and hippocampus of females (B) and males (D).

Supplementary Figure 3
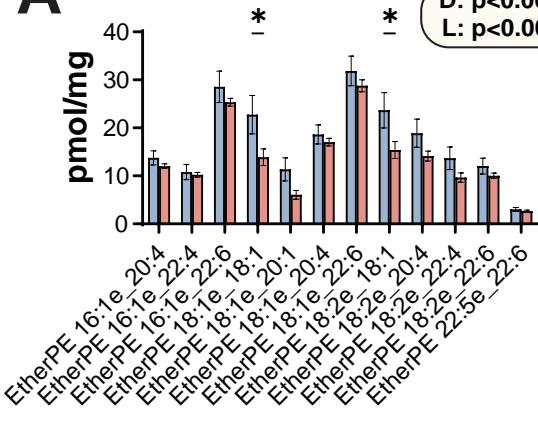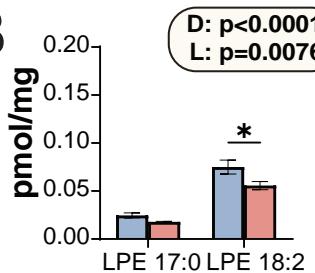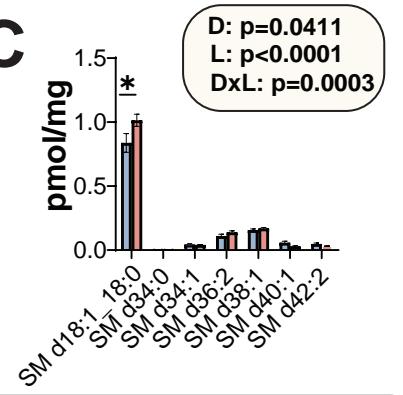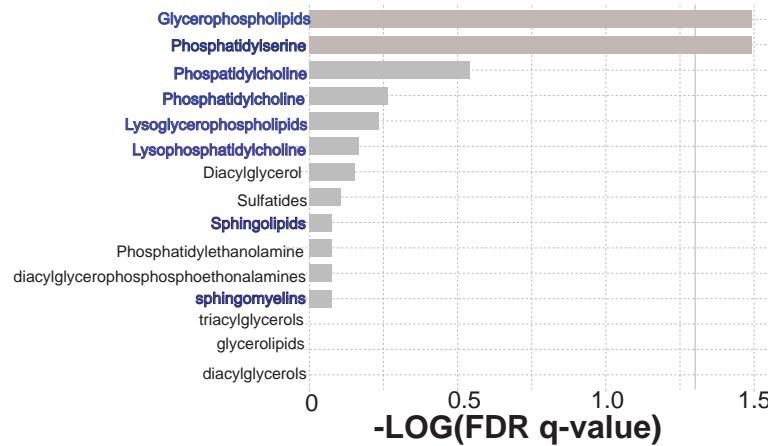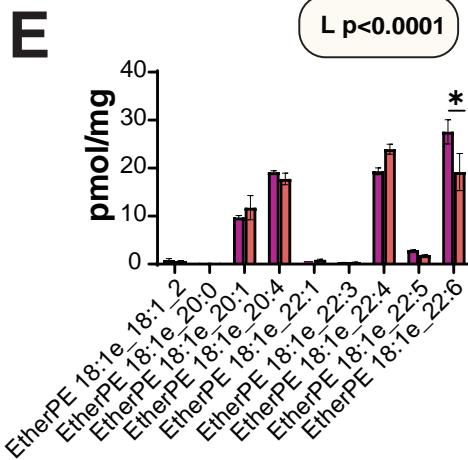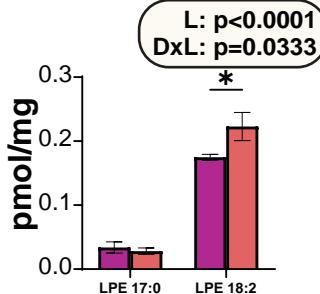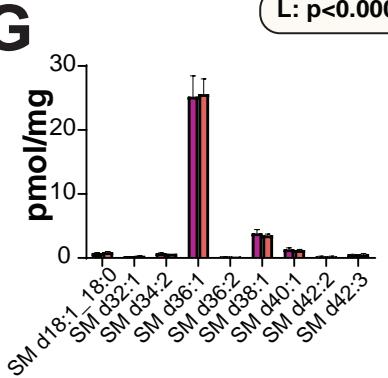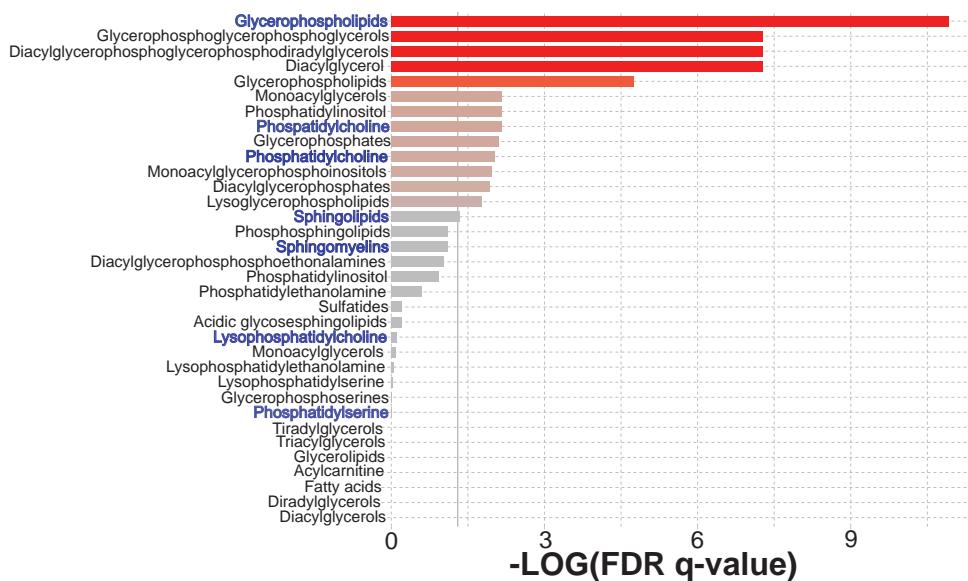
Supplementary Figure 3: PR induces sex-specific shifts in the brain lipidome of 3xTg mice.

(A-H) Lipidomic analysis was performed on the cortex of female (A-D) and male (E-H) 3xTg mice fed either a Control or PR diet. (D, H) LION ontology pathway enrichment analysis of the complete lipidomic dataset from the cortex of female (D) and male (H) 3xTg mice. The vertical gray lines indicate the threshold value for significant enrichments; names in blue are pathways significantly enriched in both sexes. (A-C, E-H) n=6 (A-C) or n=3-5 (E-H) biologically independent mice per group; statistics for the overall effects of diet, lipid and the interaction represent the p value from a 2-way ANOVA; *p<0.05, from a Sidak's post-test for the effect of PR on each lipid. Ether PE: Ether phosphatidylethanolamines; LPE: lyso-phosphatidylethanolamines; SM: sphingomyelin. Data represented as mean ± SEM.

Supplementary Figure 4

A

B

Diet: p=0.0263

p-T389 S6K1 (% of NTg)

NTg | NTg PR | 3xTg | 3xTg PR

C

Diet: p=0.0278
GT: p=0.0002

p-T37/S46-4E-BP1 (% of NTg)

NTg | NTg PR | 3xTg | 3xTg PR

D

p62 (% of NTg)

NTg | NTg PR | 3xTg | 3xTg PR
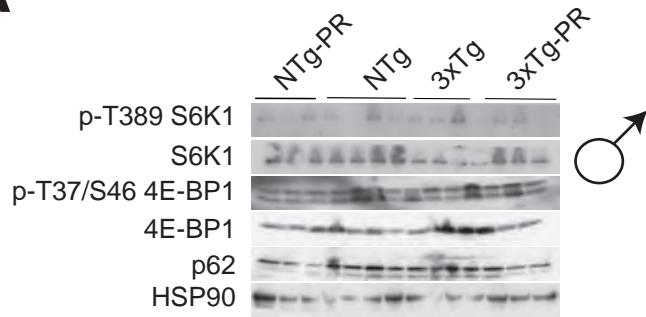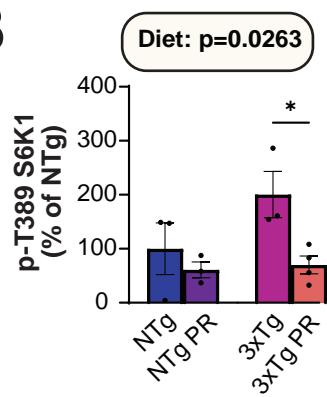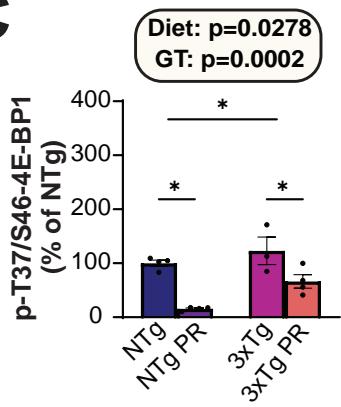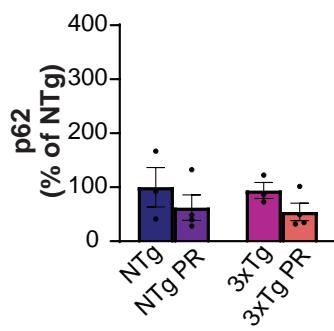
Supplementary Figure 4: PR reduces mTORC1 signaling in the brains of male 3xTg mice.
Representative immunoblots of the whole brain of male mice (A). Quantification of the mTORC1 substrates T389 S6K1 (B) and T37/S46 4E-BP1 (C). (D) Quantification of p62 expression. (A-D) n=3-5 biological independent mice per group; statistics for the overall effects of genotype (GT), diet, and the interaction represent the p value from a 2-way ANOVA, *p<0.05, from a Sidak's post-test examining the effect of parameters identified as significant in the 2-way ANOVA. Data represented as mean ± SEM.

Supplementary Figure 5

A Open Field Test
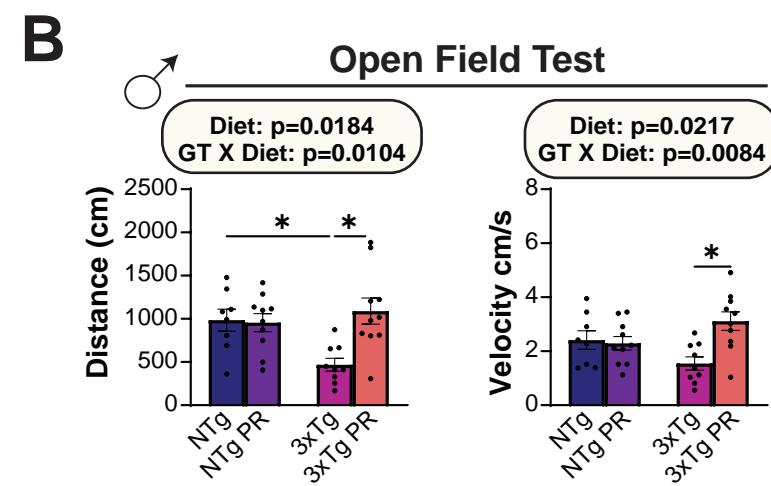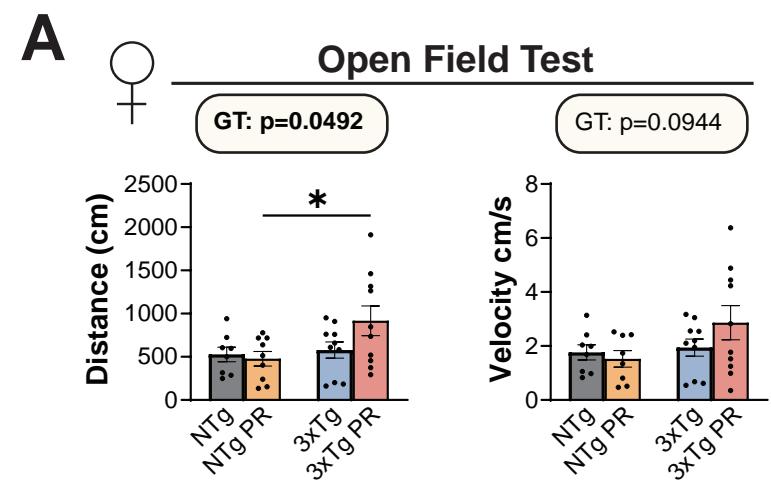
B Open Field Test

Supplementary Figure 5: Effect of PR on open field test performance. (A-B) Distance and velocity of female (A) and male (B) mice during open field test. n=6-10 biologically independent mice per group; statistics for the overall effects of genotype (GT), diet, and the interaction represent the p value from a 2-way ANOVA, *p<0.05, from a Sidak's post-test examining the effect of parameters identified as significant in the 2-way ANOVA. Data represented as mean ± SEM.

Supplemental Tables

Supplementary Table 1: Diet composition and calorie content for diets used in this study.

Supplementary Table 2: List of all 38 metabolites and their compound names identified through metabolomics.

Supplementary Table 3: Peak intensities of the 38 circulating metabolites measured in both males and females of both genotypes.

Supplementary Table 4: Log_2 fold-changes from metabolomic analysis in 3xTg females and males found in **Figure 4B**.

Supplementary Table 5: Results output from Metaboanalyst pathway analysis which shows pathway direction and p-values in both females and males.

Supplementary Table 6: Untargeted lipidomics data from mass spectrometry analysis of hippocampus and cortex in females.

Supplementary Table 7: Untargeted lipidomics data from mass spectrometry analysis of hippocampus and cortex in males

Supplementary Table 8: Results of LION lipid ontology analysis in female 3xTg mice.

Supplementary Table 9: Results of LION lipid ontology analysis in male 3xTg mice.

Supplementary Table 10: Targeted lipidomics data from male and female NTg and 3xTg mice

Supplementary Table 11: Antibodies used for both western blotting and immunohistochemistry.