

High-fat diet robustly increases CA1 stratum radiatum synaptic density and may modify *App^{NL-F}*-enhanced plasticity in old mice

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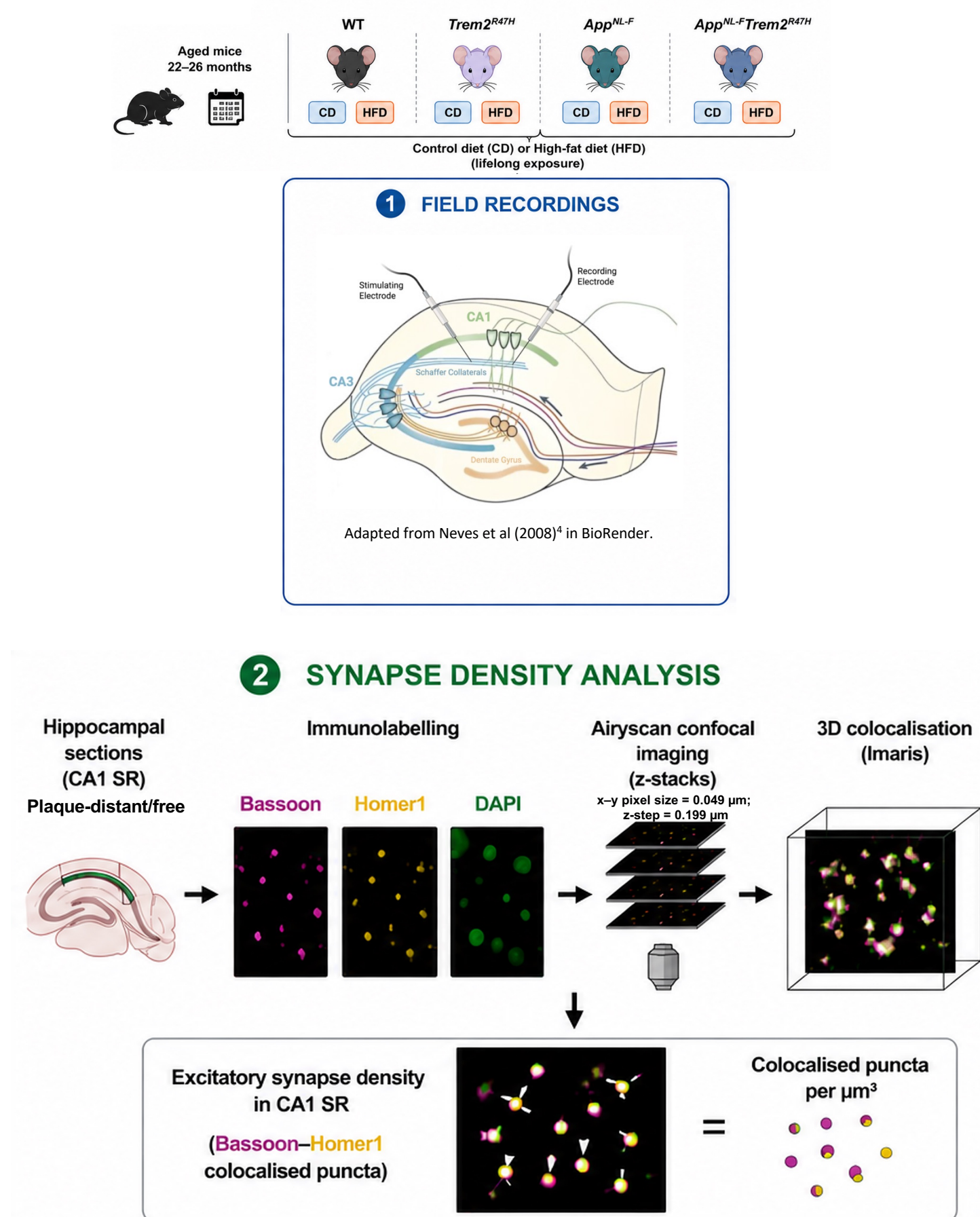
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1. Introduction

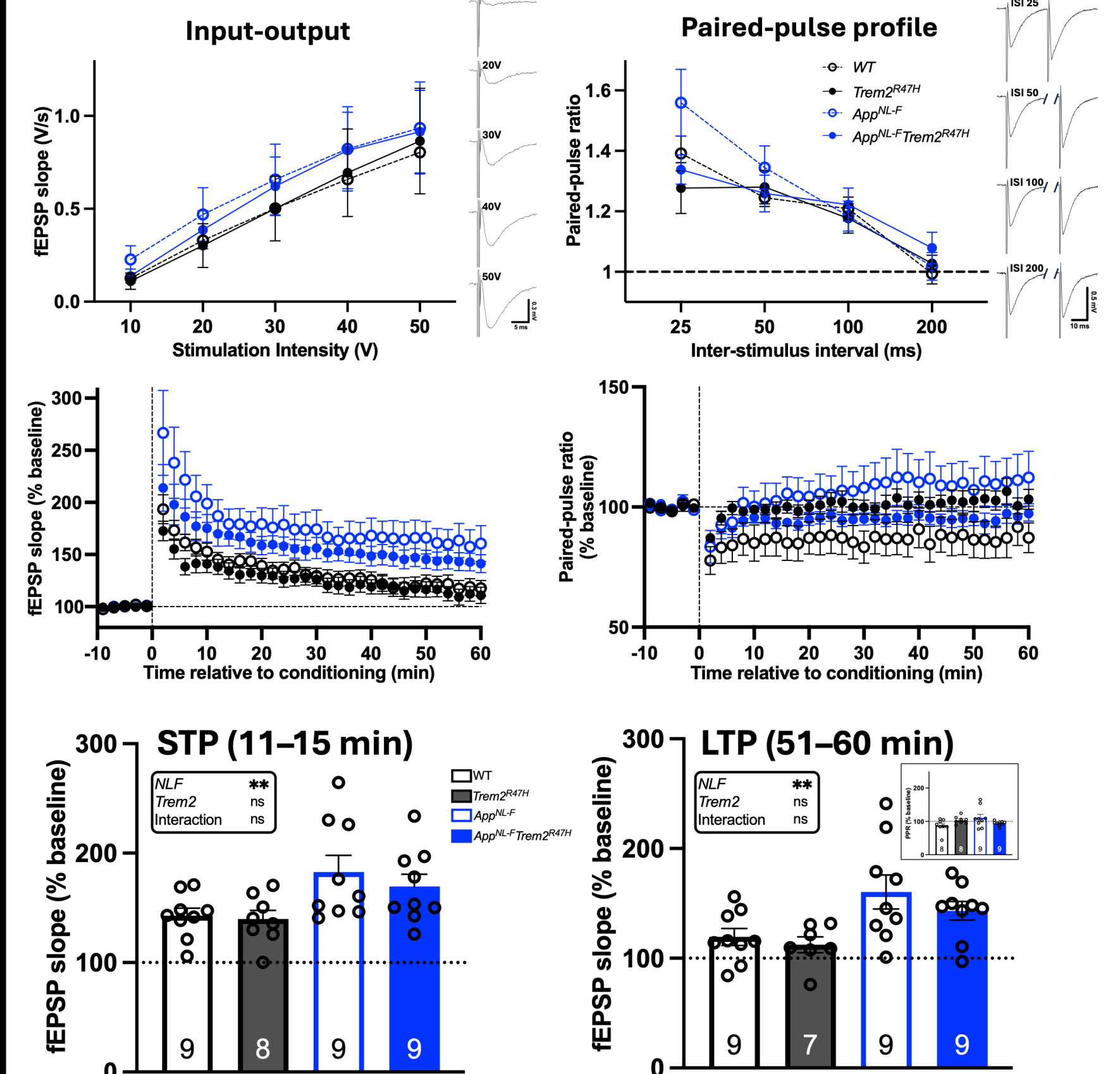
- ❖ Obesity and high-fat diet (HFD) are linked to increased Alzheimer's disease (AD) risk, but effects on aged hippocampal synapses remain unclear¹.
- ❖ *TREM2^{R47H}* is an AD risk variant that alters microglial responses to amyloid pathology and synaptic remodelling^{2,3}.
- ❖ This study tested whether long-term HFD and/or *Trem2^{R47H/R47H}* affect CA1 stratum radiatum (SR) synaptic plasticity and excitatory synapse density in aged *App^{NL-F/NL-F}* knock-in mice.

2. Methods

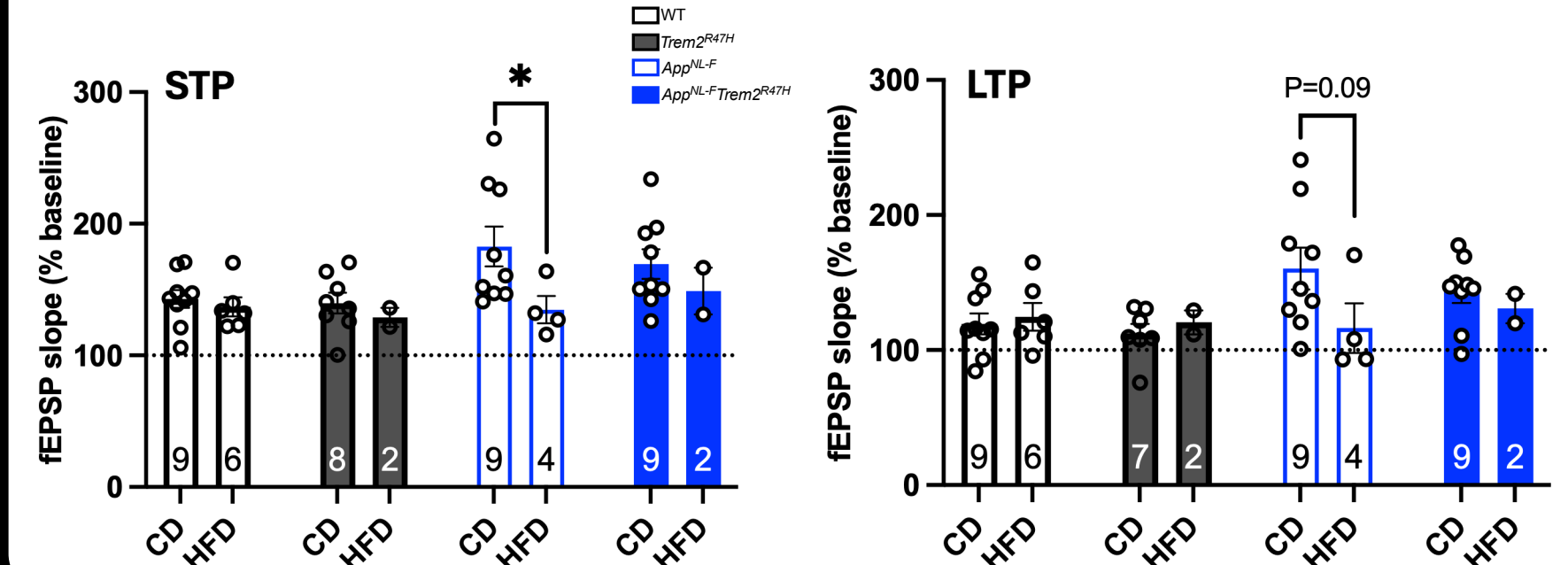


3. Results

A. *App^{NL-F}* enhances SR short- and long-term potentiation without altering basal synaptic transmission in 22–26-month-old mice under control-diet. No effect of the *Trem2^{R47H}* mutation

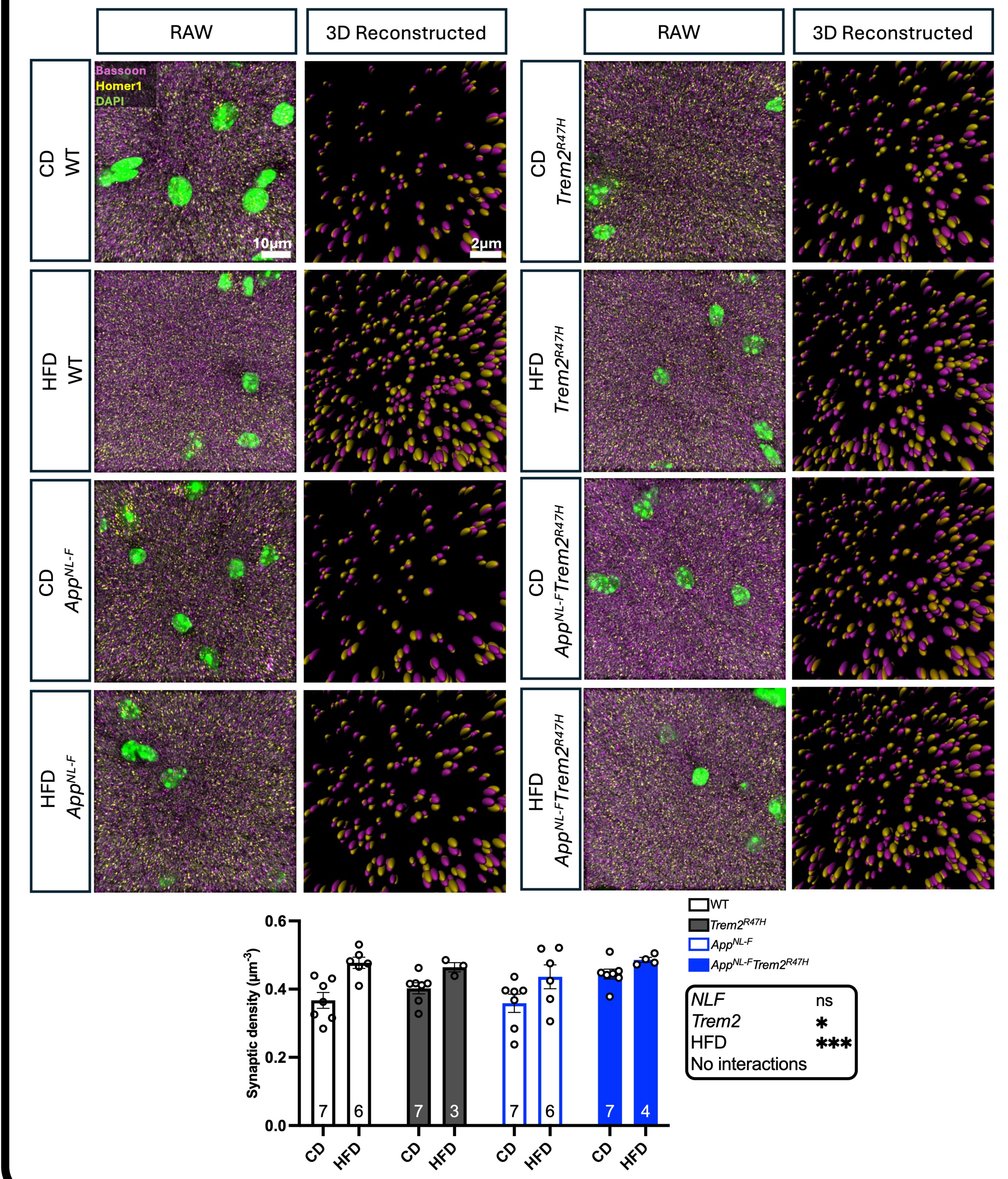


B. HFD reduces SR Short-term potentiation and trends toward lower long-term potentiation in *App^{NL-F}* in 22–26-month-old mice



Results (Cont.)

C. HFD and *Trem2^{R47H}* increase synaptic density in CA1 SR in 22–26-month-old mice



4. Conclusions

- ❖ In aged CD-fed mice, *App^{NL-F}* was associated with larger in magnitude CA1 SR short- and long-term potentiation, without clear changes in basal transmission or plaque-free excitatory synapses.
- ❖ This may suggest that synaptic strength is preserved in the presence of a toxic amyloid-β environment by enhancing synaptic plasticity (i.e. homeostatic plasticity).
- ❖ HFD tended to reduce the *App^{NL-F}*-related LTP magnitude ($P = 0.09$), while clearly increasing excitatory synapse density in plaque-distant/free SR ($P = 0.0001$).
- ❖ *Trem2^{R47H}* had no effect on synaptic transmission, but increased synapse density ($P = 0.02$), possibly reflecting altered microglial regulation of removal of unhealthy synapses.
- ❖ Overall, the data suggest that the possible homeostatic responses to amyloid-related dysfunction may be prevented by metabolic and genetic risk factors.

5. Future directions

- ❖ Extending the work by studying inhibitory synapse density (e.g. Bassoon-Gephyrin colocalisation).
- ❖ Use electron microscopy to examine synaptic ultrastructure, including excitatory and inhibitory synapse types, active-zone structure, postsynaptic density size, and vesicle organisation.
- ❖ Examining microglial-synapse interactions in plaque-distant regions and whether altered synapse density reflects changes in synaptic clearance.



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