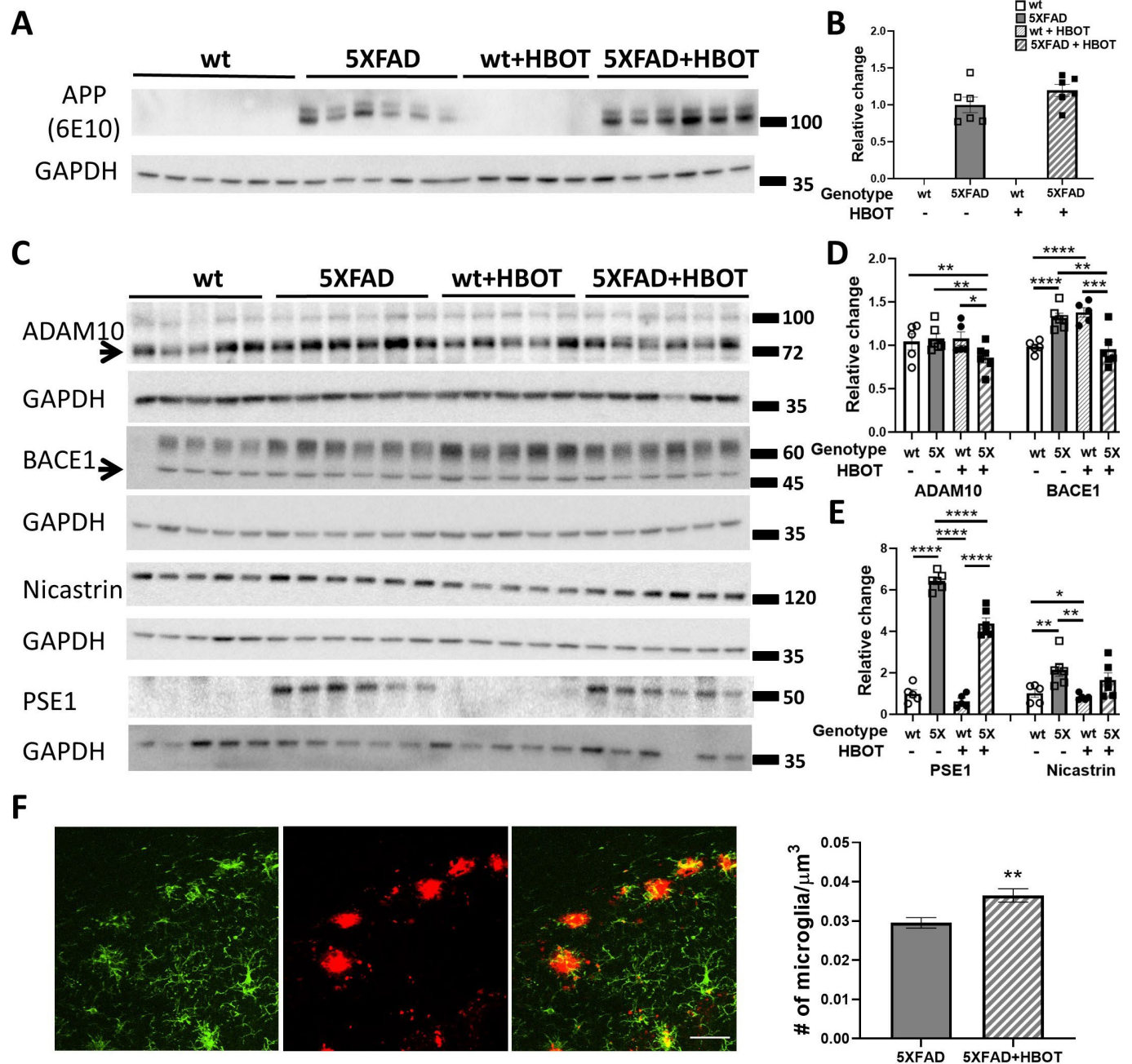
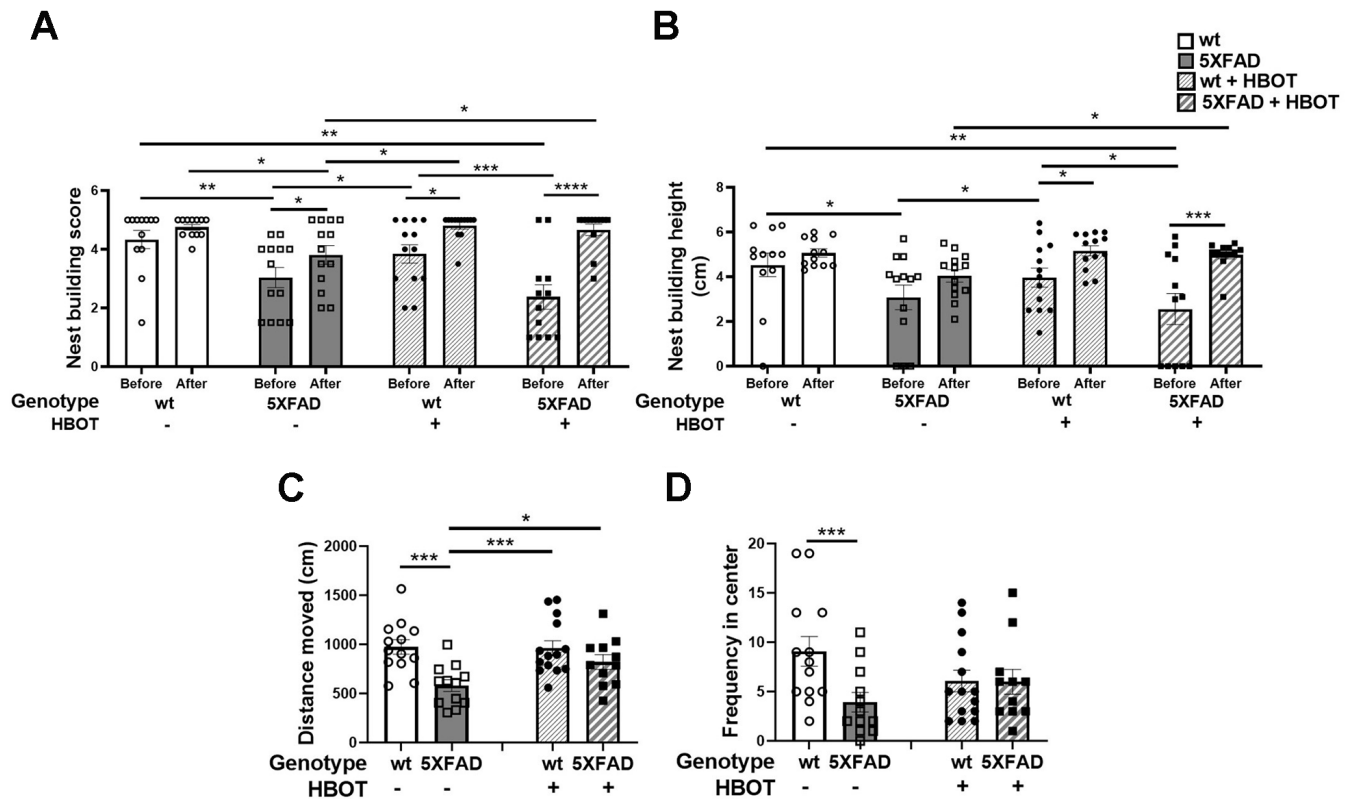


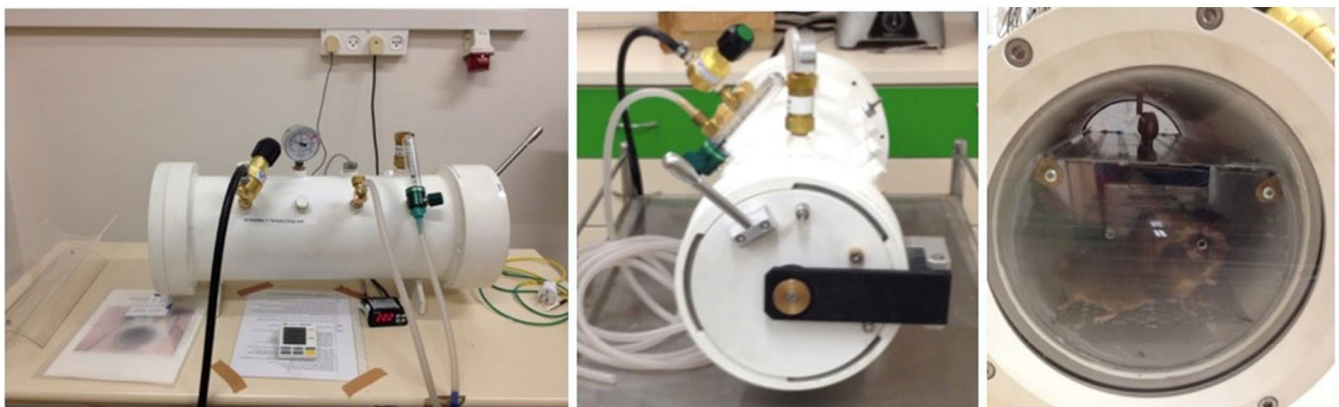
SUPPLEMENTARY FIGURES



Supplementary Figure 1. Western blots of proteins involved in the APP processing pathway in hippocampi extracted from HBO-treated and control 5XFAD mice and wt littermates. (A) Representative immunoblots of the full APP protein detected by 6E10 antibodies. (B) Quantification of western blots in (A), presented as percentages of levels in 5XFAD controls, normalized to GAPDH levels (n = 4–5/group). (C) Representative immunoblots of APP-processing enzymes (ADAM10 and BACE1) and proteins comprising the γ -secretase complex (PSE1 and nicastrin). (D, E) Quantification of the western blots in (C), presented as percentages of levels in wt controls, normalized to GAPDH levels (ADAM10: -37.67%, P = 0.0082; BACE1: -18.16%, P = 0.0011; PSE1: -25.62%, P < 0.000001; n = 4–5/group). Two-way ANOVA and post-hoc Fisher LSD tests were performed. (F). Values represent means \pm SEM. * P < 0.05, ** P < 0.01, *** P < 0.001, **** P < 0.0001. On the left panel, representative images of microglia (Iba-1 staining, green) and plaques (anti-A β 4G8 staining, red) in the hippocampal CA1 of a 5XFAD mouse. Scale bar 40 μm . On the right panel, quantification of the number of plaque-associated microglia normalized to plaque size (μm^3) in control (N= 1108 plaques) and HBOT 5XFAD (N=907 plaques) mice (n=5 per group).



Supplementary Figure 2. HBO improves performance of 5XFAD in behavioral tasks. Overnight nest building was assessed by nest building score (A) and height (B) before and after a month of HBO or control normobaric treatment of 5XFAD mice and their wt littermates. (C, D) In the open field test, HBO-treated 5XFAD mice show higher locomotive activity than control 5XFAD mice, as demonstrated by distances covered (C). No changes were observed between HBO-treated 5XFAD mice and control mice in terms of navigation in the open field, as reflected by the number of times the center of the arena was crossed (D). Values represent means \pm SEM. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, **** $P < 0.0001$.



Supplementary Figure 3. Hyperbaric oxygen therapy chamber for small animals. A custom-made chamber for small animals was used to expose 5XFAD mice to HBO. Oxygen levels in the chamber reached saturation of $\geq 96\%$, as measured by an oxygen analyzer (model 320BRC, Teledyne Analytical Instruments). Left: front view; middle: side view; right: side view with open door.