SUPPLEMENTARY DATA

Supplementary Table 1. (Statistical Analyses)

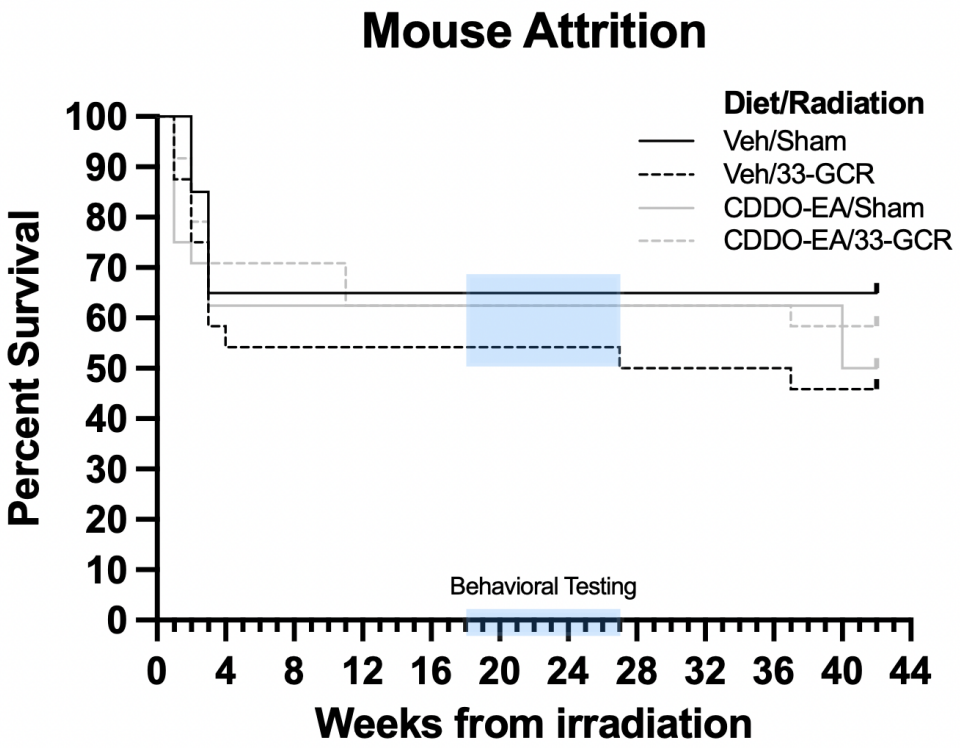
Experiment	Behavior	Figure Panel	Test Statistic	Main Effect	Dist.-Value (Dfn, Dfd)	Main Effect P-Value (bold text: *P<0.05*)	Effect Size (% variance, HR)	Post-hoc Test	Group	Sample Size (n)	Gaussian or LogNormal ?	Mean (predicted or rank)	Group Difference P-Value	Post-hoc Effect Size (Cohen's *d*)
Animal Weight		1B	Mixed Effects 3-way ANOVA	Time from Radiation (months)	F (16, 448) = 213.5	***P<0.0001***			Veh/Sham	15				
				Diet	F (1, 406) = 2.208	*P=0.1381*			Veh/33-GCR	13				
				Radiation	F (1, 28) = 0.9108	*P=0.3481*			CDDO-EA/Sham	15				
				Time from Radiation (months) x Diet	F (16, 406) = 0.9906	*P=0.466*			CDDO-EA/33-GCR	15				
				Time from Radiation (months) x Radiation	F (16, 406) = 0.3613	*P=0.9898*								
				Diet x Radiation	F (1, 406) = 0.05553	*P=0.8138*								
				Time from Radiation (months) x Diet x Radiation	F (16, 406) = 0.9120	*P=0.5555*								
Locomotor Activity Chambers	Cumulative Locomotion	2A	2-way ANOVA	Radiation x Diet	F (1, 54) = 4.160	***P=0.0463***	% Var = 7.107	Mult. Comp/ w/ Tukey Corr.	Veh/Sham	15	Yes	696.2	All Comparisons *P > 0.05*	
				Diet	F (1, 54) = 0.2471	*P=0.6212*	% Var = 0.4221		Veh/33-GCR	13	Yes	802.8		
				Radiation	F (1, 54) = 0.07420	*P=0.7864*	% Var = 0.1268		CDDO-EA/Sham	15	Yes	813.1		
									CDDO-EA/33-GCR	15	Yes	731.7		
	Ambulatory Episodes	2B	2-way ANOVA	Radiation x Diet	F (1, 54) = 4.268	***P=0.0436***	% Var = 7.204	Mult. Comp/ w/ Tukey Corr.	Veh/Sham	15	Yes	40.67	All Comparisons *P > 0.05*	
				Diet	F (1, 54) = 0.6358	*P=0.4287*	% Var = 1.073		Veh/33-GCR	13	Yes	47.38		
				Radiation	F (1, 54) = 0.2526	*P=0.6173*	% Var = 0.4264		CDDO-EA/Sham	15	Yes	48.16		
									CDDO-EA/33-GCR	15	Yes	44.07		
	Ambulatory Time	2C	2-way ANOVA	Radiation x Diet	F (1, 54) = 6.410	***P=0.0143***	% Var = 10.56	Mult. Comp/ w/ Tukey Corr.	Veh/Sham	15	Yes	30.79	All Comparisons *P > 0.05*	
				Diet	F (1, 54) = 0.2024	*P=0.6546*	% Var = 0.3333		Veh/33-GCR	13	Yes	35.95		
				Radiation	F (1, 54) = 0.03055	*P=0.8619*	% Var = 0.05031		CDDO-EA/Sham	15	Yes	46.48		
									CDDO-EA/33-GCR	15	Yes	31.98		
	Mean Velocity	2D	Kruskal-Wallis		H = 1.381	*P=0.7101*			Veh/Sham	15	No	27.47		
									Veh/33-GCR	13	No	28.54		
									CDDO-EA/Sham	15	Yes	28		
									CDDO-EA/33-GCR	15	Yes	33.87		
Elevated Plus Maze	Open Arm Exploration	3A	2-way ANOVA	Radiation x Diet	F (1, 54) = 0.4639	*P=0.4987*	% Var = 0.8309		Veh/Sham	15	Yes	25.74		
				Diet	F (1, 54) = 1.398	*P=0.2422*	% Var = 2.504		Veh/33-GCR	13	Yes	23.17		
				Radiation	F (1, 54) = 0.01066	*P=0.9181*	% Var = 0.0191		CDDO-EA/Sham	15	Yes	27.96		
									CDDO-EA/33-GCR	15	Yes	31.44		
	Open Arm Entries	3B	Kruskal-Wallis		H = 2.675	*P=0.4445*			Veh/Sham	15	Yes	24.9		
									Veh/33-GCR	13	Yes	28.12		
									CDDO-EA/Sham	15	Yes	34.7		
									CDDO-EA/33-GCR	15	No	30.1		
	Open Arm Exploration Ratio	3C	Kruskal-Wallis		H = 0.0412	*P=0.9400*			Veh/Sham	15	Yes	29.47		
									Veh/33-GCR	13	Yes	27.15		
									CDDO-EA/Sham	15	No	29.93		
									CDDO-EA/33-GCR	15	No	31.13		
	Locomotion	3D	2-way ANOVA	Radiation x Diet	F (1, 54) = 0.7894	*P=0.3782*	% Var = 1.313	Mult. Comp/ w/ Tukey Corr.	Veh/Sham	15	Yes	948.5	All Comparisons *P > 0.05*	
				Diet	F (1, 54) = 5.134	***P=0.0275***	% Var = 8.538		Veh/33-GCR	13	Yes	1008		
				Radiation	F (1, 54) = 0.03087	*P=0.8612*	% Var = 0.0513		CDDO-EA/Sham	15	Yes	1125		
									CDDO-EA/33-GCR	15	Yes	1085		
Open Field	Arena Center Exploration	4A	Kruskal-Wallis		H = 1.961	*P=0.5805*			Veh/Sham	15	Yes	28.61		
									Veh/33-GCR	13	Yes	23.86		
									CDDO-EA/Sham	15	No	30.57		
									CDDO-EA/33-GCR	15	Yes	23.81		
	Thigmotaxis	4B	Kruskal-Wallis		H = 2.122	*P=0.5475*			Veh/Sham	15	Yes	27.53		
									Veh/33-GCR	13	No	25.04		
									CDDO-EA/Sham	15	No	31.37		
									CDDO-EA/33-GCR	15	No	33.47		
	Exploration Ratio	4C	Kruskal-Wallis		H =1.823	*P=0.6100*			Veh/Sham	15	No	26.5		
									Veh/33-GCR	13	No	33.31		
									CDDO-EA/Sham	15	No	30.6		
									CDDO-EA/33-GCR	15	No	26		
	Locomotion	4D	2-way ANOVA	Radiation x Diet	F (1, 54) = 1.818	*P=0.1832*	% Var = 3.215		Veh/Sham	15	Yes	1120		
				Diet	F (1, 54) = 0.1548	*P=0.6955*	% Var = 0.2738		Veh/33-GCR	13	Yes	1333		
				Radiation	F (1, 54) = 0.5643	*P=0.4558*	% Var = 0.9983		CDDO-EA/Sham	15	Yes	1296		
									CDDO-EA/33-GCR	15	Yes	1236		
3-Chamber Social Interaction	Habituation	5A	3-way ANOVA	Chamber	F (2, 104) = 15.92	***P<0.0001***	% Var = 22.90	Mult. Comp/ w/ Tukey Corr.	Veh/Sham (Left vs Center)	14	Yes	116.2	*P = 0.0653*	
				Diet	F (1, 52) = 1.465	*P=0.2316*	% Var = 0.0010		Veh/Sham (Right vs Center)	14	Yes	66.91	*P = 0.7751*	
				Radiation	F (1, 52) = 0.1193	*P=0.7312*	% Var = 0.0001		Veh/Sham (Left vs Right)	14	Yes	49.33	*P = 0.9652*	
				Chamber x Diet	F (2, 104) = 0.2353	*P=0.7908*	% Var = 0.3385		CDDO-EA/Sham (Left vs Center)	13	Yes	63.91	*P = 0.7874*	
				Chamber x Radiation	F (2, 104) = 0.4375	*P=0.6469*	% Var = 0.6293		CDDO-EA/Sham (Right vs Center)	13	Yes	43.81	*P = 0.9814*	
				Diet x Radiation	F (1, 52) = 0.0002	*P=0.9904*	% Var = 0.0000		CDDO-EA/Sham (Left vs Right)	13	Yes	20.1	*P > 0.9999*	
				Chamber x Diet x Radiation	F (2, 104) = 1.064	*P=0.3488*	% Var = 1.531		Veh/33-GCR (Left vs Center)	15	Yes	86.23	*P = 0.4686*	
									Veh/33-GCR (Right vs Center)	15	Yes	101.3	*P = 0.2283*	
									Veh/33-GCR (Left vs Right)	15	Yes	-15.07	*P > 0.9999*	
									CDDO-EA/33-GCR (Left vs Center)	14	Yes	123.5	***P = 0.0368***	
									CDDO-EA/33-GCR (Right vs Center)	14	Yes	76.33	*P = 0.6013*	
									CDDO-EA/33-GCR (Left vs Right)	14	Yes	47.18	*P = 0.9749*	
			Pearson Correlation	Center Chamber : (Nov. Mouse 2 - Nov. Mouse 1)					Veh/Sham	14		R^2 = 0.09	*P=0.3169*	
									Veh/33-GCR	13		R^2 = 0.14	*P=0.2099*	
									CDDO-EA/Sham	15		R^2 = 0.02	*P=0.6225*	
									CDDO-EA/33-GCR	14		R^2 = 0.00	*P=0.9945*	
	Sociability	5B	3-way ANOVA	Chamber	F (1, 51) = 55.52	***P<0.0001***	% Var = 45.87	Mult. Comp/ w/ Tukey Corr.	Veh/Sham (Nov. Mouse 1)	14	Yes	325.9	***P=0.0021***	*d =0.6793 (medium)*
				Diet	F (1, 51) = 1.081	*P=0.3034*	% Var = 0.1678		Veh/Sham (Nov. Object)	14	Yes	173		
				Radiation	F (1, 51) = 1.887	*P=0.1756*	% Var = 0.2929		Veh/33-GCR (Nov. Mouse 1)	13	Yes	332.7	***P<0.0001***	*d =0.7957 (large)*
				Chamber x Diet	F (1, 51) = 4.205	***P=0.0455***	% Var = 3.474		Veh/33-GCR (Nov. Object)	13	Yes	140.8		
				Chamber x Radiation	F (1, 51) = 0.002	*P=0.9619*	% Var = 0.0019		CDDO-EA/Sham (Nov. Mouse 1)	14	Yes	313.6	***P=0.0430***	*d =0.4736 (medium)*
				Diet x Radiation	F (1, 51) = 0.058	*P=0.8115*	% Var = 0.0089		CDDO-EA/Sham (Nov. Object)	14	Yes	197.9		
				Chamber x Diet x Radiation	F (1, 51) = 1.051	*P=0.3101*	% Var = 0.8681		CDDO-EA/33-GCR (Nov. Mouse 1)	14	Yes	287	*P=0.9749*	
									CDDO-EA/33-GCR (Nov. Object)	14	Yes	80.26		
			Pearson Correlation	Center Chamber : (Nov. Mouse 2 - Nov. Mouse 1)					Veh/Sham	14		R^2 = 0.18	*P=0.1187*	
									Veh/33-GCR	13		R^2 = 0.00	*P=0.8768*	
									CDDO-EA/Sham	15		R^2 = 0.08	*P=0.3315*	
									CDDO-EA/33-GCR	14		R^2 = 0.30	*P=0.0799*	
	Preference for Social Novelty	5C	3-way ANOVA	Stranger Sniff Zone	F (1, 47) = 6.595	***P=0.0135***	% Var = 7.621	Mult. Comp/ w/ Tukey Corr.	Veh/Sham (Nov. Mouse 1)	15	Yes	35.69	***P=0.0328***	*d =0.2665 (small)*
				Diet	F (1, 47) = 0.6643	*P=0.4191*	% Var = 0.3684		Veh/Sham (Nov. Mouse 2)	15	Yes	64.31		
				Radiation	F (1, 47) = 0.1052	*P=0.7471*	% Var = 0.0583		Veh/33-GCR (Nov. Mouse 1)	11	Yes	45.61	*P=0.9510*	
				Stranger Sniff Zone x Diet	F (1, 47) = 2.768	*P=0.1028*	% Var = 3.199		Veh/33-GCR (Nov. Mouse 2)	11	Yes	54.39		
				Stranger Sniff Zone x Radiation	F (1, 47) = 2.804	*P=0.1007*	% Var = 3.240		CDDO-EA/Sham (Nov. Mouse 1)	14	Yes	45.42	*P=0.9067*	
				Diet x Radiation	F (1, 47) = 4.719	***P=0.0349***	% Var = 2.617		CDDO-EA/Sham (Nov. Mouse 2)	14	Yes	54.58		
				Stranger Sniff Zone x Diet x Radiation	F (1, 47) = 0.0347	*P=0.8531*	% Var = 0401		CDDO-EA/33-GCR (Nov. Mouse 1)	11	Yes	46	*P>0.9999*	
									CDDO-EA/33-GCR (Nov. Mouse 2)	11	Yes	54		
Novel Object Recognition	Object Exploration	6A	3-way ANOVA	Object exploration	F (1, 53) = 78.75	***P=0.0001***	% Var = 34.60	Mult. Comp/ w/ Tukey's Test, Within Group	Veh/Sham (Familiar)	15	Yes	8.67	***P<0.0001***	*d =0.5785 (medium)*
				Diet	F (1, 53) = 0.001295	*P=0.9714*	% Var = 0.0009681		Veh/Sham (Novel)	15	No	45.41		
				Radiation	F (1, 53) = 1.149	*P=0.2887*	% Var = 0.8585		Veh/33-GCR (Familiar)	12	No	9.227	***P=0.0266***	*d =0.7967(large)*
				Object x Diet	F (1, 53) = 0.04101	*P=0.8403*	% Var = 0.01801		Veh/33-GCR (Novel)	12	Yes	34.3		
				Object x Radiation	F (1, 53) = 1.176	*P=0.2832*	% Var = 0.5165		CDDO-EA/Sham (Familiar)	15	Yes	11.14	***P=0.0005***	*d =0.5537 (medium)*
				Diet x Radiation	F (1, 53) = 0.01377	*P=0.9070*	% Var = 0.01029		CDDO-EA/Sham (Novel)	15	Yes	42.22		
				Object x Diet x Radiation	F (1, 53) = 0.3964	*P=0.5316*	% Var = 0.1742		CDDO-EA/33-GCR (Familiar)	15	No	8.453	***P=0.0022***	*d =0.6492 (medium)*
									CDDO-EA/33-GCR (Novel)	15	Yes	36.43		
	Object Discrimination	6B	2-way ANOVA	Radiation x Diet	F (1, 53) = 1.317	*P=0.2563*	% Var = 2.397		Veh/Sham	15	Yes	40.67		
				Diet	F (1, 53) = 0.4505	*P=0.5050*	% Var = 0.8203		Veh/33-GCR	12	Yes	47.38		
				Radiation	F (1, 53) = 0.07541	*P=0.7847*	% Var = 0.1373		CDDO-EA/Sham	15	Yes	48.16		
									CDDO-EA/33-GCR	15	Yes	44.07		
Survival			Cox Proportional Hazards	Diet	b(CDDO-EA) = 0.02	*P = 0.94*	HR = 1.02		Veh/Sham	22				
				Radiation	b(33-GCR) = 0.12	*P = 0.71*	HR = 1.12		Veh/33-GCR	24				
									CDDO-EA/Sham	24				
									CDDO-EA/33-GCR	24				
		Supp. 1	Log-rank (Mantel-Cox)		χ2 = 2.03	*P=0.565*			Veh/Sham	22				
									Veh/33-GCR	24				
									CDDO-EA/Sham	24				
									CDDO-EA/33-GCR	24				

Supplementary Table 2. Detailed 33-GCR sequential delivery used in this study. Adapted from Simonsen et al. 2020 [12] and adjusted for a total dose of 75cGy.

Particle	Energy (MeV/n)	Dose Fraction	Dose (cGy)	LET (KeV/um)	Range in H2O (Cm)
^{1}H	1000	24.71%	18.5325	0.22	326.6
^{4}He	1000	4.98%	3.735	0.88	327.8
^{28}Si	600	1.62%	1.215	50.2	22.73
^{1}H	20	6.08%	4.56	2.59	0.43
^{1}H	23	1.34%	1.005	2.29	0.56
^{4}He	20	2.20%	1.65	10.34	0.43
^{4}He	23	0.42%	0.315	9.14	0.57
^{48}Ti	1000	0.90%	0.675	109.5	32.53
^{4}He	27	0.44%	0.33	8.06	0.75
^{4}He	32	0.46%	0.345	7.12	0.99
^{1}H	27	1.48%	1.11	2.02	0.75
^{1}H	32	1.60%	1.2	1.79	0.98
^{1}H	37	1.74%	1.305	1.58	1.3
^{1}H	43	1.86%	1.395	1.39	1.72
^{4}He	37	0.50%	0.375	6.29	1.31
^{4}He	43	0.52%	0.39	5.56	1.73
^{16}O	350	3.08%	2.31	20.8	16.95
^{4}He	50	0.54%	0.405	4.92	2.28
^{4}He	59	0.54%	0.405	4.36	3.01
^{1}H	50	2.00%	1.5	1.23	2.26
^{1}H	59	2.12%	1.59	1.09	2.99
^{1}H	69	2.22%	1.665	0.97	3.95
^{1}H	80	2.24%	1.68	0.86	5.2
^{4}He	69	0.54%	0.405	3.86	3.97
^{4}He	80	0.54%	0.405	3.43	5.23
^{12}C	1000	2.34%	1.755	7.95	110.13
^{4}He	100	1.22%	0.915	2.9	7.81
^{1}H	100	5.44%	4.08	0.73	7.76
^{1}H	150	7.00%	5.25	0.54	15.9
^{4}He	150	1.50%	1.125	2.17	16
^{56}Fe	600	0.82%	0.615	175.1	13.09
^{4}He	250	3.28%	2.46	1.56	38.3
^{1}H	250	13.77%	10.3275	0.39	38.1
		Total	**75**		

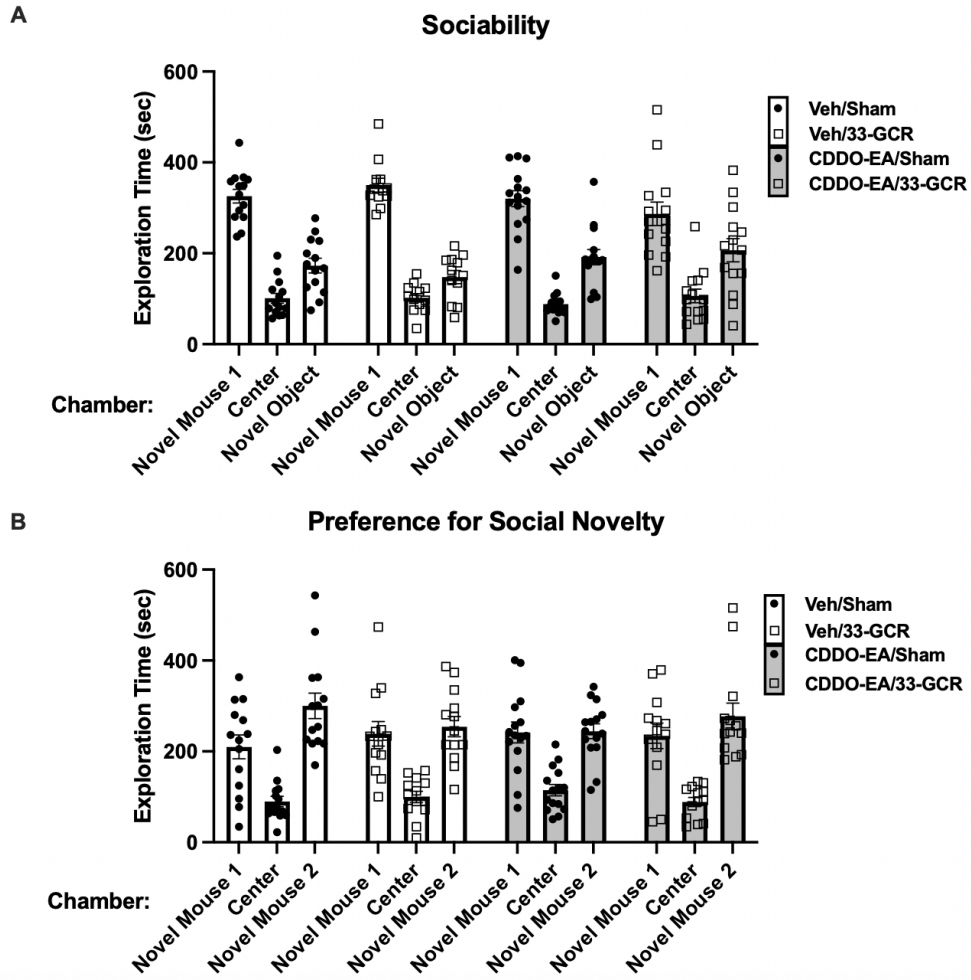
Supplemental Figures

Supp. Fig. 1



Supplemental Figure 1. Mouse attrition among groups was not significantly different throughout the study. A Kaplan-Meier survival curve of mice throughout the duration of the study with the behavioral testing period (shaded light blue regions on X axis and on lines). Mice that were singly-housed at the recommendation of veterinarians were counted as losses. Hazard ratio analysis revealed a non-significant non-significant increase in mortality due to CDDO-EA and 33-GCR; therefore, there is negligible hazard due to either Diet or Radiation. Despite a visually lower percent survival in Veh/33-GCR mice vs. the other three groups, Mantel-Cox analysis revealed that survival curves among groups are not significantly different. *n* = 22-24 per group. Details on statistics provided in **Supp. Table 1**.

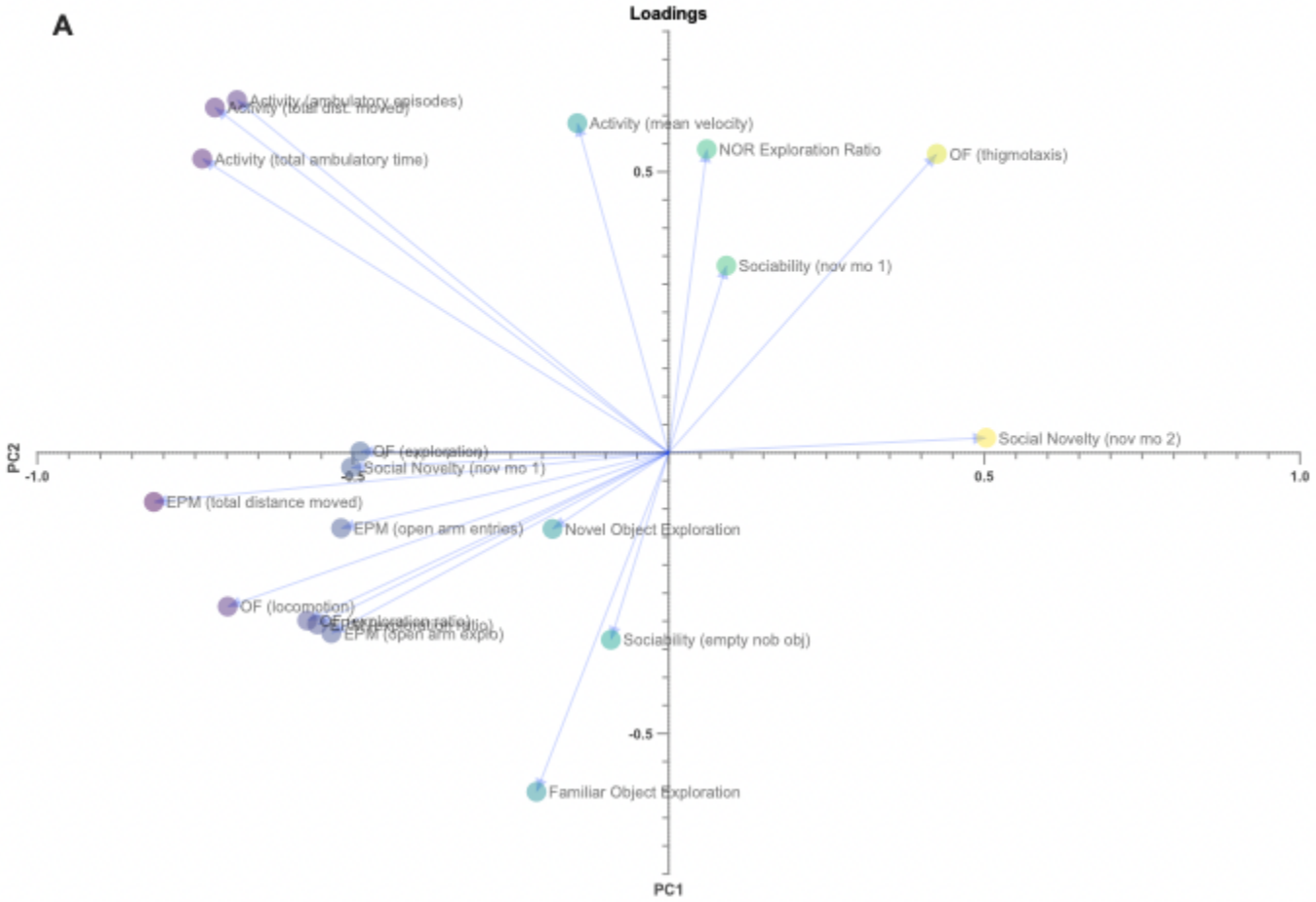
Supplemental Fig. 2



Supplemental Figure 2. Chamber exploration times for the 3-Chamber Social Interaction Test. Chamber exploration times for the (**A**) Sociability and (**B**) Preference for Social Novelty trials of the 3-CSI test. *n* = 11-15 per group.

Supplemental Fig. 3

A



B

Principal Component	Eigenvalue From: Data	Parallel Analysis
PC1	4.918613076	2.327486146
PC2	2.956978587	2.044104546
PC3	2.558436155	1.824897719
PC4	1.949593181	1.644430223
PC5	1.604507744	1.484736045
PC6	1.267684286	1.345425692
PC7	0.9333030039	1.216488637
PC8	0.7279936398	1.094529912
PC9	0.6088877099	0.9800893146
PC10	0.5953505352	0.8779302134
PC11	0.3939959864	0.7795071312
PC12	0.2545211068	0.6868438494
PC13	0.1329285672	0.6031058407
PC14	0.0471058955	0.5236361108
PC15	0.0327324336	0.4461937015
PC16	0.0106343952	0.3758879483
PC17	0.0067336981	0.3047639599

Supplemental Figure 3. Principal Components Loadings Plot containing each behavioral measure as loadings, and eigenvalues. A) Several clusters relating to Anxiety-like, Gross Locomotor Activity, and Exploration behaviors are evident along the PC1 axis, with exploration of novel mouse 2 during the third trial of the 3-chamber social interaction assay as being the behavior with the most isolated variance among all groups in PC1 and PC2. **B**) Eigenvalues of data and parallel analysis.