Cannabinoids rescue migraine symptoms caused by central CGRP administration in mice.

(Supplementary materials)

Erik Zorrilla [1,2*], Thomas L. Duong [2], Cassandra L. Piña [2], Andrew F. Russo [1,2,3,4*]

Table 1. Longitudinal representation of light aversion

Table 1

Figure 1B (Light aversion) — **Male & Female**

n = 105 (2 excl.)

Analysis — **Statistics**

Two-way RM ANOVA

	P values	Degrees of freedom	F values
Row Factor x Column Factor	**p = 0.0106*	*DFn: 10, DFd: 500*	*f = 2.338*
Row Factor	*****p < 0.0001*	*DFn: 3.87, DFd: 387*	*f = 15.36*
Column Factor	*****p < 0.0001*	*DFn: 2, DFd: 100*	*f = 12.18*
Subject	*****p < 0.0001*	*DFn: 100, DFd: 500*	*f = 13.65*

Tukey's multiple comparisons test

			5 min	10 min	15 min	20 min	25 min	30 min
PBS + Veh	*vs.*	CGRP + Veh	***p = 0.0012*	*****p < 0.0001*	*****p < 0.0001*	****p = 0.0008*	***p = 0.0014*	***p = 0.004*
PBS + Veh	*vs.*	CGRP + CBD:THC 100:1	*ns p = 0.9068*	*ns p = 0.7676*	*ns p = 0.7665*	*ns p = 0.4383*	*ns p = 0.5783*	*ns p = 0.9212*
CGRP + Veh	*vs.*	CGRP + CBD:THC 100:1	*****p < 0.0001*	****p = 0.0003*	****p = 0.0009*	**p = 0.0468*	**p = 0.046*	**p = 0.0448*

Figure 1B (Light aversion) — **Male**

n = 52

Analysis — **Statistics**

Two-way RM ANOVA

	P values	Degrees of freedom	F values
Row Factor x Column Factor	*ns p = 0.0749*	*DFn: 10, DFd: 245*	*f = 1.729*
Row Factor	*****p < 0.0001*	*DFn: 3.6, DFd: 177*	*f = 7.872*
Column Factor	**p = 0.0127*	*DFn: 2, DFd: 49*	*f = 4.776*
Subject	*****p < 0.0001*	*DFn: 49, DFd: 245*	*f = 12.80*

Tukey's multiple comparisons test

			5 min	10 min	15 min	20 min	25 min	30 min
PBS + Veh	*vs.*	CGRP + Veh	*ns p = 0.0660*	***p = 0.0052*	***p = 0.0021*	*ns p = 0.1374*	**p = 0.0436*	*ns p = 0.1855*
PBS + Veh	*vs.*	CGRP + CBD:THC 100:1	*ns p = 0.6484*	*ns p = 0.4604*	*ns p = 0.2491*	*ns p = 0.1077*	*ns p = 0.1864*	*ns p = 0.4254*
CGRP + Veh	*vs.*	CGRP + CBD:THC 100:1	*ns p = 0.1341*	*ns p = 0.1065*	*ns p = 0.2472*	*ns p = 0.9924*	*ns p = 0.7486*	*ns p = 0.8448*

Figure 1B (Light aversion) — **Female**

n = 53 (2 excl.)

Analysis — **Statistics**

Two-way RM ANOVA

	P values	Degrees of freedom	F values
Row Factor x Column Factor	*ns p = 0.4601*	*DFn: 10, DFd: 240*	*f = 0.9816*
Row Factor	*****p < 0.0001*	*DFn: 3.7, DFd: 179*	*f = 7.500*
Column Factor	****p = 0.0001*	*DFn: 2, DFd: 48*	*f = 10.83*
Subject	*****p < 0.0001*	*DFn: 48, DFd: 240*	*f = 13.88*

Tukey's multiple comparisons test

			5 min	10 min	15 min	20 min	25 min	30 min
PBS + Veh	*vs.*	CGRP + Veh	**p = 0.0297*	****p = 0.0006*	***p = 0.0017*	***p = 0.0034*	**p = 0.0444*	**p = 0.0112*
PBS + Veh	*vs.*	CGRP + CBD:THC 100:1	*ns p = 0.3141*	*ns p = 0.9122*	*ns p = 0.6767*	*ns p = 0.9016*	*ns p = 0.9298*	*ns p = 0.7421*
CGRP + Veh	*vs.*	CGRP + CBD:THC 100:1	****p = 0.0008*	***p = 0.0041*	***p = 0.0041*	**p = 0.0154*	**p = 0.0437*	**p = 0.047*

Table 2. Average light aversion, and percent resting in dark and light zone of individual mice

Table 2					
Figure 1C,1D, 1E (Light aversion)			**1C) Male & Female**	**1D) Male**	**1E) Female**
			n = 105 (2 excl.)	n = 52	n = 53 (2 excl.)
Analysis				**Statistics**	
One-way ANOVA					
P values			*****p < 0.0001*	**p = 0.0131*	****p = 0.0001*
Degrees of freedom			*DFn: 2, DFd: 100*	*DFn: 2, DFd: 49*	*DFn: 2, DFd: 48*
F values			*f = 12.3*	*f = 4.741*	*f = 10.84*
Tukey's multiple comparisons test					
PBS + Veh	*vs.*	CGRP + Veh	*****p < 0.0001*	**p = 0.0103*	***p = 0.0047*
PBS + Veh	*vs.*	CGRP + CBD:THC 100:1	*ns p = 0.6531*	*ns p = 0.1532*	*ns p = 0.6204*
CGRP + Veh	*vs.*	CGRP + CBD:THC 100:1	***p = 0.001*	*ns p = 0.4516*	****p = 0.0002*
Figure 2C, 2E, 2G (% Resting in dark)			**2C) Male & Female**	**2E) Male**	**2G) Female**
			n = 105 (2 excl.)	n = 52	n = 53 (2 excl.)
Analysis				**Statistics**	
One-way ANOVA					
P values			*****p < 0.0001*	**p = 0.0149*	*****p < 0.0001*
Degrees of freedom			*DFn: 2, DFd: 100*	*DFn: 2, DFd: 49*	*DFn: 2, DFd: 48*
F values			*f = 15.84*	*f = 4.591*	*f = 13.48*
Tukey's multiple comparisons test					
PBS + Veh	*vs.*	CGRP + Veh	*****p < 0.0001*	**p = 0.0112*	*****p < 0.0001*
PBS + Veh	*vs.*	CGRP + CBD:THC 100:1	*ns p = 0.2102*	*ns p = 0.2022*	*ns p = 0.8126*
CGRP + Veh	*vs.*	CGRP + CBD:THC 100:1	****p = 0.0009*	*ns p = 0.3858*	****p = 0.0006*
Figure 2D, 2F, 2H (% Resting in light)			**2D) Male & Female**	**2F) Male**	**2H) Female**
			n = 105 (2 excl.)	n = 52	n = 53 (2 excl.)
Analysis				**Statistics**	
One-way ANOVA					
P values			**p = 0.0293*	*ns p = 0.0812*	*ns p = 0.0686*
Degrees of freedom			*DFn: 2, DFd: 100*	*DFn: 2, DFd: 49*	*DFn: 2, DFd: 48*
F values			*f = 3.658*	*f = 2.645*	*f = 2.835*
Tukey's multiple comparisons test					
PBS + Veh	*vs.*	CGRP + Veh	**p = 0.0303*	*ns p = 0.0861*	*ns p = 0.4384*
PBS + Veh	*vs.*	CGRP + CBD:THC 100:1	*ns p = 0.8067*	*ns p = 0.2104*	*ns p = 0.5520*
CGRP + Veh	*vs.*	CGRP + CBD:THC 100:1	*ns p = 0.134*	*ns p = 0.8667*	*ns p = 0.0565*

Table 3. Longitudinal representation of percent resting in dark zone

Table 3

Figure 2A (% Resting in dark) — **Male & Female**

n = 105 (2 excl.)

Analysis — **Statistics**

Mixed-effects model (REML)

	P values	Degrees of freedom	F values
Row Factor	*****p < 0.0001*	*DFn: 3.76, DFd: 363*	*f = 187.4*
Column Factor	*****p < 0.0001*	*DFn: 2, DFd: 100*	*f = 15.46*
Row Factor x Column Factor	***p = 0.0053*	*DFn: 10, DFd: 483*	*f = 2.544*

Tukey's multiple comparisons test

			5 min	10 min	15 min	20 min	25 min	30 min
PBS + Veh	*vs.*	CGRP + Veh	****p = 0.0002*	*****p < 0.0001*	*****p < 0.0001*	*****p < 0.0001*	*****p < 0.0001*	***p = 0.0038*
PBS + Veh	*vs.*	CGRP + CBD:THC 100:1	*ns p = 0.995*	*ns p = 0.1767*	*ns p = 0.3409*	*ns p = 0.2011*	**p = 0.0256*	*ns p = 0.307*
CGRP + Veh	*vs.*	CGRP + CBD:THC 100:1	****p = 0.0006*	**p = 0.0178*	***p = 0.0033*	***p = 0.0062*	**p = 0.0439*	*ns p = 0.2319*

Figure 2A (% Resting in dark) — **Male**

n = 52

Analysis — **Statistics**

Mixed-effects model (REML)

	P values	Degrees of freedom	F values
Row Factor	*****p < 0.0001*	*DFn: 3.38, DFd: 157*	*f = 94.70*
Column Factor	**p = 0.0293*	*DFn: 2, DFd: 49*	*f = 3.798*
Row Factor x Column Factor	**p = 0.0408*	*DFn: 10, DFd: 232*	*f = 1.941*

Tukey's multiple comparisons test

			5 min	10 min	15 min	20 min	25 min	30 min
PBS + Veh	*vs.*	CGRP + Veh	*ns p = 0.1306*	**p = 0.0209*	**p = 0.0114*	*ns p = 0.0546*	**p = 0.0397*	*ns p = 0.6042*
PBS + Veh	*vs.*	CGRP + CBD:THC 100:1	*ns p = 0.983*	*ns p = 0.1911*	*ns p = 0.5462*	*ns p = 0.4075*	*ns p = 0.097*	*ns p = 0.2283*
CGRP + Veh	*vs.*	CGRP + CBD:THC 100:1	*ns p = 0.1577*	*ns p = 0.4789*	*ns p = 0.2423*	*ns p = 0.4557*	*ns p = 0.8993*	*ns p = 0.9404*

Figure 2A (% Resting in dark) — **Female**

n = 53 (2 excl.)

Analysis — **Statistics**

Mixed-effects model (REML)

	P values	Degrees of freedom	F values
Row Factor	*****p < 0.0001*	*DFn: 3.4, DFd: 162*	*f = 88.71*
Column Factor	*****p < 0.0001*	*DFn: 2, DFd: 48*	*f = 14.38*
Row Factor x Column Factor	*ns p = 0.0758*	*DFn: 10, DFd: 236*	*f = 1.726*

Tukey's multiple comparisons test

			5 min	10 min	15 min	20 min	25 min	30 min
PBS + Veh	*vs.*	CGRP + Veh	***p = 0.0012*	****p = 0.0003*	****p = 0.0004*	*****p < 0.0001*	*****p < 0.0001*	***p = 0.0019*
PBS + Veh	*vs.*	CGRP + CBD:THC 100:1	*ns p = 0.9998*	*ns p = 0.7025*	*ns p = 0.6574*	*ns p = 0.5367*	*ns p = 0.2506*	*ns p = 0.9002*
CGRP + Veh	*vs.*	CGRP + CBD:THC 100:1	***p = 0.0075*	**p = 0.0228*	***p = 0.0068*	**p = 0.0114*	**p = 0.0213*	**p = 0.0197*

Table 4. Longitudinal representation of percent resting in light zone

Table 4

Figure 2B (% Resting in light) — **Male & Female**

n = 105 (2 excl.)

Analysis — **Statistics**

Mixed-effects model (REML)

	P values	Degrees of freedom	F values
Row Factor	*****p < 0.0001*	*DFn: 3.9, DFd: 208*	*f = 19.95*
Column Factor	**p = 0.0143*	*DFn: 2, DFd: 100*	*f = 4.437*
Row Factor x Column Factor	**p = 0.0336*	*DFn: 10, DFd: 266*	*f = 2.000*

Tukey's multiple comparisons test

			5 min	10 min	15 min	20 min	25 min	30 min
PBS + Veh	*vs.*	CGRP + Veh	*ns p = 0.6033*	*ns p = 0.5577*	*ns p = 0.1507*	*ns p = 0.5078*	*ns p = 0.5394*	*ns p = 0.3967*
PBS + Veh	*vs.*	CGRP + CBD:THC 100:1	*ns p = 0.8633*	*ns p = 0.5839*	*ns p = 0.9269*	*ns p = 0.6792*	*ns p = 0.3219*	*ns p = 0.2353*
CGRP + Veh	*vs.*	CGRP + CBD:THC 100:1	*ns p = 0.8606*	*ns p = 0.9509*	*ns p = 0.1248*	*ns p = 0.2747*	*ns p = 0.0767*	*ns p = 0.0881*

Figure 2B (% Resting in light) — **Male**

n = 52

Analysis — **Statistics**

Mixed-effects model (REML)

	P values	Degrees of freedom	F values
Row Factor	*****p < 0.0001*	*DFn: 2.8, DFd: 73.5*	*f = 13.46*
Column Factor	*ns p = 0.0786*	*DFn: 2, DFd: 49*	*f = 2.681*
Row Factor x Column Factor	**p = 0.012*	*DFn: 10, DFd: 132*	*f = 2.397*

Tukey's multiple comparisons test

			5 min	10 min	15 min	20 min	25 min	30 min
PBS + Veh	*vs.*	CGRP + Veh	*ns p = 0.4573*	*ns p = 0.6302*	*ns p > 0.9999*	*ns p = 0.2451*	**p = 0.0164*	*ns p = 0.1952*
PBS + Veh	*vs.*	CGRP + CBD:THC 100:1	*ns p = 0.3444*	*ns p = 0.3155*	*ns p = 0.998*	*ns p = 0.7461*	*ns p = 0.5109*	*ns p = 0.2431*
CGRP + Veh	*vs.*	CGRP + CBD:THC 100:1	*ns p = 0.9653*	*ns p = 0.7302*	*ns p = 0.9991*	*ns p = 0.4318*	***p = 0.0046*	*ns p = 0.0656*

Figure 2B (% Resting in light) — **Female**

n = 53 (2 excl.)

Analysis — **Statistics**

Mixed-effects model (REML)

	P values	Degrees of freedom	F values
Row Factor	*****p < 0.0001*	*DFn: 2.6, DFd: 65.7*	*f = 11.67*
Column Factor	*ns p = 0.0646*	*DFn: 2, DFd: 48*	*f = 2.902*
Row Factor x Column Factor	*ns p = 0.0669*	*DFn: 10, DFd: 119*	*f = 1.804*

Tukey's multiple comparisons test

			5 min	10 min	15 min	20 min	25 min	30 min
PBS + Veh	*vs.*	CGRP + Veh	*ns p = 0.9762*	*ns p = 0.9977*	*ns p = 0.1354*	*ns p = 0.96*	*ns p = 0.7405*	*ns p = 0.9795*
PBS + Veh	*vs.*	CGRP + CBD:THC 100:1	*ns p = 0.6918*	*ns p = 0.2488*	*ns p = 0.7384*	*ns p = 0.3682*	*ns p = 0.5279*	*ns p = 0.697*
CGRP + Veh	*vs.*	CGRP + CBD:THC 100:1	*ns p = 0.6173*	*ns p = 0.4039*	*ns p = 0.0794*	*ns p = 0.5207*	*ns p = 0.8599*	*ns p = 0.8367*

Table 5. Longitudinal representation of percent rearing in dark zone

Table 5

Figure 3A (Rearing in dark) — **Male & Female**

n = 105 (2 excl.)

Analysis — **Statistics**

Mixed-effects model (REML)

	P values	Degrees of freedom	F values
Row Factor	*****p < 0.0001*	*DFn: 2.9, DFd: 292*	*f = 30.38*
Column Factor	**p = 0.0298*	*DFn: 2, DFd: 100*	*f = 3.641*
Row Factor x Column Factor	*ns p = 0.095*	*DFn: 10, DFd: 491*	*f = 1.630*

Tukey's multiple comparisons test

			5 min	10 min	15 min	20 min	25 min	30 min
PBS + Veh	*vs.*	CGRP + Veh	*ns p = 0.4922*	**p = 0.034*	**p = 0.0323*	**p = 0.0219*	*ns p = 0.0817*	*ns p = 0.1464*
PBS + Veh	*vs.*	CGRP + CBD:THC 100:1	*ns p > 0.9999*	*ns p = 0.0984*	*ns p = 0.1041*	*ns p = 0.1547*	*ns p = 0.9203*	*ns p = 0.1054*
CGRP + Veh	*vs.*	CGRP + CBD:THC 100:1	*ns p = 0.5985*	*ns p = 0.6542*	*ns p = 0.6671*	*ns p = 0.4711*	*ns p = 0.1866*	*ns p = 0.9978*

Figure 3A (Rearing in dark) — **Male**

n = 52

Analysis — **Statistics**

Mixed-effects model (REML)

	P values	Degrees of freedom	F values
Row Factor	*****p < 0.0001*	*DFn: 2.9, DFd: 140*	*f = 20.43*
Column Factor	*ns p = 0.6045*	*DFn: 2, DFd: 49*	*f = 0.5086*
Row Factor x Column Factor	*ns p = 0.054*	*DFn: 10, DFd: 240*	*f = 1.844*

Tukey's multiple comparisons test

			5 min	10 min	15 min	20 min	25 min	30 min
PBS + Veh	*vs.*	CGRP + Veh	*ns p = 0.7792*	*ns p = 0.7583*	*ns p = 0.5312*	*ns p = 0.7143*	*ns p = 0.9131*	*ns p = 0.9977*
PBS + Veh	*vs.*	CGRP + CBD:THC 100:1	*ns p = 0.9899*	*ns p = 0.1886*	*ns p = 0.1897*	*ns p = 0.6015*	*ns p = 0.7156*	*ns p = 0.0645*
CGRP + Veh	*vs.*	CGRP + CBD:THC 100:1	*ns p = 0.8933*	*ns p = 0.8019*	*ns p = 0.8832*	*ns p = 0.9997*	*ns p = 0.9754*	*ns p = 0.3461*

Figure 3A (Rearing in dark) — **Female**

n = 53 (2 excl.)

Analysis — **Statistics**

Mixed-effects model (REML)

	P values	Degrees of freedom	F values
Row Factor	*****p < 0.0001*	*DFn: 2.88, DFd: 136*	*f = 13.01*
Column Factor	***p = 0.0049*	*DFn: 2, DFd: 48*	*f = 5.959*
Row Factor x Column Factor	*ns p = 0.4633*	*DFn: 10, DFd: 236*	*f = 0.9779*

Tukey's multiple comparisons test

			5 min	10 min	15 min	20 min	25 min	30 min
PBS + Veh	*vs.*	CGRP + Veh	**p = 0.0455*	**p = 0.0261*	**p = 0.0496*	**p = 0.0283*	**p = 0.0204*	*ns p = 0.0665*
PBS + Veh	*vs.*	CGRP + CBD:THC 100:1	*ns p = 0.9836*	*ns p = 0.5115*	*ns p = 0.5662*	*ns p = 0.2379*	*ns p = 0.5633*	*ns p = 0.6236*
CGRP + Veh	*vs.*	CGRP + CBD:THC 100:1	*ns p = 0.0699*	**p = 0.0365*	*ns p = 0.1427*	*ns p = 0.182*	*ns p = 0.0788*	*ns p = 0.224*

Table 6. Longitudinal representation of percent rearing in light zone

Table 6

Figure 3B (Rearing in light) — **Male & Female**

n = 105 (2 excl.)

Analysis — **Statistics**

Mixed-effects model (REML)

	P values	Degrees of freedom	F values
Row Factor	*****p < 0.0001*	*DFn: 3.41, DFd: 170*	*f = 7.487*
Column Factor	*ns p = 0.4947*	*DFn: 2, DFd: 100*	*f = 0.7088*
Row Factor x Column Factor	*ns p = 0.4873*	*DFn: 10, DFd: 249*	*f = 0.9508*

Tukey's multiple comparisons test

			5 min	10 min	15 min	20 min	25 min	30 min
PBS + Veh	*vs.*	CGRP + Veh	*ns p = 0.8255*	**p = 0.0384*	*ns p = 0.1963*	*ns p = 0.9917*	*ns p = 0.2376*	*ns p = 0.7602*
PBS + Veh	*vs.*	CGRP + CBD:THC 100:1	*ns p = 0.9734*	*ns p = 0.4347*	*ns p = 0.5809*	*ns p = 0.721*	*ns p = 0.065*	*ns p = 0.5068*
CGRP + Veh	*vs.*	CGRP + CBD:THC 100:1	*ns p = 0.9251*	*ns p = 0.2876*	*ns p = 0.6579*	*ns p = 0.8937*	*ns p = 0.9992*	*ns p = 0.9855*

Figure 3B (Rearing in light) — **Male**

n = 52

Analysis — **Statistics**

Mixed-effects model (REML)

	P values	Degrees of freedom	F values
Row Factor	***p = 0.0017*	*DFn: 3, DFd: 75*	*f = 5.534*
Column Factor	*ns p = 0.9813*	*DFn: 2, DFd: 49*	*f = 0.01885*
Row Factor x Column Factor	*ns p = 0.1264*	*DFn: 10, DFd: 123*	*f = 1.560*

Tukey's multiple comparisons test

			5 min	10 min	15 min	20 min	25 min	30 min
PBS + Veh	*vs.*	CGRP + Veh	*ns p = 0.5551*	*ns p = 0.6916*	*ns p = 0.9449*	*ns p = 0.6356*	*ns p = 0.8585*	*ns p = 0.8169*
PBS + Veh	*vs.*	CGRP + CBD:THC 100:1	*ns p = 0.8925*	*ns p = 0.6751*	*ns p = 0.9308*	*ns p = 0.44*	*ns p = 0.0571*	*ns p = 0.7111*
CGRP + Veh	*vs.*	CGRP + CBD:THC 100:1	*ns p = 0.8276*	*ns p = 0.966*	*ns p = 0.8811*	*ns p = 0.9927*	*ns p = 0.8569*	*ns p = 0.9849*

Figure 3B (Rearing in light) — **Female**

n = 53 (2 excl.)

Analysis — **Statistics**

Mixed-effects model (REML)

	P values	Degrees of freedom	F values
Row Factor	**p = 0.0336*	*DFn: 2.6, DFd: 58.5*	*f = 3.244*
Column Factor	*ns p = 0.1561*	*DFn: 2, DFd: 48*	*f = 1.931*
Row Factor x Column Factor	*ns p = 0.6748*	*DFn: 10, DFd: 111*	*f = 0.7513*

Tukey's multiple comparisons test

			5 min	10 min	15 min	20 min	25 min	30 min
PBS + Veh	*vs.*	CGRP + Veh	*ns p = 0.1911*	*ns p = 0.1698*	*ns p = 0.1691*	*ns p = 0.28*	*ns p = 0.4114*	*ns p = 0.9712*
PBS + Veh	*vs.*	CGRP + CBD:THC 100:1	*ns p = 0.6648*	*ns p = 0.6702*	*ns p = 0.1786*	*ns p = 0.6246*	*ns p = 0.618*	*ns p = 0.7237*
CGRP + Veh	*vs.*	CGRP + CBD:THC 100:1	*ns p = 0.3618*	*ns p = 0.0998*	*ns p = 0.9281*	*ns p = 0.6149*	*ns p = 0.7761*	*ns p = 0.6947*

Table 7. Average transitions, rearing in dark and light zone and time spent in center of individual mice

Table 7					
Figure 3C, 3E, 3G (Rearing in dark)			**3C) Male & Female**	**3E) Male**	**3G) Female**
			n = 105 (2 excl.)	n = 52	n = 53 (2 excl.)
Analysis				**Statistics**	
One-way ANOVA					
P values			**p = 0.0245*	*ns p = 0.5307*	***p = 0.0047*
Degrees of freedom			*DFn: 2, DFd: 100*	*DFn: 2, DFd: 49*	*DFn: 2, DFd: 48*
F values			*f = 3.849*	*f = 0.6418*	*f = 6.002*
Tukey's multiple comparisons test					
PBS + Veh	*vs.*	CGRP + Veh	**p = 0.0185*	*ns p = 0.8429*	***p = 0.0040*
PBS + Veh	*vs.*	CGRP + CBD:THC 100:1	*ns p = 0.2424*	*ns p = 0.4987*	*ns p = 0.4605*
CGRP + Veh	*vs.*	CGRP + CBD:THC 100:1	*ns p = 0.5162*	*ns p = 0.8514*	*ns p = 0.1027*
Figure 3D, 3F, 3H (Rearing in light)			**3D) Male & Female**	**3F) Male**	**3H) Female**
			n = 105 (2 excl.)	n = 52	n = 53 (2 excl.)
Analysis				**Statistics**	
One-way ANOVA					
P values			*ns p = 0.7820*	*ns p = 0.7673*	*ns p = 0.1419*
Degrees of freedom			*DFn: 2, DFd: 100*	*DFn: 2, DFd: 49*	*DFn: 2, DFd: 48*
F values			*f = 0.2466*	*f = 0.2663*	*f = 2.035*
Tukey's multiple comparisons test					
PBS + Veh	*vs.*	CGRP + Veh	*ns p = 0.7952*	*ns p = 0.7662*	*ns p = 0.1506*
PBS + Veh	*vs.*	CGRP + CBD:THC 100:1	*ns p = 0.9950*	*ns p = 0.9878*	*ns p = 0.8961*
CGRP + Veh	*vs.*	CGRP + CBD:THC 100:1	*ns p = 0.8478*	*ns p = 0.8459*	*ns p = 0.3417*
Figure 4B, 4C, 4D (Transitions)			**4B) Male & Female**	**4C) Male**	**4D) Female**
			n = 105 (2 excl.)	n = 52	n = 53 (2 excl.)
Analysis				**Statistics**	
One-way ANOVA					
P values			***p = 0.0029*	*ns p = 0.4876*	****p = 0.0007*
Degrees of freedom			*DFn: 2, DFd: 100*	*DFn: 2, DFd: 49*	*DFn: 2, DFd: 48*
F values			*f = 6.181*	*f = 0.7289*	*f = 8.427*
Tukey's multiple comparisons test					
PBS + Veh	*vs.*	CGRP + Veh	***p = 0.0031*	*ns p = 0.5201*	***p = 0.0019*
PBS + Veh	*vs.*	CGRP + CBD:THC 100:1	*ns p = 0.6603*	*ns p = 0.5977*	*ns p = 0.9273*
CGRP + Veh	*vs.*	CGRP + CBD:THC 100:1	**p = 0.0395*	*ns p = 0.987*	***p = 0.0060*
Figure 5B (Open field)			**Male & Female**	**Male**	**Female**
			n = 37	n = 20	n = 17
Analysis				**Statistics**	
P values			*ns p = 0.1599*	*ns p = 0.0756*	*ns p = 0.6214*
Degrees of freedom			*DFn: 18, DFd: 17*	*DFn: 10, DFd: 8*	*DFn: 7, DFd: 8*
F values			*f = 2.000*	*f = 3.712*	*f = 1.434*
T values			*t = 1.269*	*t = 0.7331*	*t = 0.1351*
Unpaired t-test					
PBS + Veh	*vs.*	CGRP + Veh	*ns p = 0.2127*	*ns p = 0.4729*	*ns p = 0.1967*

Table 8. Longitudinal representation of transition behavior

Table 8

Figure 4A (Transitions) — **Male & Female**

n = 105 (2 excl.)

Analysis — **Statistics**

Two-way RM ANOVA

	P values	Degrees of freedom	F values
Row Factor x Column Factor	***p = 0.0058*	*DFn: 10, DFd: 500*	*f = 2.521*
Row Factor	*****p < 0.0001*	*DFn: 2.5, DFd: 255*	*f = 61.48*
Column Factor	***p = 0.0029*	*DFn: 2, DFd: 100*	*f = 6.181*
Subject	*****p < 0.0001*	*DFn: 100, DFd: 500*	*f = 6.612*

Tukey's multiple comparisons test

			5 min	10 min	15 min	20 min	25 min	30 min
PBS + Veh	*vs.*	CGRP + Veh	*ns p = 0.9873*	***p = 0.0019*	****p = 0.0004*	***p = 0.0048*	***p = 0.0019*	***p = 0.0073*
PBS + Veh	*vs.*	CGRP + CBD:THC 100:1	*ns p = 0.3053*	*ns p = 0.8645*	*ns p = 0.5162*	*ns p = 0.1561*	*ns p = 0.8037*	*ns p = 0.3367*
CGRP + Veh	*vs.*	CGRP + CBD:THC 100:1	*ns p = 0.6194*	*ns p = 0.1004*	**p = 0.0135*	*ns p = 0.0784*	**p = 0.0305*	*ns p = 0.1046*

Figure 4A (Transitions) — **Male**

n = 52

Analysis — **Statistics**

Two-way RM ANOVA

	P values	Degrees of freedom	F values
Row Factor x Column Factor	*ns p = 0.3105*	*DFn: 10, DFd: 245*	*f = 1.172*
Row Factor	*****p < 0.0001*	*DFn: 1.7, DFd: 83.2*	*f = 28.79*
Column Factor	*ns p = 0.4876*	*DFn: 2, DFd: 49*	*f = 0.7289*
Subject	*****p < 0.0001*	*DFn: 49, DFd: 245*	*f = 4.827*

Tukey's multiple comparisons test

			5 min	10 min	15 min	20 min	25 min	30 min
PBS + Veh	*vs.*	CGRP + Veh	*ns p = 0.8206*	*ns p = 0.168*	*ns p = 0.0985*	*ns p = 0.6853*	*ns p = 0.417*	*ns p = 0.7936*
PBS + Veh	*vs.*	CGRP + CBD:THC 100:1	*ns p = 0.723*	*ns p = 0.4358*	*ns p = 0.1907*	*ns p = 0.5659*	*ns p = 0.8499*	*ns p = 0.4216*
CGRP + Veh	*vs.*	CGRP + CBD:THC 100:1	*ns p = 0.9708*	*ns p = 0.7862*	*ns p = 0.8673*	*ns p = 0.9923*	*ns p = 0.8145*	*ns p = 0.8976*

Figure 4A (Transitions) — **Female**

n = 53 (2 excl.)

Analysis — **Statistics**

Two-way RM ANOVA

	P values	Degrees of freedom	F values
Row Factor x Column Factor	*ns p = 0.0819*	*DFn: 10, DFd: 240*	*f = 1.698*
Row Factor	*****p < 0.0001*	*DFn: 2.7, DFd: 129*	*f = 31.83*
Column Factor	****p = 0.0007*	*DFn: 2, DFd: 48*	*f = 8.427*
Subject	*****p < 0.0001*	*DFn: 48, DFd: 240*	*f = 7.131*

Tukey's multiple comparisons test

			5 min	10 min	15 min	20 min	25 min	30 min
PBS + Veh	*vs.*	CGRP + Veh	*ns p = 0.7671*	**p = 0.0159*	**p = 0.012*	***p = 0.0075*	***p = 0.0097*	**p = 0.0126*
PBS + Veh	*vs.*	CGRP + CBD:THC 100:1	*ns p = 0.3708*	*ns p = 0.9999*	*ns p = 0.9878*	*ns p = 0.2548*	*ns p = 0.9195*	*ns p = 0.607*
CGRP + Veh	*vs.*	CGRP + CBD:THC 100:1	*ns p = 0.1209*	*ns p = 0.1313*	**p = 0.0142*	**p = 0.0136*	**p = 0.0285*	***p = 0.0098*

Table 9. Average mean pixel area over 5 min for individual mice in the automated squint assay

Table 9					
Figure 6B (Squint)			**Male & Female**		
			n = 63 (1 excl.)		
Analysis			**Statistics**		
Two-way RM ANOVA					
			P values	Degrees of freedom	F values
Row Factor			**p = 0.0279*	*DFn: 24 , DFd: 94*	*f = 1.729*
Column Factor			***p = 0.0032*	*DFn: 5 , DFd: 94*	*f = 3.857*
Tukey's multiple comparisons test					
PBS + Veh (BL)	*vs.*	PBS + Veh (Tx)	*ns p > 0.9999*		
CGRP + Veh (BL)	*vs.*	CGRP + Veh (Tx)	**p = 0.0208*		
CGRP + CBD:THC 100:1 (BL)	*vs.*	CGRP + CBD:THC 100:1 (Tx)	*ns p = 0.9908*		
PBS + Veh (BL)	*vs.*	CGRP + Veh (BL)	*ns = 0.9934*		
PBS + Veh (BL)	*vs.*	CGRP + CBD:THC 100:1 (BL)	*ns = 0.9981*		
CGRP + Veh (BL)	*vs.*	CGRP + CBD:THC 100:1 (BL)	*ns p > 0.9999*		
PBS + Veh (Tx)	*vs.*	CGRP + Veh (Tx)	***p = 0.0063*		
PBS + Veh (Tx)	*vs.*	CGRP + CBD:THC 100:1 (Tx)	*ns p = 0.889*		
CGRP + Veh (Tx)	*vs.*	CGRP + CBD:THC 100:1 (Tx)	*ns p = 0.1275*		
Figure 6B (Squint)			**Male**		
			n = 33		
Analysis			**Statistics**		
Two-way RM ANOVA					
			P values	Degrees of freedom	F values
Row Factor			*ns p = 0.0808*	*DFn: 12 , DFd: 50*	*f = 1.765*
Column Factor			**p = 0.0183*	*DFn: 5 , DFd: 50*	*f = 3.029*
Tukey's multiple comparisons test					
PBS + Veh (BL)	*vs.*	PBS + Veh (Tx)	*ns = 0.9999*		
CGRP + Veh (BL)	*vs.*	CGRP + Veh (Tx)	*ns = 0.107*		
CGRP + CBD:THC 100:1 (BL)	*vs.*	CGRP + CBD:THC 100:1 (Tx)	*ns p = 0.9809*		
PBS + Veh (BL)	*vs.*	CGRP + Veh (BL)	*ns = 0.993*		
PBS + Veh (BL)	*vs.*	CGRP + CBD:THC 100:1 (BL)	*ns = 0.961*		
CGRP + Veh (BL)	*vs.*	CGRP + CBD:THC 100:1 (BL)	*ns p = 0.9996*		
PBS + Veh (Tx)	*vs.*	CGRP + Veh (Tx)	**p = 0.0206*		
PBS + Veh (Tx)	*vs.*	CGRP + CBD:THC 100:1 (Tx)	*ns = 0.9991*		
CGRP + Veh (Tx)	*vs.*	CGRP + CBD:THC 100:1 (Tx)	*ns = 0.0694*		
Figure 6B (Squint)			**Female**		
			n = 30 (1 excl.)		
Analysis			**Statistics**		
Two-way RM ANOVA					
			P values	Degrees of freedom	F values
Row Factor			*ns p = 0.0755*	*DFn: 11 , DFd: 39*	*f = 1.865*
Column Factor			*ns p = 0.2299*	*DFn: 5 , DFd: 39*	*f = 1.445*

Tukey's multiple comparisons test

PBS + Veh (BL)	*vs.*	PBS + Veh (Tx)	*ns p > 0.9999*
CGRP + Veh (BL)	*vs.*	CGRP + Veh (Tx)	*ns p = 0.4492*
CGRP + CBD:THC 100:1 (BL)	*vs.*	CGRP + CBD:THC 100:1 (Tx)	*ns p = 0.6533*
PBS + Veh (BL)	*vs.*	CGRP + Veh (BL)	*ns p > 0.9999*
PBS + Veh (BL)	*vs.*	CGRP + CBD:THC 100:1 (BL)	*ns p > 0.9999*
CGRP + Veh (BL)	*vs.*	CGRP + CBD:THC 100:1 (BL)	*ns p = 0.9992*
PBS + Veh (Tx)	*vs.*	CGRP + Veh (Tx)	*ns p = 0.5839*
PBS + Veh (Tx)	*vs.*	CGRP + CBD:THC 100:1 (Tx)	*ns p = 0.9071*
CGRP + Veh (Tx)	*vs.*	CGRP + CBD:THC 100:1 (Tx)	*ns p = 0.8829*