

Figure S1. Young adult STEP KO and Het mice showed similar performances compared to young WT mice in the MWM and Y-maze tasks. Related to Figure 1. During the MWM task, no significant difference was observed in the latency (**A**) and path length (**B**) of young (Y; 6mo old) STEP KO (n=9), STEP Het (n=9), and WT mice (n=34) ($P>0.05$; two-way ANOVA, Tukey's HSD test). During the MWM probe trial, speed (one-way ANOVA) (**C**), platform crossing (one-way ANOVA) (**D**), and time spent in the target and opposite quadrants (two-way ANOVA) (**E**) were not significantly different across all groups. (**F**) During the Y-maze, all groups spent more time in the new available arm than in the other arm previously explored during the training phase (** $P<0.01$, *** $P<0.001$; two-way ANOVA). All histograms are presented as mean values \pm s.e.m.

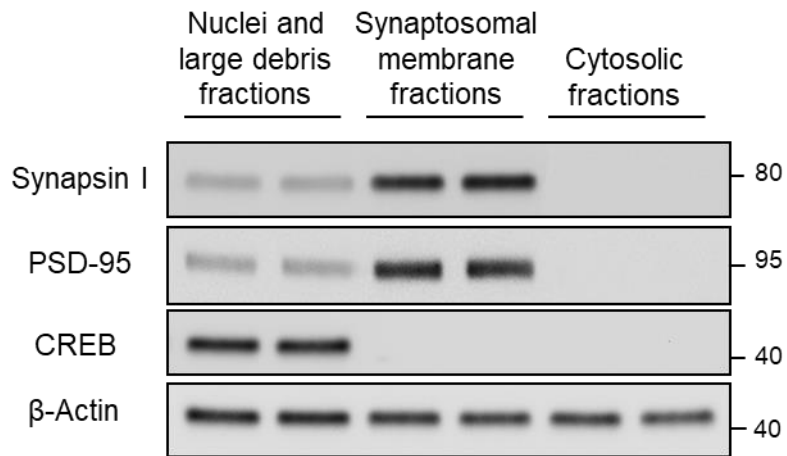


Figure S2. The synaptosomal (P2) membrane fraction prepared from hippocampus is enriched in synaptic proteins. Related to Figure 1. The different fractions were examined for levels of synapsin I and PSD-95 to confirm the enrichment of synaptic proteins in P2 fractions. The level of cAMP response element-binding (CREB), a nuclear protein, was also determined for comparison.

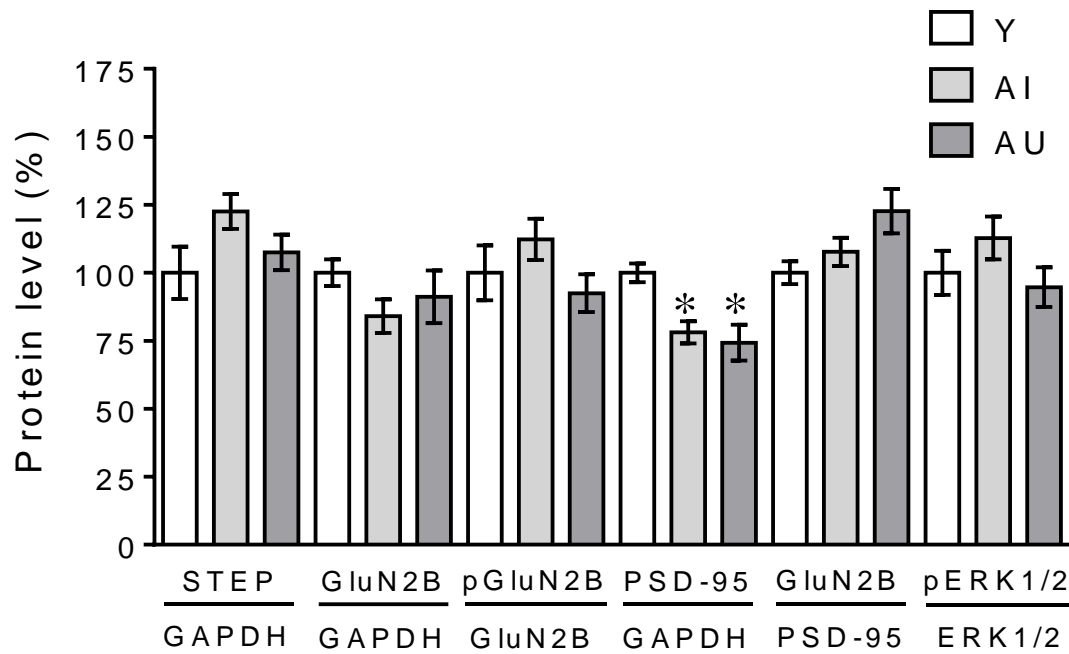


Figure S3. Densitometric quantification of P2 fractions from the occipital cortex. Related to Figure 1.

No significant difference in STEP levels and phosphorylation of GluN2B and ERK1/2 in young (Y; n=9) adult, aged memory-impaired (AI; n=9), and aged memory-unimpaired (AU; n=9) mice. * $P < 0.05$ indicates significant variations compared to Y mice (one-way ANOVA). The histogram is presented as mean values \pm s.e.m.

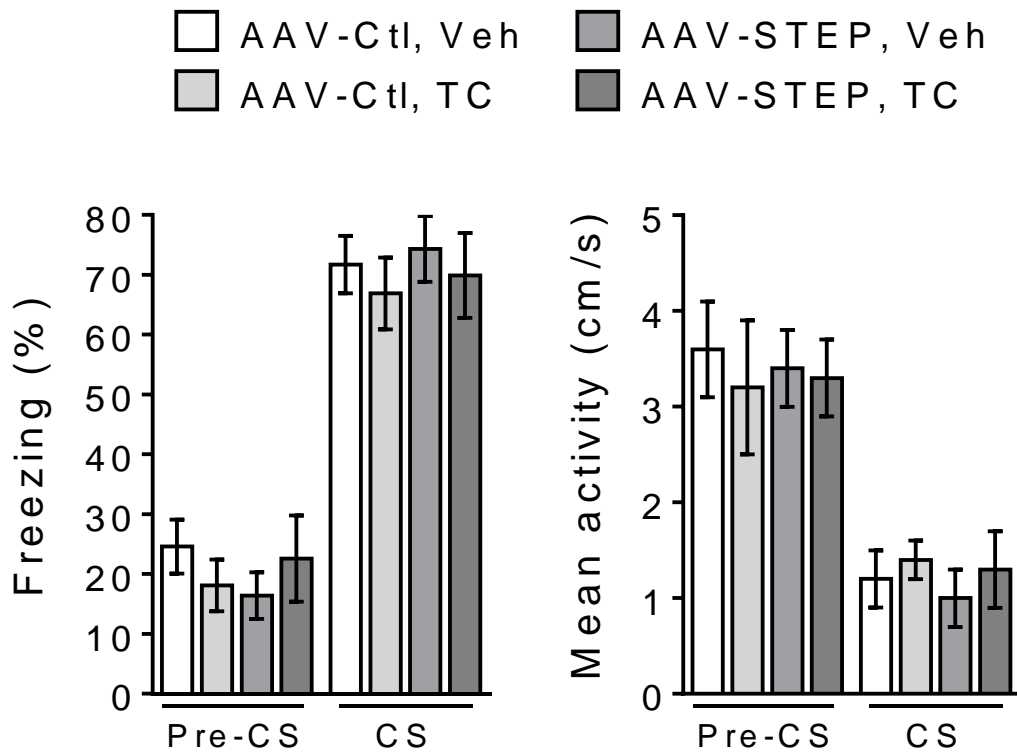


Figure S4. Amygdala-dependent auditory-cued fear conditioning is not altered by hippocampal STEP overexpression. Related to Figure 2. Tone-dependent memory test of mice injected with AAV-STEP or control (Ctl) AAV-EGFP in the CA1 region of dorsal hippocampus, and treated with TC-2153 (i.p., 10mg/kg) or vehicle (Veh; 0.1% DMSO, i.p., v/v) 3h before the training phase, where a tone (Conditioned stimulus, CS; 75dB SPL, 30s) was associated with a footshock (Unconditioned stimulus, US; 0.7mA, 2s). Twenty-four hours after training, mice were tested in a novel context to evaluate freezing and motor activity before (Pre-CS) and after (CS) auditory stimulation. AAV-STEP + Veh mice showed similar freezing and motor activity compared to the other groups after the tone ($P>0.05$; three-way ANOVA; $n=10$ in each group, two independent experiments). Histograms are presented as mean values \pm s.e.m.

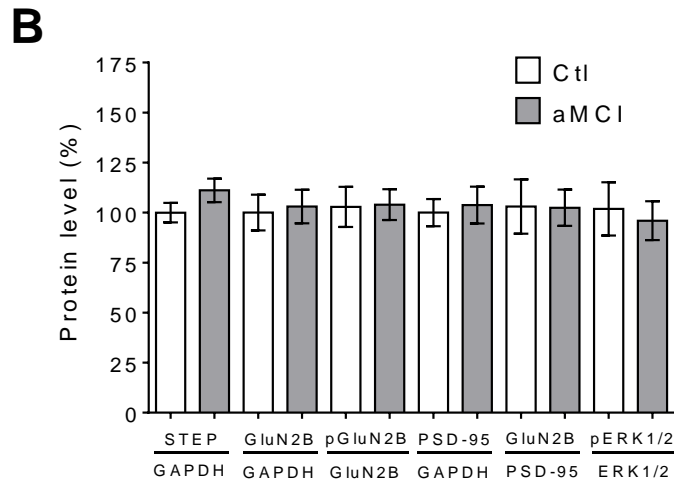
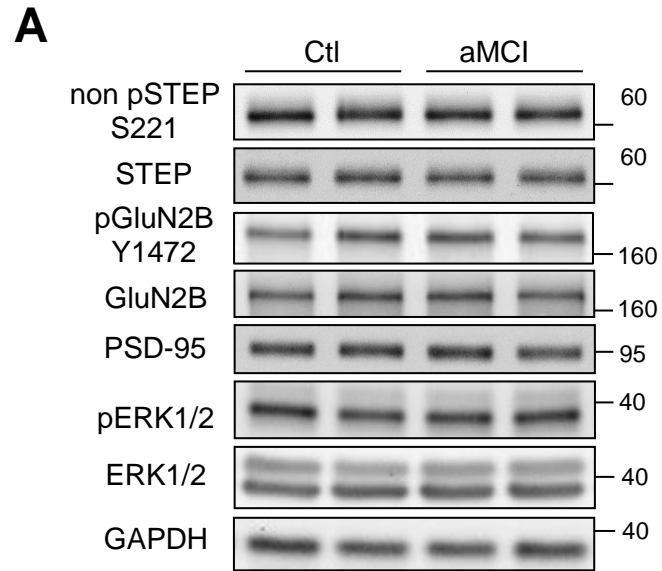


Figure S5. Representative immunoblots (A) and densitometric quantification (B) revealed no significant difference in total and phosphorylated proteins obtained from synaptosomal fraction of the occipital cortex of aMCI patients (n=6) and control (Ctl) aged non-demented subjects (n=8). Related to Figure 5. The histogram is presented as mean values \pm s.e.m.