

## Supplementary Materials

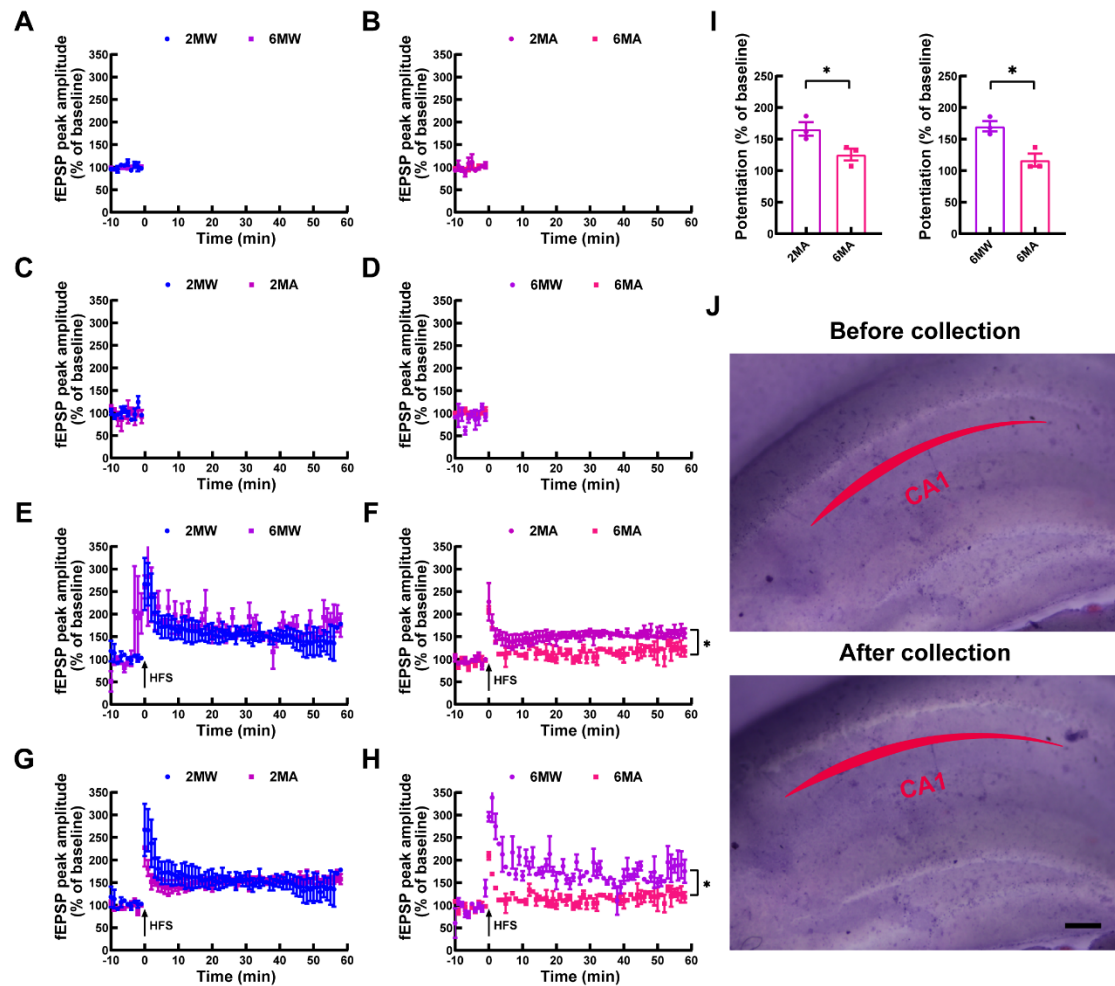
### **Long-term potentiation-based screening identifies neuronal PYGM as a synaptic plasticity regulator participating in Alzheimer's disease**

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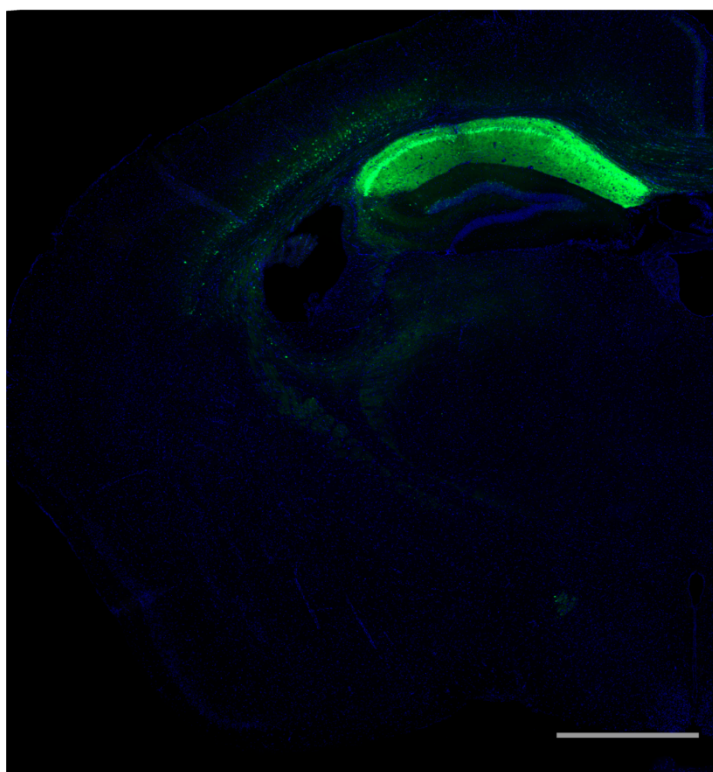
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### Supplementary Figure S1 LTP recordings in hippocampal CA3-CA1 circuit of WT and APP/PS1 AD model mice and sample collection

A–H: Mouse hippocampal slices were stabilized for 10 min. CA3 region was then subjected to high-frequency stimulation (HFS, 100 Hz for 1 s, twice, with 30 s intervals). Induced fEPSPs in CA1 region were recorded for 60 min and compared in a pairwise manner. 2MW, 2-month-old WT mice; 2MA, 2-month-old AD mice; 6MW, 6-month-old WT mice; 6MA, 6-month-old AD mice.  $n=3$  slices from three mice per group. I: Average fEPSP peak amplitudes in the last 10 min of recordings were calculated for comparison. Data represent mean  $\pm$  SEM and were analyzed by unpaired  $t$ -test. \*:  $P < 0.05$ . J: After fEPSP recordings, cells in CA1 region were collected by a capillary-based vacuum-assisted cell and tissue acquisition system for RNA-seq. Scale bars: 100  $\mu$ m.



**Supplementary Figure S2 Representative image of AAV2/9 infection in hippocampal CA1 region**

AAV2/9 expressing GFP was stereotactically injected into hippocampal CA1 region of C57BL/6 WT mice at 4–5 months of age. After 4 months, mice were sacrificed, and brain sections were stained with DAPI and observed under a fully automated digital slide scanner. Scale bar: 1 000  $\mu\text{m}$ .

**Supplementary Table S1** Genes identified by RNA-seq

**Supplementary Table S2** DEGs in WT\_2Mo\_S60 vs WT\_2M0\_NC (S2A), WT\_6Mo\_S60 vs WT\_6M0\_NC (S2B), AD\_2Mo\_S60 vs AD\_2M0\_NC (S2C), AD\_2Mo\_S60 vs AD\_2M0\_NC (S2D), and AD\_6Mo\_NC vs WT\_6M0\_NC (S2E).

**Supplementary Table S3** DEGs consistently altered upon HFS in mice with normal LTP

**Supplementary Table S4** Genes changed in one direction in mice with normal LTP but not changed or changed in the other direction in mice with impaired LTP

**Supplementary Table S5** Candidate genes mediating impaired LTP in AD

**Supplementary Tables S1–S5** are listed as a separate Excel file due to their large size.