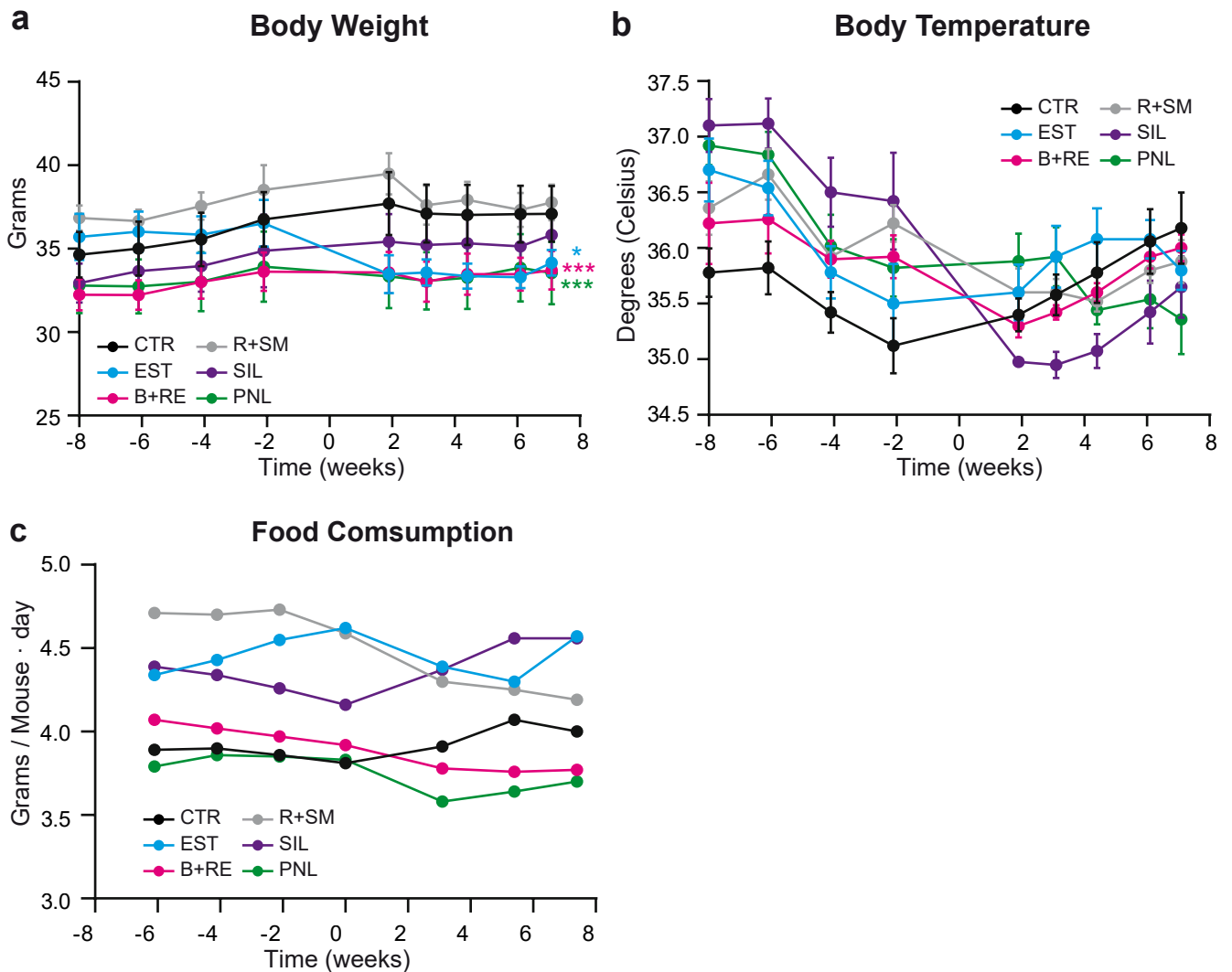
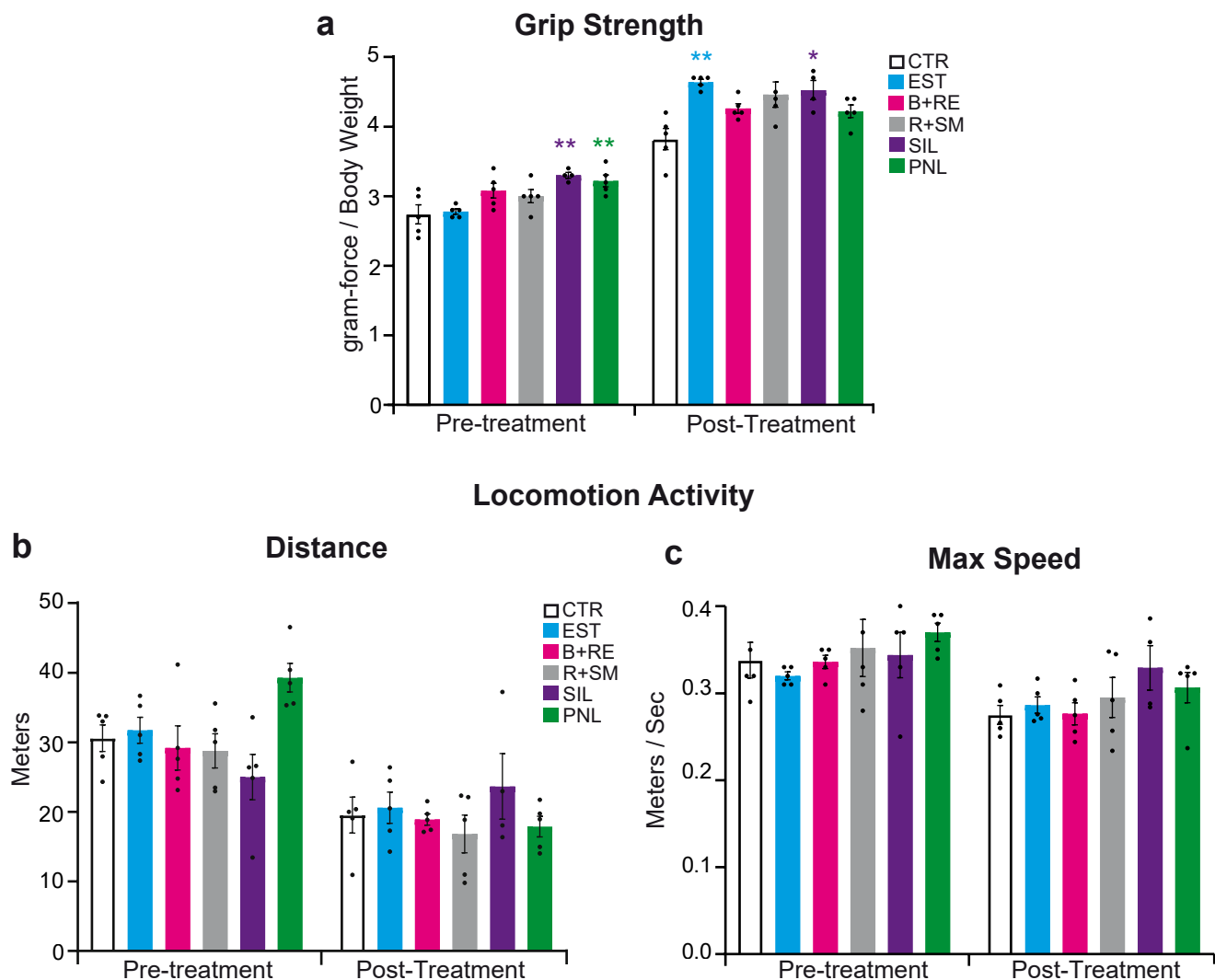
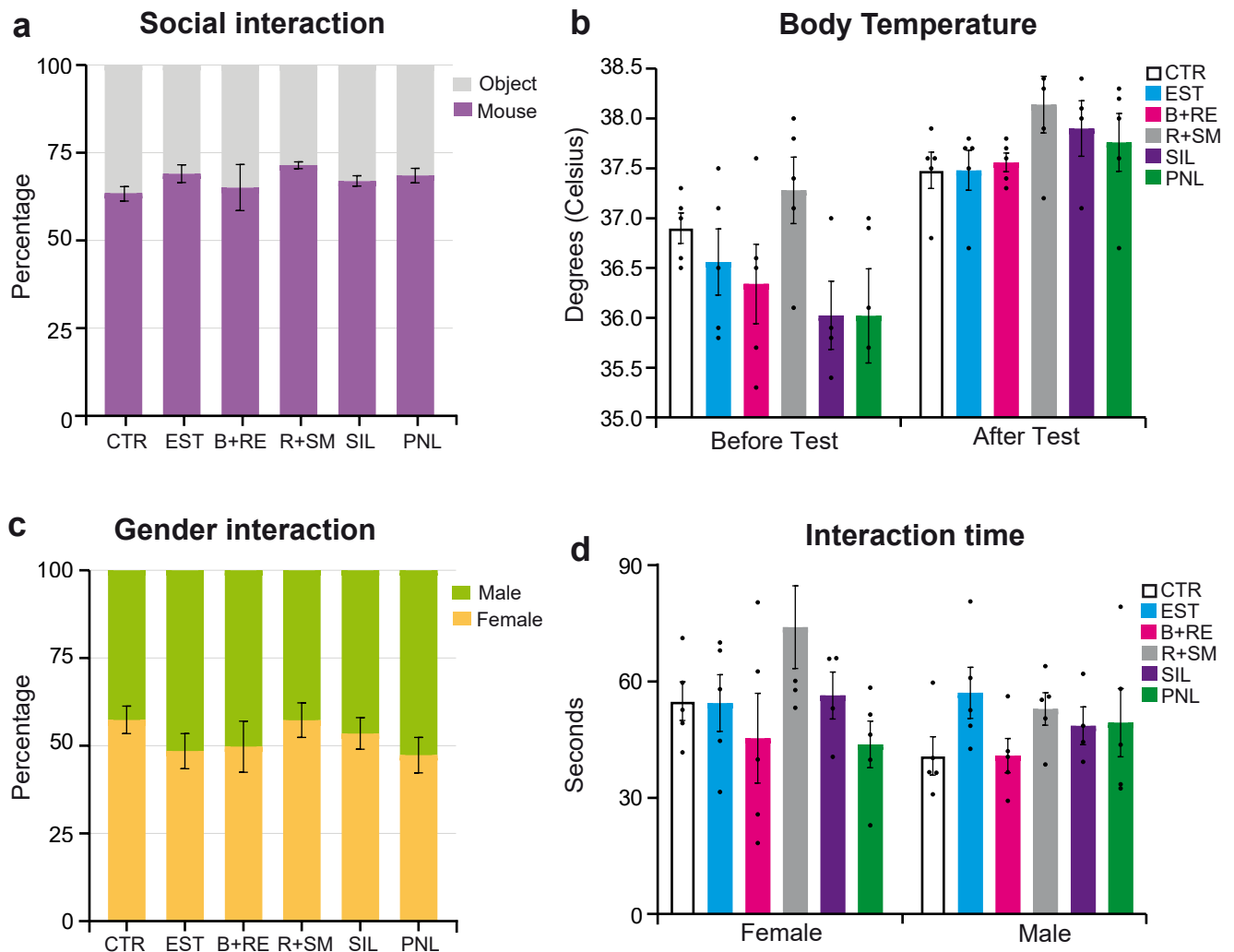




Extended Data Figure 1 | Supplemental Basic physiological parameters. **a**, Body weight in grams (g) measured and **b**, Rectal body temperature ($^{\circ}\text{C}$) measured longitudinally throughout the protocol. **c**, Daily food intake (grams/mouse/day). CTR, control; EST, 17α -estradiol; B+RE, berberine + resveratrol; R+SM, rapamycin + Smer28; SIL, sildenafil; PNL, pinealon. Data show mean $\pm$ standard error of the mean (SEM). Statistical significance was assessed by mixed-effects model (REML) with Dunnett's multiple comparisons test (**a–b**).



Extended Data Figure 2 | Supplemental physical performance. **a**, Forelimb grip strength normalized to body weight measured before (Pre) and after (Post) treatment. **b**, Total distance traveled and **c**, Maximum speed in the open field test measured pre- and post-treatment. CTR, control; EST, 17 α -estradiol; B+RE, berberine + resveratrol; R+SM, rapamycin + Smer28; SIL, sildenafil; PNL, pinealon. Data show mean $\pm$ standard error of the mean (SEM). Statistical significance was assessed by one-way ANOVA with Dunnett's multiple comparisons test (**a-pre**, **b**), Kruskal-Wallis test with Dunn's multiple comparisons test (**a-post**, **c-post**) and Welch ANOVA with Dunnett's multiple comparisons test (**c-pre**).



Extended Data Figure 3 | Supplemental cognitive function and social behavior. **a**, Percentage of interaction time with stranger mice versus objects during the social recognition test. **b**, Interaction time and **c**, Percentage of interaction time with female versus male stranger mice. **d**, Core body temperature measured before (Pre) and after (Post) the social recognition activity test. CTR, control; EST, 17 α -estradiol; B+RE, berberine + resveratrol; R+SM, rapamycin + Smer28; SIL, sildenafil; PNL, pinealon. Data show mean $\pm$ standard error of the mean (SEM). Statistical significance was assessed by Kruskal-Wallis test with Dunn's multiple comparisons test (**a**, **b-after**) and one-way ANOVA with Dunnett's multiple test (**b-before**, **c**, **d**).

Complete Blood Count

Pre-treatment (Baseline)

Mouse ID	Group	WBC 10 ⁹ /L	RBC 10 ¹² /L	HGB g/L	HCT (%)	MCV (fL)	RDW-CV (%)	RDW-SD (fL)	PLT 10 ⁹ /L	MPV (fL)	PDW (fL)
AVERAGE	CTR	8.726	10.082	148	43.84	43.54	18.38	38.6	1185.6	6.54	15.54
MOUSE_016	R+SM	10.94	10.68	153	45.6	42.7	18.7	38.8	1108	6.5	15.5
MOUSE_017†	R+SM	9.13	10.07	158	45.6	45.3	18	39.2	791	7.1	15.6
MOUSE_018	R+SM	11.25	10.63	152	45.5	42.8	17.5	36.3	1149	6.5	15.3
MOUSE_019†	R+SM	9.04	9.88	154	44.7	45.2	17.3	36.5	799	6.8	15.4
MOUSE_020	R+SM	11.91	10.95	156	46.7	42.7	18.3	38	1182	6.7	15.5

Post-treatment (Endpoint)

Mouse ID	Group	WBC 10 ⁹ /L	RBC 10 ¹² /L	HGB g/L	HCT (%)	MCV (fL)	RDW-CV (%)	RDW-SD (fL)	PLT 10 ⁹ /L	MPV (fL)	PDW (fL)
AVERAGE	CTR	8.032	9.63	142.75	41.925	43.98	16.56	34.34	579.5	6.6	16.08
MOUSE_016	R+SM	7.08	8.62	134	36.7	42.6	17	34.5	263	6.6	16.5
MOUSE_017†	R+SM	4.98	5.94	94	27.6	46.5	17.7	38.4	472	6.9	15.7
MOUSE_018	R+SM	11.17	9.43	138	40	42.4	19.2	38.6	520	6.4	15.3
MOUSE_019†	R+SM	7.71	6.54	116	31	47.4	17.9	39.6	375	7.2	15.6
MOUSE_020	R+SM	10.44	10.23	147	44.3	43.3	17.9	37	768	6.7	16.2

Supplementary Table 1 | Complete blood count analysis of rapamycin + SMER28–treated mice. Complete blood count (CBC) parameters measured at baseline (Pre-treatment) and after 8 weeks of treatment (Post-treatment) in rapamycin + Smer28 (R+SM) treated mice. Control values correspond to the mean of the control group (CTR). Mice showing hematological values consistent with anemia at endpoint are marked with † and highlighted in red. WBC, white blood cells; RBC, red blood cells; HGB, hemoglobin; HCT, hematocrit; MCV, mean corpuscular volume; RDW-CV, red cell distribution width; RDW-SD, red cell distribution width; PLT, platelets; MPV, mean platelet volume; PDW, platelet distribution width.

Urinalysis parameters

Post-treatment (Endpoint)

Group	LEU (cell/ μ)	KET (mg/dL)	NIT	URO	BIL (mg/dL)	GLU (mg/dL)	PRO (mg/dL)	SG	pH	BLD (cell/ μ)	ASC (mg/dL)	MA (mg/dL)	Ca (mg/dL)	CR (mg/dL)
EST	0	0	0	Normal	0	0	15	1.01	6.5	0	0	<2.5	30	50
B+RE	0	0	0	Normal	0	0	<15	1.02	6	0	10	<2.5	30	50
R+SM	0	0	0	Normal	0	0	<15	1.02	5.5	0	0	<2.5	20	50
SIL	0	0	0	Normal	0	0	<15	1.015	6	0	0	<2.5	20	50
PNL	0	0	0	Normal	0	0	<15	1.02	6.5	0	0	<2.5	30	50

Supplementary Table 2 | Urinalysis parameters. Urine analysis was performed after 8 weeks of treatment at the end point. Samples correspond to pooled urine collected from animals within the same treatment group. EST, 17 α -estradiol; B+RE, berberine + resveratrol; R+SM, rapamycin + Smer28; SIL, sildenafil; PNL, pinealon. Parameters include: LEU, leukocytes; KET, ketones; NIT, nitrites; URO, urobilinogen; BIL, bilirubin; GLU, glucose; PRO, protein; SG, specific gravity; BLD, blood; ASC, ascorbic acid; MA, microalbumin; Ca, calcium; CR, creatinine.