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Effect of Delaying HCA Exposure on the Development of Manic/ Depressive Behaviors in Sprague Dawley Rats

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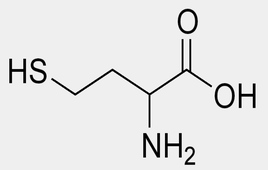
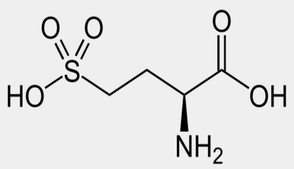
Background

Bipolar disorder (BD) is a neuropsychological disorder characterized by alternating periods of depressive and manic behaviors. The World Health Organization (WHO), citing the Global Health Data Exchange report of the Institute of Health Metrics and Evaluation, estimated 40 million people worldwide were experiencing this disorder in 2019 (1). Widespread prevalence of BD has led to therapeutic advances, however a validated and standardized animal model has yet to be introduced to the field. Research in the Chase lab aims to test a potential model to fill this need.

High levels of homocysteine, a methionine metabolism product, are associated with multiple mood disorders including BD (2). Homocysteine is readily oxidized to homocysteic acid (HCA), an endogenous NMDA receptor agonist in cells. It was therefore reasoned that exposure to HCA may induce a mood disorder phenotype thus providing an animal model.



Homocysteine



Homocysteic Acid

In 2012, the Chase lab found that early exposure to HCA led to a phenotype with a mixed manic/depressive state and behaviors consistent with those commonly observed in individuals with bipolar disorder (3). Multiple cohorts of these rats were tested and consistently displayed this phenotype as well as changes in gene expression in the prefrontal cortex that are also improperly regulated in BD (4,5). 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, providing evidence for the model's predictive validity (6).

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, rather than the previous postnatal day 3, 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 bipolar disorder.

Differences in Weight Gains between Treatment and Control Rats

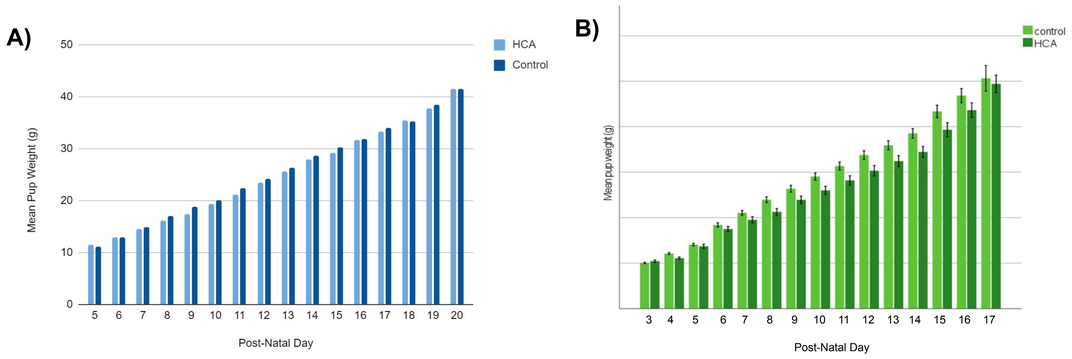


Figure 1. Comparison of mean weight gains between HCA-treated and control rats reveal no statistically significant differences. A) Data from 2023: light blue indicates mean weight of HCA-treated rats and dark blue indicates mean weight of control rats from postnatal days 5-20 showing no significant differences in weight gain between the two groups ($F=0.832$, $p=0.636$). B) Data from 2015: light green indicates mean weight of HCA-treated rats and dark green indicates mean weight of control rats from postnatal days 3-17 showing significant interaction in weight gain over time and treatment ($F_{15,504}=1.826$, $p=0.032$).

Behavioral Testing Results

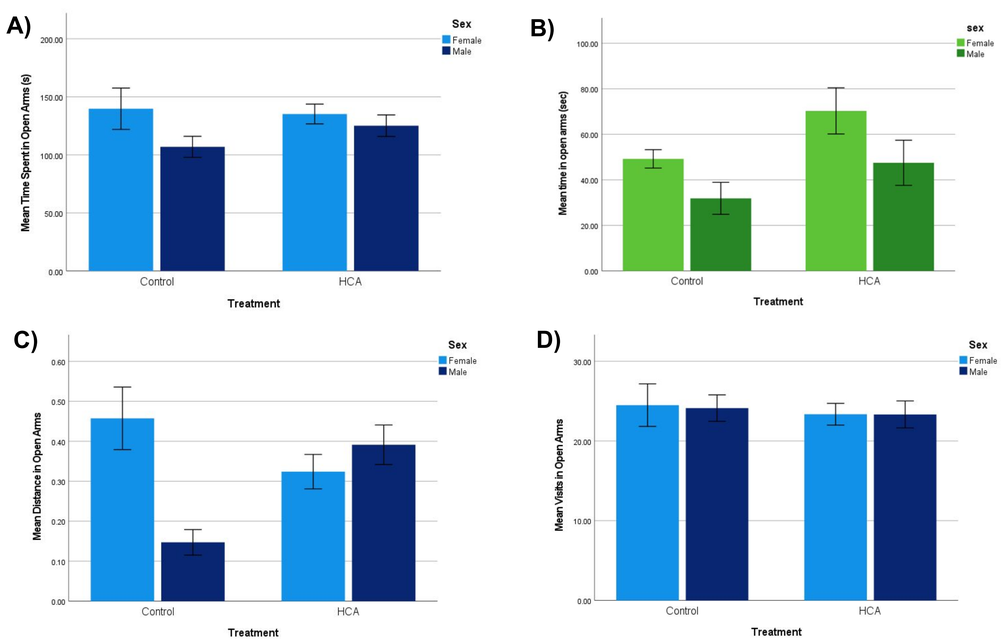


Figure 2. HCA-treated rats show little difference in risk-taking behaviors compared to control rats in elevated plus maze testing. Rats were placed individually into the maze for 5 minutes and activity was recorded. Time spent, distance covered, and visits made to open arms were compared between treatments and sexes. **A)** HCA-treatment was not found to predict statistically significant differences in time spent in open arms ($F=0.389$, $p=0.537$) nor did sex impact time spent in open arms ($F=0.389$, $p=0.537$). **B)** Spring 2015 data: HCA-treatment was not found to predict led to statistically significant increases in time spent in open arms ($F=1.826$, $p=0.032$). **C)** Treated rats showed no statistically significant differences in distance spent in open arms ($F=1.130$, $p=0.295$) however sex ($F=5.445$, $p=0.026$) and sex by treatment ($F=13.131$, $p<0.001$) was significant with control females going longer distances in the open arms than control males and HCA-treated females going shorter distances than HCA-treated males. **D)** Treated rats displayed no statistically significant differences in visits to open arms ($F=0.286$, $p=0.597$) no matter the sex ($F=0.012$, $p=0.913$).

Elevated plus testing is done to assess risk taking behaviors in rats. Generally, rats spend a majority of time in the closed arms of the maze, but manic behavior caused by HCA treatment can lead to rats spending more time in the open arm portion, indicating risk-taking behaviors.

Conclusions

- The weight gain of HCA-treated rats was not found to significantly differ from that of control rats.
- We observed that HCA treatment in Sprague Dawley rats from postnatal day 5-21 leads to little change in risk taking behavior as seen in the results of elevated plus maze testing.

Future Directions

- Throughout the rest of the semester, three more behavioral tests will be administered to determine overall trends in behavior of the two cohorts (control versus HCA treatment)
  - Behavioral tests include open field test, marble burying test for OCD-like tendencies, and re-test of saccharin preference testing due to technical difficulties with scale used to determine amount of water drank each day
- Cohort results will continue to be compared to those of previous cohorts in which HCA exposure was earlier to allow for conclusions to be made on impact, if any, of a delayed exposure period

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