Assessing Behavioral and Neurological Validity of novel Social Instability Stress Model (SIS) and the counter effects of Fluoxetine

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Background

Major Depressive Disorder (MDD) is a heterogeneous and complex disease affecting nearly 300 million people each year. Previous findings suggest that many cases of depression are linked to deregulation of the hypothalamic-pituitary-adrenal axis (HPA), an intricate set of interacting neural nuclei and endocrine glands that result in the release of the stress hormone corticosterone.

However, little research has been done to examine the effects of chronic stress on female mice because their estrus cycle adds another area of variability. In order to identify potential sex differences between male and female mice, we exposed both male and female mice to chronic administration and examined the effects on gene expression in dorsal and ventral dentate in the hippocampus and in the hypothalamus

In addition, previous preclinical models of depression have excluded females entirely or have not been compatible for female rodents.

In my research, I will be observing the novel Social Instability Model of depression which involves subjecting mice to unstable social hierarchies followed by treatment of the antidepressant fluoxetine. This research we determine whether this social model is a pharmacologically and behavioral effective model of depression for male and female mice.

Methods: SIS Model and Treatment

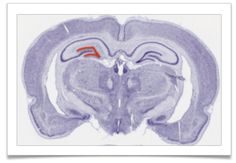
Subjects: Adult male and female C57BL/6J mice.

Treatment	Number
VEH/ FLX	40
VEH/CNTRL	40
CORT/FLX	40
CORT/CNTRL	40

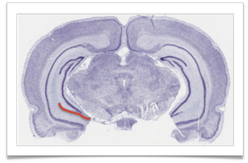
Treatment: Subjects in CORT group had cage composition changed twice a week in which mice are housed with new cage mates and a new cage during each cage composition change. VEH mice had cages changed but remained with the same cage mates.

IHC and training:

- **Perfusion** — Animals are perfused transcardially and brains are stored in PFA then in NaN3
- **Brain Collection** — Serial sections of brain are cut on a cytostat and collected through the entire hypothalamus
- **Staining** — Brains are stained for either ki67 (marker for cell proliferation) or DCX (marker of differentiation) cells
- **Cell counting** — Number of ki67+ cells and DCX+ cells in the DG are counted. Number of mature DCX counted. Maturation index (MI) calculated.

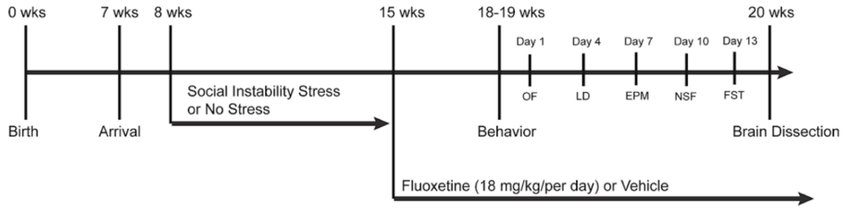


Dorsal DG



Ventral DG

Timeline



Behavioral Analysis

Open Field *Light Dark Emergence*

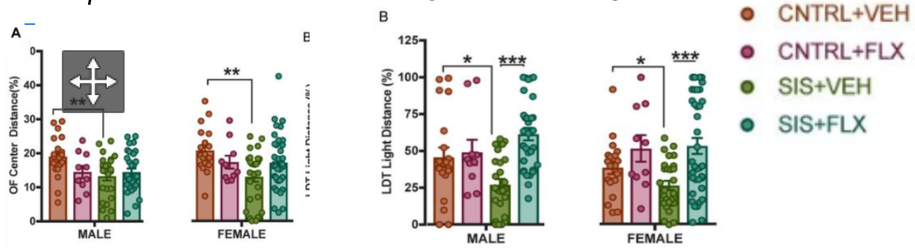


Figure 1A: SIS stress decreases OF center time in both sexes. SIS stress decreases LDT Light Distance in both sexes which is reversed by FLX. **CNTRL+VEH vsSIS+VEH, p=0.0041 in males and **CNTRL+VEH vsSIS+VEH, p=0.0019 in females. n males, **CNTRL+VEHvsSIS+VEH (p=0.029) and ***SIS+VEHvsSIS+FLX (p<0.0001). In females, *CNTRL+VEHvsSIS+VEH (p=0.0471) and ***SIS+VEHvsSIS+FLX (p<0.0001)

Novelty Suppressed Feeding

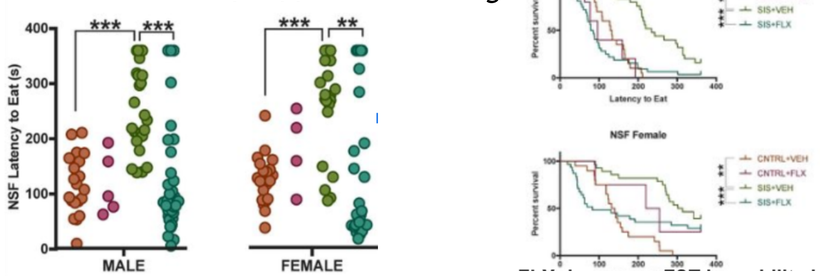
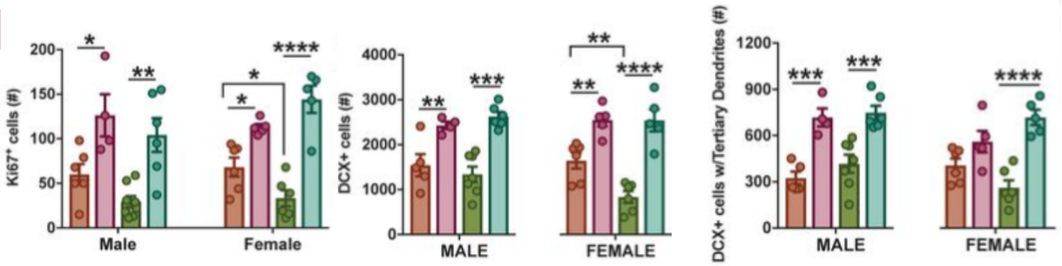


Figure 1C: SIS stress increases NSF latency to eat which is reversed by FLX. In males, ***CNTRL+VEHvsCNTRL+FlX (x2(1)= 33.7, p<0.0001) and ***CNTRL+FLXvsSIS+FLX (x2(1)= 25.1, p<0.0001). In females, ***CNTRL+VEHvsCNTRL+FlX (x2(1)= 29.5, p<0.0001) and **CNTRL+FLXvsSIS+FLX (x2(1)= 4.09, p=0.040).

Neurological Results



Conclusion (cont.)

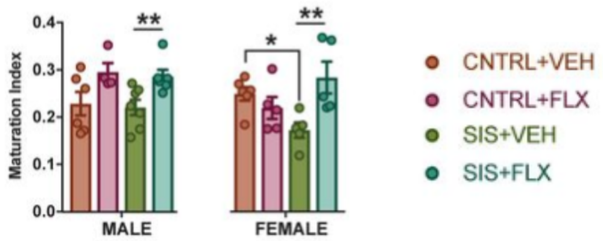


Figure 2A/C: FLX increases FlX increases ki67+ count and DCX+ count in males and females. SIS decreases cell count in females. FLX increases mature DCX+ count in males and females. FLX increases maturation index index in SIS treated male and female mice. SIS decreases maturation index in female mice.

Conclusion

Summary

- Hypothesis is partially proved
  - SIS does increase negative valence behaviors in both sexes which will be reversed by chronic FLX treatment
  - SIS does decrease adult hippocampal neurogenesis in FEMALES while FLX will increase adult hippocampal neurogenesis in both sexes
- Significance
  - A new preclinical paradigm is successful in inducing behavioral & neurological effects for females
  - A better understanding of mechanisms of depression will follow

Future Directions:

1) Testing other SSRIs for similar results
2) Testing serotonin-norepinephrine reuptake Inhibitors (SNRIs) with the SIS Model
3) Comparing and contrasting SIS directly to other stress paradigms
4) Determine the effect of estrous cycle of SIS behavior

References and Acknowledgements

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