



uOttawa

Sex differences in the effects of pubertal immune stress on adult hippocampal cellular proliferation

Houlding, Elizabeth¹; Kolmogorova, Daria¹; Ismail, Nafissa¹

¹NISE Laboratory, School of Psychology, University of Ottawa, Ottawa, Ontario, Canada



Introduction

The **pubertal** brain undergoes extensive remodeling & reorganizing → vulnerability to external stressors that activate the **immune system**¹.

Rodent models have shown that **immune activation** triggered by the bacterial endotoxin lipopolysaccharide (LPS) → various immediate deleterious effects on **neurocognitive functions** involved in learning and memory².

Male and female sex hormones, which begin to emerge during puberty, differentially affect the immune response³.

The (a) long-term effects of **pubertal immune stress** on hippocampal cellular proliferation and (b) the role of **immune-regulating sex hormones** in this relationship are unclear.

Hypotheses

Cellular proliferation:

1. LPS-injected mice < saline-injected mice
2. ♀ mice < ♂ mice, regardless of treatment
3. Gonadal hormones moderate the long-term effects of pubertal LPS *ip*

Methods

• CD-1 mice shipped to the lab

3 wks ♀: n=45 & ♂: n=45

• Single LPS (1.5 mg/kg *ip*) or saline control (1.5 mg/kg *ip*)

6 wks (puberty) ♀ & ♂: n_{saline} = 21 & n_{LPS} = 24

• Gonadectomy or Sham-operation

9 wks ♀ & ♂: SALINE: n_{Gx} = 12 & n_{sham} = 9
LPS: n_{Gx} = 12 & n_{sham} = 12

• Brain perfusion & extraction → immunofluorescence staining for Ki67 (biomarker of cellular proliferation) → fluorescence intensity measured in **SGZ**

17 wks (adulthood)



Results

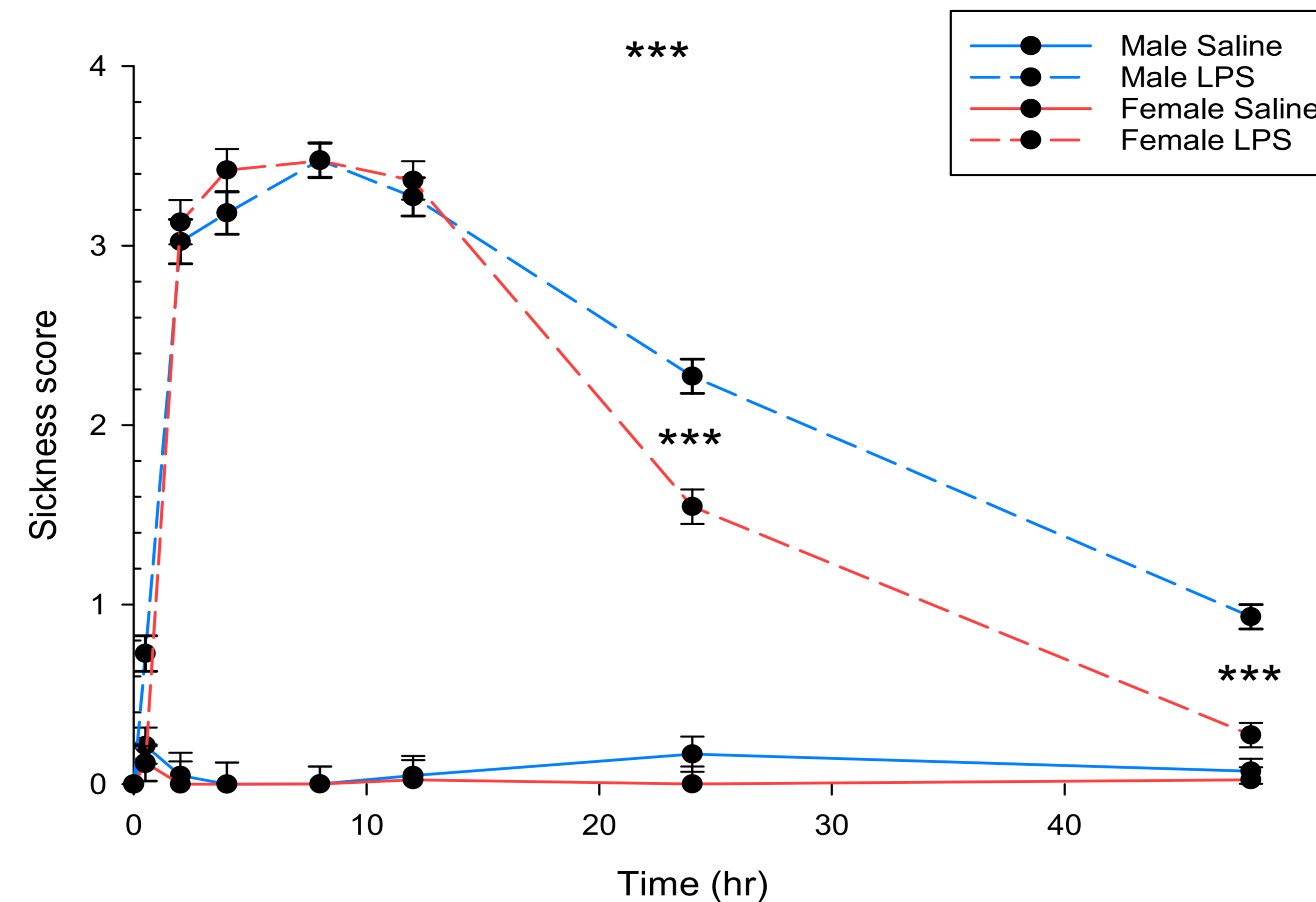


Figure 1. Impact of LPS exposure on sickness behaviours in male and female pubertal mice. Note: * = $p < .05$, ** = $p < .01$, *** = $p < .001$

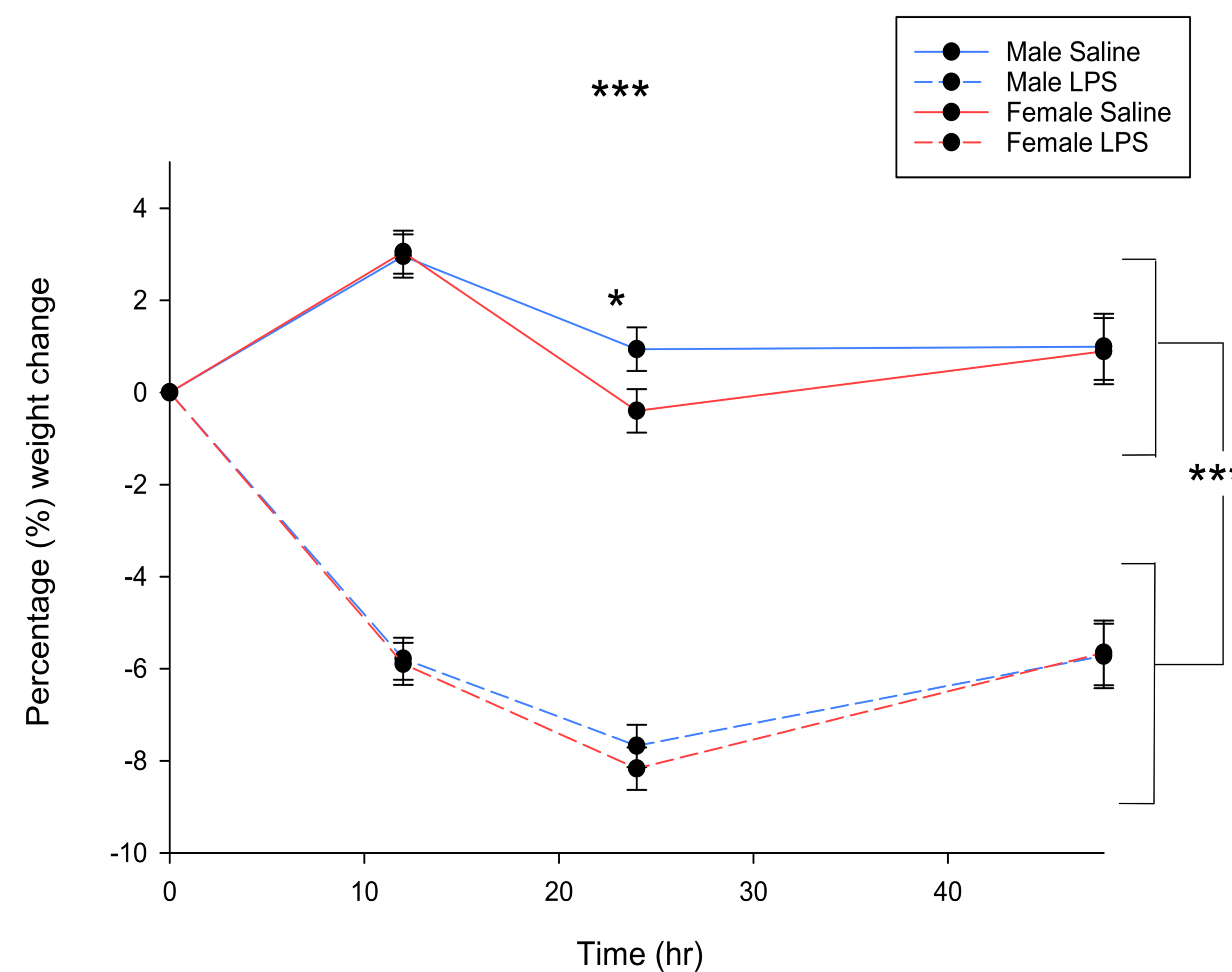


Figure 2. Impact of LPS exposure on weight gain for male and female mice. Note: * = $p < .05$, ** = $p < .01$, *** = $p < .001$

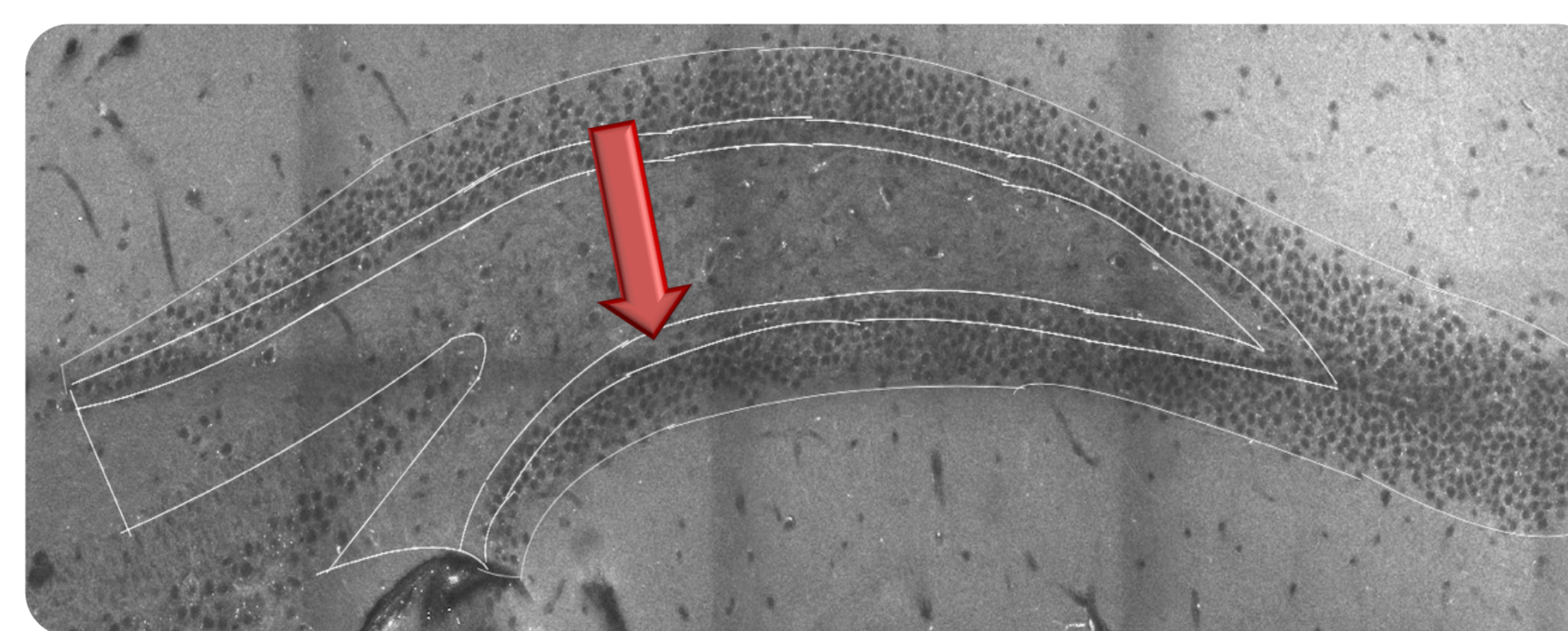


Figure 3. Subgranular zone of the hippocampus.

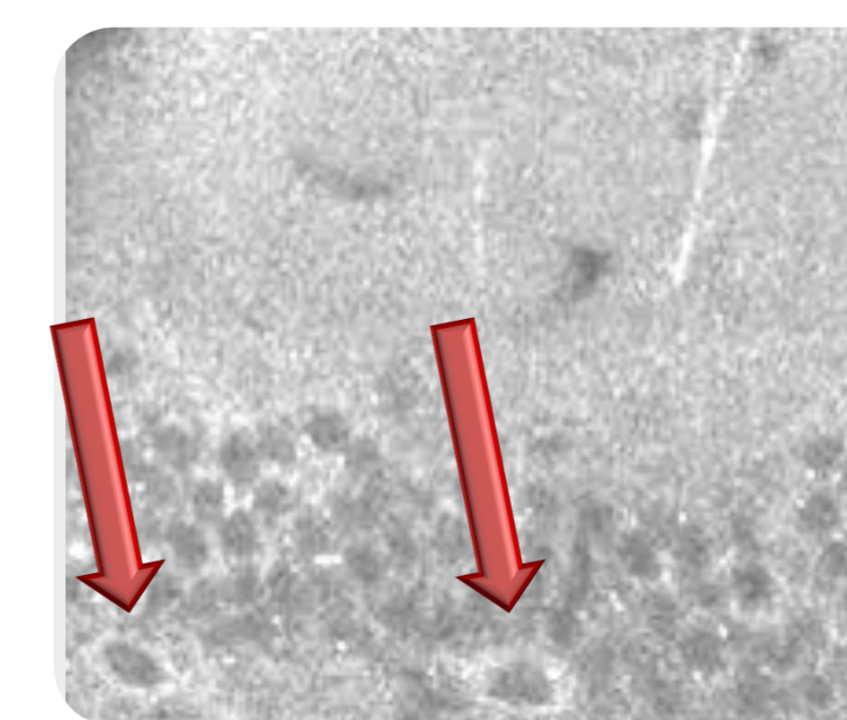


Figure 4. Ki67⁺ hippocampal cells.

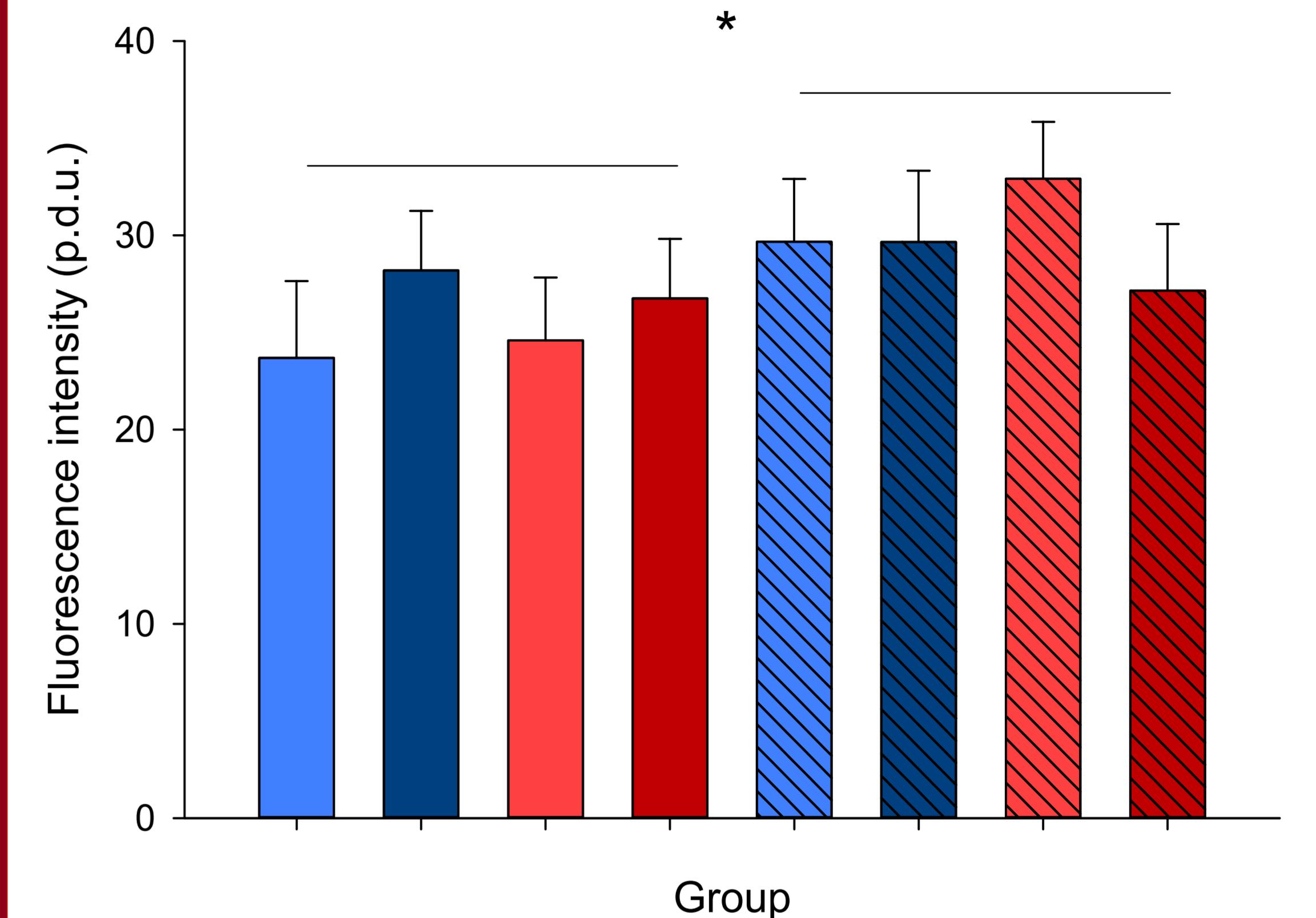
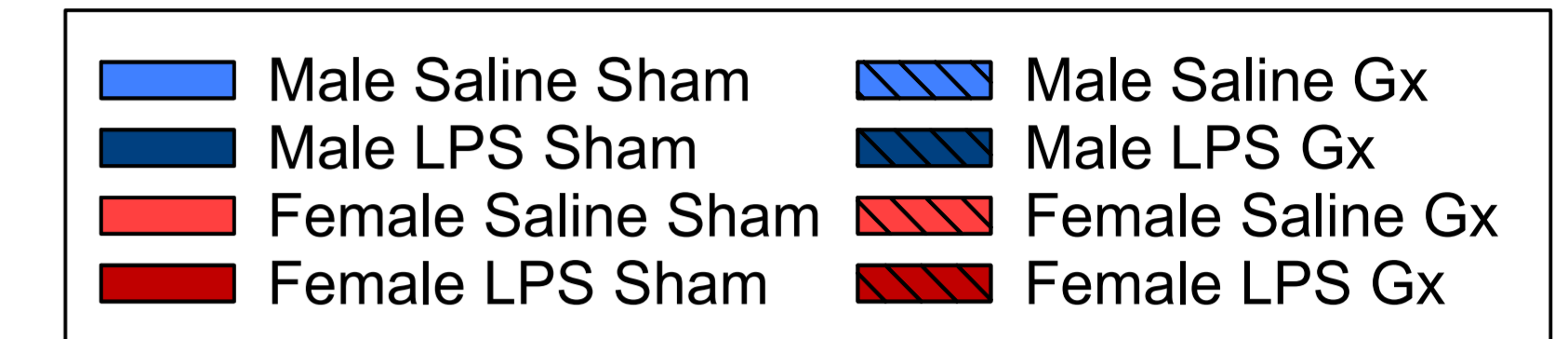


Figure 5. Mean fluorescence intensity of Ki67 in the subgranular zone of the dorsal hippocampus within each experimental group. Note: * = $p < .05$, ** = $p < .01$, *** = $p < .001$

Conclusions

As expected, there were significant sex and treatment effects on sickness behaviours as well as a significant effect of treatment on % body weight change during the 48 hr after injections. Interestingly, LPS-treated male mice displayed significantly more sickness and took longer to recover than their female counterparts ($p < .05$).

The experiment demonstrated a main effect of surgery on Ki67 fluorescence intensity in the SGZ, a neurogenic zone involved in learning and memory processes. Main effects of treatment and sex were not found.

Future Directions

Examination of the impact of prolonged (rather than acute) LPS exposure on hippocampal cellular proliferation during puberty.

Assessment of the impact of pubertal LPS exposure and the role of sex hormones on cellular proliferation in other neurogenic zones of the brain (e.g., subventricular zone)

Acknowledgements

Thank you to Dr. Ismail for such a warm welcome and for the opportunity to participate as a UROP student in the NISE laboratory.

Thank you to Daria Kolmogorova for your support, encouragement and mentoring throughout the project.

Thank you to the patient and helpful staff of NISE laboratories, particularly Sylvie and Jackie.

Bibliography

1. Holder, M.K., & Blaustein, J.D. (2014). Puberty and adolescence as a time of vulnerability to stressors that alter neurobehavioral processes. *Frontiers in Neuroendocrinology*, 35, 89-110. DOI: <http://dx.doi.org/10.1016/j.yfrne.2013.10.004>
2. Qin, L., Wu, X., Block, M.L., Liu, Y., Brees, G.R., Hong, J.S., ... Crews, L.T. (2013). Systemic LPS causes chronic neuroinflammation and progressive neurodegeneration. *GLIA*, 55, 453-462. DOI: [10.1002/glia.22467](http://dx.doi.org/10.1002/glia.22467)
3. Cai, K.C., van M, S., Murray, E., Mallet, J.-F., Matar, C., & Ismail, N. (2016). Age and sex differences in immune response following LPS treatment in mice. *Brain, Behavior, and Immunity*. DOI: <http://dx.doi.org/10.1016/j.bbi.2016.08.002>