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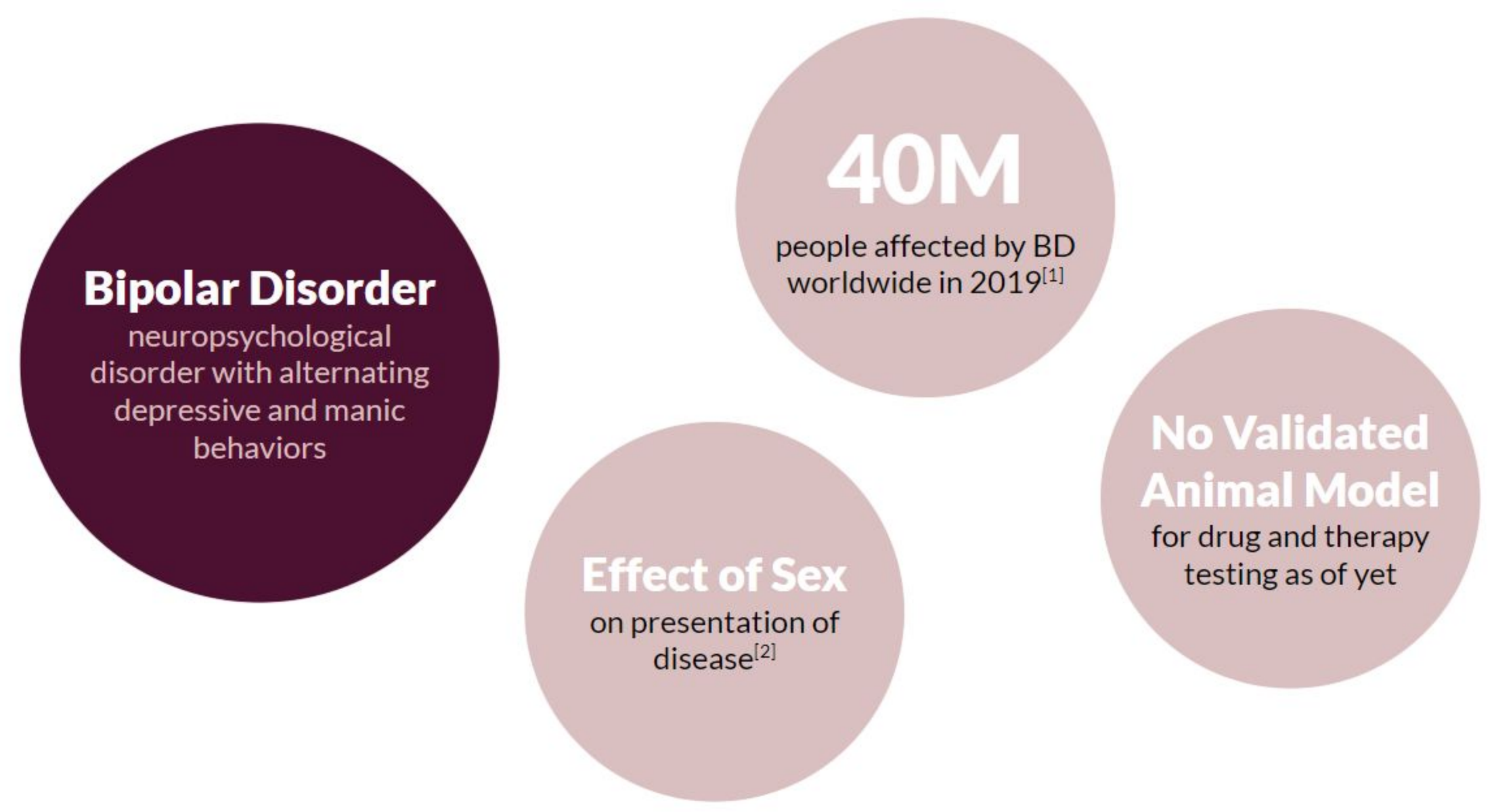
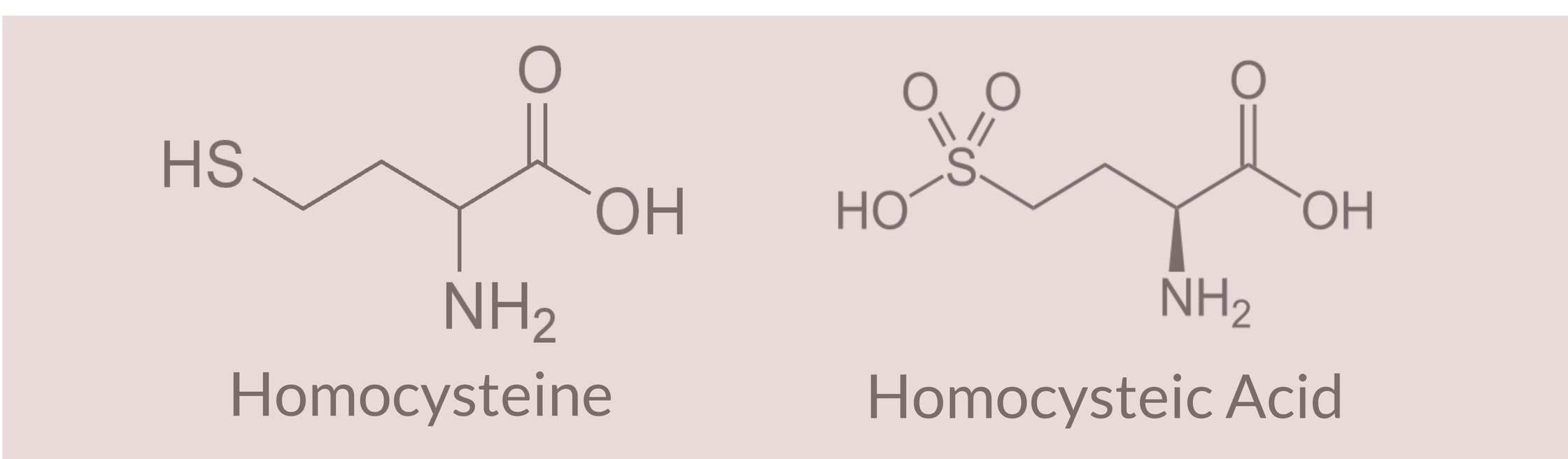
Background


Bipolar Disorder
neuropsychological disorder with alternating depressive and manic behaviors
40M
people affected by BD worldwide in 2019[1]
Effect of Sex
on presentation of disease[2]
No Validated Animal Model
for drug and therapy testing as of yet

- **High levels of homocysteine** associated with multiple mood disorders including BD[3]
- **Homocysteic acid (HCA)**: oxidized form of homocysteine
  - Endogenous **NMDA receptor agonist**
- NMDA receptors have **altered function** in those with BD

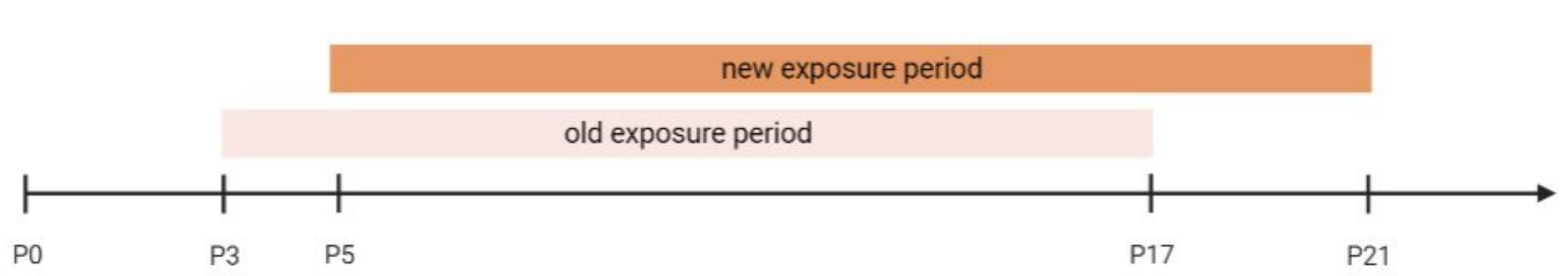
Therefore, it was reasoned that exposure to HCA may induce a BD phenotype in an animal model



- Chase lab found **prepubescent exposure to HCA in rats** leads to phenotype with **mixed manic/depressive state** and behaviors consistent with those observed in BD[4]
- Multiple cohorts showed **consistent behavioral results** and **changes in gene expression** in the prefrontal cortex that are improperly regulated in BD[5,6]
- **Lithium**, a medication commonly taken by those people experiencing BD in order to reduce severity and frequency of manic behaviors, was found to similarly **reduce manic behaviors** in the novel rat model[7]

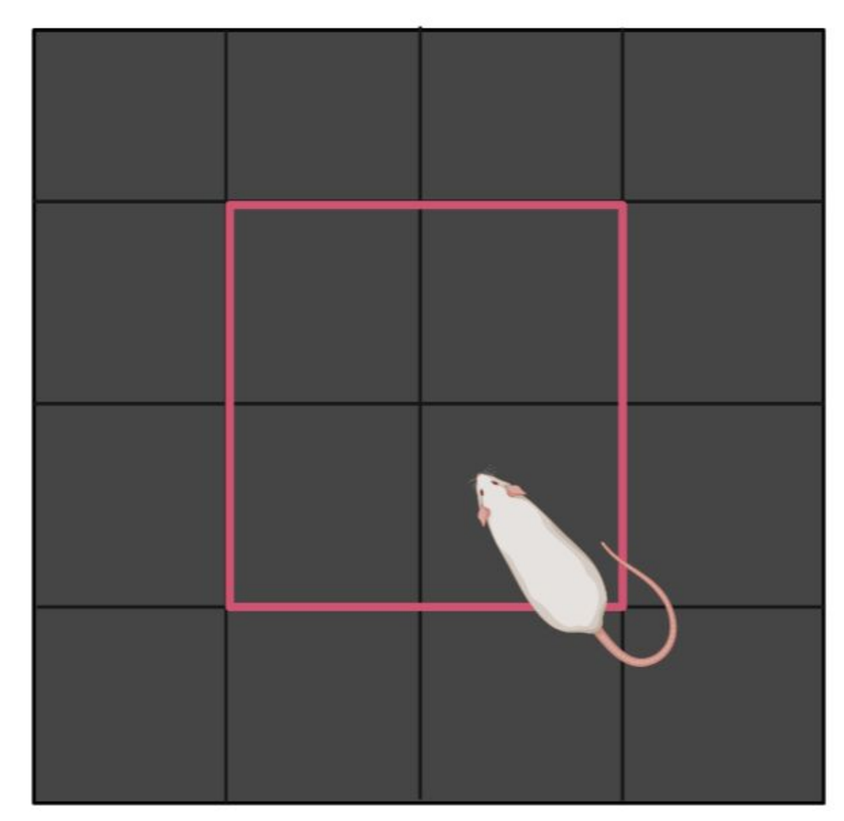
Exposure Period Hypothesis

While the rat model displayed great reproducibility across cohorts, changes were observed in the summer 2021 cohort such that more manic behaviors were displayed relative to depressive behaviors. Further investigation revealed pups within this cohort were 1.3-2.0 g heavier than previous cohorts ($F_{1,39}$=17.1, p<0.001) on the first day of injection, suggesting either the 2021 pups were around 2 days older than indicated by the vendor or they exhibited a faster growth rate than previous cohorts.



Our current study is focused on measuring behavior in rats given daily HCA injections beginning postnatal day 5 (P5), rather than the previous postnatal day 3 (P3), in order to determine the effects of a delayed treatment period. **We hypothesize this adjusted exposure window may match that of the 2021 cohort and thus produce similar resulting behaviors.** Ultimately, this work will allow us to understand how timing of HCA exposure impacts the associated behavioral changes and may provide a better understanding of the variations in behavior associated with BD.

Results



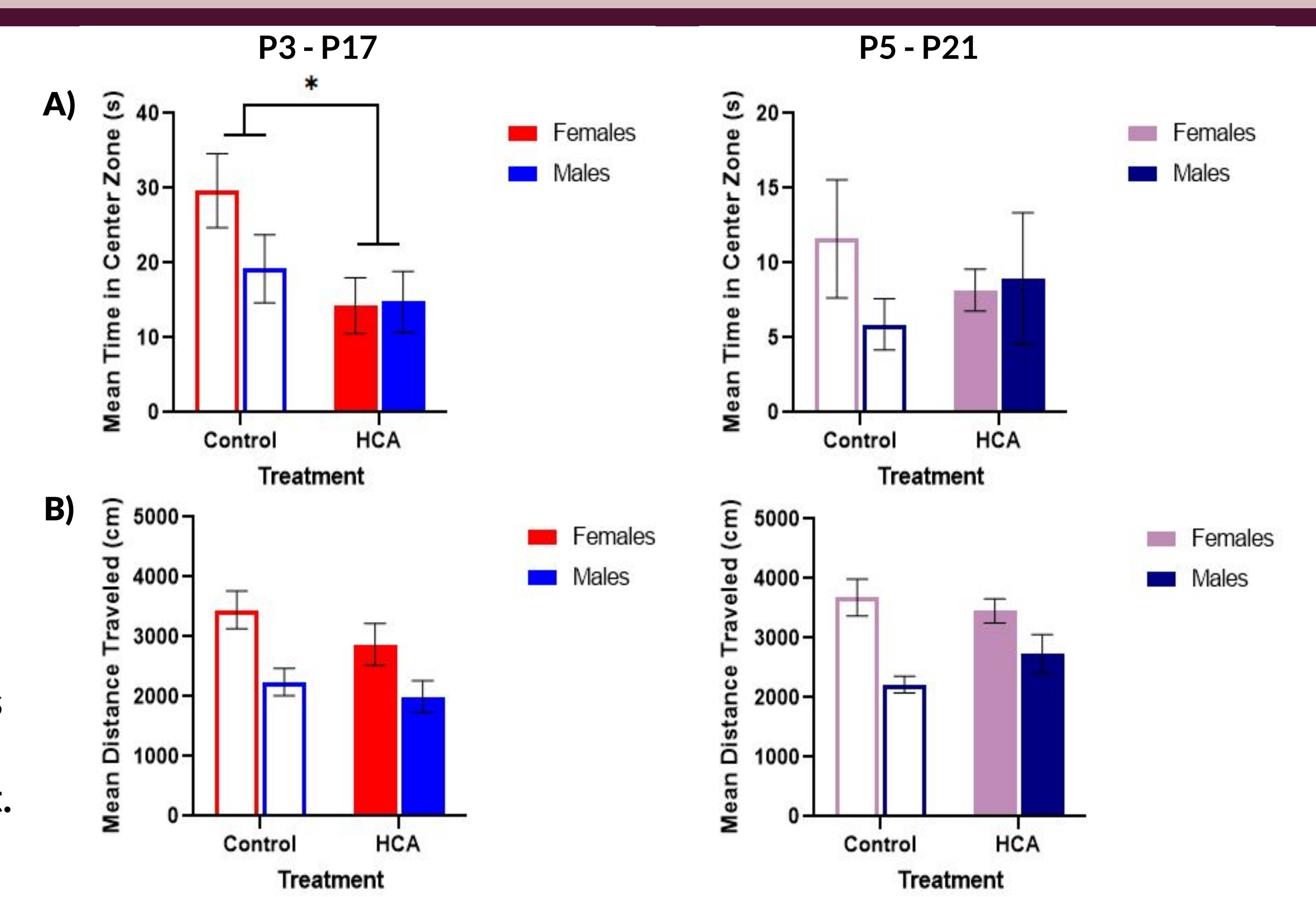
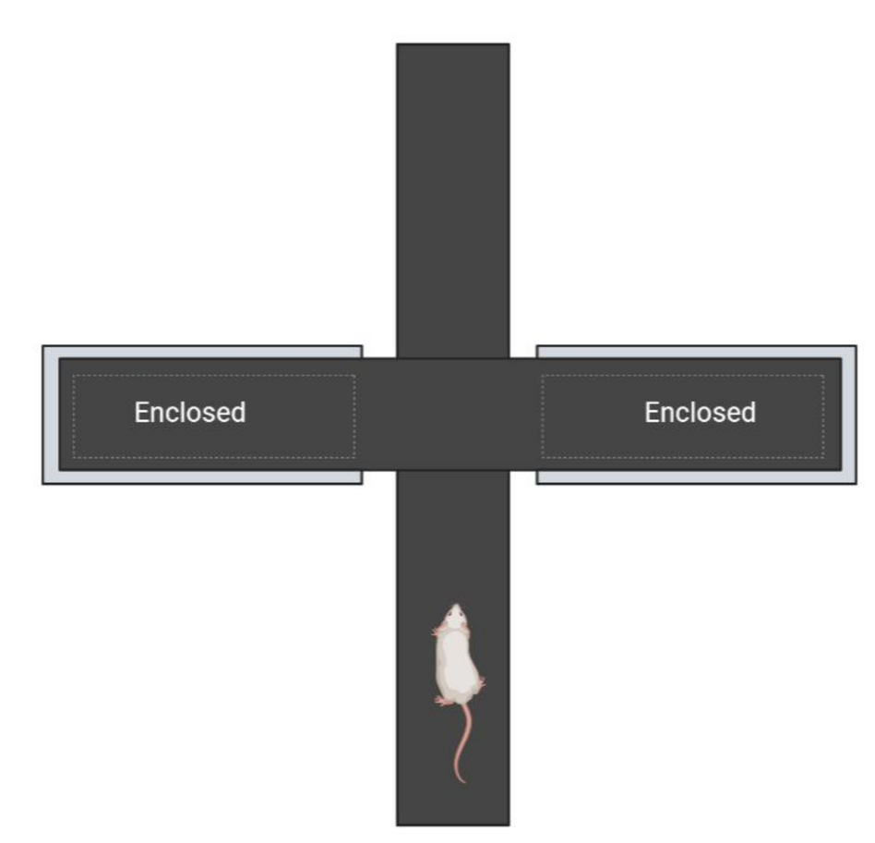


Figure 1. Unlike earlier exposure to HCA (P3-P17), later exposure (P5-P21) does not impact time spent in center zone of open field test.

A) P3-P17 exposure leads to significantly less time spent in center zone for both sexes (p=0.029; F=5.223) compared to no significant effect of treatment (p=0.953; F=0.004) or treatment by sex (p=0.272; F=1.246) for P5-P21 exposure. **B)** Mean distance traveled was not significant by treatment for either early (p= 0.177; F=1.900) or late exposure (p=0.590; F=0.296).



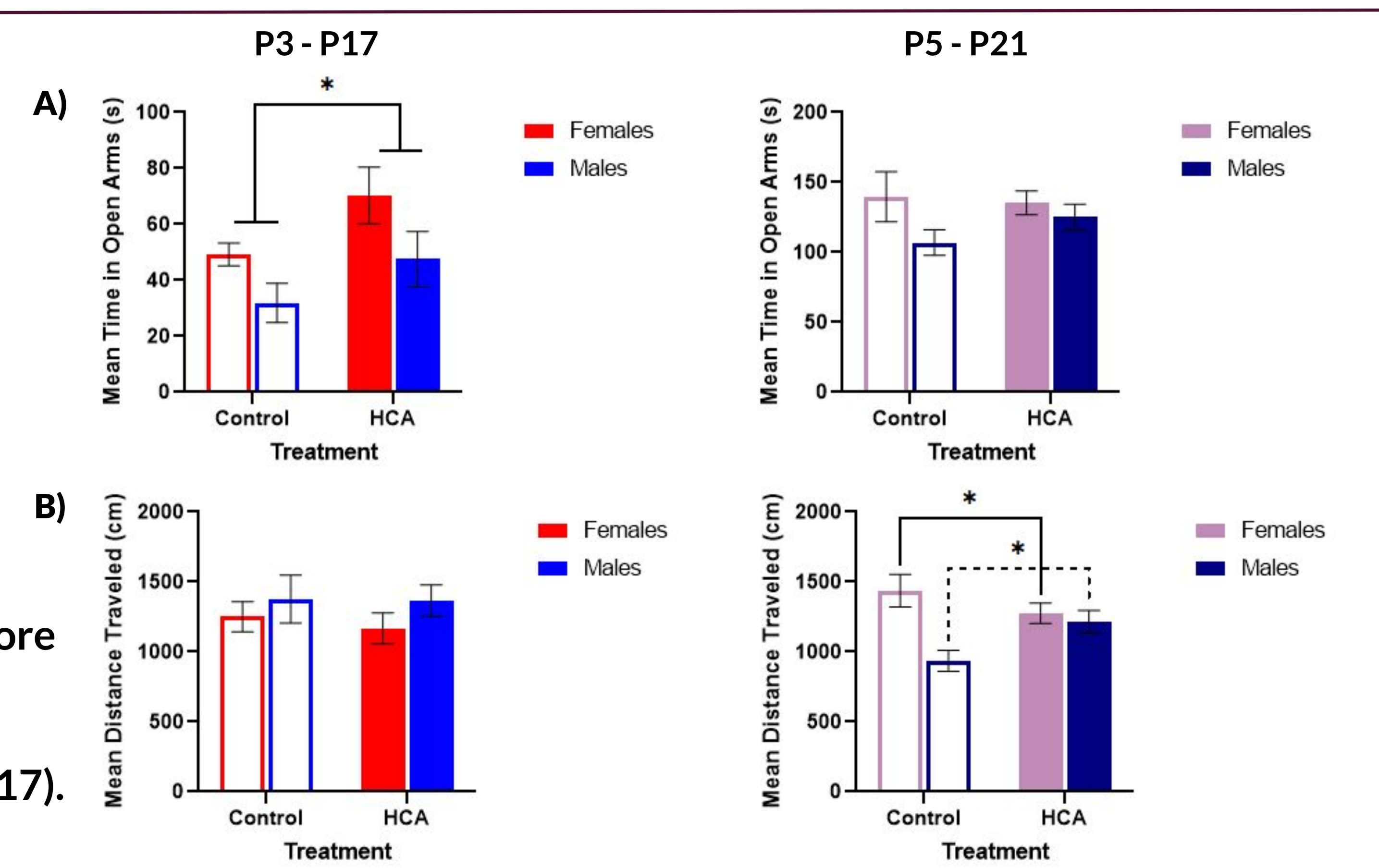


Figure 2. Delayed exposure (P5-P21) does not lead to more time spent in open arms of elevated plus maze, unlike earlier HCA exposure (P3-P17).

A) Mean time spent in open arms of elevated plus maze was significant by treatment (p=0.036; F=4.744) for an early exposure period but not late (p=0.537; F=0.389). **B)** While insignificant for the early exposure period (p=0.717; F=0.134), mean distance traveled in the maze was significant for treatment by sex (p=0.017; F=6.278) in delayed exposure period.

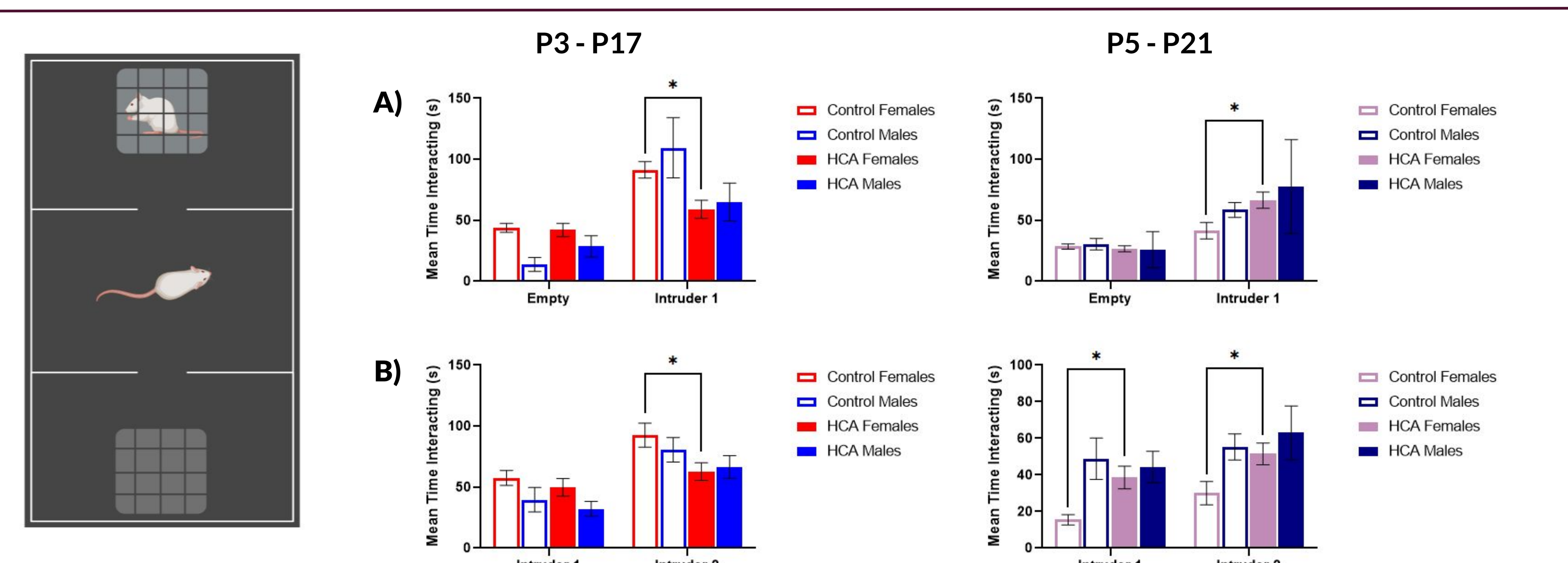


Figure 3. HCA treatment affects female behavior in the social interaction test; earlier HCA exposure (P3-P17) leads to less time socializing while delayed exposure (P5-P21) leads to more time socializing.

A) First phase of the test revealed female mean time socializing with first intruder rat was decreased in earlier exposed rats (p=0.005; F=10.304) and increased in later exposed rats (p=0.039; F=4.940). **B)** Second phase again showed less female mean time socializing in earlier HCA-treated rats (p=0.023; F=6.231) and more socializing with both the first (p=0.030; F=5.562) and second intruder (p=0.048; F=4.508).

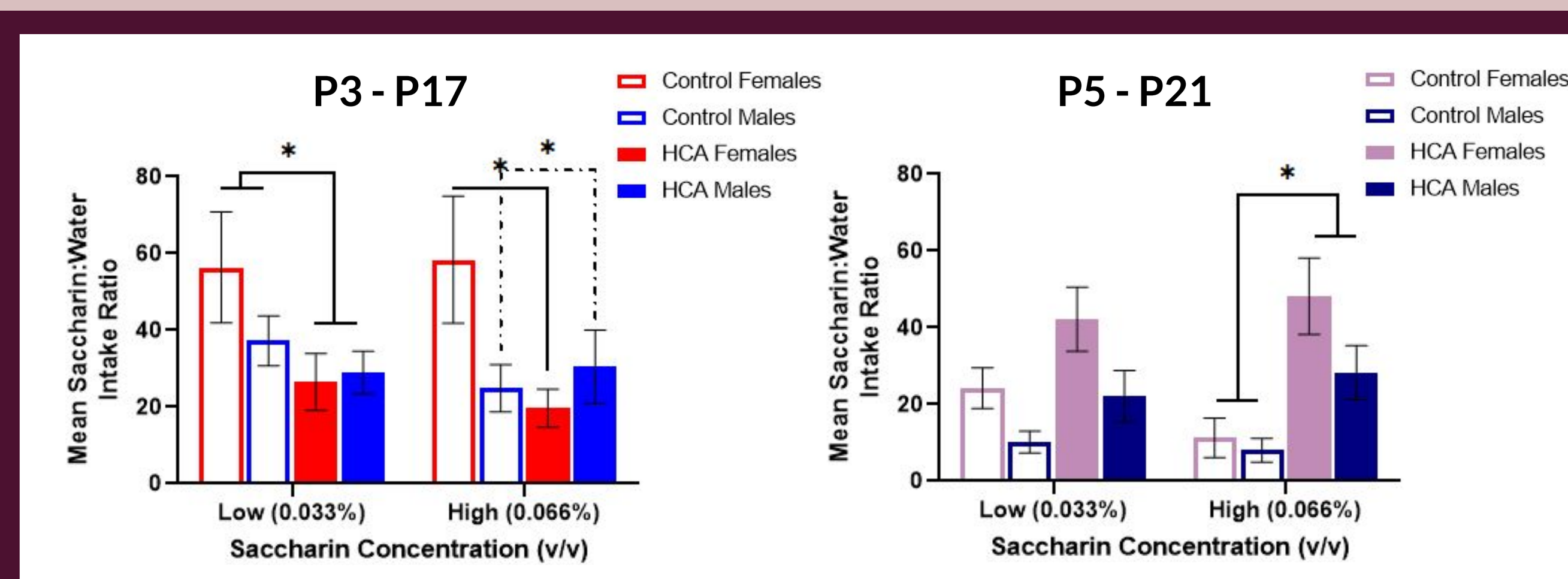


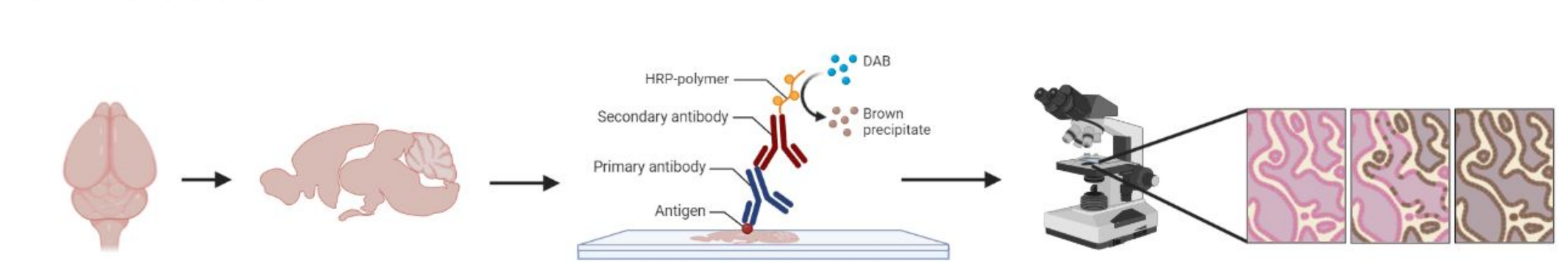
Figure 4. Early HCA exposure leads to decreased consumption of saccharin-sweetened water while later exposure leads to increased consumption. Mean ratio of 0.033% saccharin-sweetened water to water intake shows P3-P17 HCA-treated animals consumed less saccharin compared to controls (p=0.029; F=5.193). Mean ratio for 0.066% saccharin water to water intake shows greater consumption by HCA-treated animals in later exposure period (p=0.004; F=9.885).

Conclusions

HCA Exposure Period	Open Field Test	Elevated Plus Maze	Social Interaction Test	Saccharin Preference Test
P3-P17	Anxious behavior	Risk-taking behavior	Decreased socialization	Anhedonic behavior
P5-P21	No anxious behavior	No risk-taking behavior	Increased socialization	No anhedonic behavior

Future Directions

- Circadian rhythm analysis
- Immunohistochemistry to identify molecular markers of BD in brain tissue



References

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