

Protein kinase C inhibition rescues manic-like behavior and impairment of hippocampal cell proliferation induced by sleep deprivation

Abrial E¹, Bétourné A², Etievant A¹, Bétry C¹, Bourcier-Lucas C¹, Scarna H¹, Lucas G¹, Haddjeri N¹, and Lambás-Señas L¹



¹Laboratoire de Neuropsychopharmacologie, Université Lyon 1, France

²Centre de Physiopathologie de Toulouse Purpan, INSERM UMR1043, Université Toulouse III, France



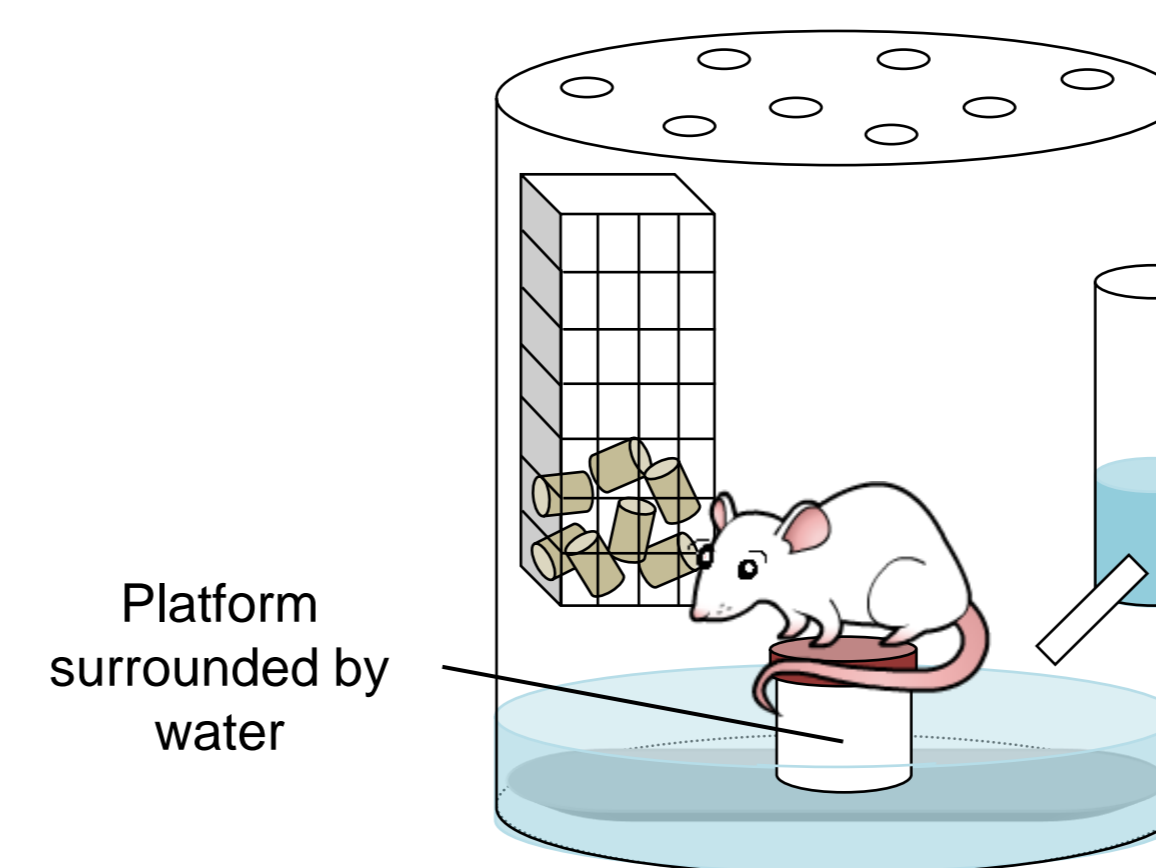
INTRODUCTION

- **Bipolar disorder** is a highly disabling chronic disease characterized by mood shifts between episodes of depression and mania.
- Tamoxifen, an antiestrogenic drug which also exhibits protein kinase C (PKC) inhibitory activity, induced significant improvements in manic symptoms in bipolar patients [1,2], highlighting the possible contribution of the **PKC signaling pathway** in mood regulation.
- Using **72h-REM sleep deprivation (SD)** as an animal model of mania [3], the present study aimed to investigate the **role of PKC in manic-like behavior**. For this purpose, we examined whether pharmacological PKC blockade could prevent SD-induced alterations in **locomotor activity** and **hippocampal cell proliferation**.

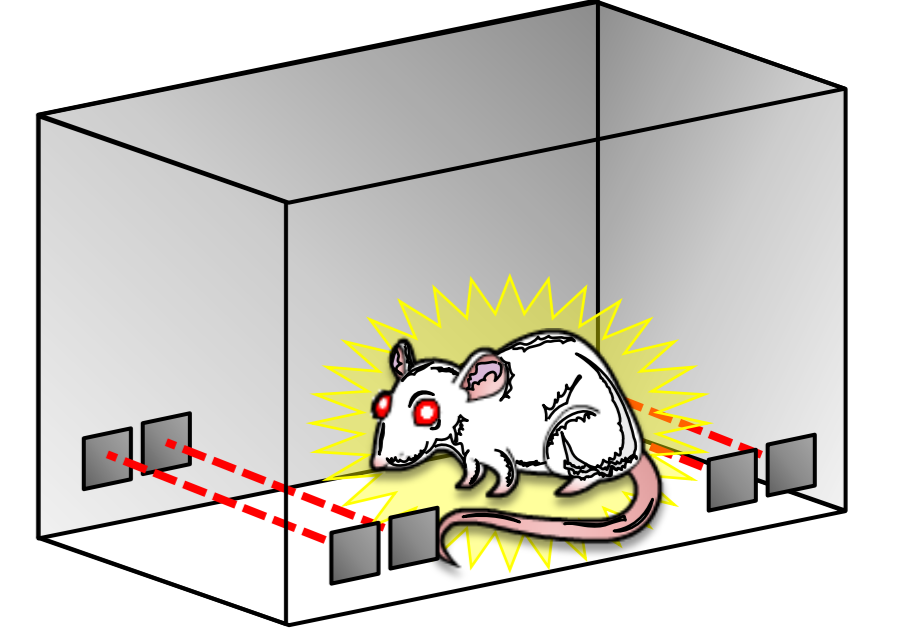
EXPERIMENTAL PROCEDURES

Model of mania:

« flower pot »
72h-REM sleep deprivation



« manic-like » hyperlocomotion behavior (actimeter)



PKC activity (western blot phospho-SNAP-25 quantification)

Hippocampal cell proliferation (BrdU-labeling in dentate gyrus)

RESULTS

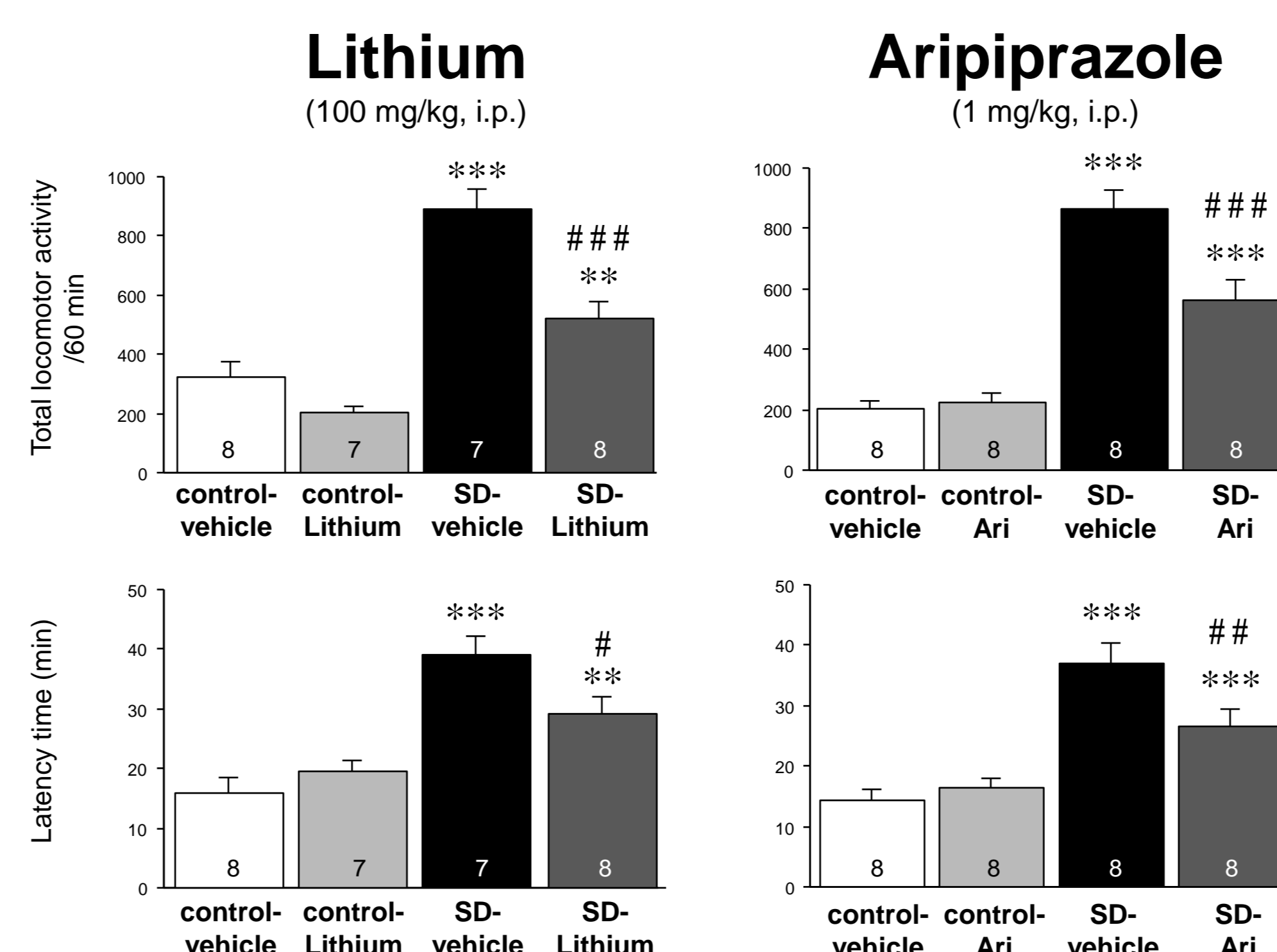
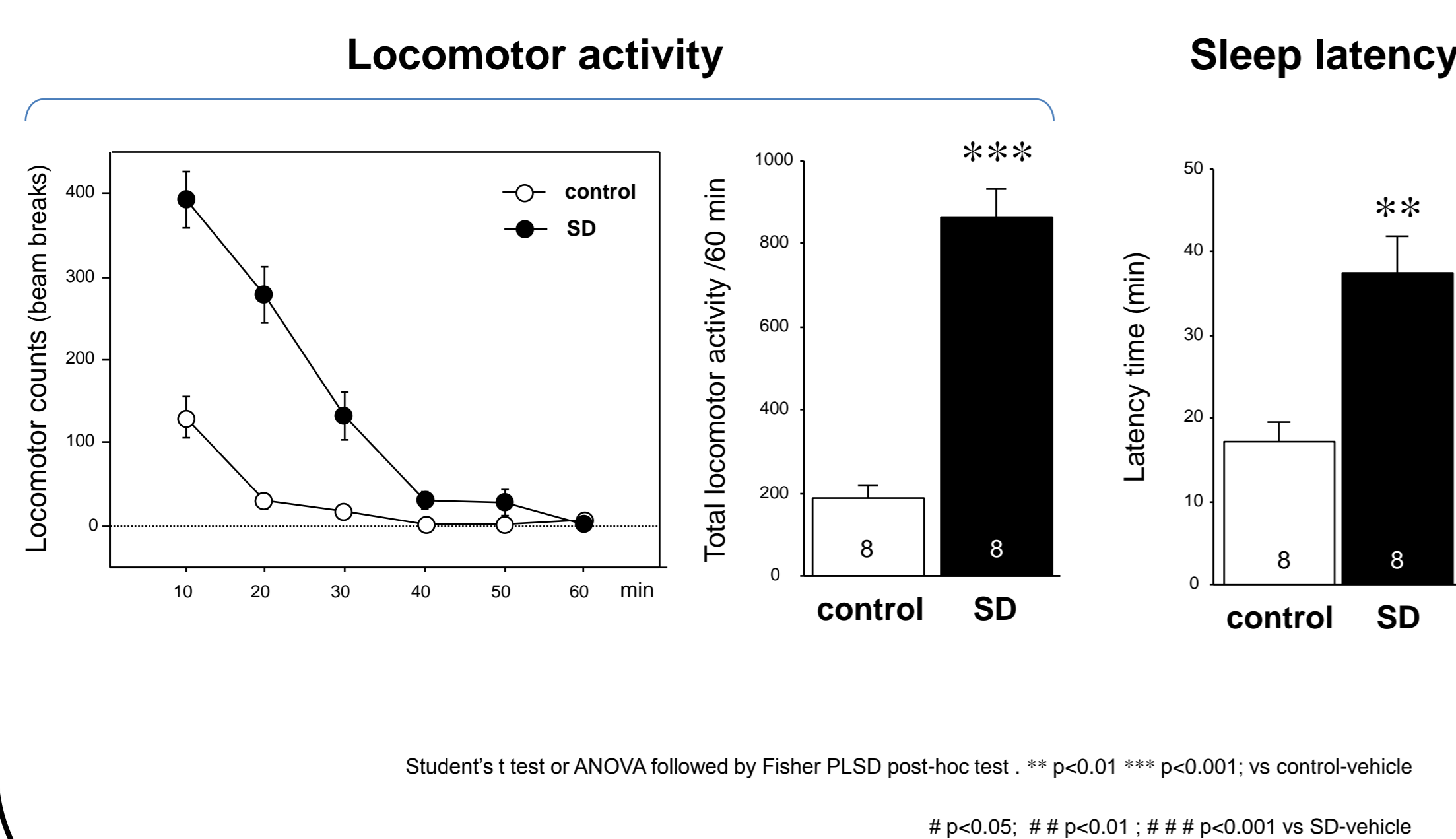
Behavioral validation of sleep deprivation (SD) animal model of mania

Face validity:

A 72h-sleep deprivation induced transient hyperlocomotion and insomnia

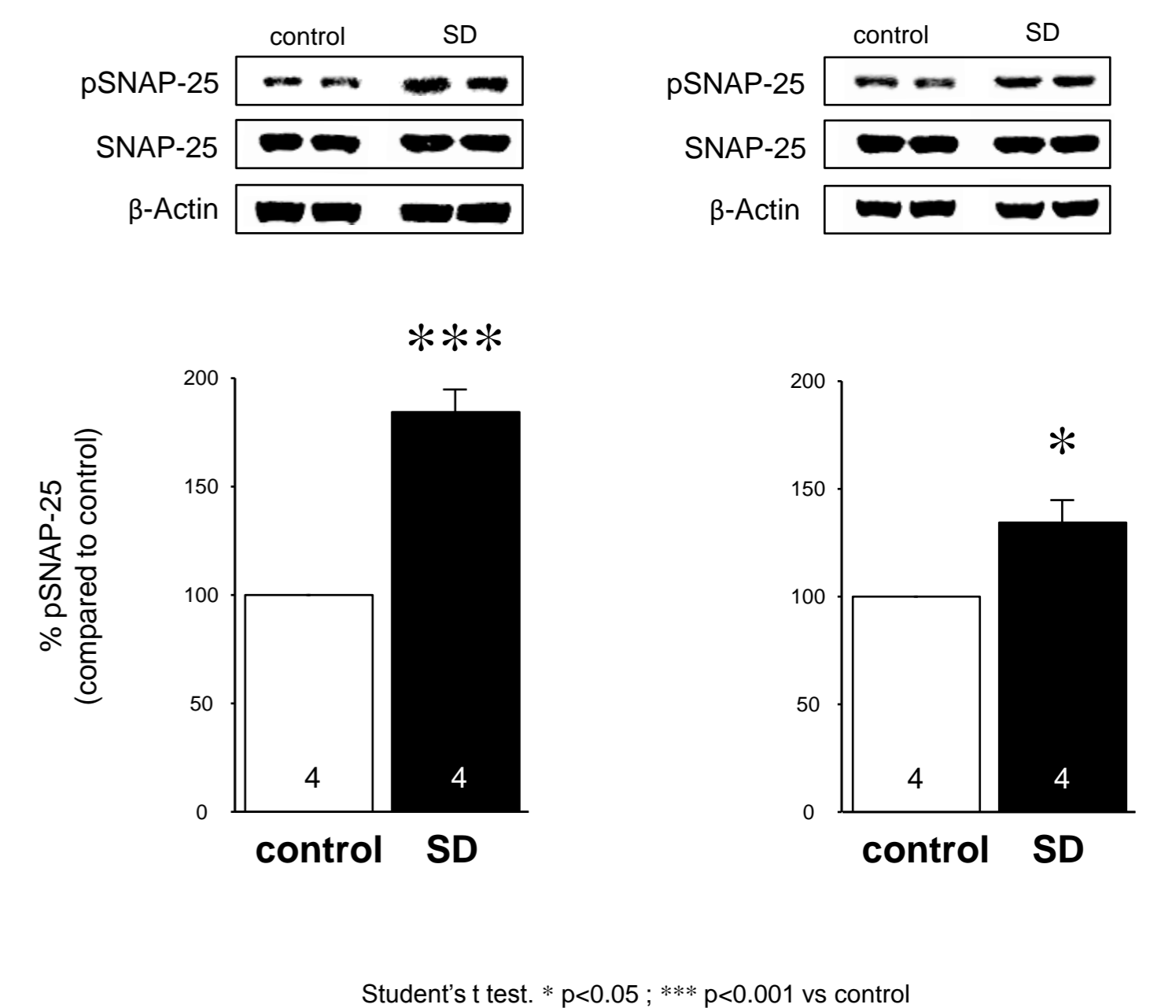
Predictive validity:

Hyperlocomotion and delayed sleep were reversed by a clinically efficient mood stabilizer (lithium) and an antimanic agent (aripiprazole)

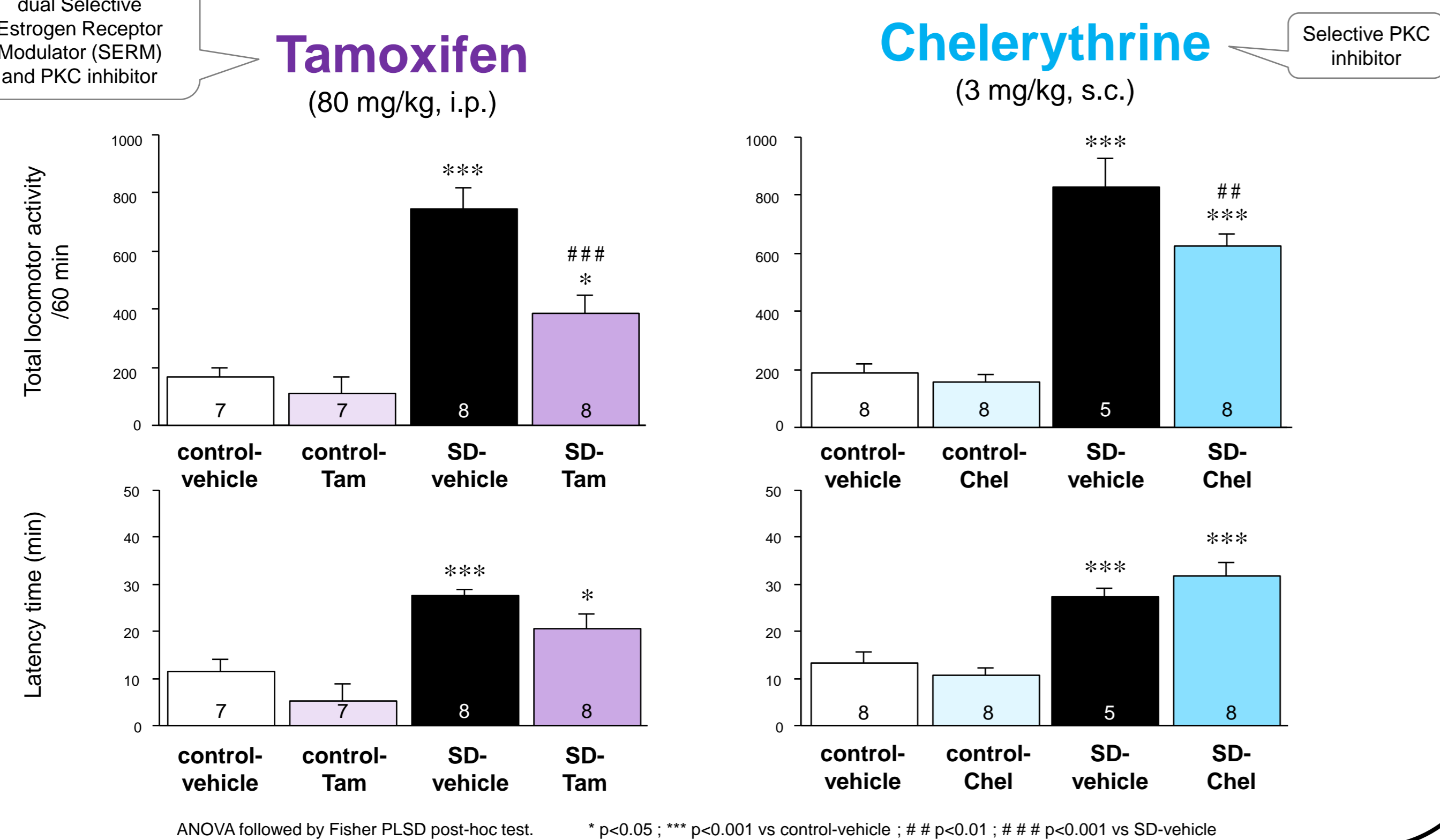


Phosphorylation of the PKC substrate SNAP-25 is enhanced in SD rats

Prefrontal cortex Hippocampus

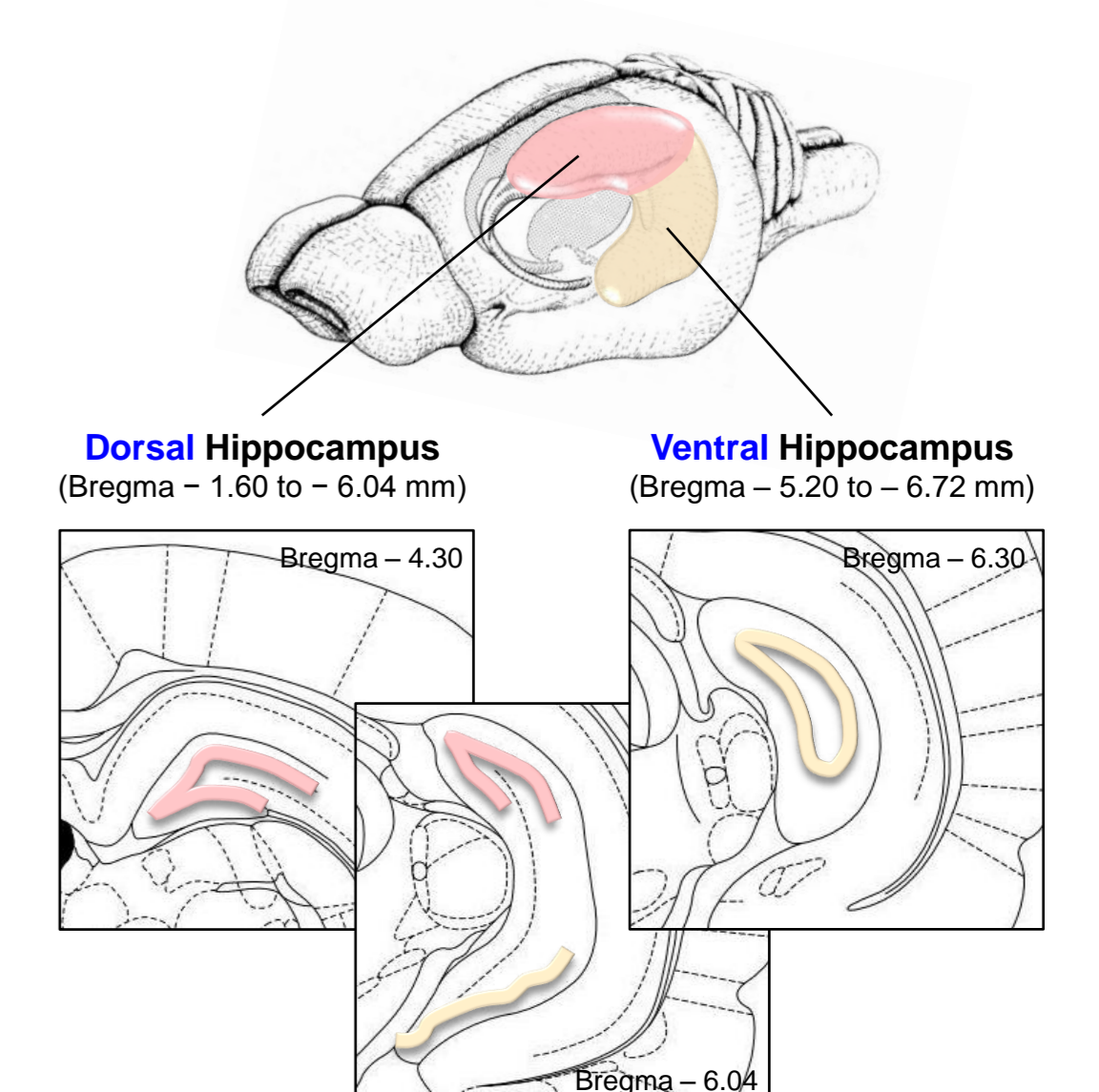
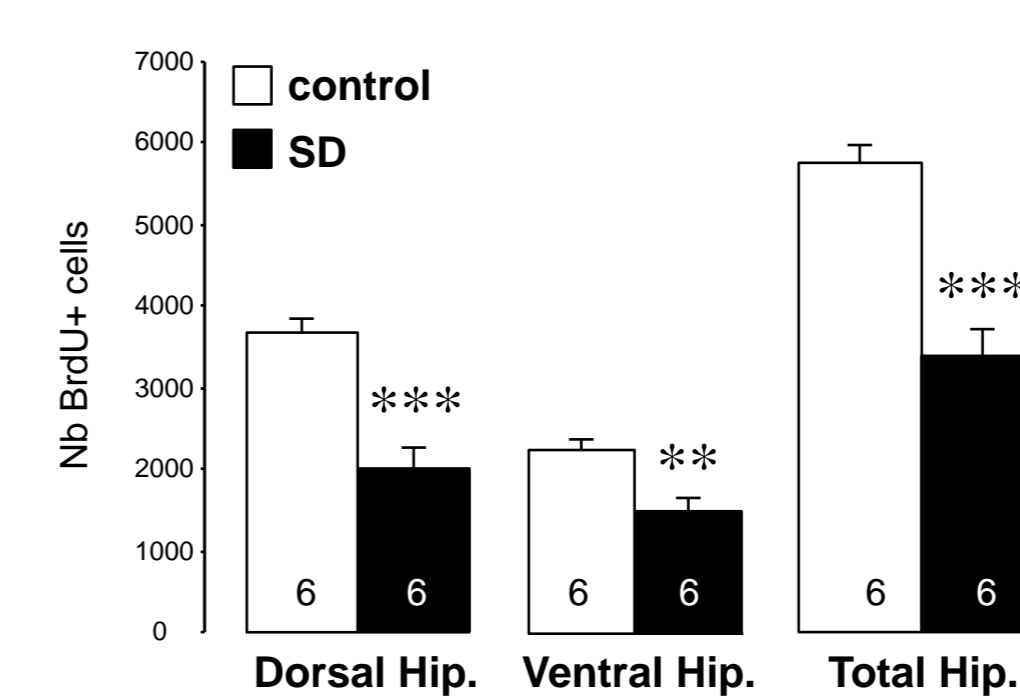
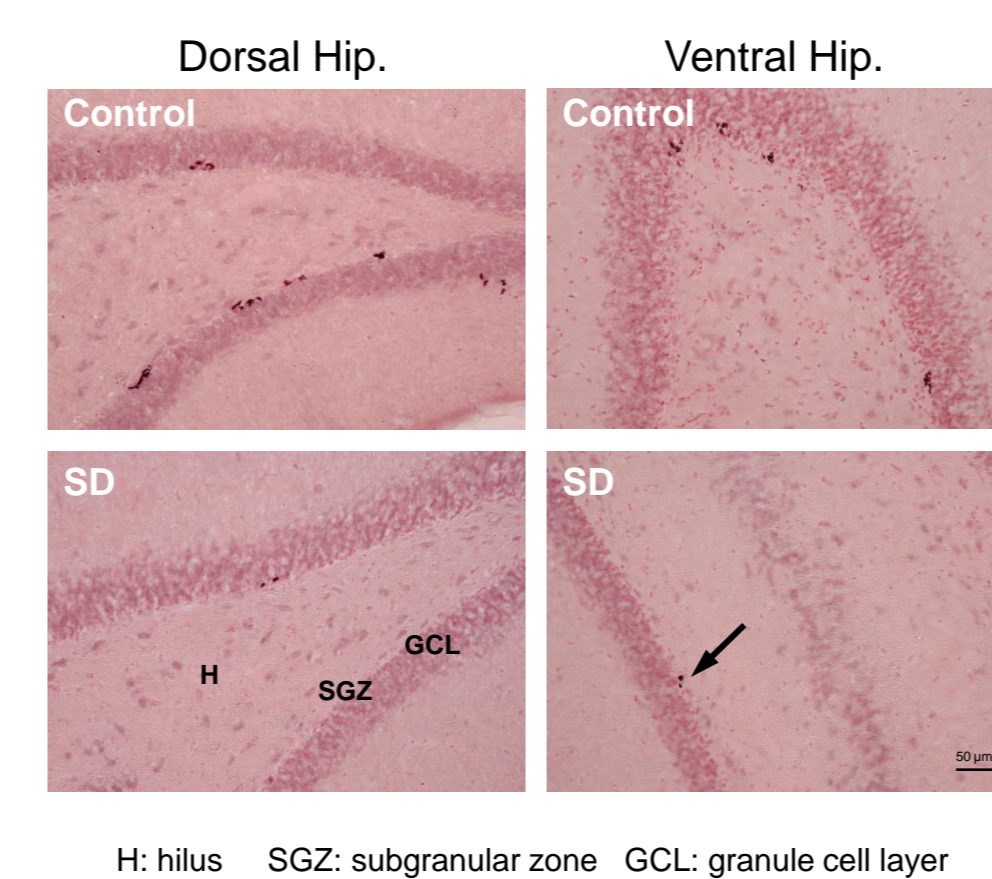


PKC inhibitors reduced hyperlocomotion of SD rats

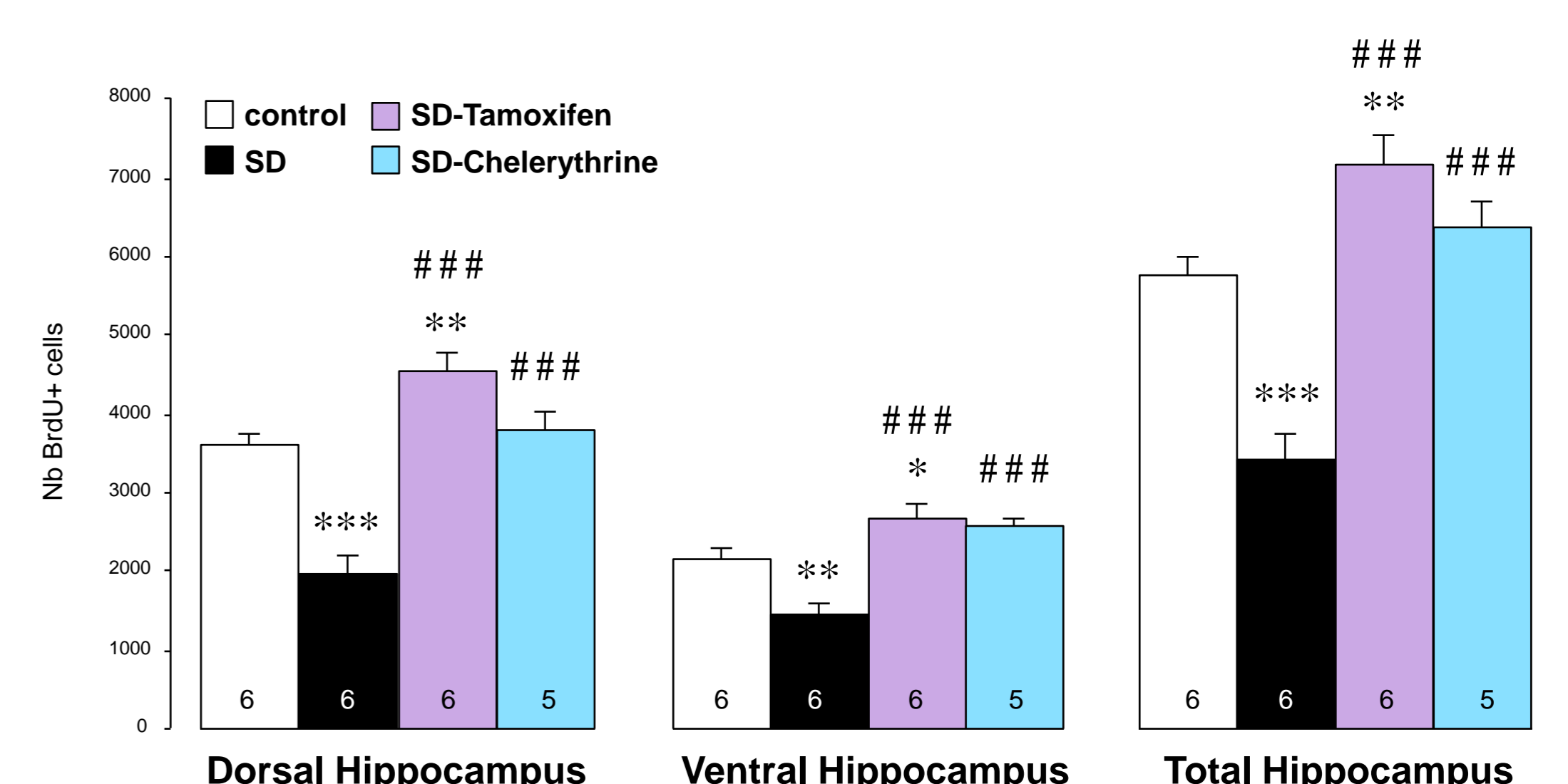
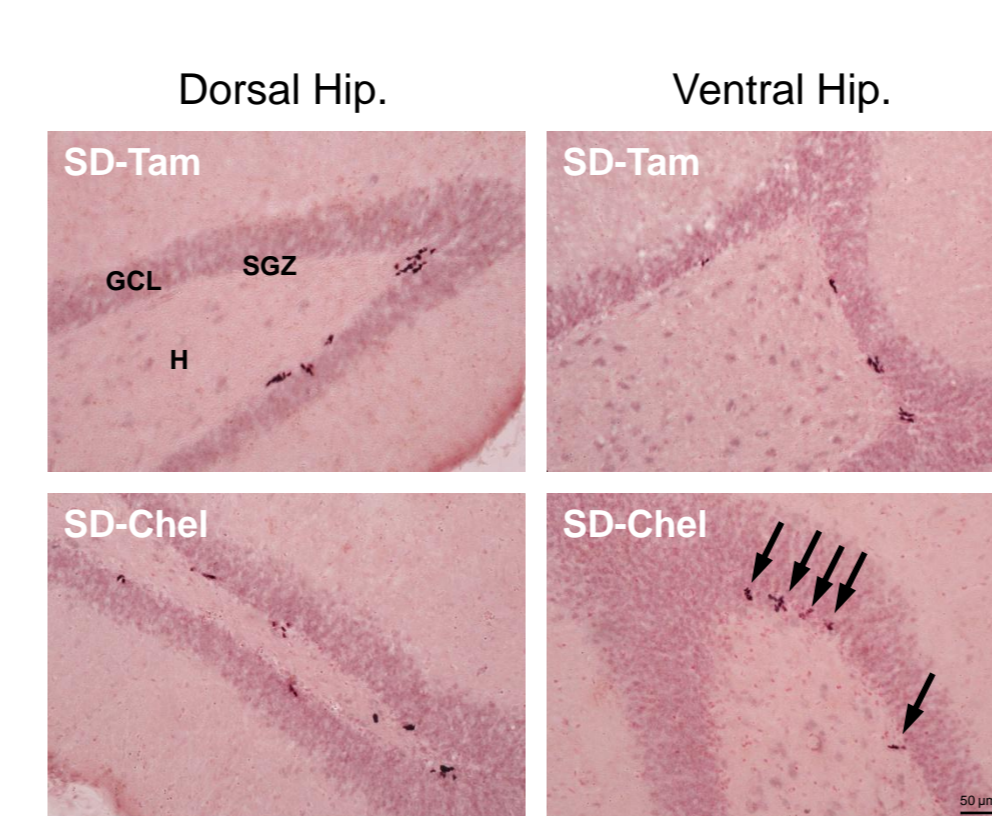


Effects of SD and PKC inhibitors on cell proliferation in the dentate gyrus

Hippocampal cell proliferation is impaired in SD rats



PKC inhibitors rescued hippocampal cell proliferation deficits induced by SD



CONCLUSIONS

The present study showed that rats exposed to 72 hours of REM SD displayed treatment-responsive behavioral alterations (hyperlocomotion, insomnia), having face validity with manic symptoms. Considering that sleep disruption is a frequent prodrome of a manic episode, this animal model appears as a valuable tool to further explore the underlying mechanisms of mania.

We evidenced that SD rats exhibited decreased hippocampal cell proliferation and enhanced PKC activity, suggesting that neurogenesis impairment and PKC overactivation may be involved in mania.

Furthermore, we demonstrated for the first time that acute PKC inhibitors attenuated the manic-like behavior and prevented the impairment of hippocampal cell proliferation triggered by SD. Our findings support a crucial role for PKC in the pathophysiology of bipolar disorder, and provide new insights on the use of PKC inhibitors as possible novel treatments for this disease.

REFERENCES

- [1] Yildiz A, Guleryuz S, Ankerst DP, Ongür D, Renshaw PF (2008) Protein kinase C inhibition in the treatment of mania: a double-blind, placebo-controlled trial of tamoxifen. Arch. Gen. Psychiatry 65:255-263.
- [2] Zarate CA, Singh JB, Carlson PJ, Quiroz J, Jolkovsky L, Luckenbaugh DA, Manji HK (2007) Efficacy of a protein kinase C inhibitor (tamoxifen) in the treatment of acute mania: a pilot study. Bipolar Disord 9:561-570.
- [3] Gessa GL, Pani L, Fadda P, Fratta W (1995) Sleep deprivation in the rat: an animal model of mania. Eur Neuropsychopharmacol 5 Suppl:89-93.

No potential conflict of interest