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### Fos Expression in Lateral Hypothalamus/Perifornical Area is Correlated with Psychosocial Stress-Induced Cocaine-Seeking Behavior in a Sex-Specific Manner

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# Fos expression in lateral hypothalamus/perifornical area is correlated with psychosocial stress-induced cocaine-seeking behavior in a sex-specific manner

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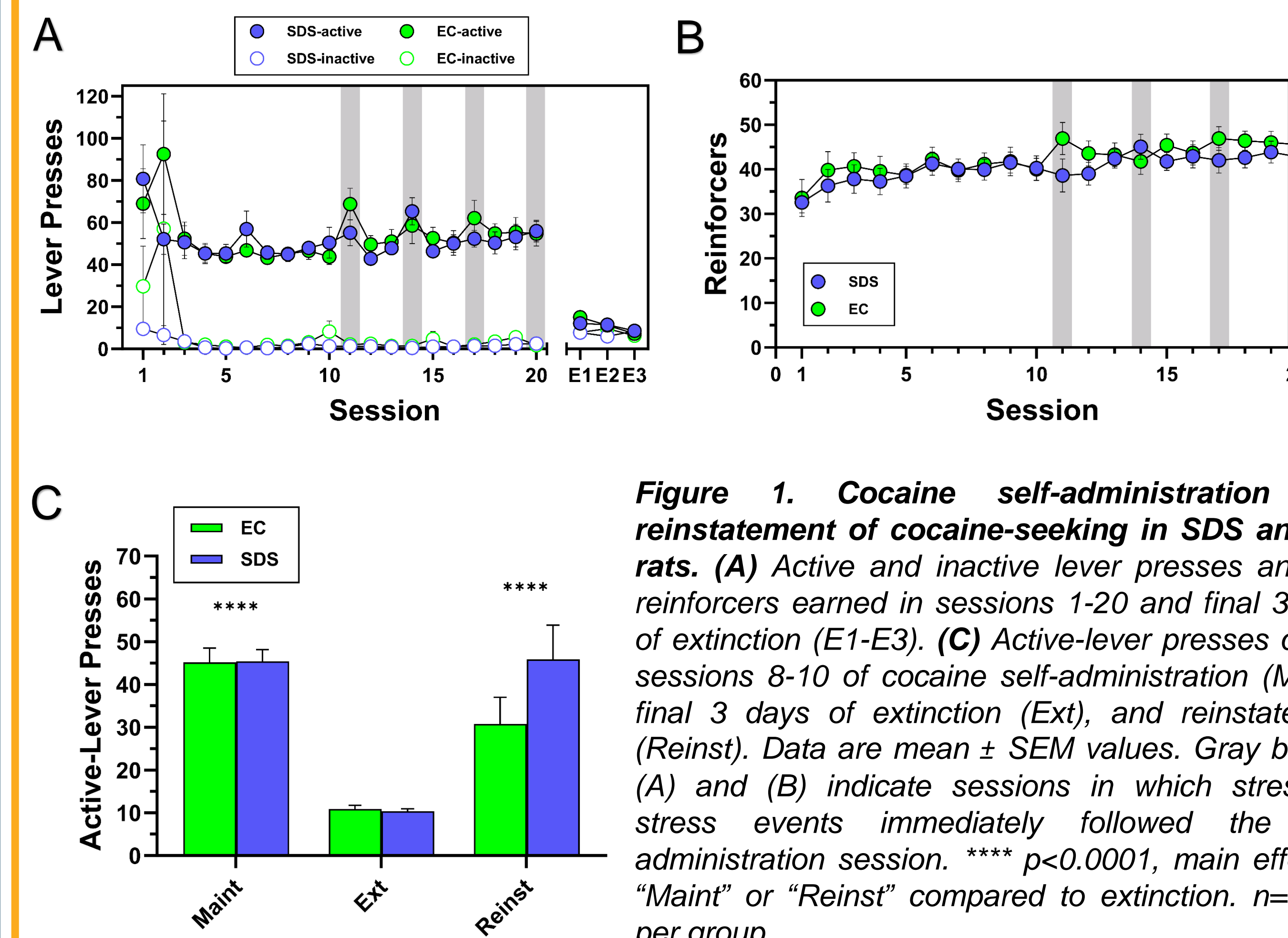
\*These authors contributed equally to this work

## Introduction

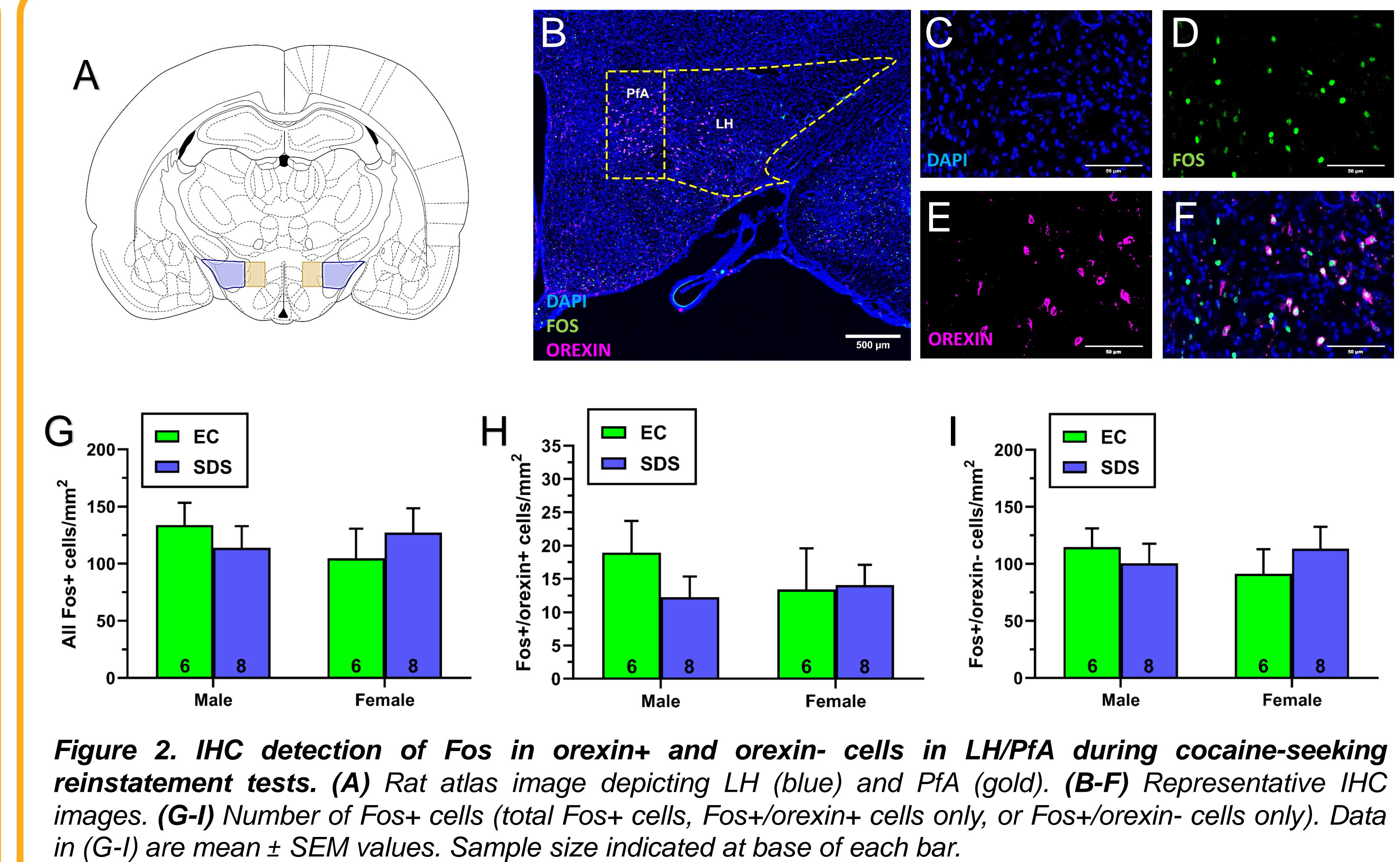
Cocaine Use Disorder persists as a significant public health concern in the United States, with recent epidemiological data indicating that rates of cocaine-involved overdose deaths are rising. Stress can precipitate cocaine craving and trigger relapse in cocaine users, but the underlying neural circuitry by which stressors drive cocaine seeking is not completely understood. Our laboratory has recently discovered that Fos expression within the rostralateral subregion of the periaqueductal gray (rIPAG) is correlated with psychosocial stress-induced cocaine-seeking behavior in rats. Neuroanatomical evidence has revealed dense reciprocal connectivity between the rIPAG and the lateral hypothalamus (LH) and neighboring perifornical area (PFA), two brain regions previously implicated in drug-seeking behaviors. However, whether activity within the LH/PfA is associated specifically with psychosocial stress-induced cocaine seeking has not been previously explored. In the present study, we used Fos immunohistochemistry to examine whether neural activation in the LH/PfA of male and female rats was associated with psychosocial stress-induced cocaine-seeking behavioral output and/or concomitant neural activity in other brain regions of interest during a cocaine-seeking episode.

## Results: Self-Administration, Reinstatement, and LH/PfA Fos Expression

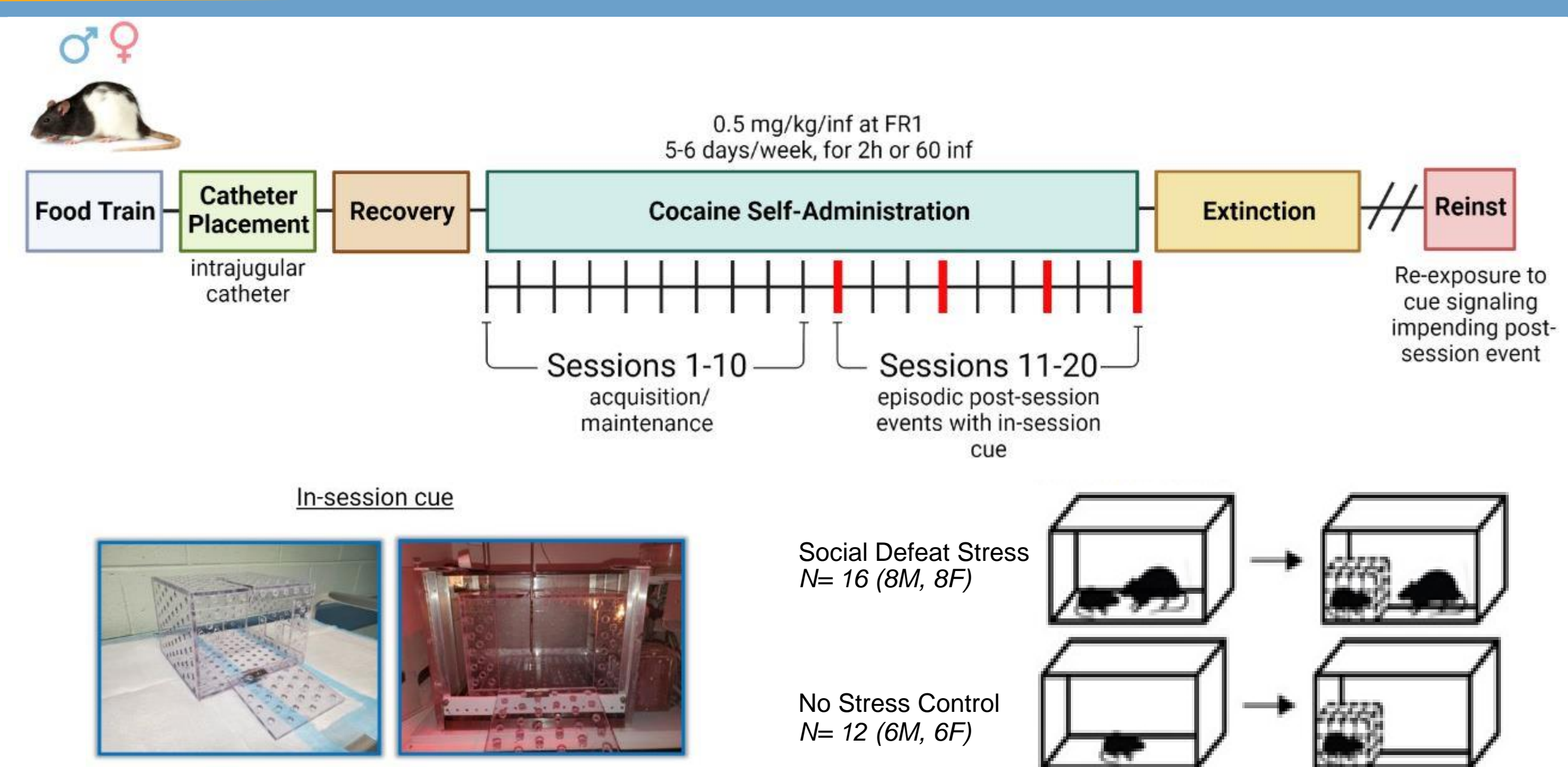
### Re-exposure to the "cue" box reinstates cocaine-seeking in SDS and EC rats



### No group differences in Fos expression during cocaine-seeking



## Methods



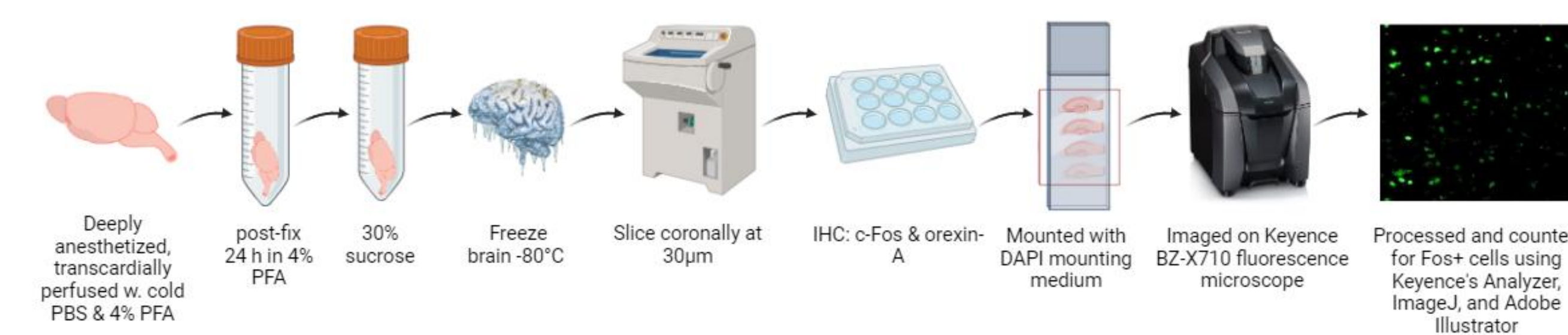
### EXPERIMENTAL GROUPS

**Social Defeat Stress (SDS):** Immediately after sessions 11, 14, 17, and 20, rats were removed from the self-administration (SA) chamber and placed into the home cage of a conspecific, same-sex aggressive Long-Evans rat until either 1) it was pinned in a submissive supine posture for 4 consecutive seconds, 2) it was bitten twice, or 3) 4 min elapsed. The rat was then placed back inside the "cue" box and returned to the resident-aggressor's home cage for 5 additional mins of "protected" threat.

**No-stress empty cage control (EC):** Rats underwent the same procedure as the SDS group with the exception that they were placed into an uninhabited resident-aggressor home cage.

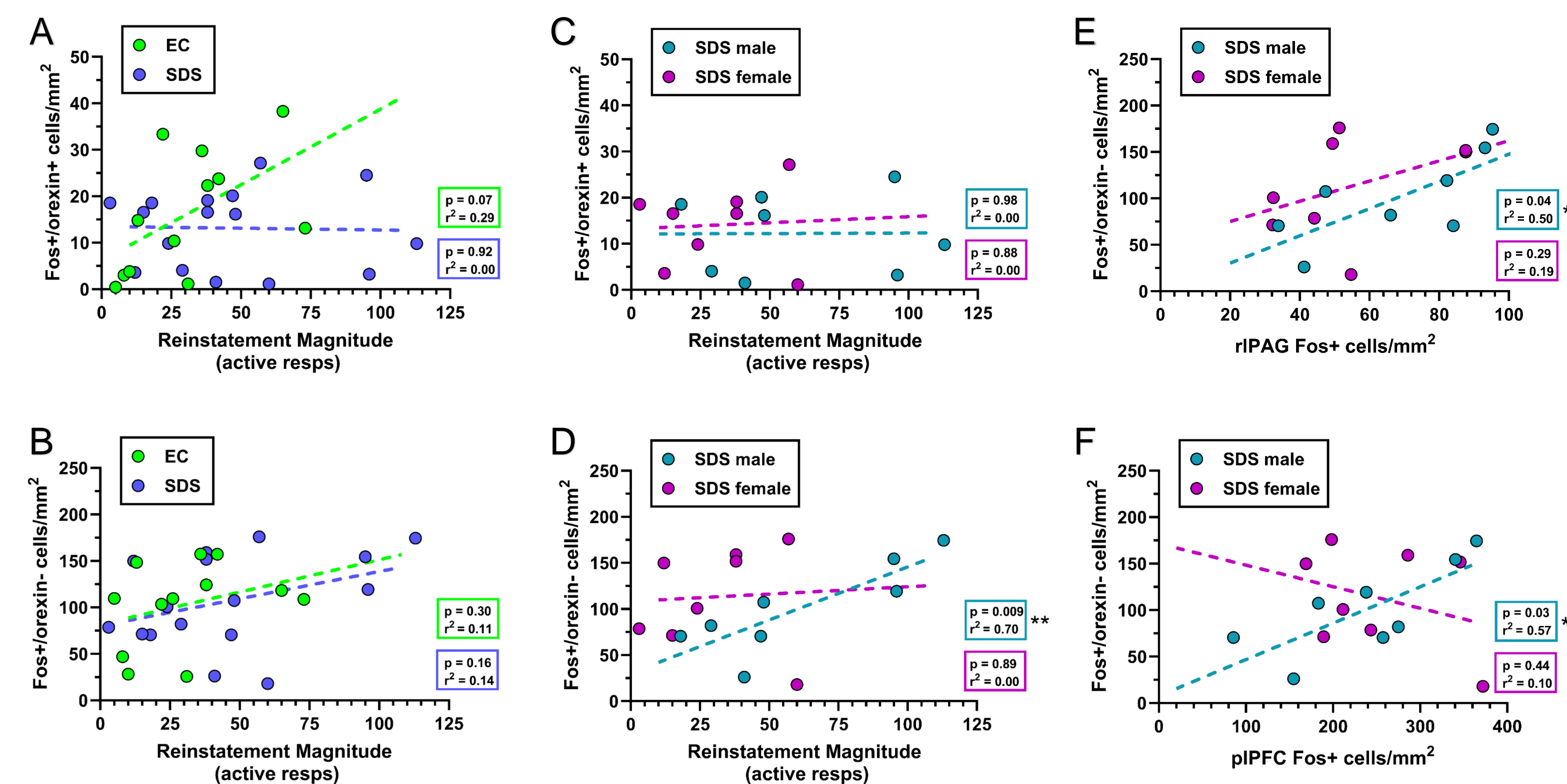
### EXTINCTION & REINSTATEMENT

Extinction sessions began on session 21 and lasted 2 h for 5-6 d/week, during which lever presses had no scheduled consequences. Extinction criteria:  $\leq 15$  active lever presses in 3 of 4 consecutive sessions. The day after criteria were met, animals were re-exposed to the "cue" box that signaled their assigned impending post-session event and were allowed to lever-press for 2 h under extinction conditions. Animals were sacrificed immediately after the session.



## Results: Correlation Analyses

### Fos expression in LH/PfA non-orexinergic cells correlates with cocaine-seeking behavior and Fos expression in rIPAG and pIPFC, but only in SDS male rats



**Figure 3. Correlation analyses for LH/PfA Fos expression with cocaine-seeking magnitude and Fos expression in rIPAG or pIPFC.** (A-B) Correlations in EC or SDS rats between cocaine-seeking and Fos expression in (A) orexin+ cells or (B) orexin- cells of LH/PfA ( $n = 12-16$ /group). (C-D) Correlations in SDS males or females between cocaine-seeking and Fos expression in (C) orexin+ cells or (D) orexin- cells in LH/PfA ( $n = 8$ /group). (E-F) Correlations in SDS males or females between Fos expression in LH/PfA orexin- cells and Fos expression in (E) rIPAG or (F) pIPFC ( $n = 8$ /group).

## Summary

- No robust group or sex differences in LH/PfA activity when cocaine-seeking is elicited via a stress-predictive vs. cocaine-predictive cue
- Psychosocial stress-induced cocaine-seeking behavior is correlated with activation of non-orexin LH/PfA cells in males
- Activity of non-orexin LH/PfA cells during psychosocial stress-induced cocaine seeking is correlated with neural activity in rIPAG and pIPFC in males
- These findings indicate the potential engagement of a neural circuit involving pIPFC, LH/PfA, and rIPAG during stress-induced cocaine-seeking behavior in males

## Support & Acknowledgements

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