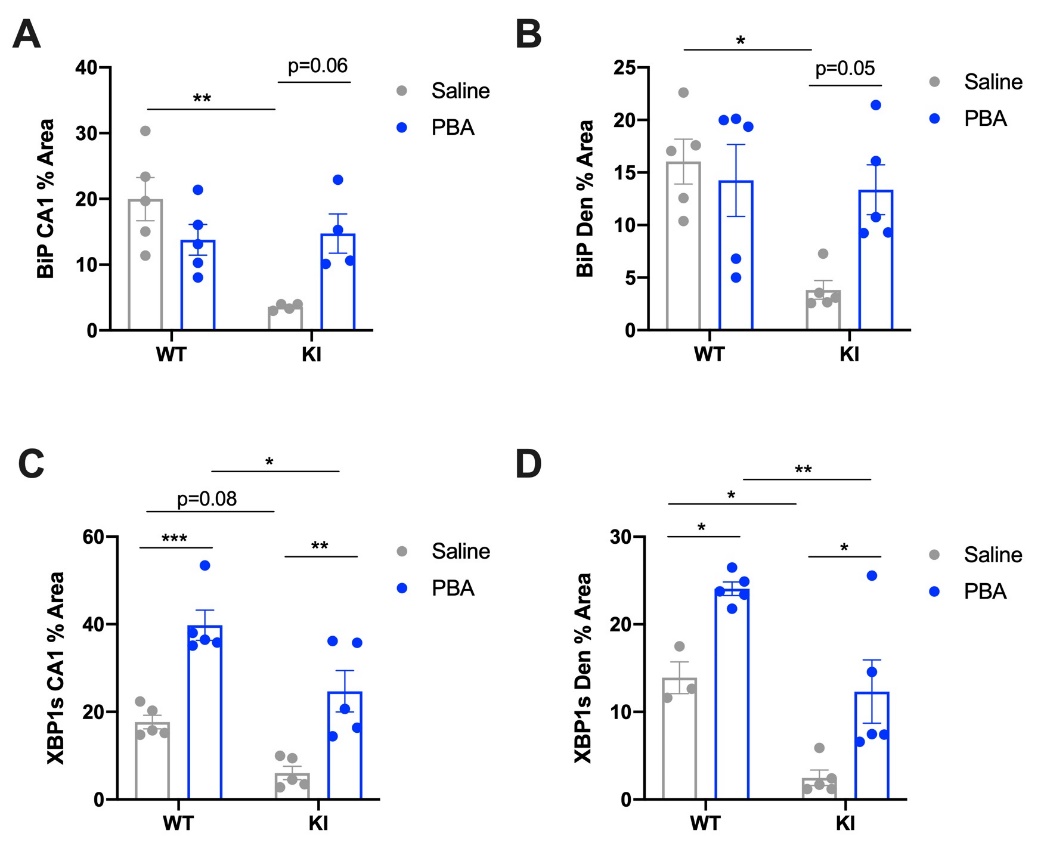
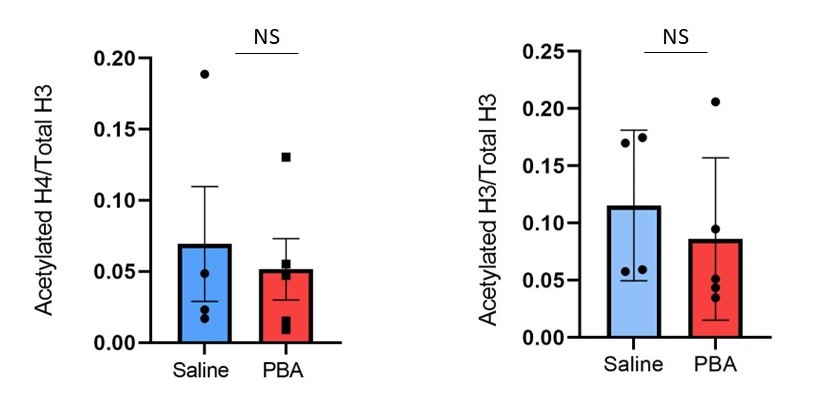
**Supplementary Materials**





**E**

**Figure S1: PBA treatment from weaning increases BiP and XBP1s in the hippocampus of *APPNL-G-F* KI mice.** Immunofluorescence quantification of BiP and XBP1s in hippocampal subregions. A: BiP in CA1; B: BiP in dentate gyrus; C: XBP1s in the CA1; D: XBP1s in dentate gyrus; E: Acetylated lysine quantification H3(K9/K14) and H4(K5) in cortical tissue from westerns of APPNL-G-F KI mice treated with saline or PBA (n=3-5 animals per group; two-way ANOVA with Tukey post-hoc correction for multiple comparisons, \*p<0.05, \*\*p<0.01, \*\*\*p<0.001).

**![Graphical user interface

Description automatically generated with medium confidence](data:image/jpeg;base64,/9j/4AAQSkZJRgABAQEAYABgAAD/4TDkRXhpZgAATU0AKgAAAAgABgALAAIAAAAmAAAIYgESAAMAAAABAAEAAAExAAIAAAAmAAAIiAEyAAIAAAAUAAAIrodpAAQAAAABAAAIwuocAAcAAAgMAAAAVgAAEUYc6gAAAAgAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAFdpbmRvd3MgUGhvdG8gRWRpdG9yIDEwLjAuMTAwMTEuMTYzODQAV2luZG93cyBQaG90byBFZGl0b3IgMTAuMC4xMDAxMS4xNjM4NAAyMDIzOjA1OjA0IDE0OjM2OjEwAAAGkAMAAgAAABQAABEckAQAAgAAABQAABEwkpEAAgAAAAMwMAAAkpIAAgAAAAMwMAAAoAEAAwAAAAEAAQAA6hwABwAACAwAAAkQAAAAABzqAAAACAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA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**Figure S2. A: Quantification of BiP immunofluorescence in the dentate gyrus following local hippocampal AAV-BiP and AAV-mCherry microinjections.** Representative confocal images of the dentate gyrus across groups. Top Row: *APPWT*WT mice Bottom Row: *APPNL-G-F* KI mice; Right: Quantification of immunofluorescence in the dentate gyrus. Mean ± SE percent area of BiP within hippocampal dentate gyrus sections (n=4-5 animals per group; two-way ANOVA with Tukey post-hoc correction for multiple comparisons, \*p<0.05, \*\*p<0.01). **B:** western blot quantification of BiP in KI bulk hippocampus and representative image following AAV-BiP microinjections.

**Chart, scatter chart

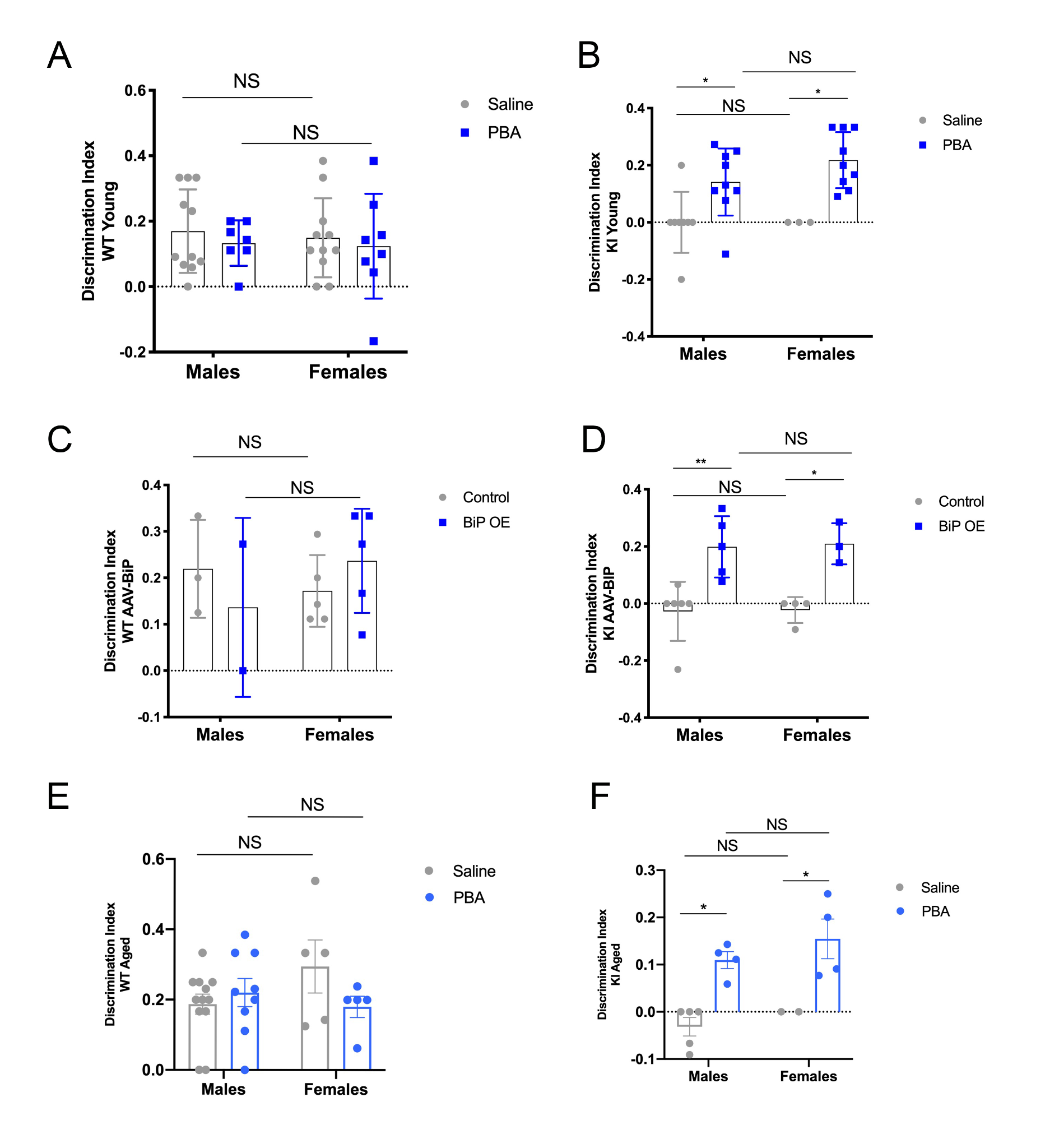
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**Figure S3: Late-stage PBA treatment increases BiP and XBP1s in 10–12-month-old *APPNL-G-F* KI mice.** Immunofluorescence quantification of BiP and XBP1s in hippocampal subregions. A: BiP in dentate gyrus; B: XBP1s in CA1. (n=3-5 animals per group; two-way ANOVA with Tukey post-hoc correction for multiple comparisons, \*p<0.05, \*\*p<0.01).

**A group of blue and orange bars

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**Figure S4: PBA improves performance in SOR test in *APPNL-G-F* KI mice.** Percentage of time spent attending to the object prior to moving (trial, blue bar) and after moving (test, orange bar) in wildtype (WT) and *APPNL-G-F* KI mice (KI) treated with PBA or saline; A: Young B: AgedData are presented as mean ± SE; two-way ANOVA. \*p < 0.05; \*\*p < 0.01, \*\*\* p<0.001

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**Figure S5: SOR discrimination index did not vary by sex in any chaperone treatment paradigm.** Discrimination index of SOR test by sex across groups. A-B: Discrimination index in mice following PBA treatment from weaning; A: *APPWT* WT mice; B: *APPNL-G-F* KI mice; C-D: Discrimination index in mice following AAV-BiP or AAV-mCherry hippocampal microinjections; C: *APPWT* WT mice; D: *APPNL-G-F* KI mice; E-F: Discrimination index in mice following late-stage PBA treatment; E: *APPWT* WT mice; F: *APPNL-G-F* KI mice. (All analyses performed using two-way ANOVA with Tukey post-hoc correction for multiple comparisons, \*p<0.05, \*\*p<0.01).

**Table S1: ANOVA interaction values for immunofluorescence assays in *APPNL-G-F* KI and *APPWT* WT mice following saline and PBA treatment from weaning.**

|  |  |  |  |
| --- | --- | --- | --- |
| **Marker** | **pint** | **Marker** | **pint** |
| BiP | **CA1: 0.005** | XBP1 | CA1: 0.59 |
| **CA3: 0.0009** | CA3: 0.88 |
| **DEN: 0.03** | DEN: 0.95 |
| pPERK | CA1: 0.61 | ADAM10 | **CA1: 0.0003** |
| CA3: 0.61 | **CA3: 0.0001** |
| DEN: 0.69 | **DEN: 0.003** |
| ATF4 | **CA1: 0.0002** | p-CREB | **DEN: 0.05** |
| CA3: 0.87 |
| **DEN: 0.008** |
| Significant values (p<0.05) in bold | | | |

**Table S2: ANOVA interaction values for immunofluorescence assays in *APPNL-G-F* KI and *APPWT* WT mice following AAV-mCherry and AAV-BiP injections.**

|  |  |  |  |
| --- | --- | --- | --- |
| Marker | pint | Marker | pint |
| BiP | **CA3: 0.02** | ADAM10 | CA3: 0.20 |
| DEN: 0.12 | DEN: 0.31 |
| pPERK | **CA3: 0.008** | p-CREB | **DEN: 0.01** |
| **DEN: 0.02** |
| Significant values (p<0.05) in bold | | | |

**Table S3: ANOVA interaction values for immunofluorescence assays in 10–12-month-old mice *APPNL-G-F* KI and *APPWT* WT mice following late-stage saline and PBA intervention.**

|  |  |  |  |
| --- | --- | --- | --- |
| Marker | pint | Marker | pint |
| BiP | **CA1: 0.03** | CHOP | CA1: 0.97 |
| **CA3: 0.03** |  | **CA3: 0.05** |
| DEN: 0.21 |  | DEN: 0.62 |
| pPERK | CA1: 0.97 | XBP1 | **CA1: 0.002** |
| CA3: 0.70 |  | **CA3: <0.0001** |
| DEN: 0.68 |  | **DEN: 0.01** |
| ATF4 | CA1: 0.35 | ADAM10 | CA1: 0.57 |
| CA3: 0.87 |  | **CA3: 0.03** |
| DEN: 0.52 |  | DEN: 0.59 |
| Significant values (p<0.05) in bold | | p-CREB | *DEN: 0.08* |

**Table S4: ANOVA interaction values for the discrimination index across SOR tests.**

|  |  |
| --- | --- |
| SOR | pint |
| PBA from weaning | **0.0002** |
| AAV-BIP | *0.06* |
| PBA from 10-12mos | **0.017** |
| Significant values (p<0.05) in bold | |

**Table S5: Mouse number distributions across all SOR experiments.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Treatment from Weaning | | | |
| Saline | | PBA | |
| Males | Females | Males | Females |
| WT | 11 | 11 | 7 | 8 |
| KI | 7 | 3 | 9 | 9 |
|  | AAV-BiP and AAV-mCherry | | | |
| AAV-mCherry | | AAV-BiP | |
| Males | Females | Males | Females |
| WT | 3 | 5 | 1 | 5 |
| KI | 6 | 4 | 5 | 5 |
|  | Late-Stage Treatment | | | |
| Saline | | PBA | |
| Males | Females | Males | Females |
| WT | 12 | 5 | 9 | 6 |
| KI | 6 | 2 | 4 | 6 |
| Table of total mouse numbers utilized across SOR behavioral experiments. | | | | |

Antibodies used in Western Analyses

Primary Antibodies: GADD34 (1:500, Protein Tech 10449-1-AP); pAKT (1:500, Cell Signaling 9271); Akt (1:500, Cell Signaling 9272); BDNF (1:500, Abcam ab108319); β-Actin (1:2000, Santa Cruz sc-47778); GluR1 (1:500, Novus NBP2-61472); H3(K9/K14) (1:500, Cell Signaling); H4(K5) (1:1000, Cell Signaling), Histone H3 (1:500, Millipore). Secondary antibodies: LiCor IRDye 680RD Goat anti-Mouse (1:10,000); LiCor IRDye 800RD Goat anti-Mouse (1:10,000); LiCor IRDye 800RD Goat anti-Rabbit (1:10,000); Odyssey IRDye 680 Goat anti-Rabbit (1:10,000).

Antibodies used for Immunohistochemistry.

Primary antibodies are as follows: pCREB (ser133) (1:300, Cell Signaling 87G3); CREB (1:200, Cell Signaling 86B10); pPERK (Thr980) (1:200, Bioss bs-3330R); ATF4 (1:500, ProteinTech, 60035-1-Ig); peIF2α (1:100, Cell Signaling 3597S); BiP/anti-KDEL (1:1000, Enzo Life Sciences ADI-SPA-827F). Secondary antibodies are as follows: Alexa Fluor 488 donkey anti-rabbit IgG (1:500); Alex Fluor 594 donkey anti-mouse IgG (1:500); Alexa Fluor 488 donkey anti-mouse IgG (1:500).