

# PKC $\gamma$ actions related to mGluR5 within NAc shell on environment elicited cocaine conditioning

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# Drug Addiction

- ▶ Principal Components:
  - ▶ Seeking and taking the drug compulsively
  - ▶ Losing the control of intake the drug
  - ▶ Developing a negative emotional response when the drug is not present.

Changes in neurotransmission systems within specific brain structures may induce drug reward effects associated with drug dependence.

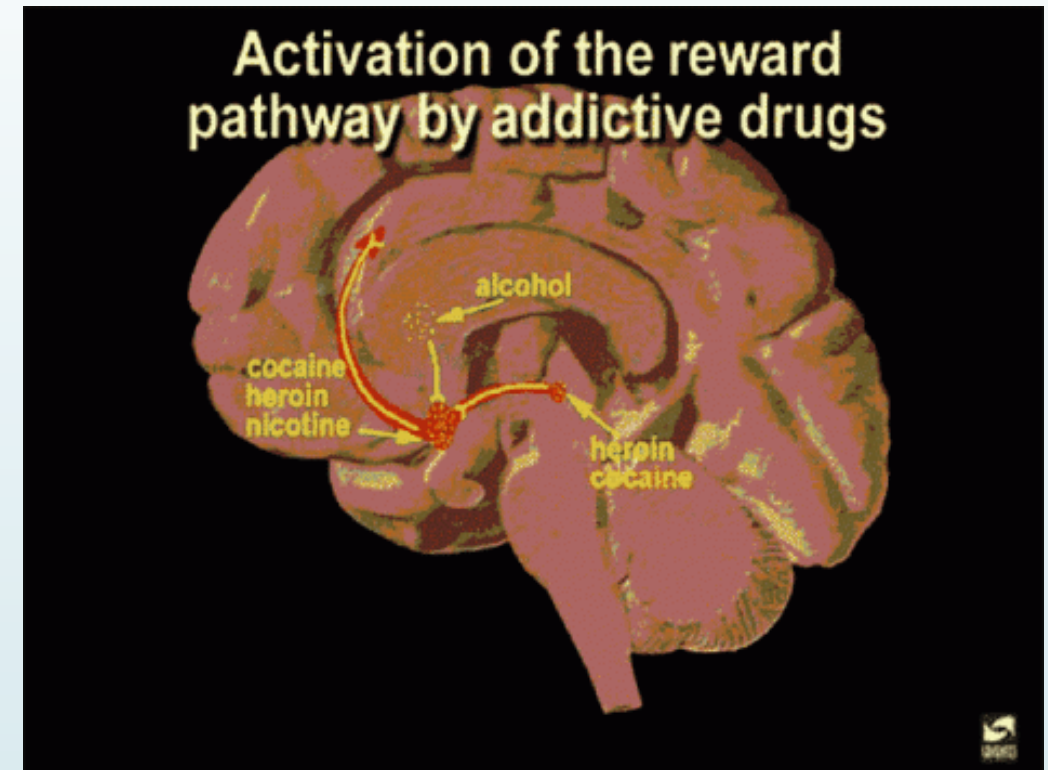


Figure 1: Mesolimbic Dopamine Reward Pathway by Addictive Drugs

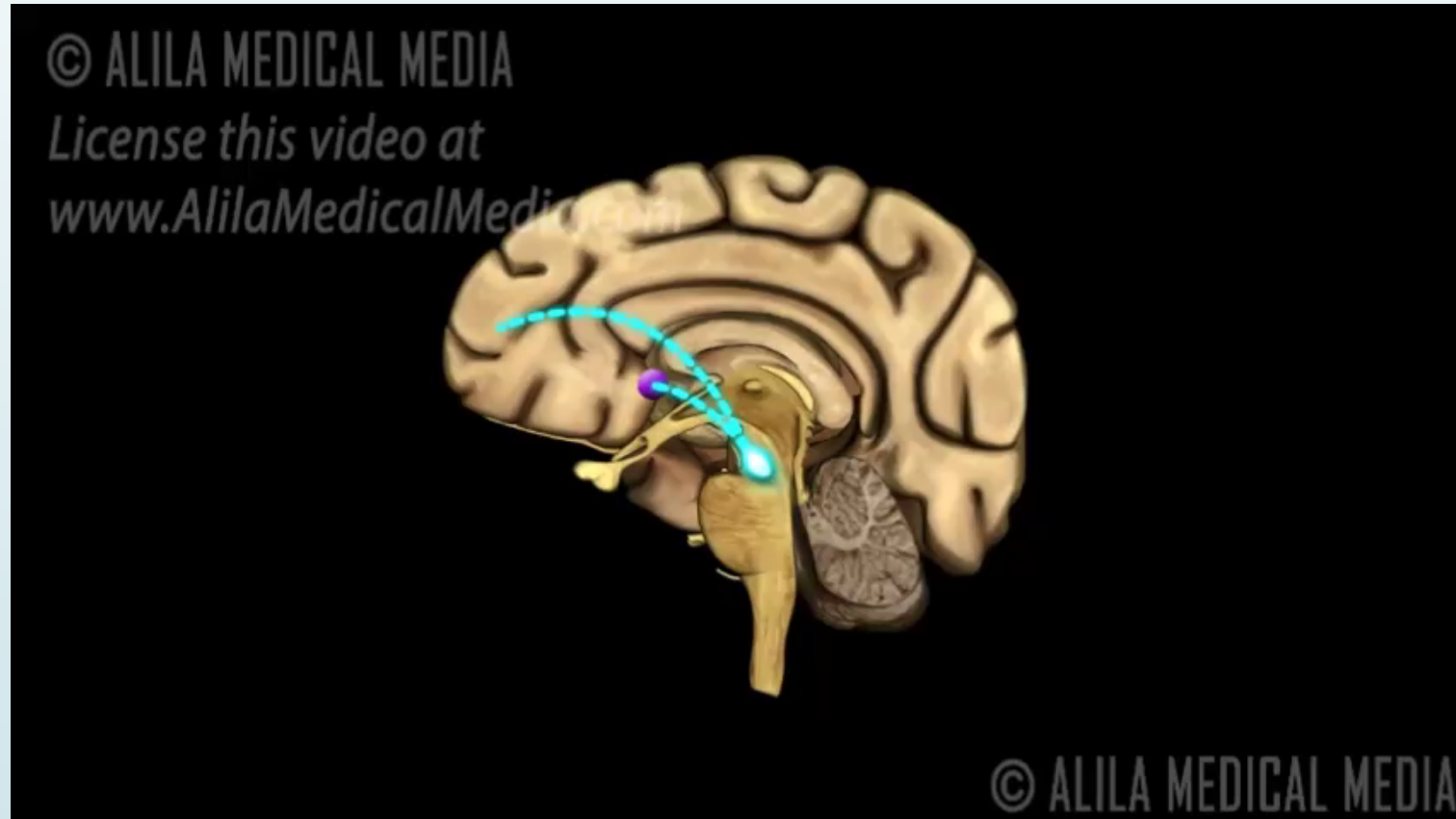
Koob, G.F., Sanna, P.P., Bloom, F.E. (1998). Neuroscience of Addiction. Neuron, Vol. 21, 467-476.

The Neurobiology of Drug Addiction. (2007) Section 7: Summary: addictive drugs activate the reward system via increasing dopamine neurotransmission. National Institute on Drug Abuse. NIH.

# Cocaine

Psychostimulant

Drug Abuse Potential



# Mesolimbic Dopamine System

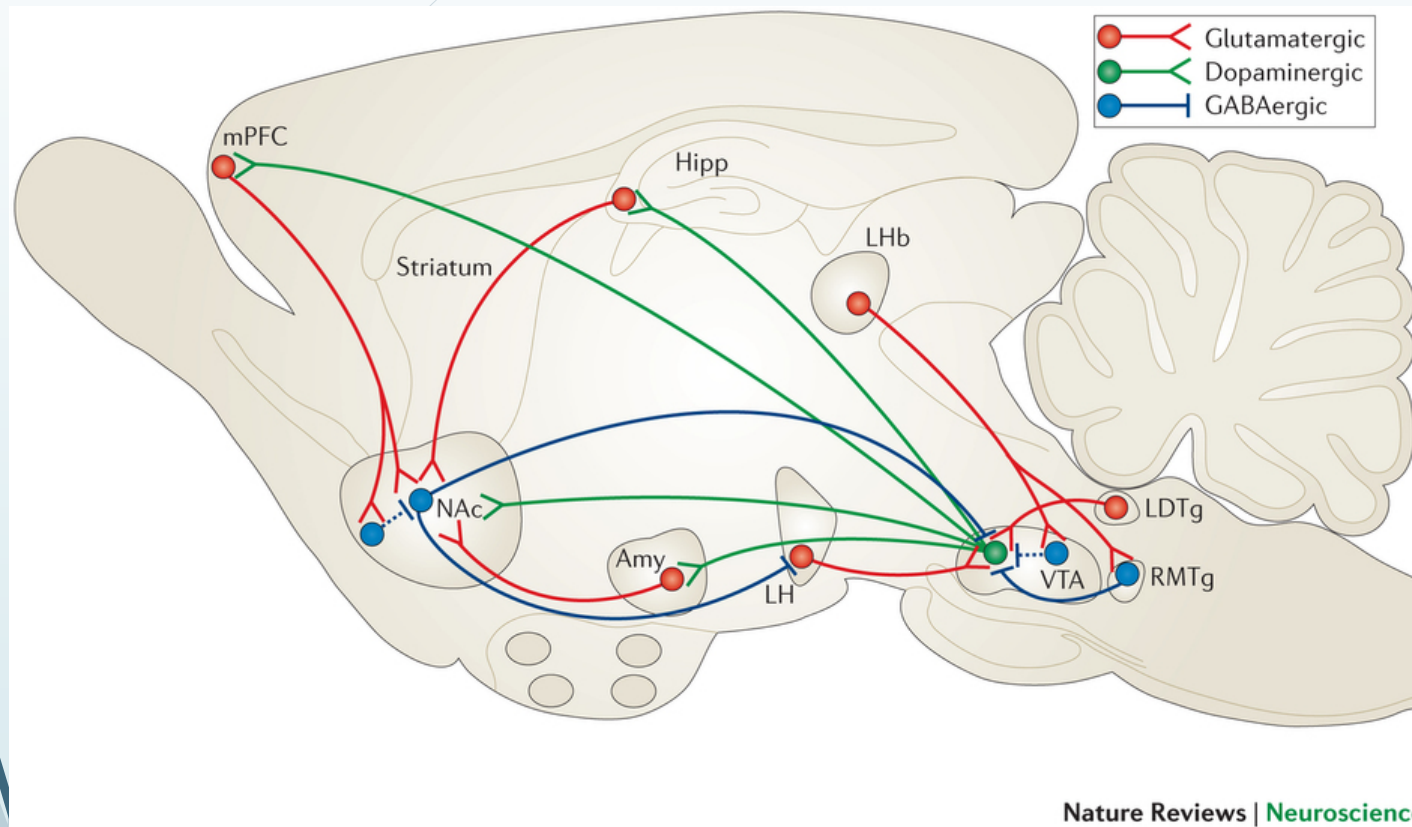
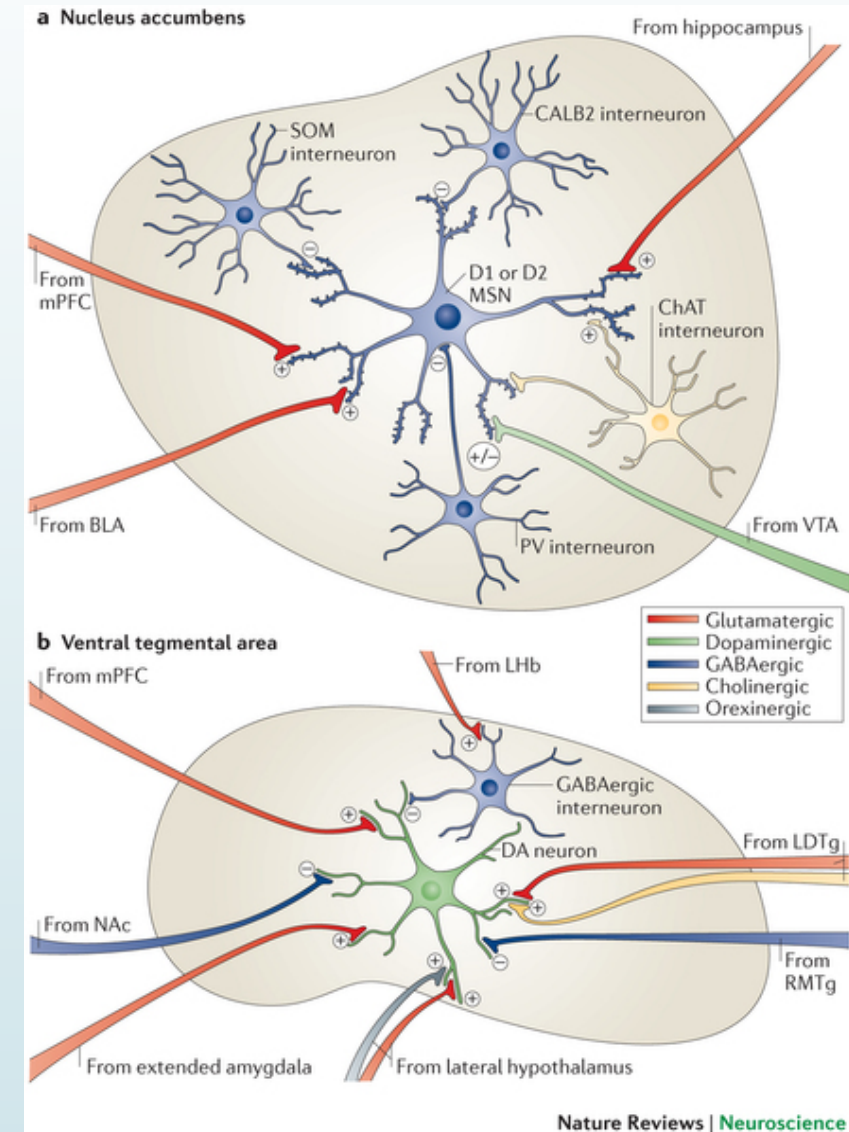


Figure 2 (above): Neurochemical neurocircuits in drug reward.

Figure 3 (right) : Neurochemical neurocircuits in drug reward within Nucleus accumbens and Ventral tegmental area

Russo, S.J., Nestler, E.J. (2013) The brain reward circuitry in mood disorders. Nature Reviews Neuroscience 14, 609-625.



# Metabotropic glutamate receptor 5

## mGluR5

All mGluRs are located within NAc subregions (core or shell).

Group I of mGluRs are critical in cocaine addiction.

If the mGluR5 stimulation is reduced, the drug-seeking behavior will be inhibited.

mGluR5 stimulation activates PKC.

Kenny, P., Markou, A. (2004). The ups and downs of addiction: role of metabotropic glutamate receptors. *Trends Pharmacological Science* 25:265-272

Schmidt, H., et. al. (2015). Group I metabotropic glutamate receptor-mediated activation of PKC gamma in the nucleus accumbens core promotes the reinstatement of cocaine seeking. *Addiction Biology*, 20(2):258-296.



# Protein Kinase C (PKC)

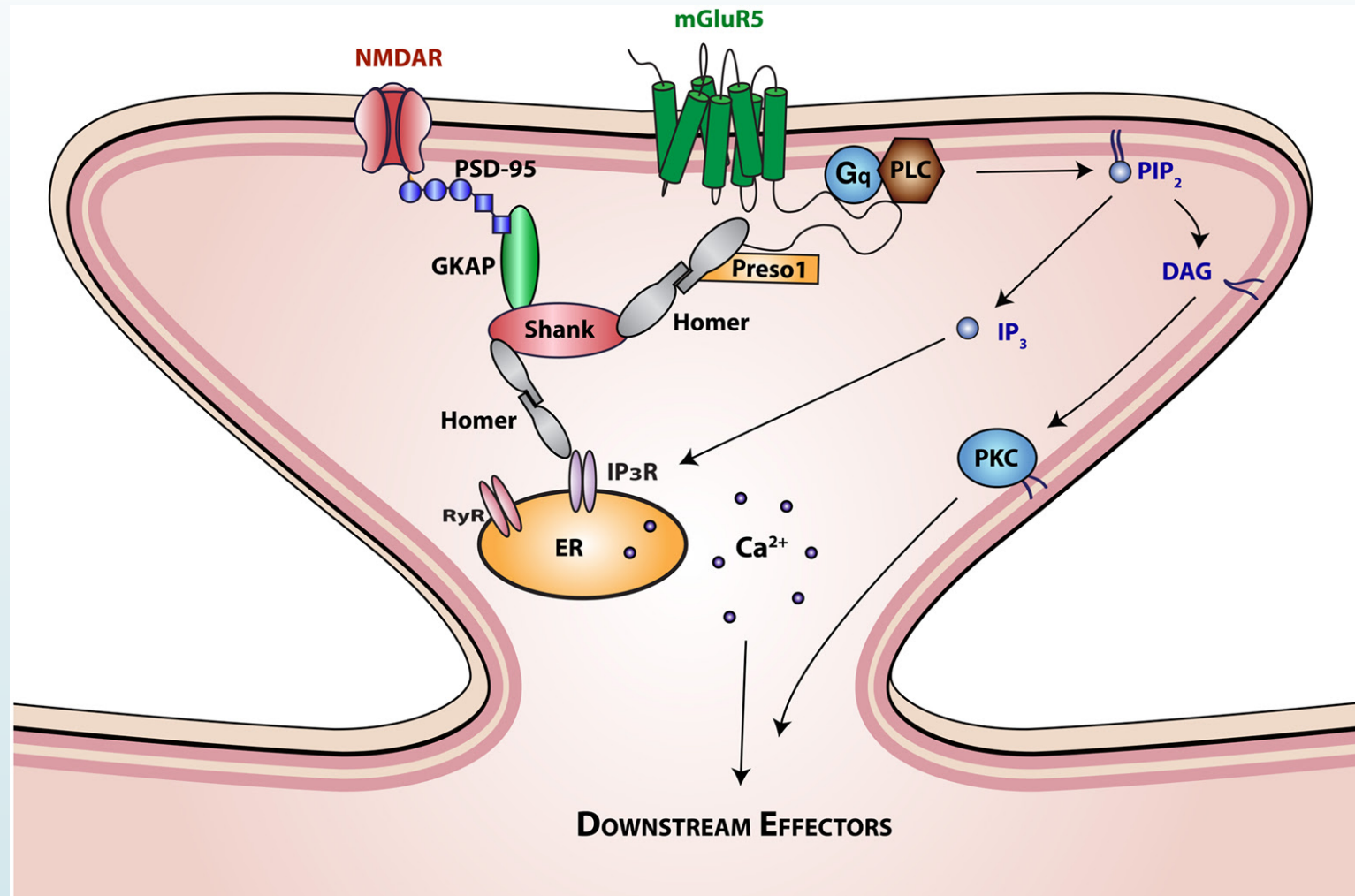


Figure 4: mGluR5 molecular pathway.

A dark grey arrow points to the right from the left edge of the slide. Several thin, light blue lines curve upwards from the bottom left corner towards the 'Objective' text.

## Objective

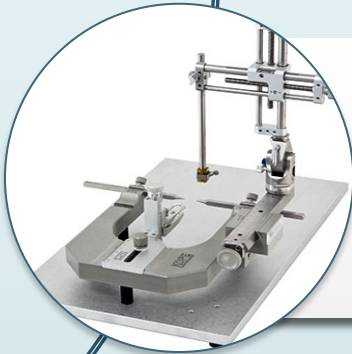
Examine the effect of blockade of PKC  $\gamma$  in the expression of cocaine conditioning.

# Methods



## Animal Model

Male Sprague Dawley Rats (250g – 275g) from PSM.  
A total of 22 rats were used.



## Surgery

Cannulae within the NAc shell were implanted in rats.  
Recovery period: 4 days



# Cocaine Conditioning in Locomotor Activity Chambers

Microinfusion ( $0.5 \mu\text{L}/\text{min}$ )  
(D1 to D5)

- **Daily infusion directly to NAc shell**
- 10  $\mu\text{M}$  Ro 31-8220 mesylate (PKC inhibitor)
- Saline 0.9%

Locomotive chambers  
(D1 to D5)

- **Exposed to a specific environment**
- Visual (black) and olfactory (orange) cues
- Systemic intraperitoneal cocaine injections (15mg/kg)

Test day (D7)

- **Animals were placed in the chambers with the environment cues, but without any pre-treatment.**



Figure 7: Harvard Pump 33 Dual Syringe Pump. Instechlabs.

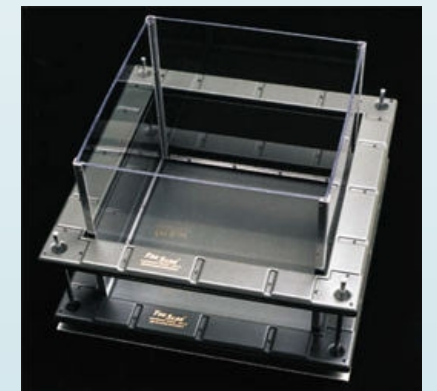
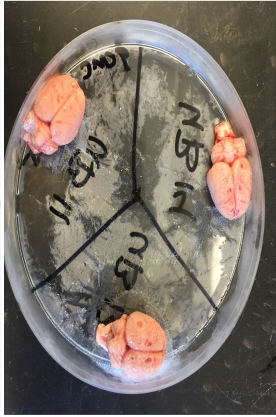


Figure 8: TruScan Photobeam Activity System

# Data analysis



After D7, rats were sacrificed and their brains were removed and frozen for further histological analysis (cannulae verification).

**\*Automatic Formula\***

	Addition of Total Hours Experimental Group (1.5 Hours) in Centimeters				
	Day 1	Day 2	Day 3	Day 4	Day 5
Total 1.5 hours					
UB 3	18730.468	6498.082	11569.7	18759.932	18817.59
UB 4	11643.106	10298.176	15771.49	19236.766	13172.44
UB 6	4725.824	5124.864	18817.886	15167.516	15946.96
UB 10	3042.92	4283.456	8795.004	10773.918	14465.046
UB 11	14117.066	20987.004	22204.934	20997.826	22044.66
UB 12	8186.578	3990.264	17462.726	23102.486	26561.03
TZ 1	17311.37	5668.772	9564.37	7963.152	10398.188
TZ 2	5245.862	4994.148	11126.684	17448.784	22545.04
TZ 4	6077.66	4263.39	16245.532	16274.542	7588.758
TZ 9	6949.518	3678.428	8620.256	9031.986	12801.254
TZ 10	4514.596	3995.674	4808.474	11585.448	6284.468
TZ 13	6825.234	10493.756	12221.972	18204.18	15587.66
AVG	9022.02517	7615.50117	14433.189	15599.793	16030.7978
SEM	1518.30453	1437.70091	2096.60454	1373.35774	1866.7522

**\*Automatic Formula\***

	Addition of Total Hours Control Group (1.5 Hours) in Centimeters				
	Day 1	Day 2	Day 3	Day 4	Day 5
Total 1.5 hours					
UB 1	5079.492	5361.432	11301.476	16112.744	23758.906
UB 2	12355.472	22887.5	20018.794	52286.946	49370.742
UB 5	9086.342	9006.586	5771.134	11519.662	12064.238
UB 14	4583.684	2043.684	12403.074	22075.646	26627.574
TZ 5	6119.368	4396.74	6123.846	3672.332	3039.106
TZ 7	6062.538	10423.896	7909.078	7794.836	8221.794
TZ 8	2921.254	1727.958	8463.026	4412.742	10260.838
TZ 12	1735.238	9472.184	10142.862	13075.158	12227.56
TZ 14	9343.888	7122.16	3544.12	6865.342	9107.7
TZ 16	5984.24	10574.528	6220.206	12208.802	9338.852
AVG	6449.1616	9419.7878	10570.5656	15205.129	16573.881
SEM	1086.86888	2665.80284	2274.61424	4491.61643	4465.8888

Data from the TruScan Photobeam Activity System was obtained and presented as mean  $\pm$  standard error of the mean (SEM).

Figure 9: Frozen rats brain of the experiment.

Figure 10: TruScan Photobeam Activity System Data spreadsheet with statistical analysis.

# Results – Training Session

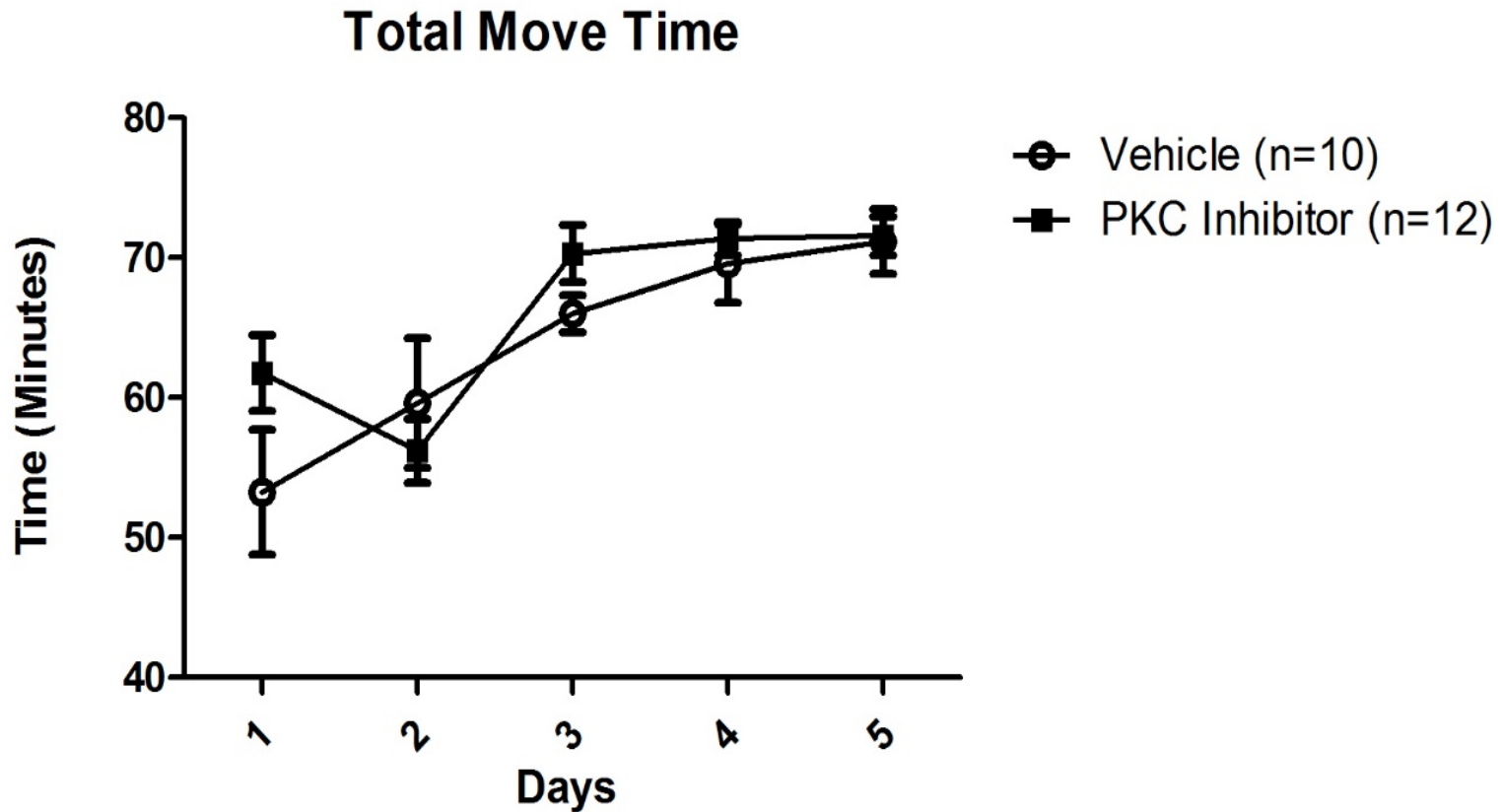


Figure 11: The effects of vehicle and PKC inhibitor infusions directly to the NAc shell during five consecutive days in the total move time of rats in the locomotor activity chamber.

# Results – Training Session

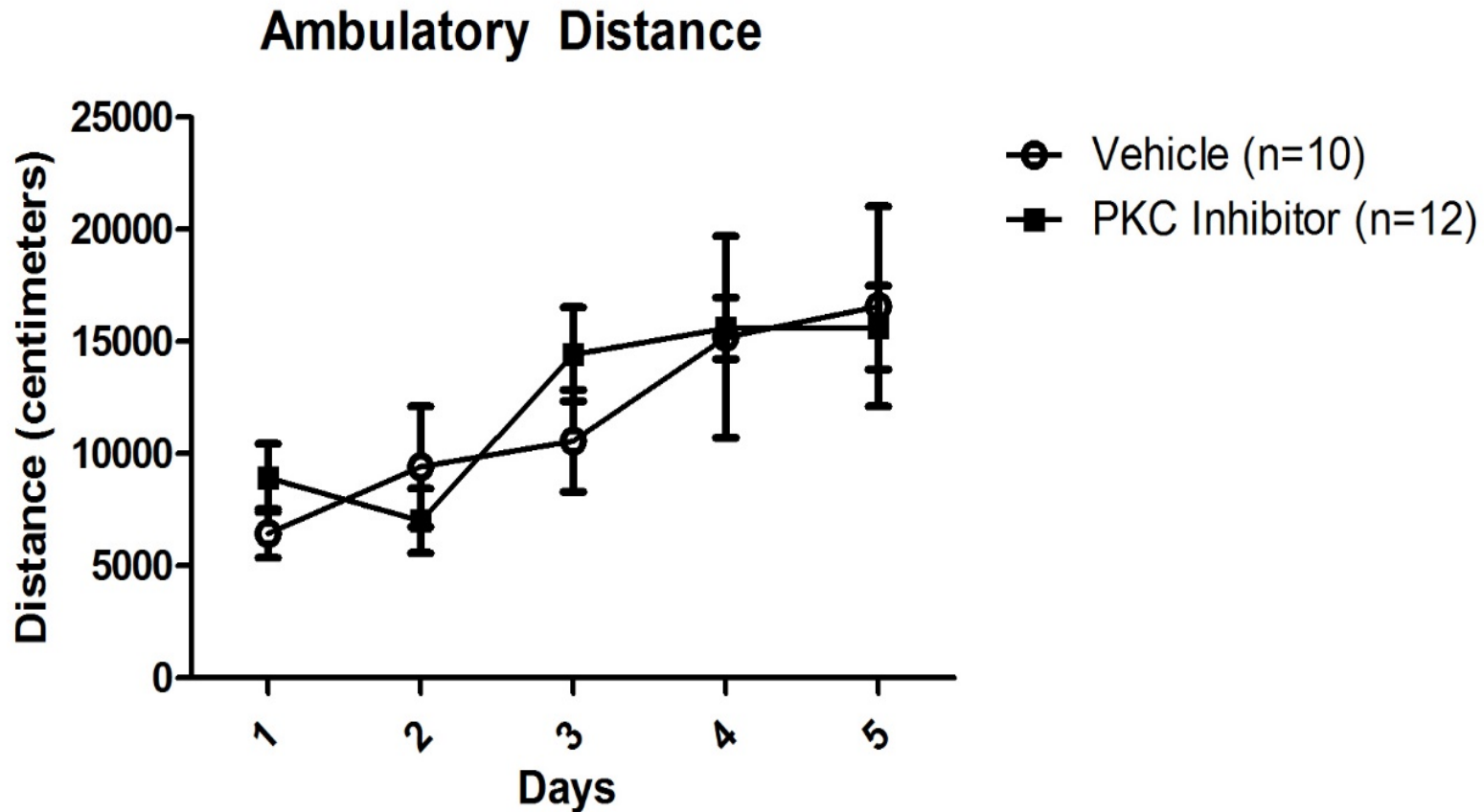


Figure 12: The effects of vehicle and PKC inhibitor infusions directly to the NAc shell during five consecutive days in the ambulatory distance of rats in the locomotor activity chamber.

# Results – Training Session

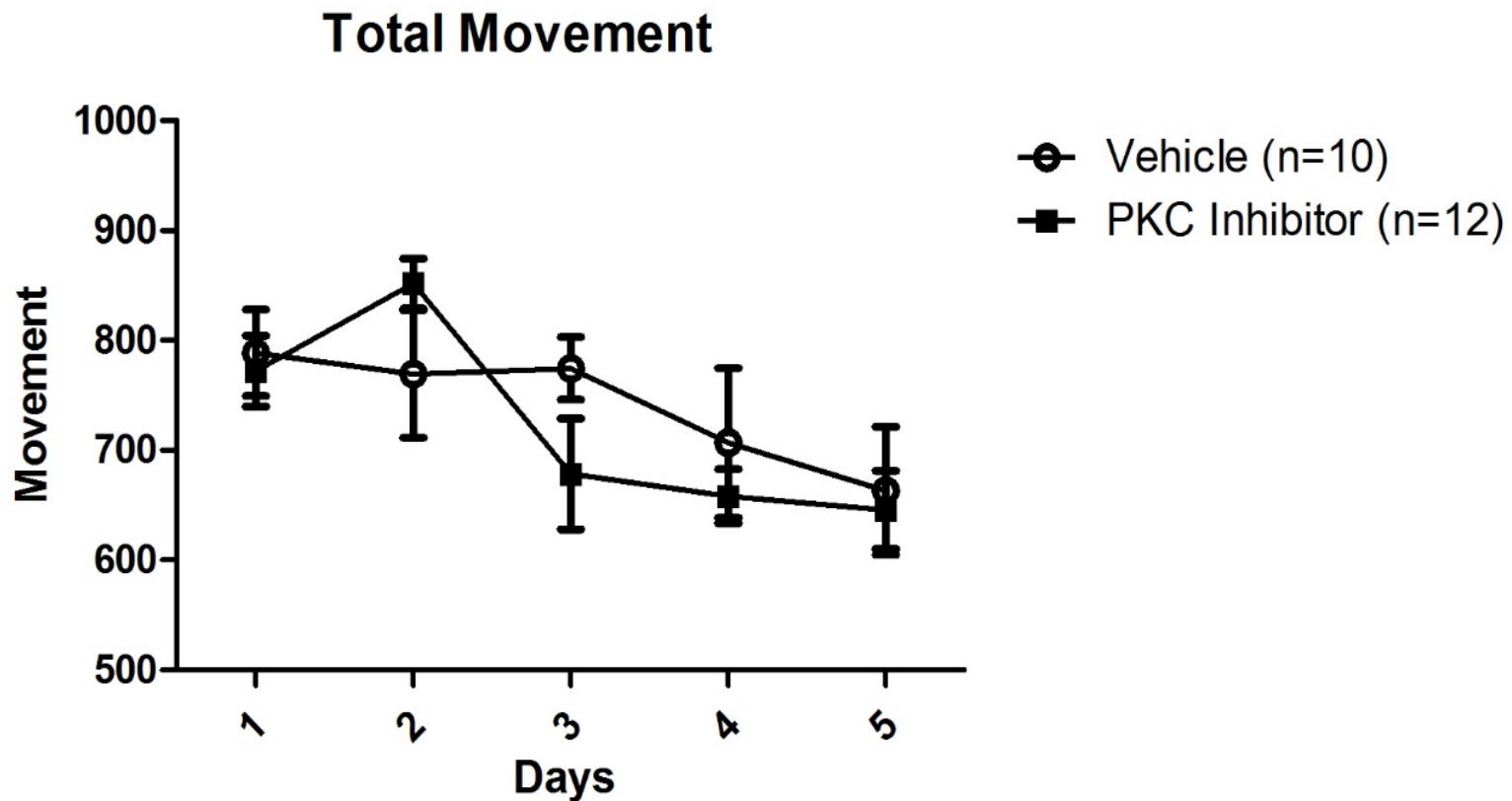


Figure 13: The effects of vehicle and PKC inhibitor infusions directly to the NAc shell during five consecutive days in the total movement of rats in the locomotor activity chamber.

# Results – Testing Session

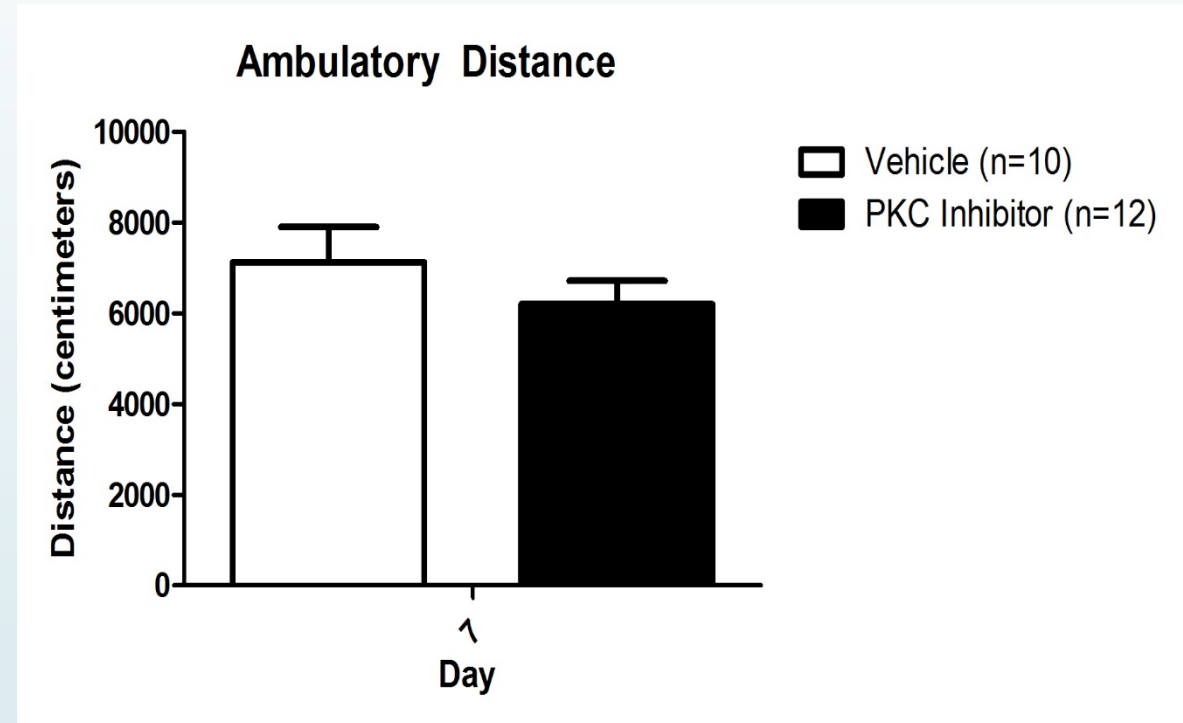
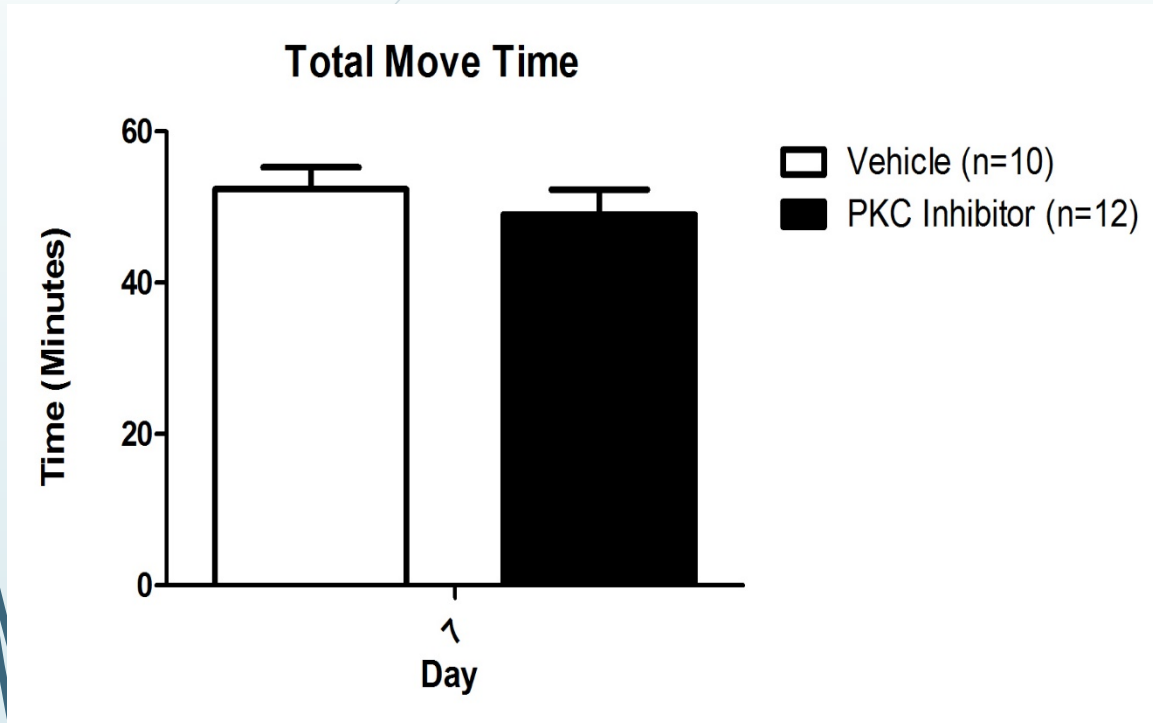
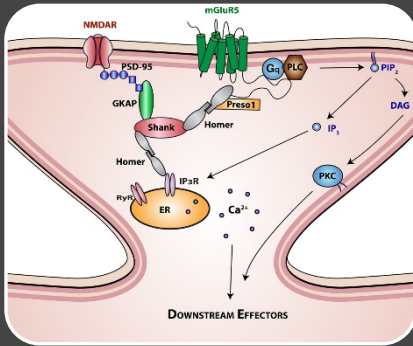


Figure 14 (left): The total move time of rats in the locomotor activity chamber with the previous environment cues, but without any pre-treatment; neither vehicle or PKC inhibitor.

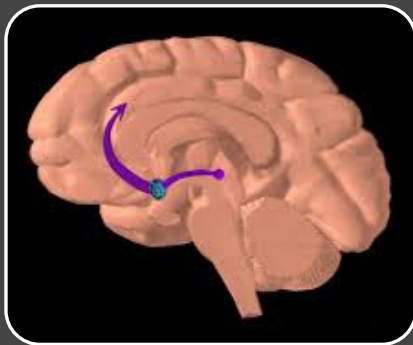
Figure 15 (right): The ambulatory distance of rats in the locomotor activity chamber with the previous environment cues, but without any pre-treatment; neither vehicle or PKC inhibitor.



# Discussion

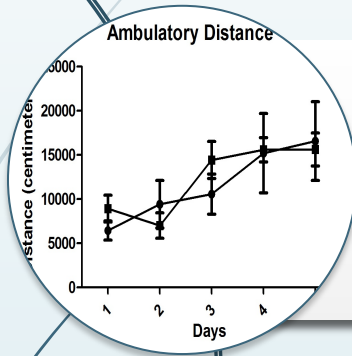


This preliminary data suggests a possible role of PKC  $\gamma$  on acquiring the association between an environment and cocaine use.

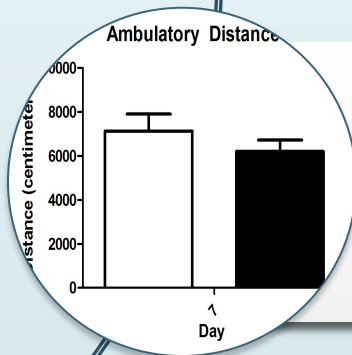


Further experiments are needed to fully characterize these findings.

# Conclusion



**There was no effect on cocaine sensitization.**



**Small effect on the cocaine conditioning expression was observed.**



# References



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