SUPPLEMENTARY INFORMATION

Supplemental Methods

Premorbid Compulsive and Anxiety-Like Behavioral Battery

1) ***Open Field Test***: Mice were placed in a testing chamber (20 cm x 43 cm x 46 cm) in a lit room (260-265 lux) and allowed to move freely for five min. Behaviors were video recorded for five min for tracking analysis (AnyMaze, Stoelting Co., Wood Dale, IL USA) where we divided the chamber into four outer zones and four inner zones. Analyses were conducted on the amount of time mice spent in any of the inner zones, the number of times mice visited all four inner zones without entering an outer zone (center sequences), and the number of times the mice visited all four outer zones without entering an inner zone (perimeter sequences). The experimenter was blinded to Genotype throughout the entire battery of behavioral tests.

2) ***Elevated Plus Maze (EPM)***: Mice were allowed to acclimate to the dark testing room (illuminated by a dim red light) for one h. Mice were then placed into the center of the EPM (Stoelting) and videotaped for five min. Mice were scored for the percentage of time spent on the closed arms, the open arms, the outer half of the open arms, and the distance traveled on the EPM.

3) ***Marble Burying***: The testing chamber (20 cm x 43 cm x 46 cm) was filled to a depth of 5 cm with wood chip bedding material that was tamped to make a flat,

even surface [85]. Six marbles were evenly spaced on top of the bedding in a 2 x 3 pattern, approximately 8 cm apart. Mice were then placed in the chamber and video recorded for five min. At the end of this period, mice were returned to the home cage, and each marble was scored based on the percentage of its surface that was covered (0, 25, 50, 75, or 100%).

4) ***Hole Board Test***: A solid platform (20 cm x 43 cm x 58 cm) was placed into the testing chamber (20 cm x 43 cm x 46 cm) and elevated (20 cm) above the chamber floor. The platform had 8 evenly-spaced holes (2 x 4) positioned directly above an instrument that generates a grid of infrared light (Kinder Scientific, Poway, CA USA). The mice were placed on the platform and video recorded for five min. Each time the animal inserted its head into any hole, the infrared beams were broken and the head-dip was recorded. We analyzed the number and pattern of head dips.

5) ***Y-maze Test.*** Mice were allowed to acclimate to the dark testing room (illuminated by a dim red light) for one h. Mice were then placed into the center of the y-maze (Stoelting; each arm 5 cm wide x 35 cm long with 10 cm-high walls) and were videotaped for five min. Mice were scored for total distance traveled, number of entries, and spontaneous alternations. A spontaneous alternation occurred when a mouse entered each of the three arms in succession without repeating an arm.

Supplemental Figure Legends

Figure S1. Combined analysis of PF intake in the B6J and D2J parental strains, B6J x D2J-F_1 and F_2 mice. A) A 2-way mixed effects ANOVA (Genotype x Day) identified a main effect of Day [$F_{5,1152} = 30.3$, $p < 0.0001$], of Genotype [$F_{3,1152} = 109.4$, $p < 0.0001$], and an interaction [$F_{15,1152} = 2.6$, $p = 0.0008$]. Specifically, the D2J strain consumed more PF than all other groups on all days (D2-D18; all ts > 3.5; all ps < 0.001; $\alpha_{adjusted} = 0.0083$; * D2J > F_1, F_2, and B6J). Additionally, F_2 mice consumed more PF than the B6J strain on D9, D11, D16, and D18 (all ts > 2.9; all ps < 0.004; $\alpha_{adjusted} = 0.0083$; # F_2 > B6J), and F_1 mice consumed more PF than the B6J strain on D18 ($t_{38} = 3.1$; $p = 0.004$; $\alpha_{adjusted} = 0.0083$; # F_1 > B6J). **B)** Analysis of slopes of escalation of PF intake over time revealed that all groups escalated intake (all Fs > 19.1; all $p < 0.0001$ vs. zero). Moreover, there was an effect of Genotype on escalation [$F_{3,1168} = 10.1$; $p < 0.0001$]. Specifically, the D2J strain showed a greater slope than all three other groups (* D2J > F_1, F_2, and B6J; all F > 6.0; all $p < 0.002$; $\alpha_{adjusted} = 0.0083$) and F_1 mice showed a greater slope than the B6J strain (#; $F_{1,236} = 7.4$; $p = 0.007$; $\alpha_{adjusted} = 0.0083$). **C)** For summed intake (% BW consumed, summed across the six training days involving food – D2, D4, D9, D11, D16, and D18), there was an effect of Genotype [$F_{3,192} = 24.4$; $p = 2 \times 10^{-13}$] in that the D2J strain showed greater intake

than all other groups (all ts > 5.6; all ps <1.6 x 10^{-6}; * D2J > F_1, F_2, and B6J; $\alpha_{adjusted}$ = 0.0083), and F_2 mice showed greater intake than the B6J strain (#; t_{154} = 3.4; p = 0.0009; 6 comparisons; $\alpha_{adjusted}$ = 0.0083). **D)** For compulsive-like intake, there was an effect of Genotype on compulsive-like PF intake in the light/dark conflict test [$F_{3,168}$ = 16.2; p = 2.8 x 10^{-9}] in that the D2J strain showed greater PF intake than any of the other three groups (*; all ts > 4.4; all ps < 8.5 x 10^{-5}; $\alpha_{adjusted}$ = 0.0083).

Figure S2. Body weight in B6J and D2J strains across BE training days. There were main effects of Genotype [$F_{1,546}$ = 42.1; p = 2 x 10^{-10}], Treatment [$F_{1,546}$ = 7.6; p = 0.006] and Day [$F_{5,546}$ = 2.8; p = 0.02]. This effect was not present at the beginning of training (D2; p = 0.27), but developed over time. Specifically, the Chow-trained, but not the PF-trained D2J strain showed greater body weight than either B6J group on D9, D11, D16, and D18 (*; all ts > 2.8; all ps < 0.008; $\alpha_{adjusted}$ = 0.0083).

Table S1. Factor analysis of B6J, D2J, and F_2 mice.

B6J variables	Heritability (h^2)	Food Seeking Activity	Generalized PF Intake & Seeking	Compulsive-Like Activity
% Variance		19	19	17
D2 PF Intake (%BW)	34%		0.67	0.14
D18 PF Intake (%BW)	56%	0.11	0.74	0.00
D18 Time in Food Triangle (s)	27%		0.33	
D18 Entries to Food Triangle	30%	0.26		
D18 Distance in Food Triangle (m)	51%	0.20	0.58	
Escalation Slope	34%	0.17	0.14	0.42
D22 Entries to Right Side	18%	0.60	-0.50	
D22 Time on the Right Side (s)	12%	0.17	0.14	0.42
D22 Distance on Right Side (m)	28%	0.99	0.12	

D22 Entries to Food Triangle	**22%**	**0.79**	**0.16**	
D22 Time in Food Triangle (s)	**2%**	**0.27**	**0.44**	**0.37**
D22 Distance in Food Triangle (m)	**17%**	**0.88**	**0.34**	
Light/dark PF Intake (%BW)	**73%**	**0.12**	**0.78**	**0.29**
Light/dark Time on Light Side (s)	**11%**		**0.30**	**0.89**
Light/dark Entries Into Light Side	**1%**	**-0.11**	**-0.22**	**0.69**
Light/dark Distance on Light Side (m)	**10%**	**-0.24**	**0.20**	**0.95**

D2J variables	**Heritability (h^2)**	**BE & Compulsive-Like Activity**	**Food Seeking Activity**	**PF CPP**
% Variance		**23**	**19**	**15**

D2 PF Intake (%BW)	**34%**		**0.18**	
D18 PF Intake (%BW)	**56%**	**0.68**	**-0.14**	**0.13**
D18 Time in Food Triangle (s)	**27%**	**0.39**		**-0.14**
D18 Entries to Food Triangle	**30%**		**0.20**	**0.62**
D18 Distance in Food Triangle (m)	**51%**	**0.46**	**0.23**	**0.18**
Escalation Slope	**34%**	**0.54**	**-0.28**	
D22 Entries to Right Side	**18%**		**0.40**	**0.71**
D22 Time on the Right Side (s)	**12%**		**0.16**	**-0.65**
D22 Distance on Right Side (m)	**28%**		**0.94**	**0.33**
D22 Entries to Food Triangle	**22%**		**0.81**	
D22 Time in Food Triangle (s)	**2%**		**0.29**	**-0.95**
D22 Distance in Food	**17%**		**0.95**	**-0.13**

Triangle (m)				
Light/dark PF Intake (%BW)	**73%**	**0.24**		
Light/dark Time on Light Side (s)	**11%**	**0.91**	**-0.20**	**-0.11**
Light/dark Entries Into Light Side	**1%**	**0.81**		
Light/dark Distance on Light Side (m)	**10%**	**0.96**	**-0.18**	

B6JxD2J-F_2 variables	**Heritability (h^2)**	**Food Seeking Activity**	**Compulsive-Like Activity**	**BE**
% Variance		**21**	**16**	**15**
D2 PF Intake (%BW)	**34%**	**-0.17**		**0.48**
D18 PF Intake (%BW)	**56%**			**1.00**
D18 Time in Food Triangle (s)	**27%**		**-0.17**	
D18 Entries to Food Triangle	**30%**	**0.36**	**0.13**	

D18 Distance in Food Triangle (m)	**51%**	**0.47**	**0.24**	**-0.15**
Escalation Slope	**34%**	**0.13**		**0.75**
D22 Entries to Right Side	**18%**	**0.72**	**0.18**	
D22 Time on the Right Side (s)	**12%**	**0.20**		
D22 Distance on Right Side (m)	**28%**	**0.98**	**0.19**	
D22 Entries to Food Triangle	**22%**	**0.82**	**0.11**	
D22 Time in Food Triangle (s)	**2%**			
D22 Distance in Food Triangle (m)	**17%**	**0.85**	**0.12**	**0.13**
Light/dark PF Intake (%BW)	**73%**			**0.68**
Light/dark Time on Light Side (s)	**11%**	**0.15**	**0.89**	**-0.11**
Light/dark Entries Into	**1%**	**0.25**	**0.77**	

Light Side			
Light/dark Distance on			
Light Side (m)	**10%**	**0.14**	**0.97**