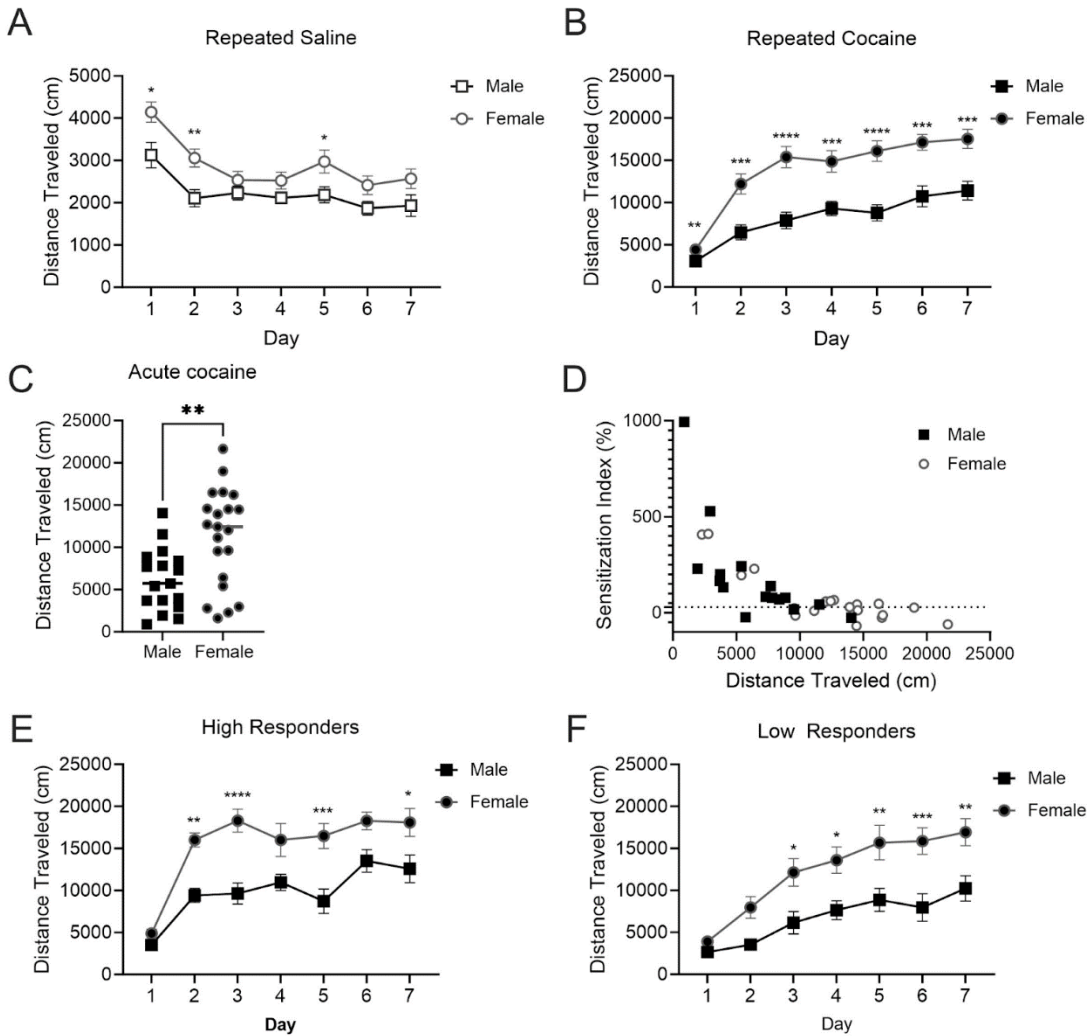


## Supplementary Figures and Tables:



**Figure S1. Sex differences in cocaine locomotor sensitization.** **A)** Distance travelled by all male and female rats exposed to saline as an initial treatment over the course of experiment 1. A two-way ANOVA revealed a main effect of day  $F_{3.57,89.28}=30.48$ ,  $p<0.0001$ , sex  $F_{1,25}=6.255$ ,  $p=0.0193$ , and a sex x day interaction  $F_{6,150}=2.162$ ,  $p=0.0498$ . \* $p<0.05$ , \*\* $p<0.01$ . **B)** Distance travelled by all male and female rats exposed to 15 mg/kg of cocaine as an initial treatment over the course of experiment 1. A main effect of day  $F_{3.64,120.2}=30.95$ ,  $p<0.0001$ , a sex  $F_{1,33}=46.2$ ,  $p<0.0001$ , and a sex x day interaction  $F_{6,198}=2.478$ ,  $p=0.0247$ . \*\*\* $p<0.001$ , \*\*\*\* $p<0.0001$ . **C)** Distance travelled by all male and female rats after acute exposure to 15 mg/kg of cocaine 1. A Mann Whitney Test revealed a significant difference in response to acute cocaine,  $p=0.0048$ . **D)** Relationship between sensitization index and distance travelled by male ( $R^2=0.4615$ ,  $p=0.0038$ ) and female ( $R^2=0.7043$ ,  $p<0.0001$ ) rats after acute exposure to cocaine. **E)** Distance travelled by rats deemed high responders to cocaine over the course of the initial treatment injections. The results of a two-way ANOVA revealed a main effect of day  $F_{6,112}=17.86$ ,  $p<0.0001$ , sex  $F_{1,112}=65.98$ ,  $p<0.0001$ , and a group x day interaction  $F_{18,186}=2.265$ ,  $p=0.0034$ . **F)** Distance travelled by rats deemed low responders to cocaine over the course of the initial treatment injections. A main effect of day  $F_{6,105}=14.45$ ,  $p<0.0001$  and sex  $F_{1,105}=55.88$ ,  $p<0.0001$  were found.

Table S1. Statistical analysis

Figure number	Test	F-value/U-value	P-value	Partial Eta <sup>2</sup>
Figure 3B	Mann-Whitney test, two-tailed	U=88	0.0343	
Figure 3C	Two-way ANOVA Treatment Sex Treatment x Sex	F(1,34) = 14.46 F(1,34) = 59.05 F(1,34) = 10.14	<u>p&lt;0.0001</u> <u>p=0.0006</u> <u>p=0.0031</u>	<u>0.634</u> <u>0.372</u> <u>0.230</u>
Figure 3D	RM Two-way ANOVA Treatment Day Treatment x Day	F(3,20) = 22.81 F(3,274, 74.49) = 9.419 F(21,140) = 4.774	<u>p&lt;0.0001</u> <u>p&lt;0.0001</u> <u>p&lt;0.0001</u>	<u>0.700</u> <u>0.320</u> <u>0.505</u>
Figure 3E	RM Two-way ANOVA Treatment Day Treatment x Day	F(3,21) = 56.70 F(3,677, 77.22) = 13.35 F(21,147) = 4.072	<u>p&lt;0.0001</u> <u>p&lt;0.0001</u> <u>p&lt;0.0001</u>	<u>0.825</u> <u>0.389</u> <u>0.675</u>
Figure 4A pAMPK  tAMPK  pAMPK/tAMPK	Two-way ANOVA Repeated Injection Acute Injection Interaction Repeated Injection Acute Injection Interaction Repeated Injection Acute Injection Interaction	F(1,37) = 0.5551 F(1,37) = 0.00116 F(1,37) = 0.2835 F(1,41) = 0.6737 F(1,41) = 0.2508 F(1,37) = 0.05196 F(1,37) = 1.130 F(1,37) = 6.580 F(1,37) = 0.01567	p=0.4609 p=0.9730 p=0.5976 p=0.4165 p=0.6192 p=0.8208 p=0.2948 <u>p=0.0145</u> p=0.9011	0.0148 0.0000313 0.0076 0.0162 0.00608 0.0013 0.0296 <u>0.1508</u> 0.000423
Figure 4B pAMPK  tAMPK  pAMPK/tAMPK	Two-way ANOVA Repeated Injection Acute Injection Interaction Repeated Injection Acute Injection Interaction Repeated Injection Acute Injection Interaction	F(1,41) = 0.6871 F(1,41) = 1.690 F(1,41) = 5.070 F(1,29) = 3.140 F(1,29) = 1.285 F(1,29) = 0.5119 F(1,29) = 0.04568 F(1,29) = 1.702 F(1,29) = 0.2289	p=0.4119 p=0.2009 <u>p=0.0298</u> <u>p=0.0869</u> p=0.2663 p=0.4800 p=0.8323 p=0.2023 p=0.6359	0.0165 0.0396 <u>0.1100</u> <u>0.0977</u> 0.0424 0.0173 0.0016 0.0555 0.0078

Figure 4C pAMPK  tAMPK  pAMPK/tAMPK	Two-way ANOVA			
	Repeated Injection	$F(1,41) = 0.1575$	$p=0.6935$	0.0038
	Acute Injection	$F(1,41) = 3.509$	<b><math>p=0.0682</math></b>	<b>0.0788</b>
	Interaction	$F(1,41) = 0.4904$	$p=0.4877$	0.0118
	Repeated Injection	$F(1,40) = 0.2308$	$p=0.6336$	0.0057
	Acute Injection	$F(1,40) = 0.3858$	$p=0.5380$	0.0096
	Interaction	$F(1,40) = 5.947$	<u><math>p=0.0193</math></u>	<u>0.1294</u>
	Repeated Injection	$F(1,40) = 0.2036$	$p=0.6543$	0.0051
	Acute Injection	$F(1,40) = 2.357$	$p=0.1326$	0.0556
	Interaction	$F(1,40) = 5.106$	<u><math>p=0.0294</math></u>	<u>0.1132</u>
Figure 4D pAMPK  tAMPK  pAMPK/tAMPK	Two-way ANOVA			
	Repeated Injection	$F(1,41) = 0.9455$	$p=0.3366$	0.0225
	Acute Injection	$F(1,41) = 0.4618$	$p=0.5006$	0.0111
	Interaction	$F(1,41) = 0.002878$	$p=0.9576$	0.000070
	Repeated Injection	$F(1,40) = 0.1673$	$p=0.6847$	0.0042
	Acute Injection	$F(1,40) = 1.382$	$p=0.2467$	0.0334
	Interaction	$F(1,40) = 1.097$	$p=0.3012$	0.0267
	Repeated Injection	$F(1,39) = 2.160$	$p=0.1497$	0.0525
	Acute Injection	$F(1,39) = 0.05351$	$p=0.8183$	0.0014
	Interaction	$F(1,39) = 1.586$	$p=0.2154$	0.0391
Figure 5A pAMPK  tAMPK  pAMPK/tAMPK	Two-way ANOVA			
	Repeated Injection	$F(1,42) = 0.2089$	$p=0.6500$	0.0049
	Acute Injection	$F(1,42) = 5.780$	<u><math>p=0.0207</math></u>	<u>0.0121</u>
	Interaction	$F(1,42) = 0.2770$	$p=0.6015$	0.0066
	Repeated Injection	$F(1,40) = 0.339$	$p=0.5637$	0.0084
	Acute Injection	$F(1,40) = 0.02257$	$p=0.8813$	0.00056
	Interaction	$F(1,40) = 0.3071$	$p=0.5825$	0.0076
	Repeated Injection	$F(1,39) = 0.5589$	$p=0.4592$	0.0141
	Acute Injection	$F(1,39) = 0.2996$	$p=0.5873$	0.0076
	Interaction	$F(1,39) = 0.09976$	$p=0.7538$	0.0026
Figure 5B pAMPK  tAMPK  pAMPK/tAMPK	Two-way ANOVA			
	Repeated Injection	$F(1,42) = 0.2300$	$p=0.6340$	0.0054
	Acute Injection	$F(1,42) = 7.687$	<u><math>p=0.0083</math></u>	<u>0.1545</u>
	Interaction	$F(1,42) = 0.1776$	$p=0.6756$	0.0042
	Repeated Injection	$F(1,35) = 1.804$	$p=0.1879$	0.049
	Acute Injection	$F(1,35) = 6.252$	<u><math>p=0.0172</math></u>	<u>0.1515</u>
	Interaction	$F(1,35) = 0.3359$	$p=0.5659$	0.0095
	Repeated Injection	$F(1,34) = 0.9479$	$p=0.3317$	0.0271
	Acute Injection	$F(1,34) = 1.749$	$p=0.1949$	0.0489
	Interaction	$F(1,34) = 0.05753$	$p=0.8119$	0.0017
Figure 5C pAMPK	Two-way ANOVA			
	Repeated Injection	$F(1,39) = 3.286$	<b><math>p=0.0776</math></b>	<b>0.0777</b>

pAMPK/tAMPK	tAMPK	Acute Injection	$F(1,39) = 1.966$	$p=0.1688$	0.0479
		Interaction	$F(1,39) = 1.241$	$p=0.2722$	0.0308
		Repeated Injection	$F(1,39) = 2.788$	$p=0.1030$	0.0667
		Acute Injection	$F(1,39) = 2.766$	$p=0.1043$	0.06620
		Interaction	$F(1,39) = 3.604$	<b><math>p=0.0681</math></b>	<b>0.0846</b>
		Repeated Injection	$F(1,39) = 0.5414$	$p=0.4663$	0.0137
pAMPK/tAMPK		Acute Injection	$F(1,39) = 0.5094$	$p=0.4769$	0.0129
		Interaction	$F(1,39) = 1.456$	$p=0.2348$	0.0360
pAMPK/tAMPK	Figure 5D	Two-way ANOVA			
		Repeated Injection	$F(1,42) = 1.904$	$p=0.1749$	0.0434
		Acute Injection	$F(1,42) = 0.239$	$p=0.6275$	0.0057
		Interaction	$F(1,42) = 1.021$	$p=0.3182$	0.0237
		Repeated Injection	$F(1,36) = 0.5738$	$p=0.4537$	0.0157
		Acute Injection	$F(1,36) = 0.4839$	$p=0.4911$	0.0133
pAMPK/tAMPK		Interaction	$F(1,36) = 0.07614$	$p=0.7842$	0.0021
		Repeated Injection	$F(1,36) = 0.5156$	$p=0.4774$	0.0141
		Acute Injection	$F(1,36) = 0.8092$	$p=0.3743$	0.0220
		Interaction	$F(1,36) = 2.623$	$p=0.1140$	0.0678
Figure 6B		Mixed-effects ANOVA			
		Treatment	$F(2,16) = 13.50$	<u><math>p&lt;0.0001</math></u>	
		Day	$F(3,263,51.80) = 19.92$	<u><math>p=0.0004</math></u>	
		Treatment x Day	$F(16,127) = 8.989$	<u><math>p&lt;0.0001</math></u>	
Figure 6C		Mixed-effects ANOVA			
		Treatment	$F(2,16) = 33.26$	<u><math>p&lt;0.0001</math></u>	
		Day	$F(3,245,51.11) = 27.88$	<u><math>p&lt;0.0001</math></u>	
		Treatment x Day	$F(16,126) = 17.34$	<u><math>p&lt;0.0001</math></u>	
Figure 6D		Two-way ANOVA			
		Treatment	$F(1,22) = 12.52$	<u><math>p=0.0007</math></u>	<u>0.414</u>
		Sex	$F(1,22) = 4.346$	<u><math>p=0.0489</math></u>	<u>0.165</u>
		Treatment x Sex	$F(1,22) = 0.3714$	$p=0.5485$	0.017
Figure 6E		Two-way ANOVA			
		Treatment	$F(1,23) = 14.03$	<u><math>p=0.0011</math></u>	<u>0.3789</u>
		Sex	$F(1,23) = 1.219$	$p=0.2809$	0.0503
		Treatment x Sex	$F(1,23) = 0.9697$	$p=0.9697$	0.000064
Figure 7A		One-way ANOVA			
		pAMPK	$F(2,35) = 0.1595$	$p=0.8532$	0.0090
		tAMPK	$F(2,34) = 0.3029$	$p=0.7403$	0.0175
		pAMPK/tAMPK	$F(2,34) = 0.1790$	$p=0.1824$	0.0953

Figure 7B	One-way ANOVA pAMPK tAMPK pAMPK/tAMPK	F(2,34) = 0.1923 F(2,34) = 1.337 F(2,34) = 0.9907	p=0.8260 p=0.2762 p=0.3818	0.0112 0.0729 0.0551
Figure 7C	One-way ANOVA pAMPK tAMPK pAMPK/tAMPK	F(2,35) = 0.2295 F(2,35) = 1.121 F(2,35) = 0.7364	p=0.7961 p=0.3373 p=0.4861	0.0129 0.0602 0.0404

Figure 7D	One-way ANOVA pAMPK tAMPK pAMPK/tAMPK	F(2,35) = 0.3209 F(2,35) = 0.2616 F(2,35) = 0.1448	p=0.7276 p=0.7713 p=0.8657	0.0180 0.0147 0.0082
Figure 8A	One-way ANOVA pAMPK tAMPK pAMPK/tAMPK	F(2,28) = 0.6681 F(2,30) = 1.485 F(2,28) = 0.9776	p=0.5207 p=0.2427 p=0.3887	0.0455 0.0901 0.0653
Figure 8B	One-way ANOVA pAMPK tAMPK pAMPK/tAMPK	F(2,33) = 0.3278 F(2,33) = 3.373 F(2,33) = 0.4295	p=0.7228 <u>p=0.0465</u> p=0.6544	0.0195 <u>0.1697</u> 0.0254
Figure 8C	One-way ANOVA pAMPK tAMPK pAMPK/tAMPK	F(2,31) = 3.353 F(2,32) = 2.456 F(2,31) = 0.1661	<u>p=0.0481</u> p=0.1018 p=0.8477	<u>0.1778</u> 0.1331 0.0106
Figure 8D	One-way ANOVA pAMPK tAMPK pAMPK/tAMPK	F(2,35) = 1.295 F(2,35) = 1.738 F(2,34) = 0.9889	p=0.2868 p=0.1907 p=0.3827	0.0689 0.0904 0.0549
Figure 9A	Two-way ANOVA pAMPK Treatment Sex Treatment x Sex tAMPK Treatment Sex Treatment x Sex pAMPK/tAMPK Treatment Sex Treatment x Sex	F(2,32) = 0.1577 F(1,32) = 0.04786 F(2,32) = 1.269 F(2,31) = 0.2182 F(1,31) = 8.214 F(2,31) = 3.228 F(2,30) = 1.569 F(1,30) = 5.389 F(2,30) = 1.266	p=0.8547 p=0.8282 p=0.2947 p=0.8052 <u>p=0.0074</u> <b>p=0.0533</b> p=0.2248 <u>p=0.0272</u> p=0.2965	0.00976 0.00149 0.0735 0.0139 <u>0.2094</u> <b>0.1723</b> 0.0947 <u>0.1523</u> 0.0779

Figure 9B pAMPK  tAMPK  pAMPK/tAMPK	Two-way ANOVA			
	Treatment	$F(2,31) = 0.06162$	$p=0.9404$	0.00396
	Sex	$F(1,31) = 2.561$	$p=0.1196$	0.0763
	Treatment x Sex	$F(2,31) = 1.681$	$p=0.2027$	0.0979
	Treatment	$F(2,31) = 1.317$	$p=0.2825$	0.0783
	Sex	$F(1,31) = 0.1926$	$p=0.6648$	0.0062
	Treatment x Sex	$F(2,31) = 1.018$	$p=0.3732$	0.0616
	Treatment	$F(2,31) = 1.003$	$p=0.3784$	0.0608
	Sex	$F(1,31) = 1.889$	$p=0.1792$	0.0574
	Treatment x Sex	$F(2,31) = 0.5864$	$p=0.5624$	0.0364
Figure 9C pAMPK  tAMPK  pAMPK/tAMPK	Two-way ANOVA			
	Treatment	$F(2,32) = 0.2176$	$p=0.8056$	0.0134
	Sex	$F(1,32) = 0.3811$	$p=0.5414$	0.0118
	Treatment x Sex	$F(2,32) = 0.3608$	$p=0.6999$	0.0221
	Treatment	$F(2,32) = 1.141$	$p=0.3322$	0.0666
	Sex	$F(1,32) = 0.4297$	$p=0.5168$	0.0132
	Treatment x Sex	$F(2,32) = 1.602$	$p=0.2172$	0.0910
	Treatment	$F(2,32) = 0.793$	$p=0.4612$	0.0472
	Sex	$F(1,32) = 1.245$	$p=0.2728$	0.0374
	Treatment x Sex	$F(2,32) = 2.157$	$p=0.1322$	0.1188
Figure 9D pAMPK  tAMPK  pAMPK/tAMPK	Two-way ANOVA			
	Treatment	$F(2,32) = 0.3444$	$p=0.7112$	0.0211
	Sex	$F(1,32) = 0.07341$	$p=0.7882$	0.0023
	Treatment x Sex	$F(2,32) = 2.776$	<b><math>p=0.0773</math></b>	<b>0.1478</b>
	Treatment	$F(2,32) = 0.321$	$p=0.7277$	0.0197
	Sex	$F(1,32) = 3.241$	<b><math>p=0.0813</math></b>	<b>0.0920</b>
	Treatment x Sex	$F(2,32) = 4.096$	<u><math>p=0.0261</math></u>	<u>0.2038</u>
	Treatment	$F(2,32) = 0.1382$	$p=0.8714$	0.0086
	Sex	$F(1,32) = 0.5035$	$p=0.4831$	0.0155
	Treatment x Sex	$F(2,32) = 0.4055$	$p=0.6700$	0.0247
Figure 10A pAMPK  tAMPK  pAMPK/tAMPK	Two-way ANOVA			
	Treatment	$F(2,25) = 0.4995$	$p=0.6127$	0.0384
	Sex	$F(1,25) = 0.9859$	$p=0.3303$	0.0379
	Treatment x Sex	$F(2,25) = 0.6118$	$p=0.5503$	0.0466
	Treatment	$F(2,27) = 1.165$	$p=0.3270$	0.0794
	Sex	$F(1,27) = 4.874$	<u><math>p=0.0359</math></u>	<u>0.1529</u>
	Treatment x Sex	$F(2,27) = 0.695$	$p=0.5078$	0.0489
	Treatment	$F(2,25) = 0.0852$	$p=0.4386$	0.0638
	Sex	$F(1,25) = 2.856$	$p=0.1034$	0.1025
	Treatment x Sex	$F(2,25) = 0.00245$	$p=0.9976$	0.0002
Figure 10B pAMPK	Two-way ANOVA			
	Treatment	$F(2,30) = 0.3171$	$p=0.7303$	0.0207

pAMPK/tAMPK	tAMPK	Sex	F(1,30) = 1.184	p=0.2853	0.0380
		Treatment x Sex	F(2,30) = 0.4754	p=0.6263	0.0307
		Treatment	F(2,30) = 3.236	<b>p=0.0534</b>	<b>0.1775</b>
		Sex	F(1,30) = 0.9416	p=0.3396	0.0304
		Treatment x Sex	F(2,30) = 0.4460	p=0.6443	0.0289
		Treatment	F(2,30) = 0.4034	p=0.6716	0.0262
		Sex	F(1,30) = 0.4794	p=0.4940	0.0157
		Treatment x Sex	F(2,30) = 0.2953	p=0.7465	0.0193
pAMPK/tAMPK	Figure 10C	Two-way ANOVA			
	pAMPK	Treatment	F(2,28) = 3.298	<b>p=0.0517</b>	<b>0.1906</b>
		Sex	F(1,28) = 0.3147	p=0.5793	0.0111
		Treatment x Sex	F(2,28) = 0.2950	p=0.7468	0.0206
	tAMPK	Treatment	F(2,29) = 2.287	p=0.1196	0.1362
		Sex	F(1,29) =	p=0.9828	0.000016
		Treatment x Sex	0.0004716	p=0.6359	0.0307
		Treatment	F(2,29) = 0.4599	p=0.5765	0.0386
pAMPK/tAMPK		Sex	F(2,28) = 0.5618	p=0.6349	0.0082
		Treatment x Sex	F(1,28) = 0.2304	p=0.9236	0.0057
			F(2,28) = 0.07974		
	Figure 10D	Two-way ANOVA			
	pAMPK	Treatment	F(2,32) = 1.231	p=0.3056	0.0714
		Sex	F(1,32) = 1.210	p=0.2796	0.0364
		Treatment x Sex	F(2,32) = 0.02928	p=0.9712	0.0018
	tAMPK	Treatment	F(2,32) = 1.754	p=0.1894	0.0988
pAMPK/tAMPK		Sex	F(1,32) = 1.598	p=0.2153	0.0476
		Treatment x Sex	F(2,32) = 0.9478	p=0.3982	0.0559
		Treatment	F(2,31) = 1.077	p=0.3530	0.0650
		Sex	F(1,31) = 2.941	p=0.0963	0.0866
		Treatment x Sex	F(2,32) = 2.006	p=0.1517	0.1145

Footnote: Significant effects as demonstrated by  $p < 0.05$  are indicated by underlining whereas trend-level results with  $p > 0.05$  but  $p < 0.10$  are indicated by bolding.