Galactic cosmic radiation produces sex-specific, circuit-selective cognitive vulnerability: countermeasure trade-offs revealed by multi-domain assessment

Sheridan A. O'Connor,[1,2,3] Pragatee Narain,[1^] Amishi Mahajan,[1,4^] Grace L. Bancroft,[1,4^] Harley A. Haas,[1,4^] Elise Wallen-Friedman,[1,4] Shubha Vasisht,[1,4] Hajime Takano,[5] Frederico C. Kiffer,[1] Amelia J. Eisch,[1,6-8] Sanghee Yun[1,7,8*]

^Equal contribution, *Corresponding author

[1]Department of Anesthesiology and Critical Care Medicine, The Children's Hospital of Philadelphia (CHOP) Research Institute, Philadelphia, PA, USA

[2]Department of Pathobiology, University of Pennsylvania School of Veterinary Medicine, Philadelphia, PA, USA

[3]Department of University Laboratory Animal Resources,University of Pennsylvania, Philadelphia, PA, USA

[4]University of Pennsylvania, School of Arts and Sciences, Philadelphia, PA, USA

[5]Division of Neurology, The Children's Hospital of Philadelphia (CHOP) Research Institute, Philadelphia, PA, USA

[6]Department of Neuroscience, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA

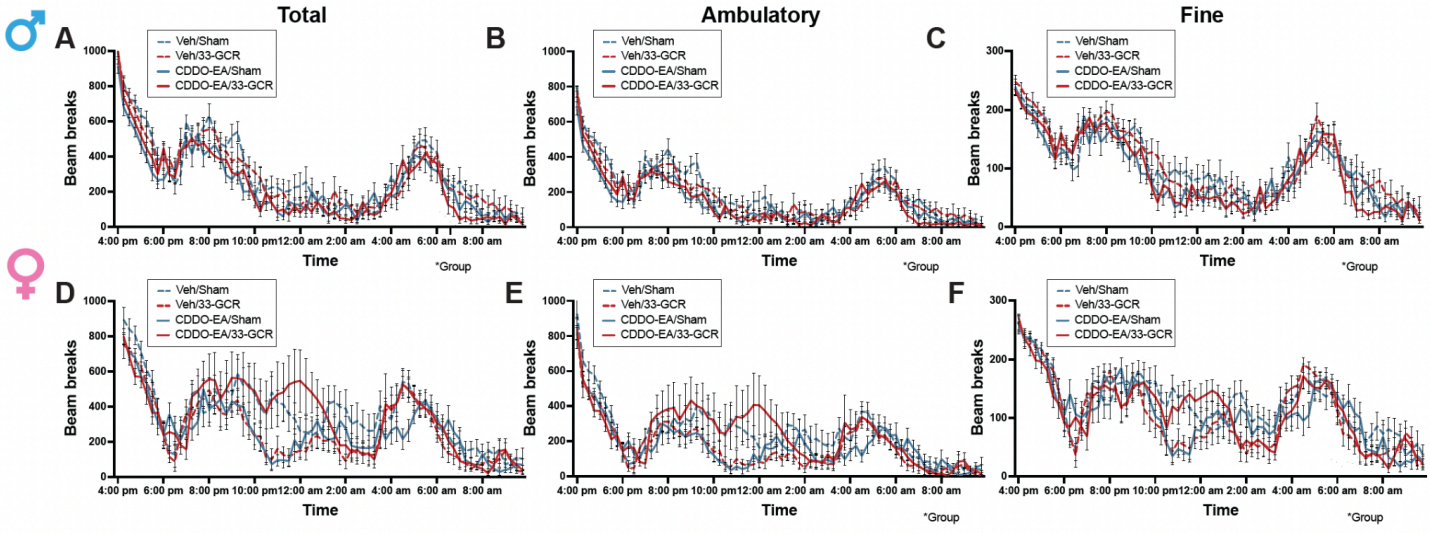
[7]Neuroscience Graduate Group, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA

[8]Department of Anesthesiology and Critical Care Medicine, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA

Supplementary Fig1.

Supplementary Table 1.

Supplementary Table 2.



Supplementary Fig1. CDDO-EA reduces locomotor activity across the circadian cycle in both sexes. **(A–F)** Locomotor activity measured over 18 hours (4pm–10am) via photobeam breaks in 15-minute bins in males **(A–C)** and females **(D–F)**. Total activity **(A, D)**, ambulatory activity **(B, E)**, and fine activity **(C, F)**. Data are presented as mean ± SEM (n=10–12/group). Statistical analysis: 2-way ANOVA (IRR × Drug) on summed light phase (4pm–7pm, 7am–10am) and dark phase (7pm–7am) data. *p<0.05. Post-hoc: Veh/Sham vs CDDO-EA/Sham, ^{b} p<0.05, $^{b'}$ p<0.01; Veh/Sham vs CDDO-EA/33-GCR, ^{c} p<0.05; Veh/33-GCR vs CDDO-EA/Sham, ^{d} p<0.05; # 0.05<p<0.08. Complete subject numbers and detailed statistical analyses are provided in Supplementary Table 1.

Supplementary Table 1. Statistical analysis

Experiment	Measure	Test Phase	Load (Difficulty)	Figure Panel	Group	Sample Size: n (Event*)		Mean (predicted or rank) or Median			Passed Normality test?	Test Statistic	Main Effect or Interaction (bold text: P<0.05)	Dist.-Value (Dfn, Dfd)	Main Effect P-Value (bold text: p<0.05)	% of Total Variation	Post-hoc Test Correction	Group Difference P-Value (bold text: P<0.05). Lower case italicized letter (e.g. a, b, c, etc) indicates specific group differences. Apostrophe indicates gradations of P values. Post-hoc values of 0.05<P<0.08 are only considered notable (and indicated below and on graph by #) when two additional conditions are met: if effect size is medium or large and if post-hoc 95% CI does not include zero
								Object 1	***Object 2***	***Object 3***								
Male d-SLR Sample	% object exploration	--	d	2B	Veh/Sham	10		29.944	32.957	37.1	Yes	3-way RM ANOVA	**Object**	**F(2, 70)=9.3076**	***p<0.001***		Tukey's	
					Veh/33-GCR	10		24.333	25.299	30.367	Yes		Drug	F(1, 35)= 0.0008	*p=0.978*			
					CDDO-EA/Sham	9		24.628.88889	22.96888.89	52.4.0111111	Yes		Radiation	F(1, 35)=0.0008	*p=0.978*			
					CDDO-EA/33-GCR	10		24.554	26.952	48.495	Yes		Object x Drug	F(2, 70)=0.5637	*p=0.572*			
													Object x Radiation	F(2, 70)= 0.2728	*p=0.762*			
													Drug x Radiation	F(1, 35)=1.0589	*p=0.311*			
													Object x Drug x Radiation	F(2, 70)=0.9425	*p=0.395*			
Male d-SLR Test	d2 ratio	--	d	2C	Veh/Sham	10					Yes	2-way ANOVA	Radiation	F(1, 35)=0.953	*p=0.336*		Tukey's	
					Veh/33-GCR	10					Yes		Drug	F(1, 35)=0.055	*p=0.816*			
					CDDO-EA/Sham	9					Yes		Radiation x Drug	F(1, 35)=0.312	*p=0.580*			
					CDDO-EA/33-GCR	10					Yes							
Male d-SLR Test	Locomotion	--	d	2D	Veh/Sham	10					Yes	2-way ANOVA	Radiation	F(1, 35)=0.314	*p=0.579*		Tukey's	
					Veh/33-GCR	10					Yes		Drug	F(1, 35)=0.0005	*p=0.982*			
					CDDO-EA/Sham	9					Yes		Radiation x Drug	F(1, 35)=0.314	*p=0.581*			
					CDDO-EA/33-GCR	10					Yes							
								Object 1	***Object 2***	***Object 3***								
Male s-SLR Sample	% object exploration	--	s	2F	Veh/Sham	10		28.36	39.95	31.69	Yes	3-way RM ANOVA	Object	F(2,70)=1.089	*p=0.342*		Tukey's	
					Veh/33-GCR	10		36.87	30.98	32.15	Yes		Drug	F(1, 35)=0.08115	*p=0.777*			
					CDDO-EA/Sham	9		35.61	29.18	35.21	Yes		Radiation	F(1, 35)=0.1268	*p=0.724*			
					CDDO-EA/33-GCR	10		38.06	22.83	39.11	Yes		**Object x Drug**	**F(2, 70)=3.615**	***p=0.032***			
													Object x Radiation	F(2, 70)=2.508	*p=0.089*			
													Drug x Radiation	F(1, 35)=2.683	*p=0.110*			
													Object x Drug x Radiation	F(2, 70)=0.3709	*p=0.692*			
Male s-SLR Test	d2 ratio	--	s	2G	Veh/Sham	10					Yes	2-way ANOVA	Radiation	F(1, 35)=0.003	*p=0.955*		Tukey's	
					Veh/33-GCR	10					Yes		Drug	F(1, 35)=0.483	*p=0.492*			
					CDDO-EA/Sham	9					Yes		Radiation x Drug	F(1, 35)=0.060	*p=0.807*			
					CDDO-EA/33-GCR	10					Yes							
Male s-SLR Test	Locomotion	--	s	2H	Veh/Sham	10					Yes	2-way ANOVA	Radiation	F(1, 35)=0.279	*p=0.601*		Tukey's	
					Veh/33-GCR	10					Yes		**Drug**	**F(1, 35)= 4.242**	***p=0.047***			
					CDDO-EA/Sham	9					Yes		Radiation x Drug	F(1, 35)=2.078	*p=0.158*			
					CDDO-EA/33-GCR	10					Yes							
								Object 1	***Object 2***	***Object 3***								
Male xs-SLR Sample	% object exploration	--	xs	2J	Veh/Sham	10		32.56	33.5	33.94	Yes	3-way RM ANOVA	Object	F(2,70)=0.454	*p=0.637*		Tukey's	
					Veh/33-GCR	10		37.3	29.58	33.12	Yes		Drug	F(1, 35)= 3.236	*p=0.081*			
					CDDO-EA/Sham	9		31.3	35.57	33.13	Yes		**Radiation**	**F(1, 35)= 6.88**	***p=0.013***			
					CDDO-EA/33-GCR	10		34.08	38.91	27.01	Yes		Object x Drug	F(2, 70)= 1.520	*p=0.226*			
													Object x Radiation	F(2, 70)= 0.806	*p=0.451*			
													Drug x Radiation	F(1, 35)= 1.130	*p=0.295*			
													Object x Drug x Radiation	F(1, 70)= 0.6497	*p=0.525*			
Male xs-SLR Test	d2 ratio	--	xs	2K	Veh/Sham	10				-0.1077	Yes	2-way ANOVA	Radiation	F(1, 35)= 1.972	*p=0.169*		Tukey's	VehGCR vs. Veh/Sham: ***a p<0.05***
					Veh/33-GCR	10				0.1952	Yes		**Drug**	**F(1, 35)= 4.567**	***p=0.040***			
					CDDO-EA/Sham	9				-0.0827	Yes		**Radiation x Drug**	**F(1, 35)= 6.063**	***p=0.019***			VehGCR vs. CDDO-EA/GCR: ***e p<0.05***
					CDDO-EA/33-GCR	10				-0.165	Yes							
Male xs-SLR Test	Locomotion	--	xs	2L	Veh/Sham	10					Yes	2-way ANOVA	Radiation	F(1, 35)=0.008	*p=0.931*		Tukey's	
					Veh/33-GCR	10					Yes		Drug	F(1, 35)=0.816	*p=0.373*			
					CDDO-EA/Sham	9					Yes		Radiation x Drug	F(1, 35)=0.880	*p=0.355*			
					CDDO-EA/33-GCR	10					Yes							
								Object 1	***Object 2***	***Object 3***								
Female d-SLR Sample	% object exploration	--	d	3B	Veh/Sham	12		29.88	36.93	33.19	Yes	3-way RM ANOVA	**Object**	**F(2, 80)=3.893**	***p=0.0244***		Tukey's	
					Veh/33-GCR	12		32.2	33.99	33.82	Yes		**Drug**	**F(1, 40)=4.390**	***p=0.0425***			
					CDDO-EA/Sham	9		31.8	37.65	30.55	Yes		Radiation	F(1, 40)=0.1031	*p=0.750*			
					CDDO-EA/33-GCR	11		35.17	37.12	27.71	Yes		Object x Drug	F(2, 80)=1.900	*p=0.156*			
													Object x Radiation	F(2, 80)=0.8132	*p=0.447*			
													Drug x Radiation	F(1, 40)=0.6308	*p=0.432*			
													Object x Drug x Radiation	F(2, 80)=0.3119	*p=0.733*			
Female d-SLR Test	d2 ratio	--	d	3C	Veh/Sham	12					Yes	2-way ANOVA	Radiation	F(1, 40)=0.088	*p=0.768*		Tukey's	
					Veh/33-GCR	12					Yes		Drug	F(1, 40)=0.294	*p=0.591*			
					CDDO-EA/Sham	9					Yes		Radiation x Drug	F(1, 40)=1.433	*p=0.238*			
					CDDO-EA/33-GCR	11					Yes							
Female d-SLR Test	Locomotion	--	d	3D	Veh/Sham	12				2184.418	Yes	2-way ANOVA	**Radiation**	**F(1, 40)= 12.711**	***p<0.01***		Tukey's	VehGCR vs. Veh/Sham: ***a p<0.05***
					Veh/33-GCR	12				1756.65	Yes		**Drug**	**F(1, 40)=4.821**	***p=0.034***			
					CDDO-EA/Sham	9				1888.934	Yes		Radiation x Drug	F(1, 40)=0.746	*p=0.393*			
					CDDO-EA/33-GCR	11				1628.008	No							
								Object 1	***Object 2***	***Object 3***								
Female s-SLR Sample	% object exploration	--	s	3F	Veh/Sham	12		34.84	32.83	32.33	Yes	3-way RM ANOVA	Object	F(2,80)=0.5429	*p=0.581*		Tukey's	
					Veh/33-GCR	12		33.76	30.56	35.68	Yes		Drug	F(1, 40)=0.01778	*p=0.895*			
					CDDO-EA/Sham	9		36.89	28.31	34.8	Yes		Radiation	F(1, 40)=0.0058	*p=0.939*			
					CDDO-EA/33-GCR	11		23.86	38.59	37.55	Yes		Object x Drug	F(2, 80)=0.6754	*p=0.512*			
													Object x Radiation	F(2, 80)=2.188	*p=0.119*			
													Drug x Radiation	F(1, 40)=0.0058	*p=0.940*			
													Object x Drug x Radiation	F(2, 80)=2.191	*p=0.119*			
Female s-SLR Test	d2 ratio	--	s	3G	Veh/Sham	12					Yes	2-way ANOVA	Radiation	F(1, 40)=0.031	*p=0.861*		Tukey's	
					Veh/33-GCR	12					Yes		Drug	F(1, 40)=0.276	*p= 0.602*			
					CDDO-EA/Sham	9					Yes		Radiation x Drug	F(1, 40)=2.613	*p=0.114*			
					CDDO-EA/33-GCR	11					Yes							
Female s-SLR Test	Locomotion	--	s	3H	Veh/Sham	12				1668.442	Yes	2-way ANOVA	Radiation	F(1, 40)=3.872	*p=0.056*		Tukey's	CDDO/Sham vs. Veh/Sham: ***b p<0.05***
					Veh/33-GCR	12				1424.134	Yes		**Drug**	**F(1, 40)=9.612**	***p=0.004***			
					CDDO-EA/Sham	9				1325.551	Yes		Radiation x Drug	F(1, 40)=0.705	*p=0.406*			
					CDDO-EA/33-GCR	11				1227.38	No							
								Object 1	***Object 2***	***Object 3***								
Female xs-SLR Sample	% object exploration	--	xs	3J	Veh/Sham	12		33.13	28.92	37.95	Yes	3-way RM ANOVA	Object	F(2, 80)=1.547	*p=0.219*		Tukey's	
					Veh/33-GCR	12		31.54	32.89	35.58	Yes		Drug	F(1, 40)=1.143	*p=0.292*			
					CDDO-EA/Sham	9		33.82	28.88	37.31	Yes		Radiation	F(1, 40)=2.121	*p=0.153*			
					CDDO-EA/33-GCR	11		32.48	35.38	32.14	Yes		Object x Drug	F(2, 80)=0.2584	*p=0.773*			
													Object x Radiation	F(2, 80)=1.788	*p=0.174*			
													Drug x Radiation	F(1, 40)=3.453	*p=0.071*			
													Object x Drug x Radiation	F(2, 80)=0.1457	*p=0.865*			
Female xs-SLR Test	d2 ratio	--	xs	3K	Veh/Sham	12					Yes	2-way ANOVA	Radiation	F(1, 40)=0.971	*p=0.330*		Tukey's	
					Veh/33-GCR	12					Yes		Drug	F(1, 40)=0.134	*p=0.716*			
					CDDO-EA/Sham	9					Yes		Radiation x Drug	F(1, 40)=0.042	*p=0.839*			
					CDDO-EA/33-GCR	11					Yes							
Female xs-SLR Test	Locomotion	--	xs	3L	Veh/Sham	12					Yes	2-way ANOVA	**Radiation**	**F(1, 40)=5.138**	***p=0.029***		Tukey's	
					Veh/33-GCR	12					Yes		Drug	F(1, 40)=2.179	*p=0.148*			
					CDDO-EA/Sham	9					Yes		Radiation x Drug	F(1, 40)=1.233	*p=0.273*			
					CDDO-EA/33-GCR	11					No							
								0 Mon post-IRR	**1 Mon post-IRR**	**2 Mon post-IRR**	**3 Mon post-IRR**	**4 Mon post-IRR**	**6 Mon post-IRR**	**7 Mon post-IRR**				
Male Animal	Weight	--	--	4A	Veh/Sham	12		29.62	30.93	36.58	37.61	34.03	43.16	44.15	Yes		Radiation	F(1,43)=0.3024	*p=0.585*			
					Veh/33-GCR	12		30.08	30.39	35.49	36.36	33.4	41.66	43.28	Yes		Drug	F(1,43)=2.8160	*p=0.101*			
					CDDO-EA/Sham	11-10		29.31	30.9	36.32	37.42	34.2	43.3	46.09	Yes	3-way Mixed effect RM	**Time**	**F(6,258)=353.618**	***p<0.001***		Bonferroni	

Weights	**(Long-term)**	--	--	[illegible]	CDDO-EA/33-GCR	12	30.67	32.13	38.6	39.83	35.68	45.88	46.85					Yes	ANOVA	Radiation x Drug Radiation x Time Drug x Time Radiation x Drug x Time	F(1,43)=2.0611 F(6,258)=0.2278 F(6,258)=1.9330 F(6,258)=0.9517	*p=0.158* *p=0.967* *p=0.076* *p=0.459*	Bonferroni	
Female Animal Weights	**Weight (Long-term)**	--	--	**4B**	Veh/Sham Veh/33-GCR CDDO-EA/Sham CDDO-EA/33-GCR	12 12 11 12	**0 Mon post-IRR** 22.88 23.26 24.41 23.35	**1 Mon post-IRR** 22.39 23.19 24.33 23.11	**2 Mon post-IRR** 24.79 27.1 26.12 25.33	**3 Mon post-IRR** 28.6 32.33 29.42 29.53	**4 Mon post-IRR** 31.92 36.21 30.95 34.06	**6 Mon post-IRR** 30.97 36.52 31 34.23	**7 Mon post-IRR** 33.16 39.23 32.34 36.09					Yes Yes Yes Yes	3-way RM ANOVA	**Radiation** Drug **Time** Radiation x Drug **Radiation x Time** **Drug x Time** Radiation x Drug x Time	**F(1,43)=6.28** F(1,43)=0.47 **F(6,258)=250.06** F(1,43)=1.76 **F(6,258)=12.13** **F(6,258)=3.25** F(6,258)=0.47	***p=0.016*** *p=0.495* ***p<0.001*** *p=0.192* ***p<0.001*** ***p=0.004*** *p=0.829*	Bonferroni	Veh/Sham vs Veh/GCR: ***a p<0.05*** Months 2, 3, 4, ***a' p<0.01*** Months 6, 7 Veh/Sham vs CDDO-EA/Sham: ***b' p<0.01*** Months 0, 1
Male Phase Locomotion - Total	**Beam Breaks**	--	--	**4C**	Veh/Sham Veh/33-GCR CDDO-EA/Sham CDDO-EA/33-GCR	12 12 10 12	**Mean beam breaks** 22191.42 20844.58 17333.8 17189.42											No No No No	Kruskal-Wallis	Group	df=3	***p=0.01***	Dunn's test	Veh/Sham vs. CDDO/Sham: ***b p=0.0446*** Veh/GCR vs. CDDO-EA/Sham: ***d p=0.0483*** Veh/Sham vs. CDDO-EA/GCR: ***c# p=0.0560*** Veh/GCR vs. CDDO-EA/GCR: ***e# p=0.0606***
Male Phase Locomotion - Ambulatory	**Beam Breaks**	--	--	**4D**	Veh/Sham Veh/33-GCR CDDO-EA/Sham CDDO-EA/33-GCR	12 12 10 12	**Mean beam breaks** 14406.667 13009.25 10625.2 10515.083											No No No No	Kruskal-Wallis	Group	df=3	***p=0.02***	Dunn's test	Veh/Sham vs. CDDO/Sham: ***b p=0.0242*** Veh/Sham vs. CDDO-EA/GCR: ***c p=0.0404***
Male Phase Locomotion - Fine	**Beam Breaks**	--	--	**4E**	Veh/Sham Veh/33-GCR CDDO-EA/Sham CDDO-EA/33-GCR	12 12 10 12	**Mean beam breaks** 7784.75 7835.33 6708.6 6674.33											No No No No	Kruskal-Wallis	Group	df=3	*p=0.11*		
Female Phase Locomotion - Total	**Beam Breaks**	--	--	**4F**	Veh/Sham Veh/33-GCR CDDO-EA/Sham CDDO-EA/33-GCR	12 12 11 12	**Mean beam breaks** 26594.33 19679.67 19999.64 25288.42											No No No No	Kruskal-Wallis	Group	df = 3	***p=0.012***	Dunn's test	Veh/Sham vs. Veh/GCR: ***a p=0.0154*** Veh/Sham vs. CDDO/Sham: ***b p=0.0112***
Female Phase Locomotion - Ambulatory	**Beam Breaks**	--	--	**4G**	Veh/Sham Veh/33-GCR CDDO-EA/Sham CDDO-EA/33-GCR	12 12 11 12	**Mean beam breaks** 17690.58 12189.25 12113.18 17236.75											No No No No	Kruskal-Wallis	Group	df=3	***p=0.019***	Dunn's test	Veh/Sham vs. Veh/GCR: ***a p=0.0327*** Veh/Sham vs. CDDO/Sham: ***b p=0.0127***
Female Phase Locomotion - Fine	**Beam Breaks**	--	--	**4H**	Veh/Sham Veh/33-GCR CDDO-EA/Sham CDDO-EA/33-GCR	12 12 11 12	**Mean beam breaks** 8903.75 7490.417 7886.455 8051.667											No No No No	Kruskal-Wallis	Group	df=3	***p=0.02***	Dunn's test	Veh/Sham vs. Veh/GCR: ***a' p<0.01*** Veh/Sham vs. CDDO/Sham: ***b# p=0.06***
Male Autoshaping	**Reward approaches (CS+ trials)**	Acquisition	--	**5B**	Veh/Sham Veh/33-GCR CDDO-EA/Sham CDDO-EA/33-GCR	10 11 10 10	***Day 1*** 4 3.182 2.6 2.2	***Day 2*** 2.2 2.636 4.6 2.8	***Day 3*** 2.9 2.182 4 2.9	***Day 4*** 4.5 9.455 9 10	***Day 5*** 7.1 9.455 8.2 12.7	***Day 6*** 2.4 7.545 3.9 7.8	***Day 7*** 3.4 5.364 4.8 9.2	***Day 8*** 5.2 5 3.8 6.8	***Day 9*** 3.9 5.273 1.9 4.6	***Day 10*** 2.6 3.545 2.9 3.4	***Day 11*** 2.1 1 2.3 3.9	Yes Yes Yes Yes	3-way RM ANOVA	**Time** Radiation Drug Time x Drug Time x Radiation Drug x Radiation Time x Drug x Radiation	**F(10,370)=10.45** F(1, 37)= 0.4703 F(1, 37)= 1.336 F(10,370)= 1.7339 F(10,370)= 0.8985 F(1, 37)= 0.0197 F(10,370)= 0.6270	***p<0.0001*** *p=0.4971* *p=0.2551* *p=0.07159* *p=0.53468* *p=0.8891* *p=0.79081*	Tukey's	Veh/GCR: ***p=0.0344*** Day 4 vs Day 11 Veh/GCR: ***p=0.0344*** Day 5 vs Day 11 CDDO/SHAM: ***p=0.0387*** Day 4 vs Day 11 CDDO/SHAM: ***p=0.0212*** Day 4 vs Day 9
Male Autoshaping	**Δ Approaches (CS+ vs. CS-)**	Acquisition	--	**5C**	Veh/Sham Veh/33-GCR CDDO-EA/Sham CDDO-EA/33-GCR	10 11 10 10	***Day 1*** -0.7 -0.7273 -0.2 -0.3	***Day 2*** -0.1 0.3636 1.2 1	***Day 3*** -0.6 -0.5455 1.1 0.7	***Day 4*** -1.7 1 2.9 0.2	***Day 5*** 3 3.909 5.2 2.4	***Day 6*** 1.3 3.909 5.4 0.3	***Day 7*** 0.6 2.727 2.8 3.7	***Day 8*** 1.4 3.273 2.6 4.1	***Day 9*** 0.9 4.636 2.4 2.7	***Day 10*** -1 3.909 3.1 3.6	***Day 11*** 1.3 3.364 3.1 2.9	Yes Yes Yes Yes	3-way RM ANOVA	**Time** Drug Radiation Time x Drug Time x Radiation Drug x Radiation Time x Drug x Radiation	**F(10,370)= 5.942** F(1, 37)= 1.810 F(1, 37)= 0.7282 F(10,370)= 0.4081 F(10,370= 1.299 F(1, 37)= 3.737 F(10, 370= 1.234	***p<0.0001*** *p=0.1867* *p=0.3989* *p=0.9426* *p=0.2293* *p=0.0609* *p=0.2674*	Tukey's	
Male Autoshaping	**% Accuracy to CS+ approach**	Acquisition	--	**5D**	Veh/Sham Veh/33-GCR CDDO-EA/Sham CDDO-EA/33-GCR	10 11 10 10	***Day 1*** 30.69 35.84 28.62 39.62	***Day 2*** 46.65 36.24 33.85 42.13	***Day 3*** 45.68 41.17 44.76 41.72	***Day 4*** 37.18 43.83 54.88 34.52	***Day 5*** 42 44.3 52 48.04	***Day 6*** 41.99 47.56 46.07 36.07	***Day 7*** 44.74 48.14 48.19 48.5	***Day 8*** 47.88 52.29 44.11 38.09	***Day 9*** 41.73 54.23 52.42 45.91	***Day 10*** 34 53.85 59.38 51.56	***Day 11*** 49.33 66.05 60.92 48.01	Yes Yes Yes Yes	3-way RM ANOVA	**Time** Drug Radiation Time x Drug Time x Radiation Drug x Radiation Time x Drug x Radiation	**F(10,370)= 3.261** F(1, 37)= 0.01333 F(1, 37)= 0.0077 F(10,370)= 0.7706 F(10,370)= 0.4470 F(1, 37)= 0.8658 F(10,370)= 1.441	***p=0.0005*** *p=0.9087* *p=0.9305* *p=0.6572* *p=0.9224* *p=0.3581* *p=0.160*	Tukey's	
Female Autoshaping	**Reward approaches (CS+ trials)**	Acquisition	--	**5E**	Veh/Sham Veh/33-GCR CDDO-EA/Sham CDDO-EA/33-GCR	12 12 10 11	***Day 1*** 1.25 0.6667 2.4 1.727	***Day 2*** 2.25 1.333 2.8 1.818	***Day 3*** 2.667 2 2.8 6.909	***Day 4*** 4.417 4.167 3.9 6	***Day 5*** 3.833 6.833 8 7.909	***Day 6*** 2.333 4.667 6.8 13.09	***Day 7*** 1.5 4.5 2.7 8.273	***Day 8*** 2.75 5.333 5 4.727	***Day 9*** 1.25 3.333 3.9 7.818	***Day 10*** 1.917 0.9167 2.9 3.364	***Day 11*** 1.5 1 3.7 3.636	Yes Yes Yes Yes	3-way RM ANOVA	**Time** **Drug** Radiation Time x Drug **Time x Radiation** Drug x Radiation Time x Drug x Radiation	**F(10, 410)= 7.0647** **F(1, 41)= 7.3475** F(1, 41)= 2.5751 F(10 , 410)= 1.6730 **F(10, 410)= 2.0311** F(1, 41)= 0.3783 F(10, 410)= 0.9068	***p<0.0001*** ***p= 0.009762*** *p=0.116233* *p= 0.084764* ***p=0.029098*** *p=0.541936* *p= 0.526739*	Tukey's	CDDO/Sham vs. Veh/Sham: ***b p=0.0164*** Day 5 Veh/Sham vs. Veh/GCR: ***a# p=0.0558*** Day 5 CDDO/Sham vs. Veh/Sham: ***b p=0.0344*** Day 6 CDDO/GCR vs. Veh/GCR: ***e p=0.0446*** Day 6 CDDO/Sham vs. CDDO/GCR: ***f p=0.0492*** Day 7 Veh/Sham vs. Veh/GCR: ***a# p=0.0623*** Day 7 Veh/Sham vs. Veh/GCR: ***a p=0.0249*** Day 9 CDDO/GCR vs. Veh/GCR: ***e p=0.0466*** Day 10
Female Autoshaping	**Δ Approaches (CS+ vs. CS-)**	Acquisition	--	**5F**	Veh/Sham Veh/33-GCR CDDO-EA/Sham CDDO-EA/33-GCR	12 12 10 11	***Day 1*** -0.1667 0.3333 1 0.8182	***Day 2*** 0.25 -0.5 -1.9 -0.4545	***Day 3*** -2.083 -1.083 1.2 -0.1818	***Day 4*** -0.1667 -2.667 0.6 -0.6364	***Day 5*** 0 -0.25 1.9 1.273	***Day 6*** 1.917 0.5833 1.9 0.9091	***Day 7*** 3.583 1 1.1 1.273	***Day 8*** 1.917 1.167 1.6 1.909	***Day 9*** 1.333 1.167 2.8 1.091	***Day 10*** 3.083 1.917 3.3 1.273	***Day 11*** 2.5 3.583 2.2 0.2727	Yes Yes Yes Yes	3-way RM ANOVA	**Time** Drug Radiation Time x Drug Time x Radiation Drug x Radiation Time x Drug x Radiation	**F(10,410)= 4.7645** F(1, 41)= 0.1414 F(1, 41)= 0.9454 F(10,410)=1.4105 F(10,410)=0.4741 F(1, 41)= 0.0064 F(10,410)=0.7709	***p<0.0001*** *p=0.7088* *p=0.3366* *p=0.1729* *p=0.9066* *p=0.9367* *p=0.6570*	Tukey's	
Female Autoshaping	**% Accuracy to CS+ approach**	Acquisition	--	**5G**	Veh/Sham Veh/33-GCR CDDO-EA/Sham CDDO-EA/33-GCR	12 12 10 11	***Day 1*** 42.18 47.7 46.83 50.52	***Day 2*** 37.74 42.64 31.91 37.82	***Day 3*** 50.94 42.67 49.83 51.89	***Day 4*** 38.92 39.43 42.18 36.46	***Day 5*** 40.5 42.39 38.41 40.13	***Day 6*** 48.43 37.59 33.13 34.18	***Day 7*** 54.4 38.14 32.46 44.02	***Day 8*** 42.16 46.71 39.55 44.07	***Day 9*** 46.71 46.16 38.95 31.78	***Day 10*** 56.58 56.53 44.64 37.1	***Day 11*** 49.75 61.54 53.07 36.65	Yes Yes Yes Yes	3-way RM ANOVA	**Time** Drug Radiation Time x Drug Time x Radiation Drug x Radiation Time x Drug x Radiation	**F(10,410)= 2.4388** F(1, 41)= 1.5502 F(1, 41)= 0.0206 F(6.800, 278.8)= 1.1896 F(6.800, 278.8)= 0.4370 F(1, 41)= 0 F(6.800, 278.8)= 1.4199	***p=0.007817*** *p=0.220181* *p=0.886528* *p=0.295874* *p=0.928075* *p=0.995829* *p=0.168733*	Tukey's	
Male Autoshaping	**Approaches to lit CS+**	Reversal	--	**6B**	Veh/Sham Veh/33-GCR CDDO-EA/Sham CDDO-EA/33-GCR	10 11 10 10	***Day 1*** 5.3 6 5 3.3	***Day 2*** 7.4 5.909 4.7 5.4	***Day 3*** 8.4 6.727 5.5 4.3	***Day 4*** 6.9 5.455 6.3 5.5	***Day 5*** 7 7 6.3 5							Yes Yes Yes Yes	3-way RM ANOVA	**Time** Drug Radiation Time x Drug Time x Radiation Drug x Radiation Time x Drug x Radiation	**F(4, 148)= 3.642** F(1, 37)= 3.732 F(1, 37)= 1.149 F(4, 148)= 2.006 F(4, 148)= 0.5453 F(1, 37)= 0.0026 F(4, 148)= 2.239	***p=0.00733*** *p=0.0611* *p=0.2906* *p=0.0966* *p=0.7027* *p=0.9596* *p=0.0676*	Tukey's	
Male Autoshaping	**% Accuracy to CS+ approach**	Reversal	--	**6C**	Veh/Sham Veh/33-GCR CDDO-EA/Sham CDDO-EA/33-GCR	10 11 10 10	***Day 1*** 36.41 40.43 33.33 22.33	***Day 2*** 49.33 39.52 31.33 36	***Day 3*** 56.83 46.31 36.67 28.67	***Day 4*** 46 39.82 42.14 38.12	***Day 5*** 49 50.5 42.14 34.3							Yes Yes Yes Yes	3-way RM ANOVA	**Time** **Drug** Radiation Time x Drug Time x Radiation Drug x Radiation Time x Drug x Radiation	**F(4, 148)= 4.364** **F(1, 37)= 4.803** F(1, 37)= 0.8976 F(4, 148)= 2.011 F(4, 148)= 0.4512 F(1, 37)= 0.011 F(4, 148)= 2.034	***p=0.002299*** ***p=0.0348*** *p=0.3496* *p=0.09589* *p=0.7714* *p=0.9171* *p=0.0926*	Tukey's	Veh/33-GCR vs. CDDO/33-GCR: ***e' p=0.00846*** Day 1 Veh/Sham vs. CDDO/Sham: ***b p<0.05*** Days 2,3
					Veh/Sham	12	***Day 1*** 5.75	***Day 2*** 6.833	***Day 3*** 7.417	***Day 4*** 7.5	***Day 5*** 9.75									**Time**	**F(4, 164)= 12.61**	***p<0.0001***		Veh/Sham vs. Veh/33-GCR: ***a p=0.0341*** Day 6

Female Autoshaping	Approaches to lit CS+	Reversal	–	6D	Veh/33-GCR	12		5	5.583	5.833	6.417	7.25									
					CDDO-EA/Sham	10		4.8	4.6	5.5	7.1	8.5									
					CDDO-EA/33-GCR	11		6.273	6.455	5.182	5.182	7.455									
															3-way RM ANOVA	Drug	F(1, 41)= 0.7074	*p=0.4052*		CDDO/Sham vs. CDDO/33-GCR: ***f p=0.0232*** Day 6
																Radiation	F(1, 41)= 0.9073	*p=0.3464*		
																Time x Drug	F(4, 164)= 0.7324	*p=0.5711*	Tukey's	
																Time x Radiation	**F(4, 164)= 2.645**	***p=0.0354***		
																Drug x Radiation	F(1, 41)= 0.9307	*p=0.3404*		
																Time x Drug x Radiation	F(4, 164)= 1.425	*p=0.228*		
Female Autoshaping	% Accuracy to CS+ approach	Reversal	–	6E				***Day 1***	***Day 2***	***Day 3***	***Day 4***	***Day 5***									
					Veh/Sham	12		38.33	47.5	49.44	50	65									
					Veh/33-GCR	12		33.61	37.92	38.89	42.78	49.7									
					CDDO-EA/Sham	10		32.41	33.42	37.83	51.9	58									
					CDDO-EA/33-GCR	11		42.1	43.03	34.55	34.7	49.7									
															3-way RM ANOVA	**Time**	**F(4, 164)= 12.41**	***p<0.0001***		
																Drug	F(1, 41)= 0.5290	*p=0.4712*		
																Radiation	F(1, 41)= 1.355	*p=0.2511*		Veh/Sham vs. Veh/33-GCR: ***a p=0.0277*** Day 6
																Time x Drug	F(4, 164)= 0.6330	*p=0.640*	Tukey's	CDDO/Sham vs. CDDO/33-GCR: ***f p=0.0462*** Day 4
																Time x Radiation	**F(4, 164)= 2.599**	***p=0.03815***		
																Drug x Radiation	F(1, 41)= 0.6011	*p=0.4426*		
																Time x Drug x Radiation	F(4, 164)= 1.763	*p=0.139*		
Male EPM	Time spent in open arms (s)	--	–	7A				**Mean time**													
					Veh/Sham	12		35.13						Yes	2-way ANOVA	Drug	F(1, 43)= 1.387	*p=0.245*		
					Veh/33-GCR	12		45.87						Yes		Radiation	F(1, 43)= 0.163	*p=0.688*	Tukey's	
					CDDO-EA/Sham	11		37.2						Yes		Drug x Radiation	F(1, 43)= 2.417	*p=0.127*		
					CDDO-EA/33-GCR	12		30.89						Yes						
Male EPM	Number of entries into open arms	--	–	7B				**Mean number of entries**													
					Veh/Sham	12		5.5						Yes	2-way ANOVA	Drug	F(1, 43)= 0.345	*p=0.560*		
					Veh/33-GCR	12		7.75						Yes		Radiation	F(1, 43)= 0.005	*p=0.944*	Tukey's	
					CDDO-EA/Sham	11		8.273						Yes		**Drug x Radiation**	**F(1, 43)= 4.629**	***p=0.037***		
					CDDO-EA/33-GCR	12		6.167						Yes						
Male EPM	Ratio time spent in open:closed arms ("Exploration Index")	--	–	7C				**Mean Ratio**													
					Veh/Sham	12		0.1662						Yes	2-way ANOVA	Drug	F(1, 43)= 1.097	*p=0.301*		
					Veh/33-GCR	12		0.2584						Yes		Radiation	F(1, 43)= 0.441	*p=0.510*	Tukey's	
					CDDO-EA/Sham	11		0.1907						Yes		Drug x Radiation	F(1, 43)= 2.772	*p=0.103*		
					CDDO-EA/33-GCR	12		0.151						Yes						
Male EPM	Total distance traveled	--	–	7D				**Mean distance**													
					Veh/Sham	12		1011						Yes	2-way ANOVA	Drug	F(1, 43)= 0.005	*p=0.945*		
					Veh/33-GCR	12		1008						Yes		Radiation	F(1, 43)=0.015	*p=0.904*		
					CDDO-EA/Sham	11		1005						Yes		Drug x Radiation	F(1, 43)= 0.116	*p=0.735*		
					CDDO-EA/33-GCR	12		1029						Yes					Tukey's	
Female EPM	Time spent in open arms (s)	--	–	7E				**Mean time**													
					Veh/Sham	12		52.91						Yes	2-way ANOVA	Drug	F(1, 43)= 0.1555	*p=0.695*		
					Veh/33-GCR	12		61.91						Yes		Radiation	F(1, 43)= 1.774	*p=0.190*	Tukey's	CDDO-EA/Sham vs. CDDO-EA/GCR: ***f p=0.0379***
					CDDO-EA/Sham	11		73.65						Yes		**Drug x Radiation**	**F(1, 43)= 7.048**	***p=0.011***		
					CDDO-EA/33-GCR	12		46.54						Yes						
Female EPM	Number of entries into open arms	--	–	7F				**Mean number of entries**													
					Veh/Sham	12		9.167						Yes	2-way ANOVA	Drug	F(1, 43)= 3.104	*p=0.085*		Veh:Sham vs. CDDO-EA:Sham: ***b' p=0.0068***
					Veh/33-GCR	12		11.25						Yes		Radiation	F(1, 43)= 1.739	*p=0.194*	Tukey's	
					CDDO-EA/Sham	11		14.73						Yes		**Drug x Radiation**	**F(1, 43)= 10.02**	***p=0.003***		CDDO-EA:Sham vs. CDDO-EA:33-GCR: ***f' p=0.0157***
					CDDO-EA/33-GCR	12		9.667						Yes						
Female EPM	Ratio time spent in open:closed arms ("Exploration Index")	--	–	7G				**Mean ratio**													
					Veh/Sham	12		0.3067						Yes	2-way ANOVA	Drug	F(1, 43)= 0.042	*p=0.839*		
					Veh/33-GCR	12		0.3936						Yes		Radiation	F(1, 43)= 0.764	*p=0.387*	Tukey's	
					CDDO-EA/Sham	11		0.4568						Yes		**Drug x Radiation**	**F(1, 43)= 5.555**	***p=0.023***		
					CDDO-EA/33-GCR	12		0.2674						Yes						
Female EPM	Total distance traveled	--	–	7H				**Mean distance**													
					Veh/Sham	12		1333						Yes	2-way ANOVA	Drug	F(1, 43)= 0.742	*p=0.3940*		Veh:33-GCR vs. CDDO-EA:Sham: ***c p=0.0323***
					Veh/33-GCR	12		1275						Yes		**Radiation**	**F(1, 43)= 10.36**	***p=0.002***	Tukey's	
					CDDO-EA/Sham	11		1527						Yes		**Drug x Radiation**	**F(1, 43)= 5.212**	***p=0.027***		CDDO-EA:Sham vs. CDDO-EA:33-GCR: ***f' p=0.0021***
					CDDO-EA/33-GCR	12		1187						Yes						
PCA	PC1 score	--	–	8D		M	F	**Male**					**Female**								
					Veh/Sham	9	12	-0.390361323					-0.2995025795	Yes	2-way ANOVA	Sex	F(1, 74)=2.294	*p=0.134*		
					Veh/33-GCR	9	12	0.04779781591					-0.6394011499	Yes		**Treatment**	**F(3, 74)=3.005**	***p=0.035***	Tukey's	Veh:33-GCR vs. CDDO-EA:33-GCR ***p=0.022***
					CDDO-EA/Sham	9	10	0.5290672458					-0.1122118777	Yes		Sex x Treatment	F(3, 74)=0.581	*p=0.629*		
					CDDO-EA/33-GCR	10	11	0.6373606878					0.3942566367	No						
PCA	PC2 score	--	–	8E	Veh/Sham	9	12	-0.3802076372					-0.1063386657	Yes	2-way ANOVA	Sex	F(1, 74)=0.191	*p=0.663*		
					Veh/33-GCR	9	12	0.3349109752					0.1297192855	Yes		Treatment	F(3, 74)=1.397	*p=0.250*	Tukey's	
					CDDO-EA/Sham	9	10	0.3600741083					0.2345554561	Yes		Sex x Treatment	F(3, 74)=0.316	*p=0.813*		
					CDDO-EA/33-GCR	10	11	-0.06681617758					-0.4355415673	No						
PCA	PC3 score	--	–	8F	Veh/Sham	9	12	-0.3.305734688					-0.5993657053	Yes	2-way ANOVA	Sex	F(1, 74)=0.016	*p=0.898*		
					Veh/33-GCR	9	12	-0.1.008596522					0.1206707392	Yes		**Treatment**	F(3, 74)=3.990	***p=0.010***	Tukey's	
					CDDO-EA/Sham	9	10	-0.192014.6258					-0.03512035985	Yes		Sex x Treatment	F(3, 74)=0.322	*p=0.808*		
					CDDO-EA/33-GCR	10	11	0.6644760938					0.4608520142	No						
Male FP	d2 ratio	--	d xs	9C				D-SLR			xs-SLR										
					Veh/Sham	3		0.237357897			-0.1513636432				2-way ANOVA	load x Radiation	F (1, 5) = 1.437	*p=0.2843*		
					Veh/33-GCR	4		0.1572280179			0.2144738396					load	F (1, 5) = 0.7941	*p=0.4137*		
																Radiation	F (1, 5) = 0.06145	*p=0.8141*		
Male FP	Signal Rate-Sample	--	d	9E				***Object 1***	***Object 2***	***Object 3***				No							
					Veh/Sham	3 (124°)		3.455	3.209	3.409				No	Kruskal-Wallis			*p=0.7974*	Dunn's test	
					Veh/33-GCR	4 (97°)		3.093	3.061	3.464							dfn6			
Male FP	Signal Amplitude-Sample	--	d	9F				***Object 1***	***Object 2***	***Object 3***				No						Veh/Sham_Obj 1 vs Veh/Sham_Obj 2 ***p<0.0001***
					Veh/Sham	3 (124°)		0.01777595479	-0.005032736500	-0.009792353521				No						Veh/Sham_Obj 1 vs Veh/Sham_Obj 3 ***p<0.0001***
					Veh/33-GCR	4 (97°)		0.04183	0.008583	0.002671										Veh/Sham_Obj 1 vs Veh/GCR_Obj 2 ***p=0.0036***
																				Veh/Sham_Obj 1 vs Veh/GCR_Obj 3 ***p=0.0001***
															Kruskal-Wallis			***p<0.0001***		Veh/Sham_Obj 2 vs Veh/GCR_Obj 1 ***p<0.0001***
																	dfn6			Veh/Sham_Obj 3 vs Veh/GCR_Obj 1 ***p<0.0001***
																				Veh/Sham_Obj 3 vs Veh/GCR_Obj 3 ***p=0.0398***
																				Veh/GCR_Obj 1 vs Veh/GCR_Obj 2 ***p<0.0001***
																				Veh/GCR_Obj 1 vs Veh/GCR_Obj 3 ***p<0.0001***
Male FP	Signal Rate-Sample	--	xs	9G				***Object 1***	***Object 2***	***Object 3***				No						Veh/Sham_Obj 3 vs. Veh/GCR_Obj 2 ***p=0.0005***
					Veh/Sham	3 (118°)		3.29	3.164	3.714				No	Kruskal-Wallis			***p=0.0002***		Veh/Sham_Obj 3 vs. Veh/GCR_Obj 3 ***p=0.0187***
					Veh/33-GCR	4(105°)		3.35	2.416	2.653							dfn6			Veh/GCR_Obj 1 vs. Veh/GCR_Obj 2 ***p=0.0392***
Male FP	Signal Amplitude-Sample	--	xs	9H				***Object 1***	***Object 2***	***Object 3***				Yes		Object x Radiation	F (2, 267) = 0.5401	*p=0.5834*		***Veh/Sham vs. Veh/33-GCR p<0.0001 Obj 1,2,3***
					Veh/Sham	3 (118°)		0.02124	0.007508	0.0069				Yes	2-way ANOVA	**Object**	F (2, 267) = 6.681	***p=0.0015***		Veh/GCR_Obj 1 vs. Veh/GCR_Obj 2 ***p=0.0034***
					Veh/33-GCR	4(105°)		0.06576	0.03995	0.04251						**Radiation**	F (1, 267) = 61.07	***p<0.0001***		Veh/GCR_Obj 1 vs. Veh/GCR_Obj 3 ***p=0.0135***
Male FP	Signal Rate-Test	--	d	9I				***Familiar***	***Novel***											Veh/Sham_F vs. Veh/GCR_Novel ***p=0.0022***
					Veh/Sham	3 (53°)		4.19	3.653						Kruskal-Wallis			***p=0.0011***		Veh/Sham_N vs. Veh/GCR_Novel ***p=0.0169***
					Veh/33-GCR	4(23°)		2.689	2.19								dfn4			
Male FP	Signal Amplitude-Test	--	d	9J				***Familiar***	***Novel***											Veh/Sham_F vs. Veh/GCR_Familiar ***p<0.0001***
					Veh/Sham	3 (53°)		0.04757	0.04306						Kruskal-Wallis			***p<0.0001***		Veh/Sham_F vs. Veh/GCR_Novel ***p=0.0013***
					Veh/33-GCR	4(23°)		-0.001335	0.01522								dfn4			Veh/Sham_N vs. Veh/GCR_Familiar ***p<0.0001***
Male FP	Signal Rate-Test	--	xs	9K				***Familiar***	***Novel***											
					Veh/Sham	3 (34°)		3.738	2.947						Kruskal-Wallis					
					Veh/33-GCR	4(57°)		3.266	3.186								dfn4	*p=0.5420*		
Male FP	Signal Amplitude-Test	--	xs	9L				***Familiar***	***Novel***											
					Veh/Sham	3 (34°)		0.03284	0.04062						Kruskal-Wallis			***p=0.0002***		Veh/Sham_Novel vs. Veh/GCR_Familiar ***p=0.006***
					Veh/33-GCR	4(57°)		0.003559	0.02044								dfn4			Veh/GCR_Familiar vs. Veh/GCR_Novel ***p=0.0002***
Male DCX	total DCX+ immature neurons	--	–	10B																	
					Veh/Sham	11		1057						Yes							
					Veh/33-GCR	10		849.6						Yes	2-way ANOVA	Drug	F(1, 37)= 0.406	*p=0.528*		
					CDDO-EA/Sham	9		868						Yes		Radiation	F(1, 37)= 0.755	*p=0.39*	Tukey's	
					CDDO-EA/33-GCR	11		937.6						Yes		Drug x Radiation	F(1, 37)= 3.052	*p=0.089*		
								Bregma -0.82	**Bregma -1.18**	**Bregma -1.54**	**Bregma -1.9**	**Bregma -2.26**	**Bregma -2.62**	**Bregma -2.98**	**Bregma -3.34**	**Bregma -3.7**	**Bregma -4.06**	**Bregma -4.42**	**Bregma -4.78**						
					Veh/Sham	11		0	0.181818181818	6.636363636	11.45454545	8.545454545	7.454545455	7	6.272727273	6.363636364	3.909090909	0.909090991	0	Yes		**Bregma**	**F(11,407)= 47.764**	***p<0.0001***		

Male DCX	immature neurons x Bregma	--	--	10C	Veh/Sham	10		0	1.3	5.3	5.9	5.8	6.9	6.3	6.4	4.6	2.6	0.8	0	Yes	3-way RM ANOVA	Drug	F(1, 37)= 0.2584	p=0.6142			
					Veh/3-GCR	9		0	0.6666666667	5	8.555555556	6.555555556	5.888888889	8.333333333	5.888888889	5.222222222	2.111111111	0	0	Yes		Radiation	F(1, 37)= 1.114	p=0.2980			
					CDDO-EA/Sham	11		0	1.181818182	8.363636364	8.727272727	7.818181818	5.727272727	7.363636364	8	4.454545455	0.454545455	0	0	Yes		Bregma x Drug	F(11, 407)= 0.888	p=0.552	Tukey's		
					CDDO-EA/3-GCR																	Bregma x Radiation	F(11, 407)= 1.372	p=0.183			
																						Drug x Radiation	F(1, 37)= 3.871	p=0.0570			
																						Bregma x Drug x Radiation	F(11,407)= 1.336	p=0.202			
Female DCX	total DCX+ immature neurons	--	--	10D	Veh/Sham	12		1253												Yes							
					Veh/3-GCR	11		1065												Yes	2-way ANOVA	Drug	F(1, 37)= 0.550	p=0.463	Tukey's		
					CDDO-EA/Sham	10		1400												No		Radiation	F(1, 37)= 4.045	p=0.052			
					CDDO-EA/3-GCR	8		1098												Yes		Drug x Radiation	F(1, 37)= 0.224	p=0.639			
								Bregma -0.82	**Bregma -1.18**	**Bregma -1.54**	**Bregma -1.9**	**Bregma -2.26**	**Bregma -2.62**	**Bregma -2.98**	**Bregma -3.34**	**Bregma -3.7**	**Bregma -4.06**	**Bregma -4.42**	**Bregma -4.78**								
					Veh/Sham	12		0	0.4166666667	3.916666667	9.583333333	9.916666667	9.833333333	8.916666667	9.75	8.083333333	5.916666667	3.25	0	Yes		**Bregma**	**F(11, 407)= 52.286**	***p<0.0001***			
					Veh/3-GCR	11		0	0.5454545455	4.727272727	8.363636364	11.72727273	8.545454545	6.727272727	8	7	3.545454545	0	0	Yes		Drug	F(1, 37)= 0.425	*p=0.518*		CDDO/Sham vs. CDDO/GCR: ***f p = 0.0353*** Bregma -1.90	
Female DCX	immature neurons x Bregma	--	--	10E	CDDO-EA/Sham	10		0	0.1	6.6	12.7	11.3	10.2	11.2	10.6	8	5.7	1.4	0	Yes	3-way RM ANOVA	**Radiation**	**F(1, 37)= 4.460**	***p=0.042***			
					CDDO-EA/3-GCR	8		0	0.125	3.875	7.875	11.25	9.625	8.375	7.875	6.875	3.625	1	0.5	Yes		Bregma x Drug	F(11,407)= 0.366	*p=0.968*	Tukey's		
																						Bregma x Radiation	F(11, 407= 1.435	*p=0.154*			
																						Drug x Radiation	F(1, 37)= 0.322	*p=0.574*			
																						Bregma x Drug x Radiation	F(11, 407)= 0.676	*p=0.762*			
Male DCX	total DCX+ progenitor cells	--	--	10F	Veh/Sham	11		3096												Yes							
					Veh/3-GCR	10		2707												Yes	2-way ANOVA	Drug	F(1, 37)= 0.4362	*p=0.513*	Tukey's		
					CDDO-EA/Sham	9		2946												Yes		Radiation	F(1, 37)= 3.368	*p=0.075*			
					CDDO-EA/3-GCR	11		2589												Yes		Drug x Radiation	F(1, 37)= 0.006	*p=0.939*			
								Bregma -0.82	**Bregma -1.18**	**Bregma -1.54**	**Bregma -1.9**	**Bregma -2.26**	**Bregma -2.62**	**Bregma -2.98**	**Bregma -3.34**	**Bregma -3.7**	**Bregma -4.06**	**Bregma -4.42**	**Bregma -4.78**								
					Veh/Sham	11		0	1.818181818	14	28.09090909	26.45454545	21.27272727	21	27.90909091	22.18181818	7	2.272727273	0	Yes		**Bregma**	**F(11 , 407)= 76.43**	***p<0.0001***			
					Veh/3-GCR	10		0	2.5	13.1	20.3	19.2	18.6	18.1	22.7	20.6	7.3	3	0	Yes		Drug	F(1, 37)= 0.201	*p=.656*			
					CDDO-EA/Sham	9		0	1	18.88888889	26.88888889	21.44444444	18.77777778	21.55555556	25	19.33333333	10.77777778	0	0	Yes		**Radiation**	**F(1, 37)= 4.415**	***p=0.0420***		VehSham vs. Veh/GCR: ***all p=0.0764*** Bregma -1.90	
Male DCX	progenitor cells x Bregma	--	--	10G	CDDO-EA/3-GCR	11		0	3.636363636	18.81818182	25.54545455	18.36363636	15.81818182	21.45454545	21.54545455	15.72727273	2.636363636	0.272727273	0	Yes	3-way RM ANOVA	Bregma x Drug	F(11,470)= 1.289	*p=.228*	Tukey's	CDDO/Sham vs. CDDO/GCR: ***f ll p=0.0694*** Bregma -4.06	
																						Bregma x Radiation	F(11,407)= 0.978	*p=.466*			
																						Drug x Radiation	F(1, 37)= 0.093	*p=.762*			
																						Bregma x Drug x Radiation	F(11,407)= 0.628	*p=.805*			
Female DCX	total DCX+ progenitor cells	--	--	10H	Veh/Sham	12		3101												Yes							
					Veh/3-GCR	11		2739												Yes		Drug	F(1, 37)= 1.412	*p=.242*	Tukey's		
					CDDO-EA/Sham	10		3530												No	2-way ANOVA	**Radiation**	**F(1, 37)= 6.948**	***p=0.012****			
					CDDO-EA/3-GCR	8		2801												Yes		Drug x Radiation	F(1, 37)= 0.789	*p=.380*			
								Bregma -0.82	**Bregma -1.18**	**Bregma -1.54**	**Bregma -1.9**	**Bregma -2.26**	**Bregma -2.62**	**Bregma -2.98**	**Bregma -3.34**	**Bregma -3.7**	**Bregma -4.06**	**Bregma -4.42**	**Bregma -4.78**								
					Veh/Sham	12		0	0.8333333333	13.58333333	2.5	24.58333333	22	22.75	24.41666667	21.58333333	14	3.5	0	Yes		**Bregma**	**F(11,407)= 54.06**	***p<0.0001***			
					Veh/3-GCR	11		0	0.6363636364	11.90909091	21.36363636	23.63636364	17.27272727	21.09090909	21.54545455	24.18181818	10.36363636	0	0	Yes		Drug	F(1, 37)= 1.345	*p=.254*		CDDO/Sham vs. CDDO/GCR: ***f p = 0.0456*** Bregma -1.90	
Female DCX	progenitor cells x Bregma	--	--	10I	CDDO-EA/Sham	10		0	0.8	15.1	29.1	25.3	23.7	20.8	31.6	30.2	16.4	3.1	0	Yes	3-way RM ANOVA	**Radiation**	**F(1, 37)= 7.212**	***p=.011***			
					CDDO-EA/3-GCR	8		0	0.125	12	18	22.875	21.75	20.875	23.75	21	10.5	3.875	0			Bregma x Drug	F(11,407)= 0.339	*p=.977*	Tukey's		
																						Bregma x Radiation	F(11,407)= 0.658	*p=.778*			
																						Drug x Radiation	F(1, 37)= 0.846	*p=.364*			
																						Bregma x Drug x Radiation	F(11,407)= 0.607	*p=.824*			
Male Interval Locomotion - Total Light	Beam Breaks	--	--	Supp 1A	Veh/Sham	12														Yes							
					Veh/3-GCR	12														Yes	2-way ANOVA	**Drug**	**F(1, 42)= 8.261**	***p=0.006***			
					CDDO-EA/Sham	10														Yes		Radiation	F(1, 42)= 0.330	*p=0.568*			
					CDDO-EA/3-GCR	12														Yes		Drug x Radiation	F(1, 42)= 0.006	*p=0.940*			
Male Interval Locomotion - Total Dark	Beam Breaks	--	--	Supp 1B	Veh/Sham	12														Yes		**Drug**	**F(1, 42)= 5.043**	***p=0.030***			
					Veh/3-GCR	12														No	2-way ANOVA	Radiation	F(1, 42)= 0.239	*p=0.627*			
					CDDO-EA/Sham	10														Yes		Drug x Radiation	F(1, 42)= 0.192	*p=0.663*			
					CDDO-EA/3-GCR	12														No							
Male Interval Locomotion - Ambulatory Light	Beam Breaks	--	--	Supp 1C	Veh/Sham	12														Yes		**Drug**	**F(1, 42)= 11.750**	***p=0.001***			
					Veh/3-GCR	12														Yes	2-way ANOVA	Radiation	F(1, 42)= 0.365	*p=0.549*			
					CDDO-EA/Sham	10														Yes		Drug x Radiation	F(1, 42)= 0.436	*p=0.513*			
					CDDO-EA/3-GCR	12														Yes							
Male Interval Locomotion - Ambulatory Dark	Beam Breaks	--	--	Supp 1D	Veh/Sham	12														Yes		**Drug**	**F(1, 42)= 5.544**	***p=0.023***			
					Veh/3-GCR	12														Yes	2-way ANOVA	Radiation	F(1, 42)= 0.556	*p=0.460*			
					CDDO-EA/Sham	10														No		Drug x Radiation	F(1, 42)= 0.329	*p=0.569*			
					CDDO-EA/3-GCR	12														Yes							
Male Interval Locomotion - Fine Light	Beam Breaks	--	--	Supp 1E	Veh/Sham	12														Yes		Drug	F(1, 42)= 5.471	*p= 0.024*			
					Veh/3-GCR	12														Yes	2-way ANOVA	Radiation	F(1, 42)= 0.0000988	*p=0.992*			
					CDDO-EA/Sham	10														Yes		Drug x Radiation	F(1, 42)= 0.394	*p=0.534*			
					CDDO-EA/3-GCR	12														Yes							
Male Interval Locomotion - Fine Dark	Beam Breaks	--	--	Supp 1F	Veh/Sham	12														No		Drug	F(1, 42)= 3.148	*p=0.083*			
					Veh/3-GCR	12														Yes	2-way ANOVA	Radiation	F(1, 42)= 0.000614	*p=0.980*			
					CDDO-EA/Sham	10														Yes		Drug x Radiation	F(1, 42)= 0.029000	*p=0.867*			
					CDDO-EA/3-GCR	12														Yes							
Female Interval Locomotion - Total Light	Beam Breaks	--	--	Supp 1G	Veh/Sham	12														Yes		Drug	F(1, 43)= 1.338	*p=0.254*			
					Veh/3-GCR	12														Yes	2-way ANOVA	Radiation	F(1, 43)= 2.865	*p=0.098*			
					CDDO-EA/Sham	11														No		Drug x Radiation	F(1, 43)= 1.210	*p=0.277*			
					CDDO-EA/3-GCR	12														Yes							
Female Interval Locomotion - Total Dark	Beam Breaks	--	--	Supp 1H	Veh/Sham	12														Yes		Drug	F(1, 43)= 0.007	*p=0.936*			
					Veh/3-GCR	12														Yes	2-way ANOVA	Radiation	F(1, 43)= 0.007	*p=0.935*			
					CDDO-EA/Sham	11														Yes		**Drug x Radiation**	**F(1, 43)= 5.561**	***p=0.023***			
					CDDO-EA/3-GCR	12														No							
Female Interval Locomotion - Ambulatory Light	Beam Breaks	--	--	Supp 1I	Veh/Sham	12														Yes		Drug	F(1, 43)= 1.204	*p=0.279*			
					Veh/3-GCR	12														Yes	2-way ANOVA	Radiation	F(1, 43)= 2.481	*p=0.123*			
					CDDO-EA/Sham	11														Yes		Drug x Radiation	F(1, 43)= 1.507	*p=0.226*			
					CDDO-EA/3-GCR	12														Yes							
Female Interval Locomotion - Ambulatory Dark	Beam Breaks	--	--	Supp 1J	Veh/Sham	12														Yes		Drug	F(1, 43)= 0.013	*p=0.910*			
					Veh/3-GCR	12														Yes	2-way ANOVA	Radiation	F(1, 43)= 0.064	*p=0.802*			
					CDDO-EA/Sham	11														Yes		**Drug x Radiation**	**F(1, 43)= 5.007**	***p=0.030***			
					CDDO-EA/3-GCR	12														No							
Female Interval Locomotion - Fine Light	Beam Breaks	--	--	Supp 1K	Veh/Sham	12														Yes		Drug	F(1, 43)= 1.214	*p=0.277*			
					Veh/3-GCR	12														Yes	2-way ANOVA	Radiation	F(1, 43)= 2.888	*p=0.096*			
					CDDO-EA/Sham	11														No		Drug x Radiation	F(1, 43)= 0.275	*p=0.603*			
					CDDO-EA/3-GCR	12														Yes							
Female Interval Locomotion - Fine Dark	Beam Breaks	--	--	Supp 1L	Veh/Sham	12														Yes		Drug	F(1, 43)= 0.024	*p=0.877*			
					Veh/3-GCR	12														Yes	2-way ANOVA	Radiation	F(1, 43)= 1.193	*p=0.281*			
					CDDO-EA/Sham	11														Yes		**Drug x Radiation**	**F(1, 43)= 4.859**	***p=0.033***			
					CDDO-EA/3-GCR	12														Yes							

Supplementary Table 2. Sample omission

Experiment	Figure	Sex	Group	Number of animals omitted from data analysis	Animal IDs omitted	Reason for omission	n/group	n/sex	n total	Criteria for omission
Overall	1	Male	Veh/Sham	0	NA	NA	12	47	94	Live vs. died
			Veh/33-GCR	0	NA	NA	12			
			CDDO/Sham	1	9	Died after locomotion - but excluded from all stats	11			
			CDDO/33-GCR	0	NA	NA	12			
	1	Female	Veh/Sham	0	NA	NA	12	47		
			Veh/33-GCR	0	NA	NA	12			
			CDDO/Sham	1	28	Died before locomotion	11			
			CDDO/33-GCR	0	NA	NA	12			
Spontaneous Location Recognition (SLR)	2	Male	Veh/Sham	2	91, 92	Did not reach either test or sample criteria for inclusion	10	39	83	**Sample** criteria: animals spent >2 sec/obj, >10 sec total exploration, and did not display unequal exploration (<3%/obj) **Test** Criteria: animals spent >1sec/obj, >5 sec total exploration
			Veh/33-GCR	2	28, 41		10			
			CDDO/Sham	2	47, 76, 9 (died)		9			
			CDDO/33-GCR	2	49, 50		10			
	3	Female	Veh/Sham	0	NA	NA	12	44		
			Veh/33-GCR	0	NA	NA	12			
			CDDO/Sham	2	25, 26, 28 (died)	Did not reach either test or sample criteria for inclusion	9			
			CDDO/33-GCR	1	29		11			
Locomotion	4	Male	Veh/Sham	0	NA	NA	12	46	93	Recording integrity
			Veh/33-GCR	0	NA	NA	12			
			CDDO/Sham	1	10, 9 (died)	Recording malfunction	10			
			CDDO/33-GCR	0	NA	NA	12			
	4	Female	Veh/Sham	0	NA	NA	12	47		
			Veh/33-GCR	0	NA	NA	12			
			CDDO/Sham	0	28 (died)	NA	11			
			CDDO/33-GCR	0	NA	NA	12			
Autoshaping	5	Male	Veh/Sham	2	91, 94	Did not reach acquisition criteria for inclusion	10	41	86	Each animal has to reach at least **25** trials in **2 out of 3** consecutive days (out of 11 total days) of acquisition training.
			Veh/33-GCR	1	25		11			
			CDDO/Sham	1	76, 9 (died)		10			
			CDDO/33-GCR	2	16, 50		10			
	6	Female	Veh/Sham	0	NA		12	45		
			Veh/33-GCR	0	NA		12			
			CDDO/Sham	1	12, 28 (died)		10			
			CDDO/33-GCR	1	31		11			
Elevated Plus Maze (EPM)	7	Male	Veh/Sham	0	NA	NA	12	47	94	Total distance traveled (cm) outlier test
			Veh/33-GCR	0	NA	NA	12			
			CDDO/Sham	0	9 (died)	NA	11			
			CDDO/33-GCR	0	NA	NA	12			
	7	Female	Veh/Sham	0	NA	NA	12	47		
			Veh/33-GCR	0	NA	NA	12			
			CDDO/Sham	0	28 (died)	NA	11			
			CDDO/33-GCR	0	NA	NA	12			
Double-Cortin X (DCX)	10	Male	Veh/Sham	1	3	Not able to count DCX cells	11	43	84	Damage to L **and** R dentate gyrus (DG) in at least one countable brain section, or outlier on statistics
			Veh/33-GCR	2	5, 8		10			
			CDDO/Sham	2	75, 12, 9 (died)		9			
			CDDO/33-GCR	1	81		11			
	10	Female	Veh/Sham	0	NA	NA	12	41		
			Veh/33-GCR	1	22	Not able to count DCX cells	11			
			CDDO/Sham	1	11, 28 (died)		10			
			CDDO/33-GCR	4	16, 29, 46, 48		8			