Reducing astrogliosis rescues early cognitive impairment in APP/PS1 mice

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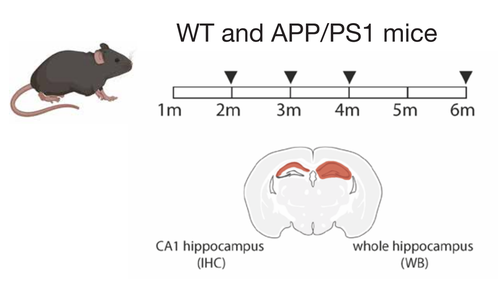
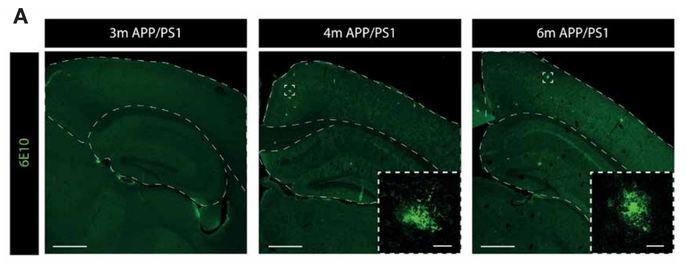
Introduction

In **Alzheimer's disease (AD)**, astrocytes become reactive, displaying a hypertrophic morphology and increased expression of intermediate filament proteins **GFAP and Vimentin**. While this is a key hallmark of AD pathology, the effect of astrogliosis on disease progression is unclear. Some studies decreasing astrogliosis reported rescued pathology, while other studies using Gfap$^{-/-}$Vim$^{-/-}$ mice reported an increase in Aβ plaques in late AD. But whether astrogliosis may be causal to early AD and cognitive dysfunction is unknown.

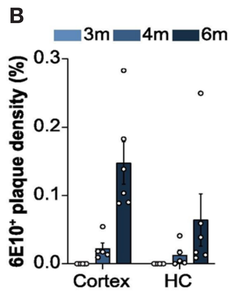
Aim: To characterize how astrocyte reactivity contributes to early AD, we crossed **APP/PS1** mice, an amyloidogenic model of AD, with **Gfap$^{-/-}$Vim$^{-/-}$ mice** and examined its effect on Aβ pathology, microgliosis, cognition and the hippocampal proteome.

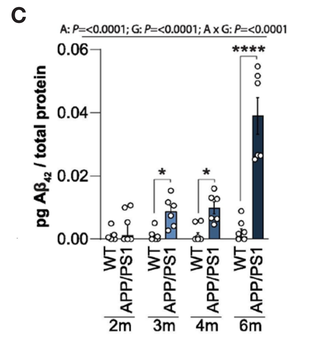
1. Astrogliosis appears before plaques in APP/PS1 mice

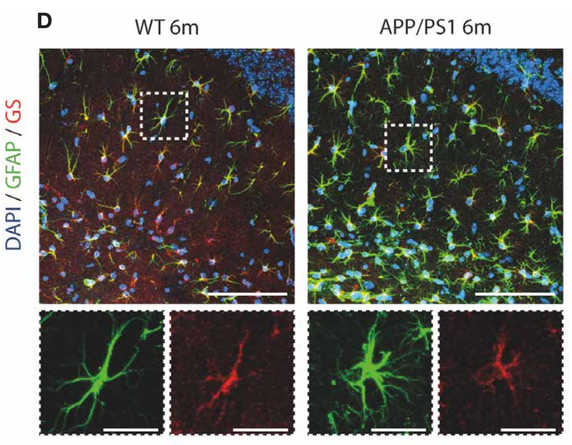


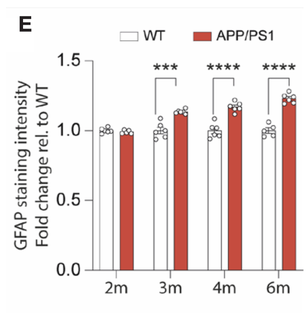


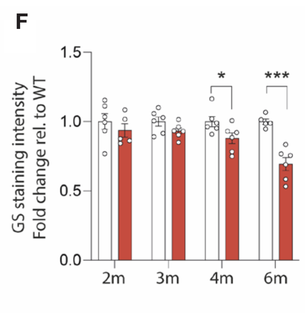
Timeline of pathology in APP/PS1 mice.
(A, B) Aβ plaque deposition starts from 4-6 months (6E10 antibody), (C) while at 3 months there is an increase in Aβ peptide (ELISA).
(D, E, F) Astrogliosis starts from 3 months based on increased GFAP and decreased glutamine synthetase (GS).





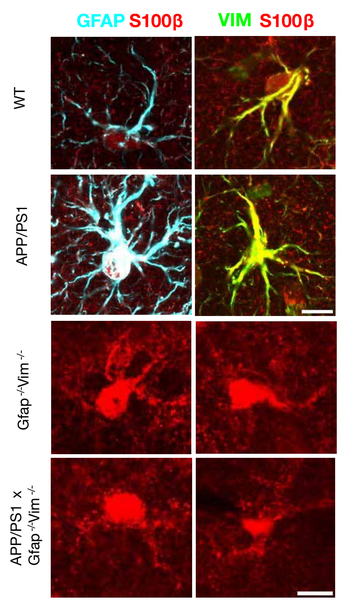


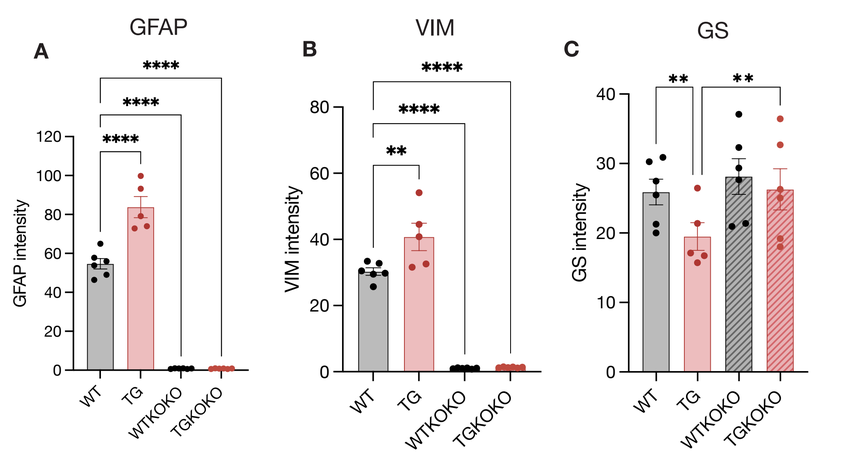




Two-way ANOVA with pairwise comparisons (n = 5-6 mice per group), Kater et al., BBI, 2023

2. Deletion of GFAP and Vimentin attenuates astrogliosis

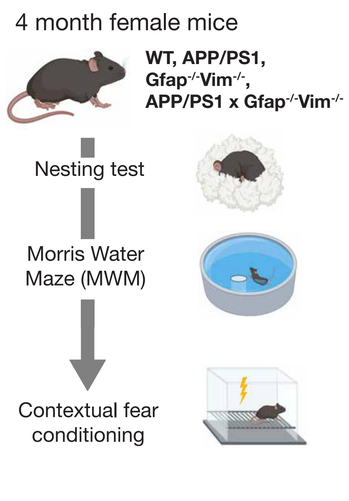


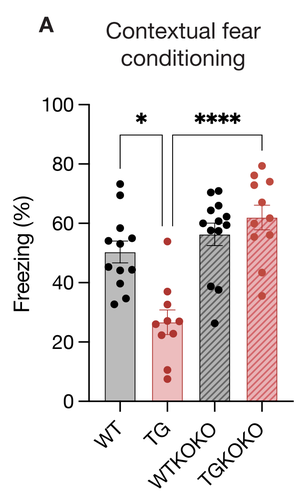


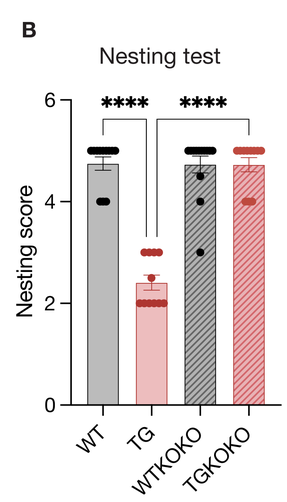
4 month APP/PS1 mice crossed with Gfap$^{-/-}$Vim$^{-/-}$ present a complete abscence of (A) GFAP and (B) Vimentin, and (C) a rescue of other astrogliosis markers, such as glutamine synthetase (GS), revaled through immunohistochemistry.

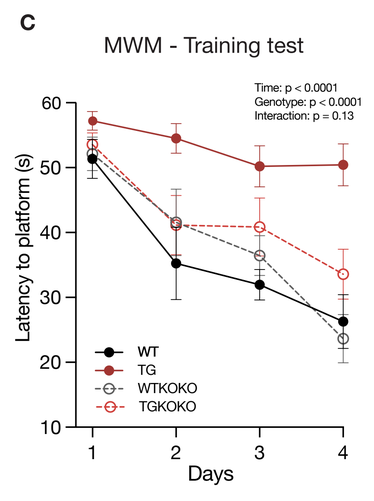
Nested One-way ANOVA, n = 5-6 mice

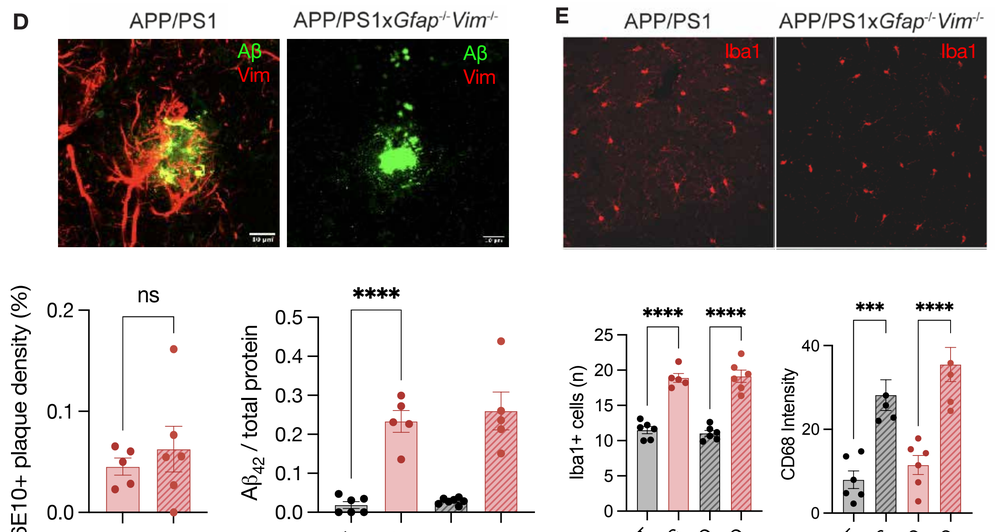
3. GFAP/Vim KO rescues cognitive decline in early AD, independently of Aβ plaques or microgliosis







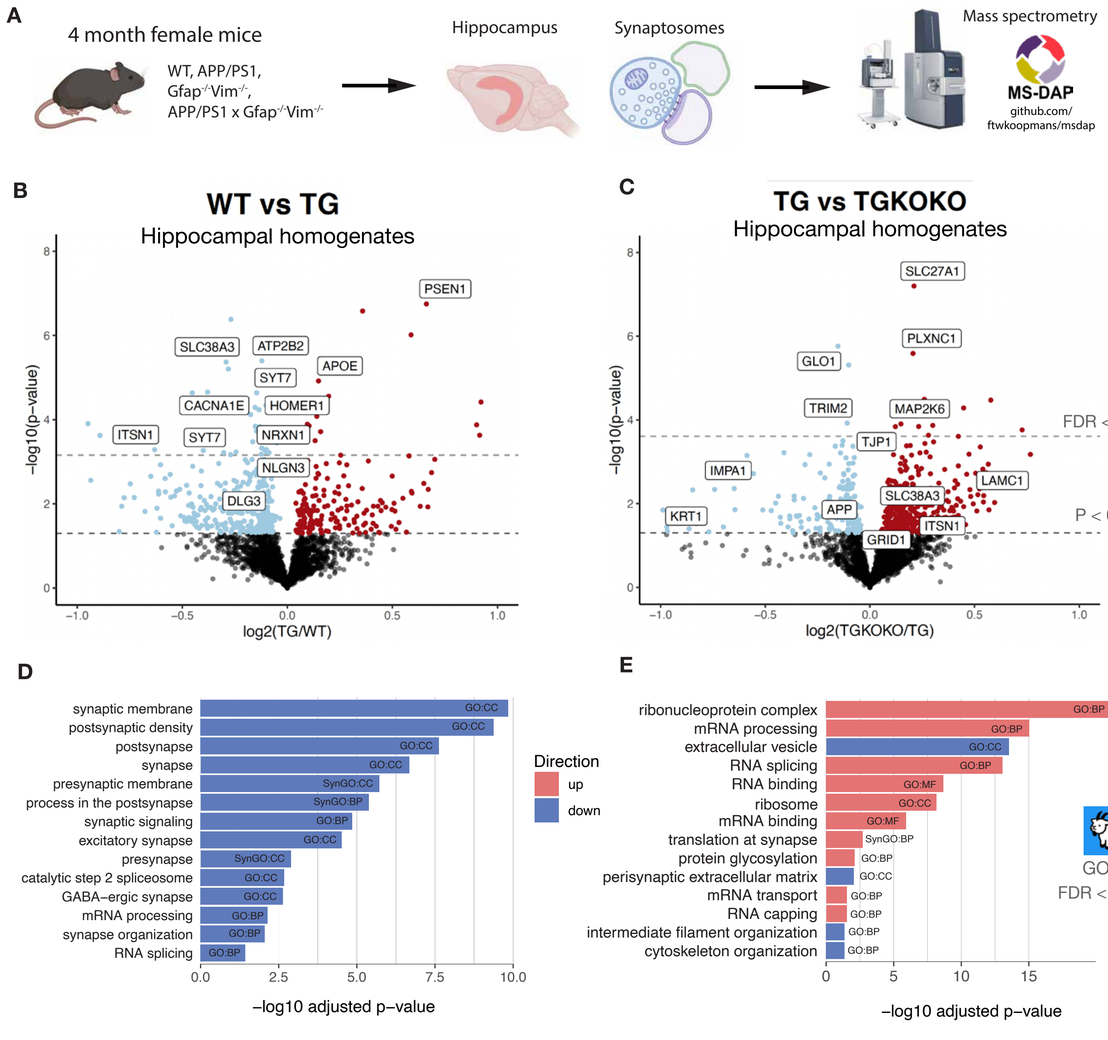




4-month APP/PS1 already exhibit clear cognitive deficits which are rescued by the deletion of GFAP and Vimentin, however, they still present (D) Aβ pathology and (E) microgliosis based on Iba1 and CD68 staining.

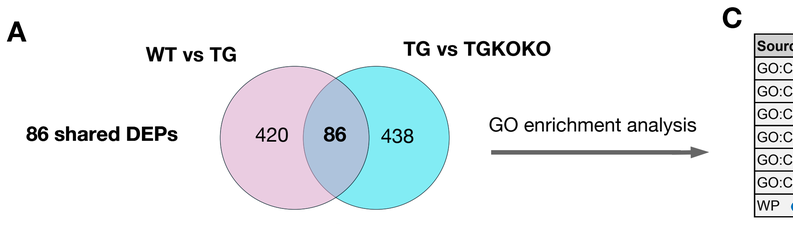
A, B) Kruskal-Wallis test; C) Repeated measures ANOVA (n = 9-13 mice). D) Unpaired t-test; One-way ANOVA; E) Nested one-way ANOVA (n = 5-6 mice)

4. GFAP/Vim KO partly rescues the AD proteomic profile

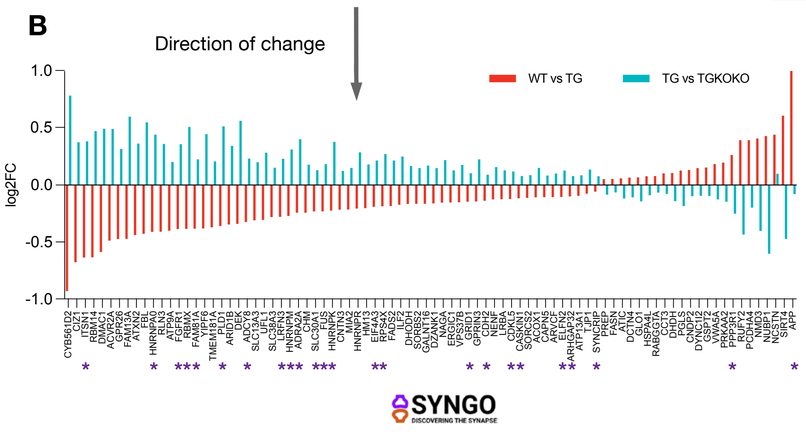


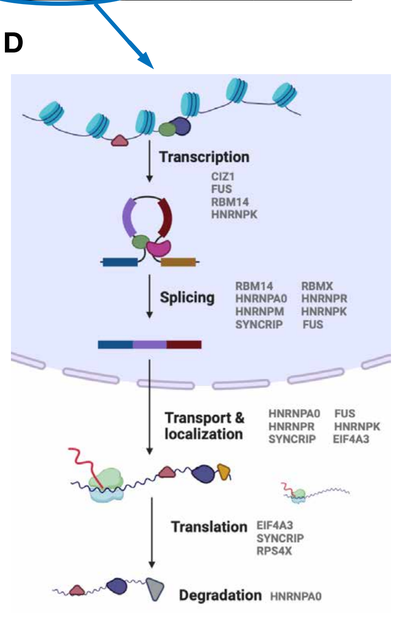
Mass-spectrometry proteomics was performed on hippocampus and synaptosomes from 4-month female mice (A) Volcanoplots of WT vs TG (B) and TG vs TGKOKO (C) illustrating the significantly differentially expressed proteins (DEPs) Gene Set Enrichment Analysis (GSEA) performed in GOAT indicates enriched upregulated and downregulated gene ontology terms, highlighting a downregulation of synaptic proteins and mRNA processing in WT vs TG (D) and an upregulation of mRNA processing in TG vs TGKOKO (E).

5. Synaptic protein synthesis is rescued by the GFAP/Vim KO



Source	Term	FDR	Term ID
GO:CC	postsynaptic density	0,003	GO:0014069
GO:CC	catalytic step 2 spliceosome	0,003	GO:0071013
GO:CC	neuron to neuron synapse	0,003	GO:0098984
GO:CC	postsynapse	0,009	GO:0098794
GO:CC	spliceosomal complex	0,040	GO:0005681
GO:CC	ribonucleoprotein complex	0,048	GO:1990904
WP	mRNA processing	0,0003	WP:WP310





Venn diagram shows the overlap between DEPs in WT vs TG and TG vs TGKOKO, and shows that 86 proteins (20%) of DEPs in WT vs TG are rescued in TG vs TGKOKO, since they show an opposite direction of change (B). These rescued DEPs are enriched in synaptic proteins (C, *SynGO proteins marked with an asterisk) and proteins involved in several steps of mRNA processing and protein synthesis (C, D).

The rescue in protein synthesis was confirmed in synaptosomes (not shown).

Conclusion

- **GFAP/Vim KO reduces astrogliosis and prevents early cognitive decline,** without affecting microglial reactivity and Aβ accumulation. This results in a **rescue of synaptic protein synthesis** liked with a partial rescue of the early AD hippocampal and synaptic proteome.
- This suggests a direct causal link between astrogliosis and synaptic dysfunction, thereby rescuing memory deficits, which we aim to functionally validate in the future

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