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Exploring the Relationship between Bipolar Disorder, Alcohol Use, and Obsessive Compulsive Disorder in the HCA Animal Model

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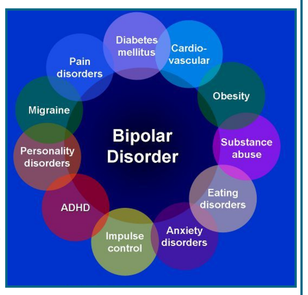
Background: Bipolar Disorder and the HCA Animal Model

- It is becoming increasingly apparent that symptoms of and comorbidities associated with bipolar disorder can vary between men and women.
- Recent research has shown that men diagnosed with bipolar disorder are more likely to exhibit alcohol use disorders and obsessive compulsive behaviors while women have a higher incidence of panic disorder.
- Homocysteic Acid (HCA) is a glutamate analog that has been demonstrated to induce a mixed manic/depressive state in rats when administered during a critical phase in development (P3-P21).



Hypothesis

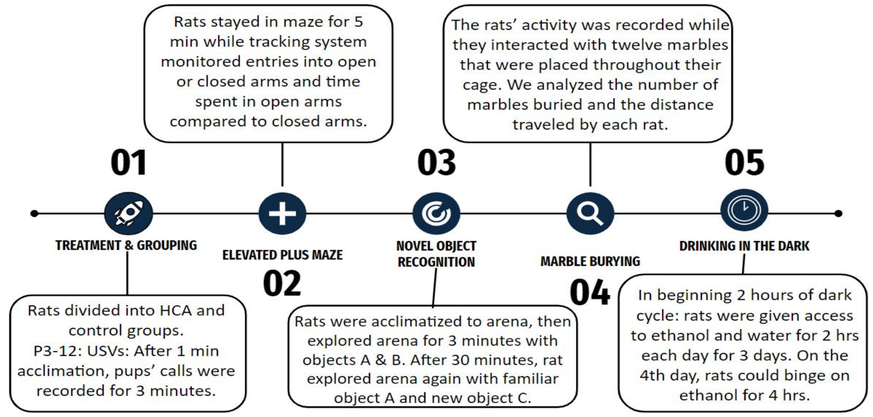
The present study aimed to replicate findings from previous studies of the HCA animal model, while also investigating the effects of HCA on alcohol use, obsessive-compulsive behaviors, and measures of stress in a sex-dependent manner.

This study will allow us to develop a more comprehensive understanding of the ability of the HCA animal model to replicate the complex phenotype of bipolar disorder.

Summary of Behavioral Assessment

Marble Burying	Repetitive/compulsive behaviors
Ultrasonic Vocalizations	Anxious behaviors
Novel Object Recognition	Memory
Elevated Plus Maze	Risk taking behaviors
Drinking in the Dark	Alcohol use

Methods



HCA Induces Manic-Like Behaviors in the Elevated Plus Maze

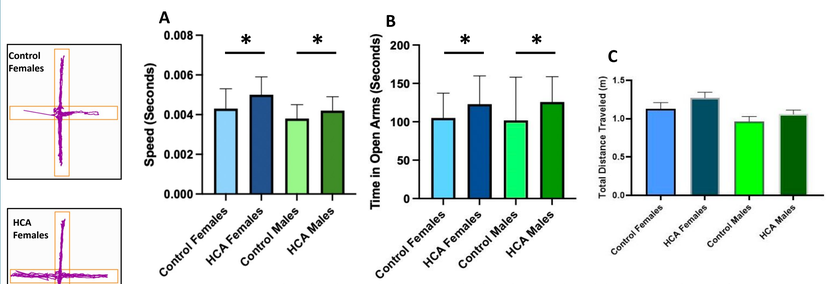


Figure 1A. Mean Speed in the Elevated Plus Maze. The female animal models were significantly faster in comparison to the males, $F(1, 35) = 7.511$, $p = 0.01$. Similarly, the HCA models were significantly faster than the controls $F(1, 35) = 5.378$, $p = 0.027$. **Figure 1B. Time Spent in the Open Arms of the Elevated Plus Maze.** The HCA treatment models spent significantly more time in the open arms than the controls, $F(1, 35) = 4.300$, $p = 0.46$. In contrast, comparison of the males and females showed no significant difference, $F(1, 35) = 0.010$, $p = 0.920$. **Figure 1C. Total Distance Traveled in the Elevated Plus Maze.** The females traveled significantly more distance within the open arms of the elevated plus maze in comparison to the males, $F(1, 35) = 7.247$, $p = 0.011$. In contrast, there was no significant difference in distance traveled between the HCA models and the controls, $F(1, 35) = 2.983$, $p = 0.094$.

HCA Did Not Induce EtOH Binge Behavior

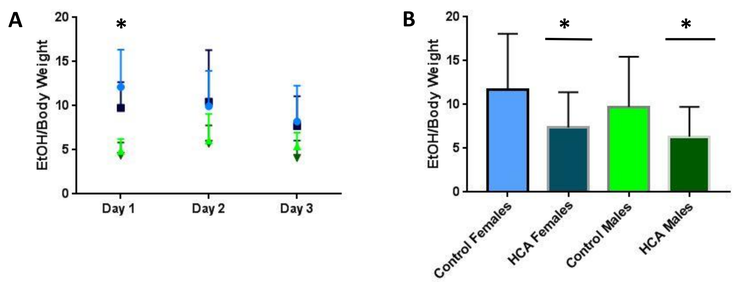
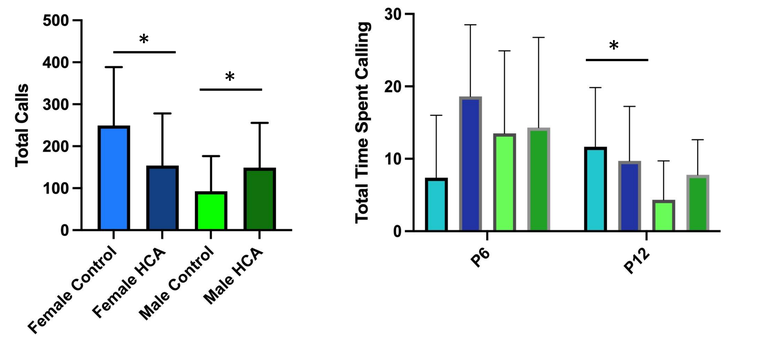


Fig. 2A Ethanol Consumed for Three Days Preceding the Binge Period. Rats slightly reduced their ethanol consumption throughout the three days $F(1) = 5.5$, $p = .025$, with females consuming more ethanol than males $F(1) = 6.6$, $p = .015$. **Fig. 2B Ethanol Consumption the Day Allotted to Binge Drink Ethanol in the Drinking in the Dark Assay.** Both female and male rats treated with HCA had a reduced desire to binge on ethanol when compared to control male and female rats $F(1) = 6.24$, $p = .017$. * indicates p<.05. ** indicates p<.01. *** indicates p<.001.

HCA Reduced USVs in Female Pups and Increased USVs in Male Pups on P12



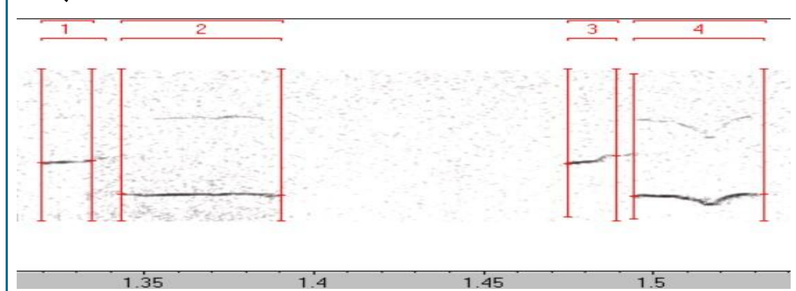


Fig. 5A Total Amount of Ultrasonic Vocalization Calls on Postnatal Day 12. On postnatal day 12, female rats called about twice as many times as male rats $F(1) = 4.75$, $p = .036$. HCA reduced the total amount of calls for female rats by about 40%, and increased the total amount of calls for male rats by about 38% $F(1) = 4.16$, $p = .049$. **Fig. 5B Total Time Spent Making USV Calls.** The total time spent calling on postnatal day six did not differ. On postnatal day 12, female rats spent about 40% more time calling than did male rats $F(1) = 4.70$, $p = .037$. * indicates p<.05. ** indicates p<.01. *** indicates p<.001. **Fig. 5C Example Ultrasonic Vocalization (USV) Call.** Lines one, two, three, and four indicate the length of the call. The frequency of the call is indicated on the Y axis.

HCA Did Not Induce Repetitive OCD Behaviors in Marble Burying

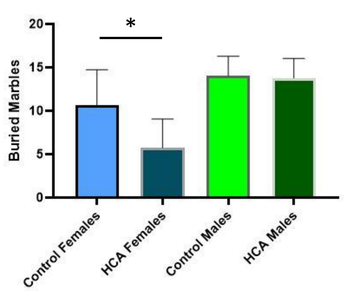


Fig. 3A Number of Buried Marbles in the Marble Burying Assay. The marble-burying assay was conducted to determine the potential comorbidity of bipolar disorder and obsessive-compulsive disorder in the HCA animal model. An overall effect of sex revealed that males buried more marbles than females $F(1) = 31.2$, $p < .001$. An interaction effect revealed that female rats treated with HCA buried fewer marbles than control rats, and HCA had no effect on the number of marbles buried for male rats $F(1) = 5.1$, $p = .03$. * indicates p<.05. ** indicates p<.01. *** indicates p<.001.

While these results deviate from our hypothesis, we can infer that the HCA females had less anxiety and less risk averse and therefore did not bury as many marbles. This is consistent with their behavior on the elevated plus maze.

HCA Decreased Preference for the Novel Object in Females

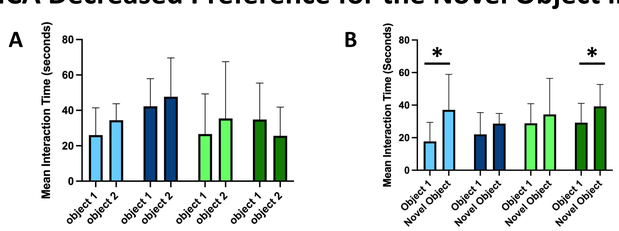


Figure 3A. To assess memory and cognition as it relates to bipolar phenotypes in rodents, the novel object recognition task assessed the mean time the rodents spent interacting (seconds) with an object between two rounds. This figure shows the mean interaction times of the rats in round 1. T-test analyses indicated that control females, HCA females, control males, and HCA males all presented no significant difference in the spent interacting between the two objects. **Figure 3B.** This figures shows the mean interaction times of the rats in round 2. T-test analyses revealed that HCA females and control males had no difference in interaction times. However, control females spent a significantly higher amount of time interacting with the novel object *t(9) = -2.256, p = 0.025.* Furthermore, HCA males exhibited a significantly higher amount of time spent interacting with the novel object *t(8) = -1.942, p = 0.044.*

Summary of Main Findings

1. The HCA model of BD contains valuable face validity for studying manic-like behavior
2. HCA impacts males and females differently, much the same way BD can present differently between the sexes.
3. As far as comorbidities, the HCA model of BD impacts behavior differently than hypothesized, thereby warranting further research.

Future Directions

1. Further research is warranted in order to continue to understand the relationship between BD and other comorbidities.
2. Previous research has implicated stress as an underlying factor in the development and progression of BD.
3. In the future, we would like to examine the role that stress plays in the development of BD and its comorbidities.

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