

Supplementary Materials

Table S1. Repeat experiments of 12-day food intake in *Bdnf-e1^{-/-}* mice.

| Repeat number | Age (month) | Daily food intake (g) | | p value [#] |
|---------------|-------------|------------------------------|----------------|----------------------|
| | | <i>Bdnf-e1^{-/-}</i> | WT littermates | |
| 1* | 5 | 4.97±0.14 | 4.81±0.24 | 0.5464 |
| 2 | 4 | 4.01±0.29 | 3.68±0.10 | 0.2646 |

* This repeat experiment was performed by a independent CRO. # Data were presented as mean ± SEM. p value for RM two-way ANOVA.

Figure S1

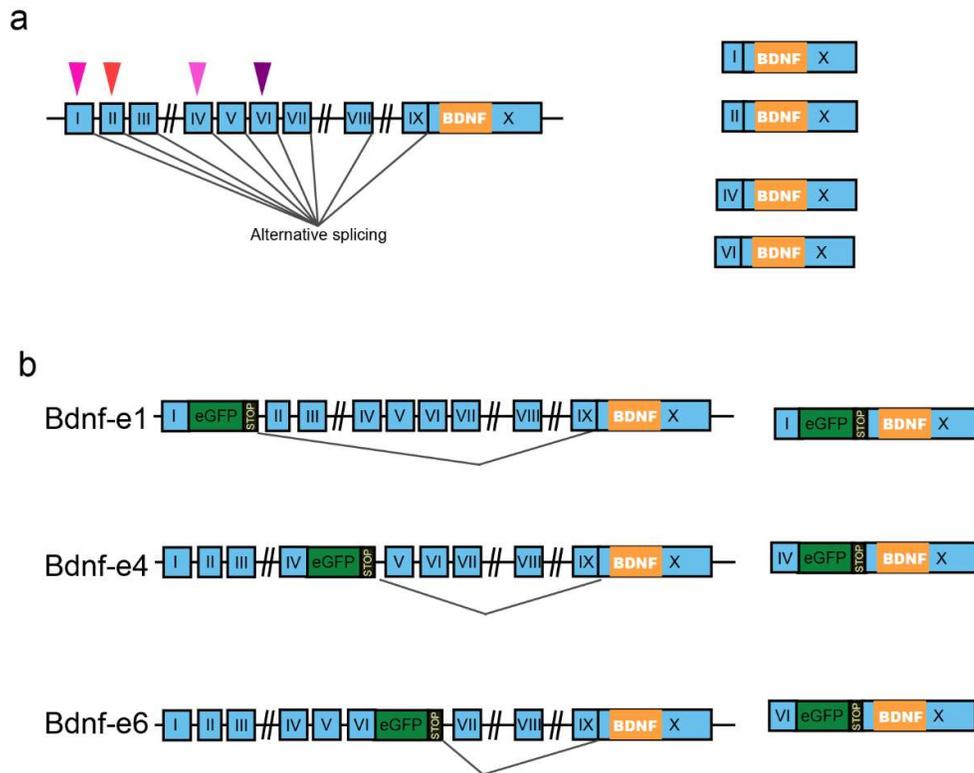


Figure S1: Schematic diagrams of WT and mutant *Bdnf* gene.

(a) Schematic diagrams for the genomic structure of *Bdnf* and four transcripts driven by promoter I, II, IV and VI. **(b)** Schematic diagrams of splicing and the consequent transcripts in *Bdnf-e1*^{-/-}, *Bdnf-e4*^{-/-} and *Bdnf-e6*^{-/-} mice.

Figure S2

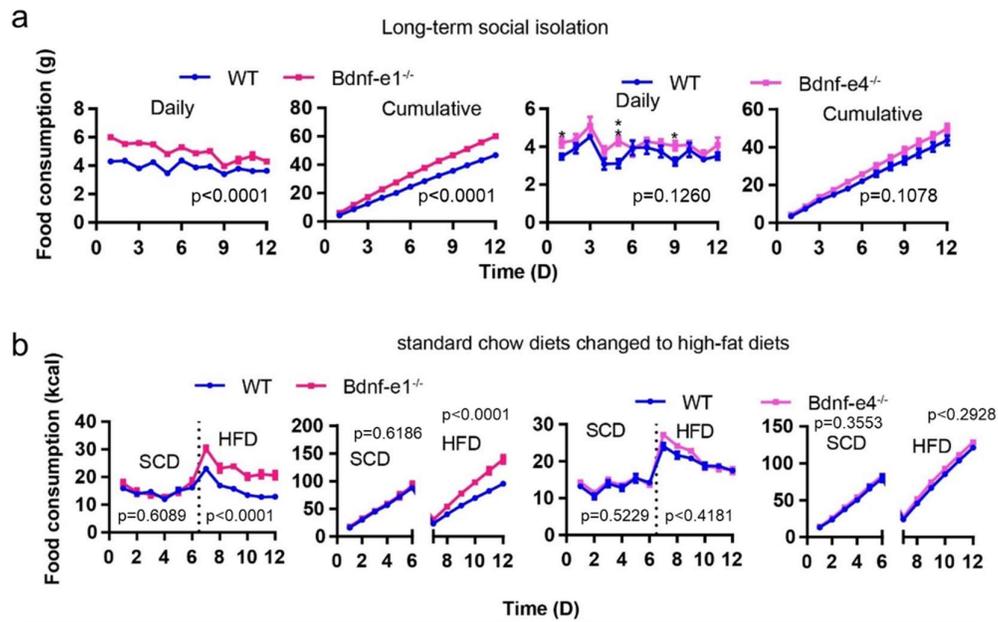


Figure S2: Food intake analysis under the stress of social isolation or high-fat diets. **(a)** Daily and cumulative food consumption of *Bdnf-e1^{-/-}*, *Bdnf-e4^{-/-}* and WT littermates, after long-term social isolation for more than one month. **(b)** Daily and cumulative food consumption of *Bdnf-e1^{-/-}*, *Bdnf-e4^{-/-}* and WT littermates, when food was changed from standard chow diets (SCD) to high-fat diets (HFD). p values of two-way RM ANOVA for daily and cumulative data were labeled correspondingly in panels.

Figure S3

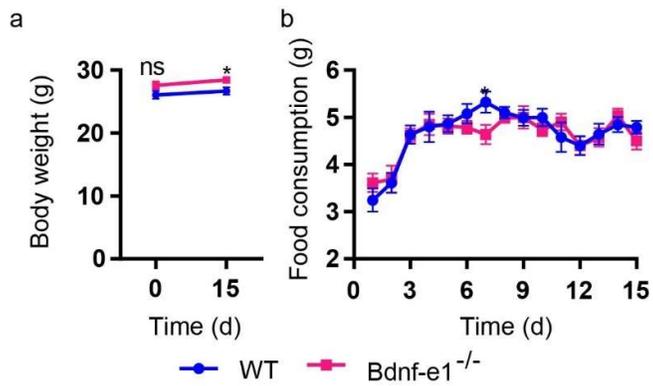


Figure S3: Food consumption in *Bdnf-e1*^{-/-} mice.

(a) Food consumption and body weight of *Bdnf-e1*^{-/-} mice and their WT littermates during the onset of obesity (n=8~9/group). (b) Food consumption of *Bdnf-e1*^{-/-} mice and their WT littermates (n=5~6/group).

Figure S4

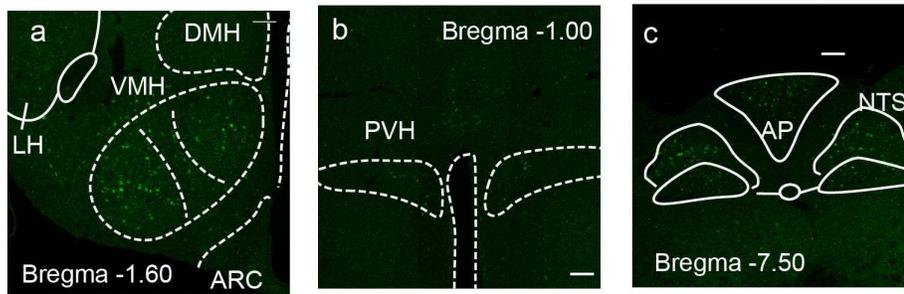


Figure S4: Large images of pII-driven GFP immunostaining.
(a,b) Hypothalamus and (c) DVC. Scale bar: 50 μm.

Figure S5

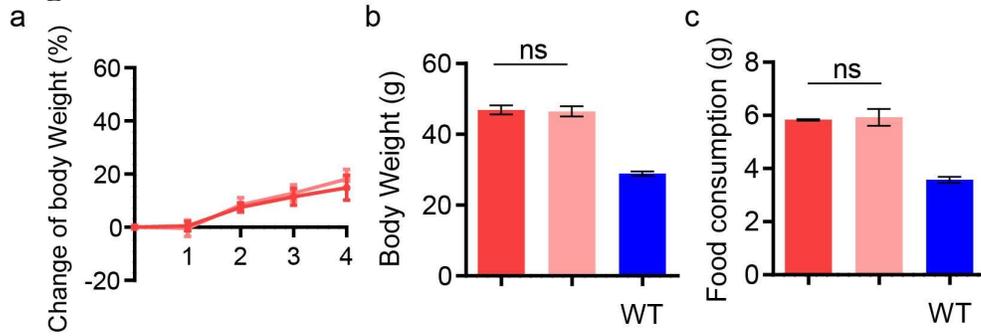


Figure S5: Injection of AAV- e2-BDNF-Myc into DVC.

(a) Change of body weight after injection of AAVs into DVC in *Bdnf-e2^{-/-}* mice (n=3~4/group). p value of two-way RM ANOVA was 0.7783. (b) Body weight of *Bdnf-e2^{-/-}* mice 4 weeks with injection of AAVs into DVC (n=3~4/group), compared with WT littermates (n=7). (c) Average daily food intake of *Bdnf-e2^{-/-}* mice 4 weeks with injection of AAVs into DVC (n=3~4/group), compared with WT littermates (n=7).

Figure S6

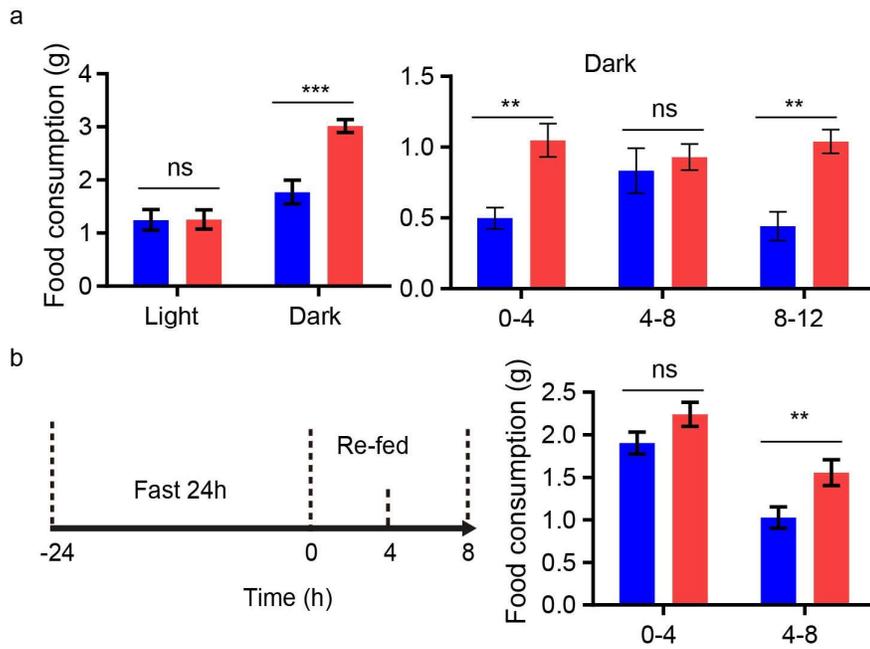


Figure S6: Less satiety in *Bdnf-e2^{-/-}* mice.

(a) Food consumption during different periods. Numbers in the bottom indicate 0-4, 4-8, 8-12 hours during darkness. (b) Food consumption after 24h fasting. *Bdnf-e2^{-/-}* mice, red; WT mice, blue. n=5~7/group.

Figure S7

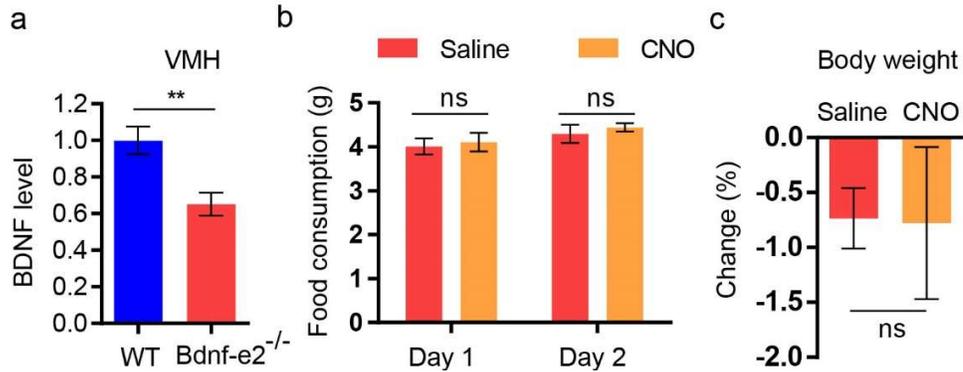


Figure S7: CNO treatment without AAV infection.

(a) Relative levels of BDNF protein in VMH of *Bdnf-e2^{-/-}* and WT mice. (b,c) Food consumption (b) and change of body weight (c) after treatment of CNO or saline in *Bdnf-e2^{-/-}* mice without AAV infection.

Figure S8

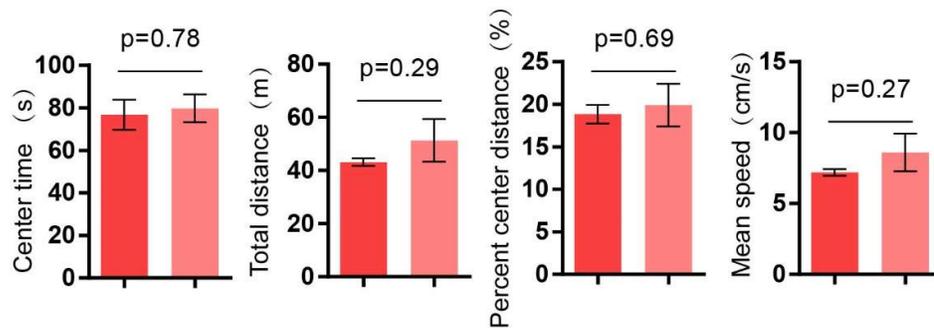


Figure S8: Effects of TrkB agonistic antibody injected into VMH of *Bdnf-e2^{-/-}* mice on open field test.

Center time, total distance, percent center distance and mean speed during 10 minutes of open field test on the third day of *Bdnf-e2^{-/-}* mice injected with TrkB-ago or IgG into VMH (n=4/group).