MEASURING NEGATIVE AFFECTIVE WITHDRAWAL IN CFW MICE: IMPLICATIONS FOR GWAS

Riley Marchin[1], Emma White[1], Abed Abbas[1], Miko Dai[3], Jay-Ho Chung[1], Sonya Farrell[1], Levi Gavette[1], Pranav Kumar[1], Connor Montgomery[2], Samuel Pelletier[2], JT Titmus[1], Olivia Peterson[1], Anna Spiro[1], JT Titmus[1], Abraham Palmer[4], Clarissa C Parker[1, 2]

[1] Program in Neuroscience, Middlebury College; [2] Department of Psychology, Middlebury College; [3] Program in Molecular Biology and Biochemistry, Middlebury College; [4] Institute for Genomic Medicine, University of California San Diego

BACKGROUND

- Negative mood states that characterize drug withdrawal are partly under genetic control and have been associated with craving and relapse to drug use in humans.

- Mice can be used to model aspects of the negative mood states associated with amphetamine (**AMP**) withdrawal and offer a number of advantages relative to studies in humans; yet conventional experimental crosses lack resolution required for fine mapping.

- We investigated negative mood states associated with acute AMP withdrawal using ~1000 highly recombinant commercially available, outbred CFW mice to conduct future QTL mapping studies.

METHODS

- CFW mice were tested in the Elevated Zero Maze (**EZM**), Porsolt Forced Swim Test (**FST**), and Sucrose Preference Test to assess changes in anxiety-like behavior, dysphoria, and anhedonia before and after 14 consecutive days of 2.5 mg/kg d-AMP administration.
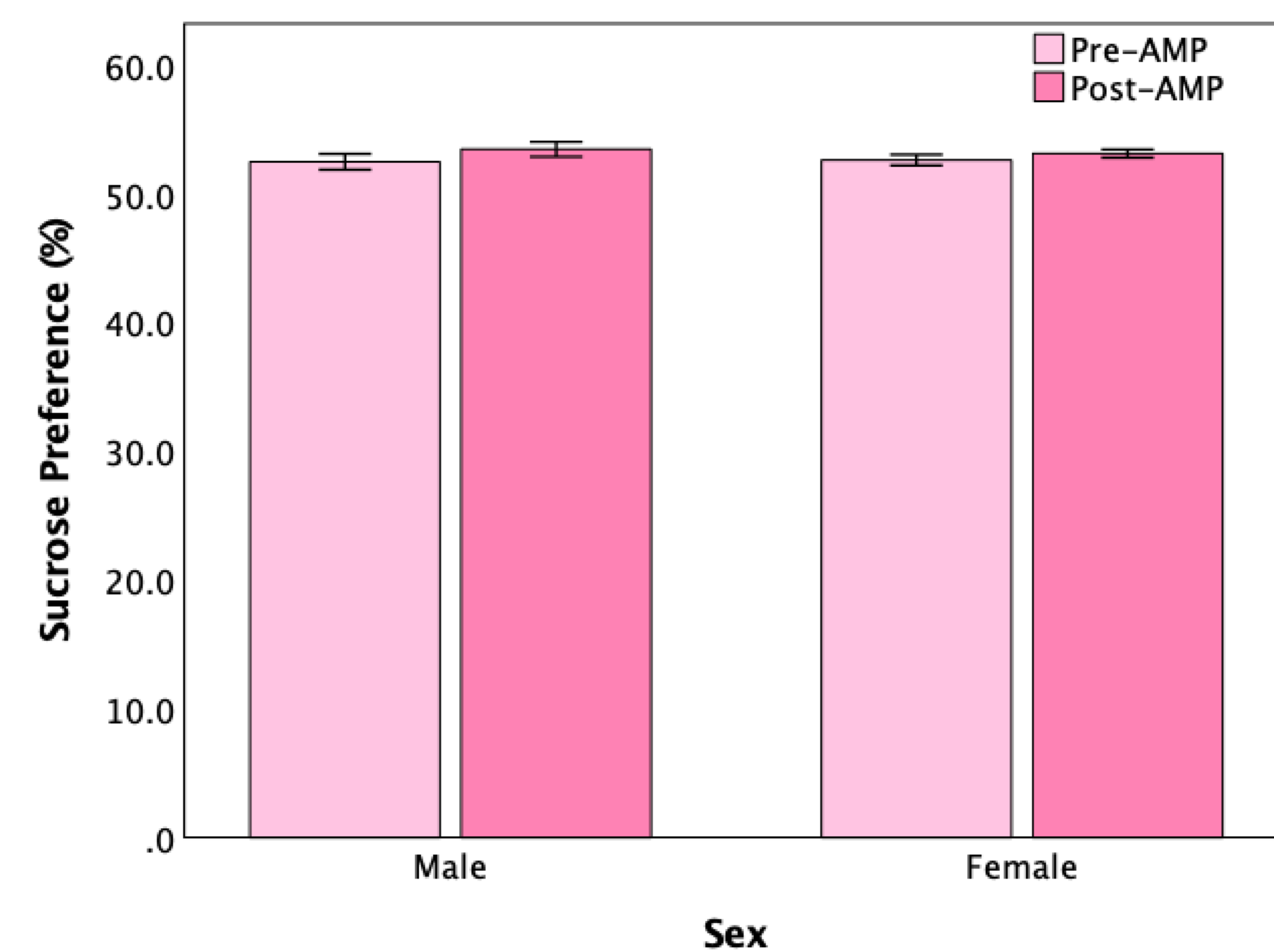

Mean LD decay rates across six mouse mapping populations

Testing Timeline
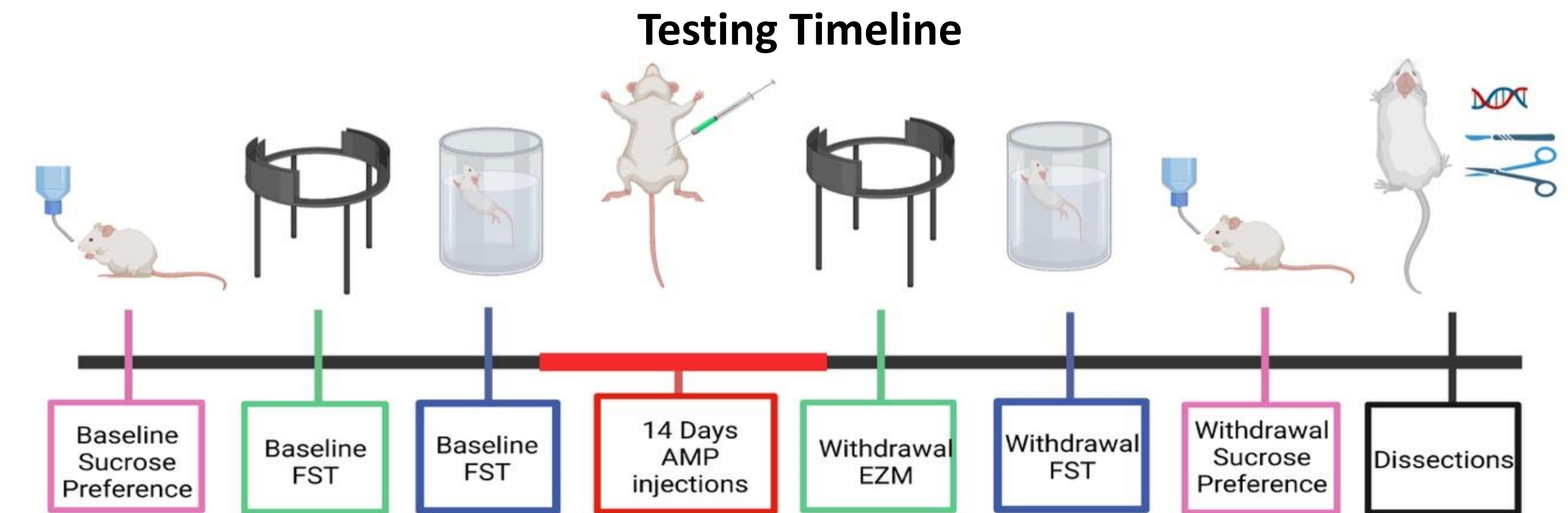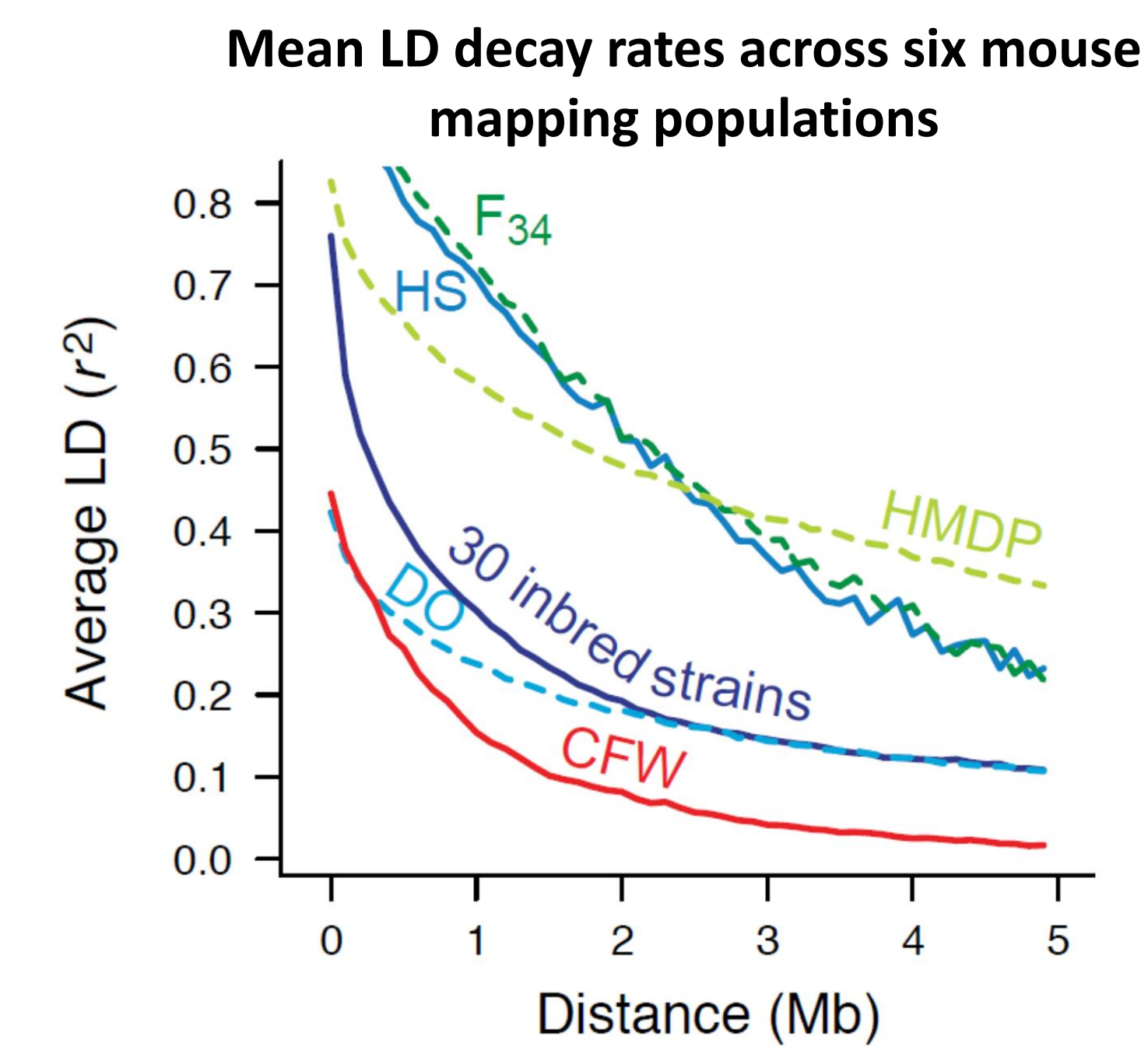
SUCROSE PREFERENCE

Figure 1. There was no significant decrease in sucrose preference during AMP withdrawal.

Figure 2. Distribution of AMP Withdrawal-Induced Changes in Sucrose Preference (N = 857).
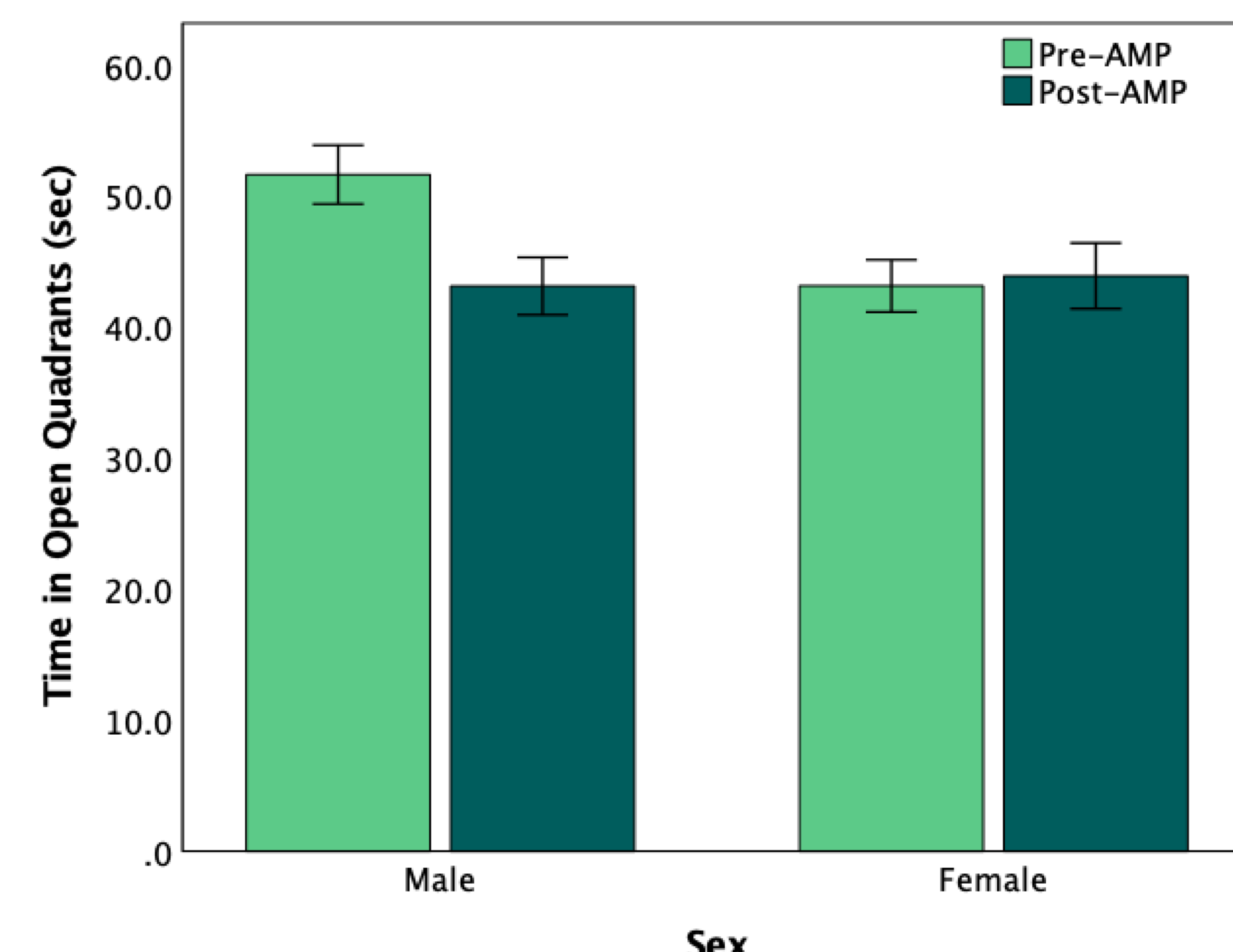
ELEVATED ZERO MAZE

Figure 3. AMP withdrawal significantly enhanced anxiety-like behavior as measured by decreased time spent on the open quadrants, $F(1, 877) = 5.321$, $p < 0.05$, $\eta_p^2 = 0.01$.
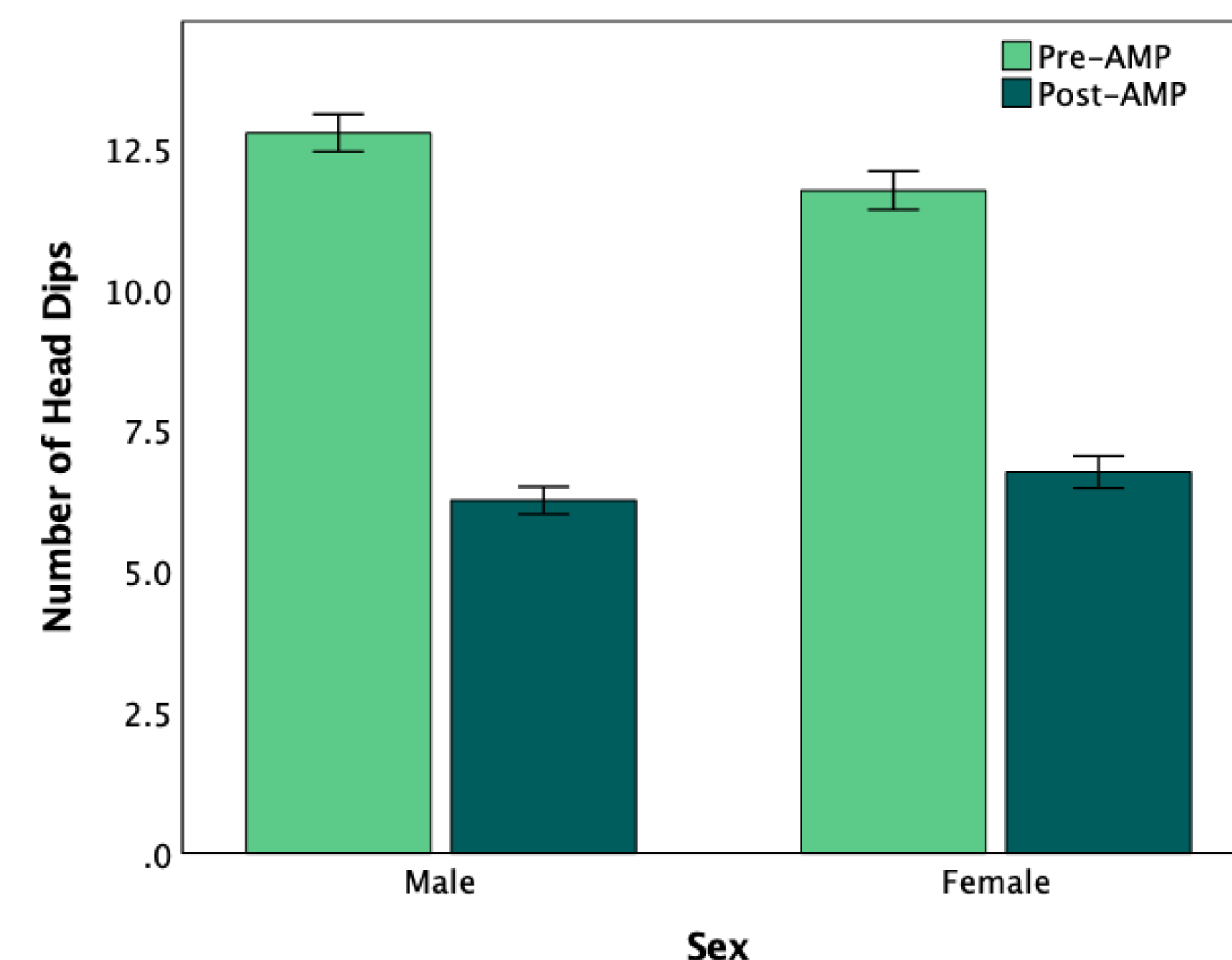

Figure 4. Distribution of AMP Withdrawal-Induced Changes in Time Spent in Open Quadrants of EZM (N = 657).

Figure 5. AMP withdrawal significantly decreased exploratory/risk assessment behaviors as measured by head dips, $F(1, 878) = 638.90$, $p < 0.001$, $\eta_p^2 = 0.42$.

Figure 6. AMP withdrawal significantly decreased exploratory/risk assessment behaviors as measured by stretch-attends, $F(1, 878) = 316.35$, $p < 0.001$, $\eta_p^2 = .27$.
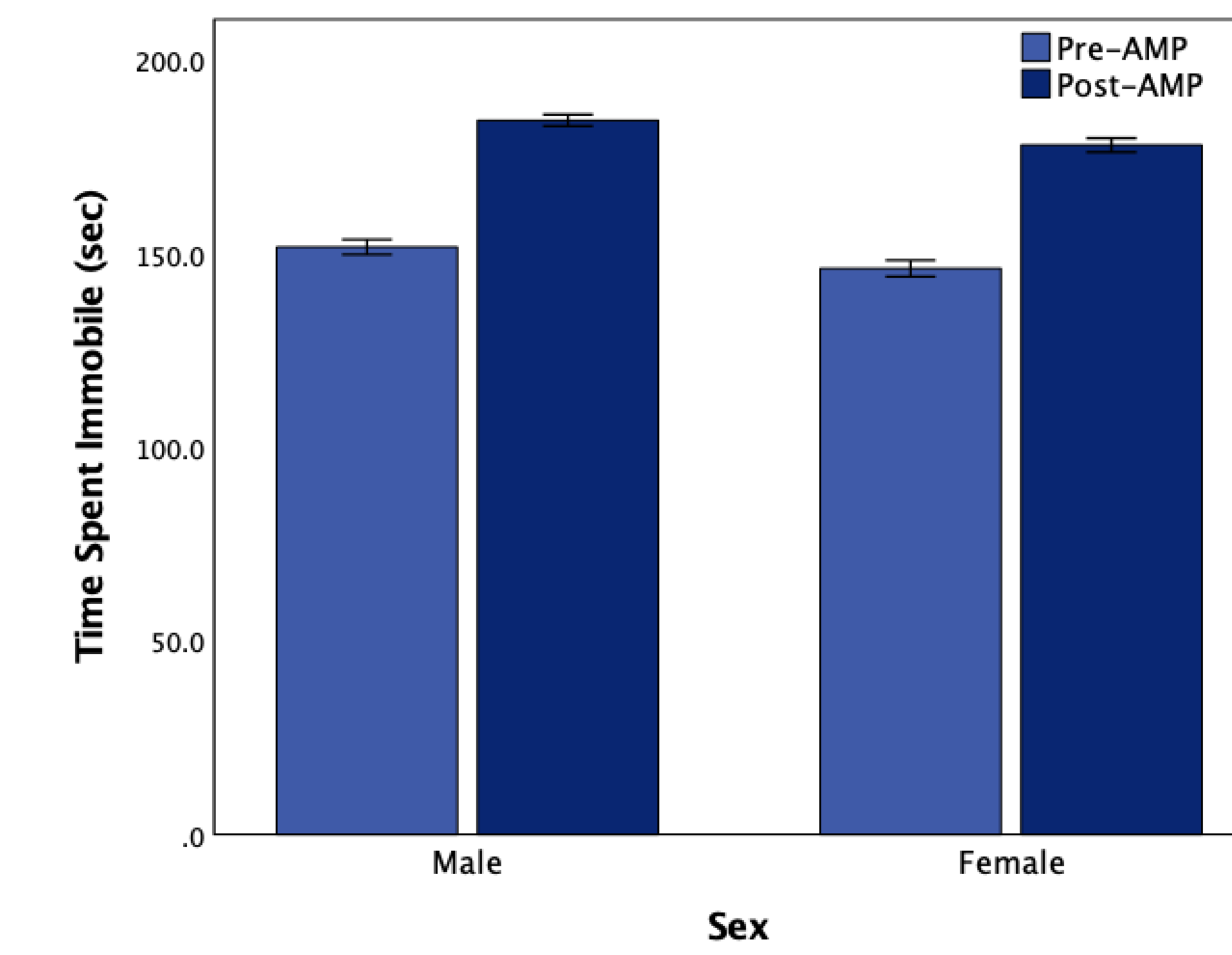
FORCED SWIM TEST

Figure 7. AMP withdrawal significantly increased depressive-like behaviors as measured by time spent immobile, $F(1, 1014) = 808.60$, $p < 0.001$, $\eta_p^2 = .44$.
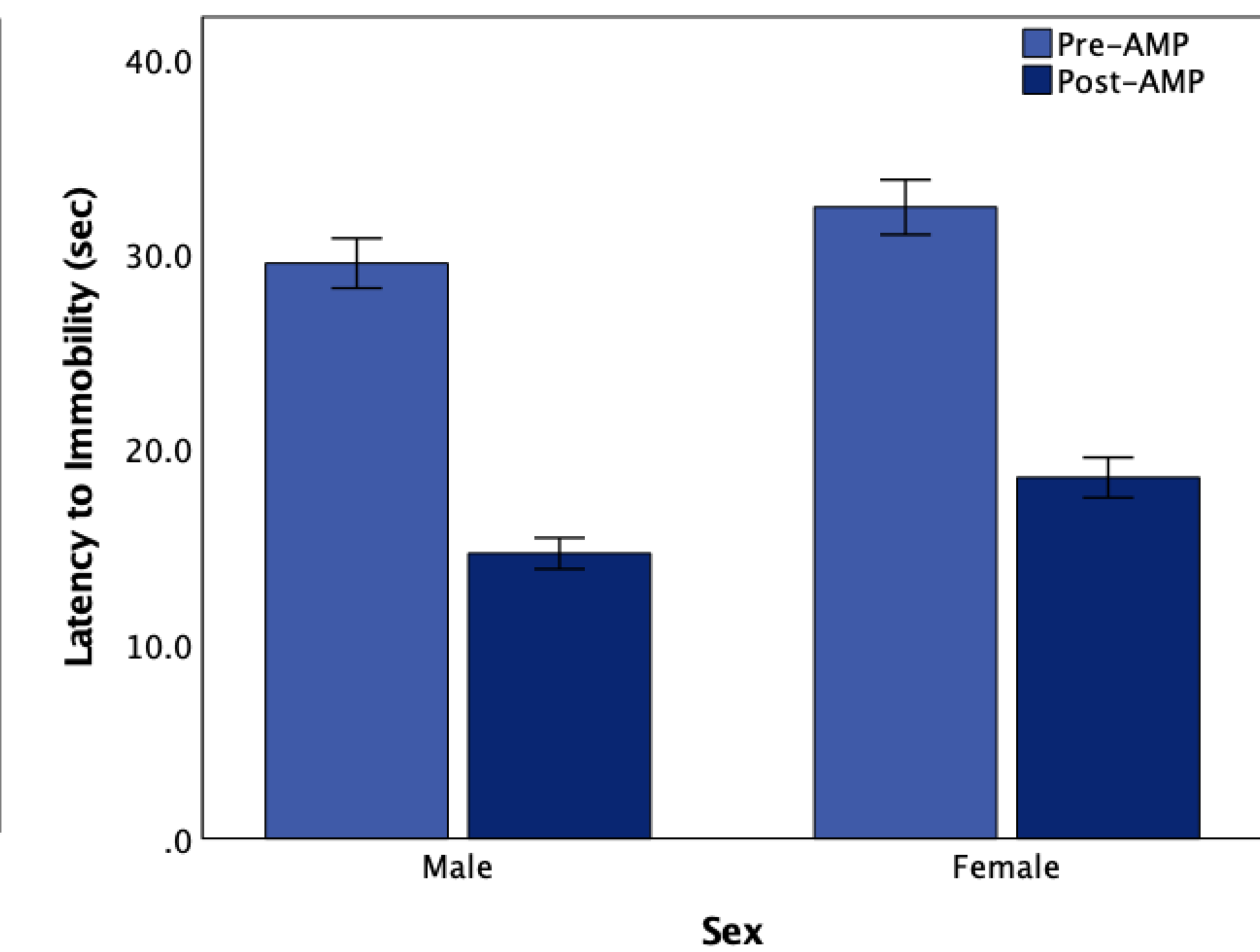

Figure 9. AMP withdrawal significantly increased depressive-like behavior as measured by latency to immobility, $F(1, 1010) = 243.17$, $p < 0.001$, $\eta_p^2 = .19$.
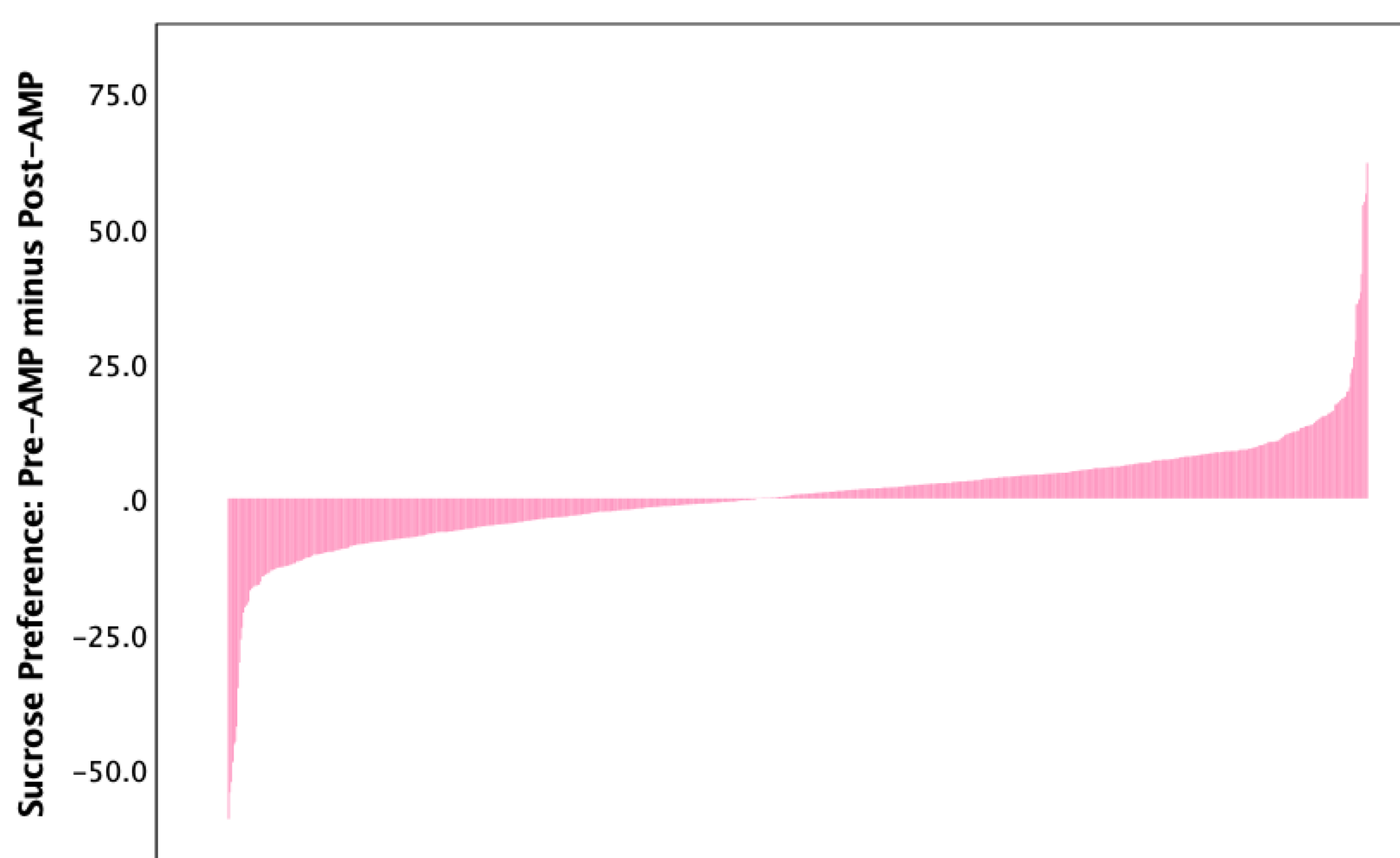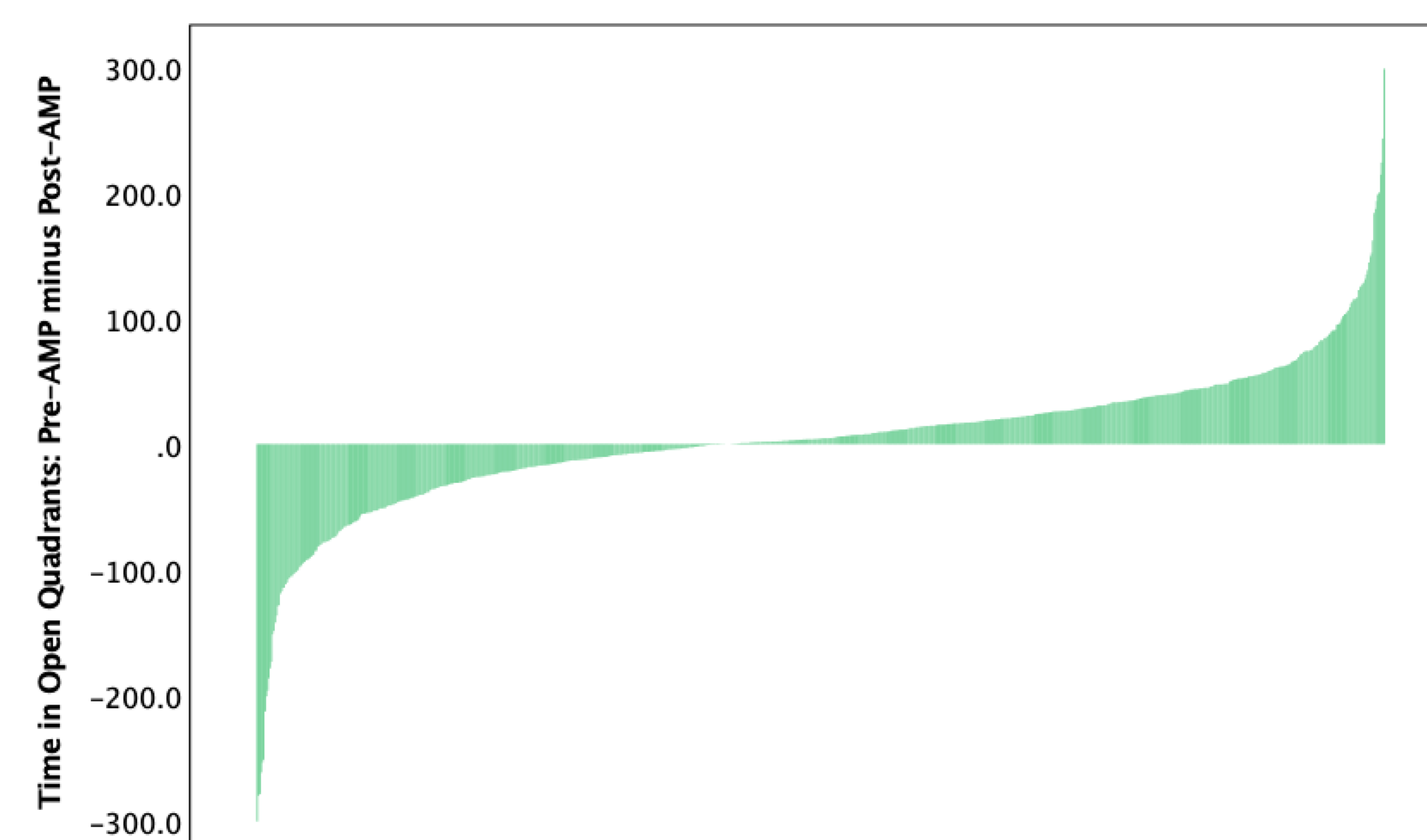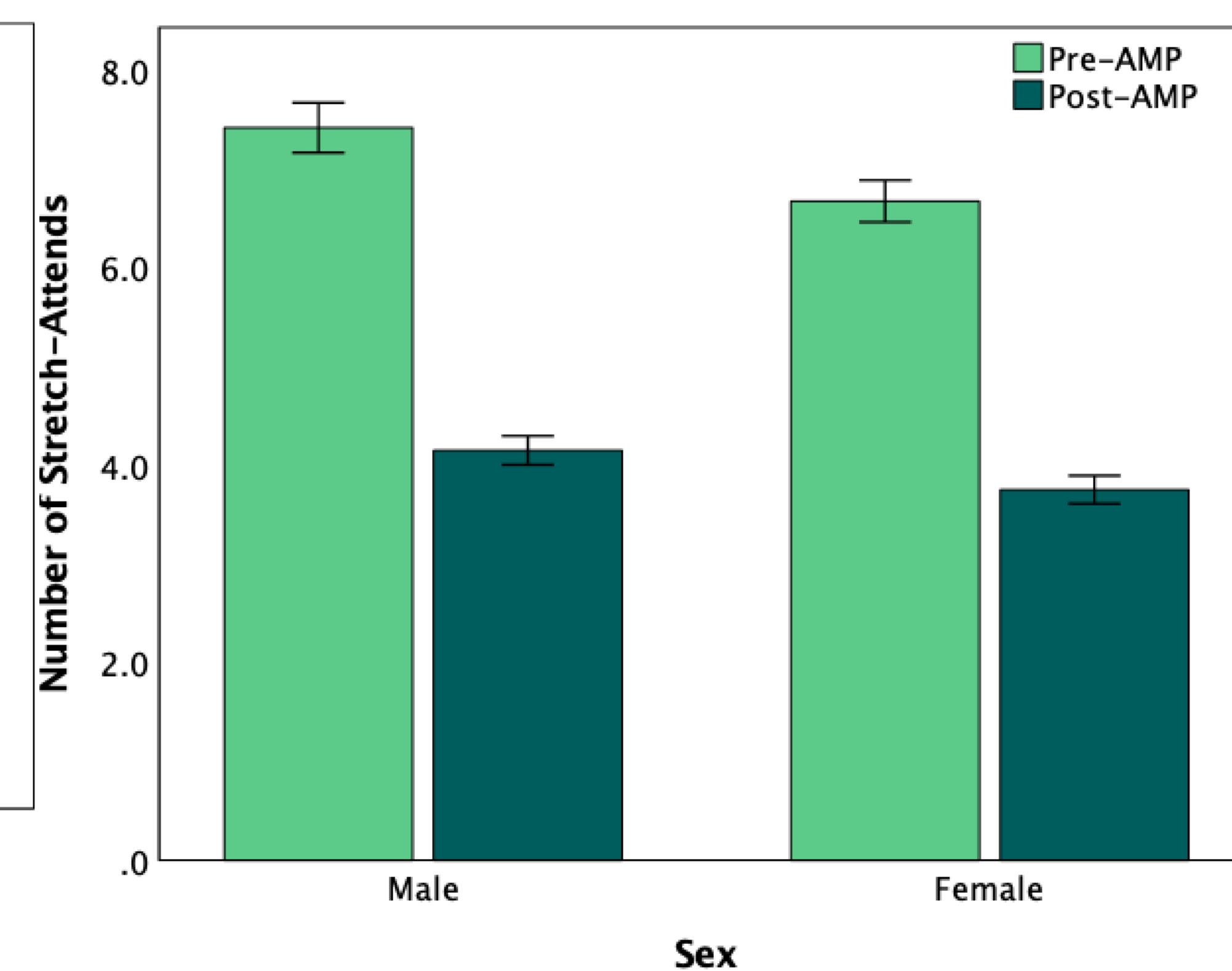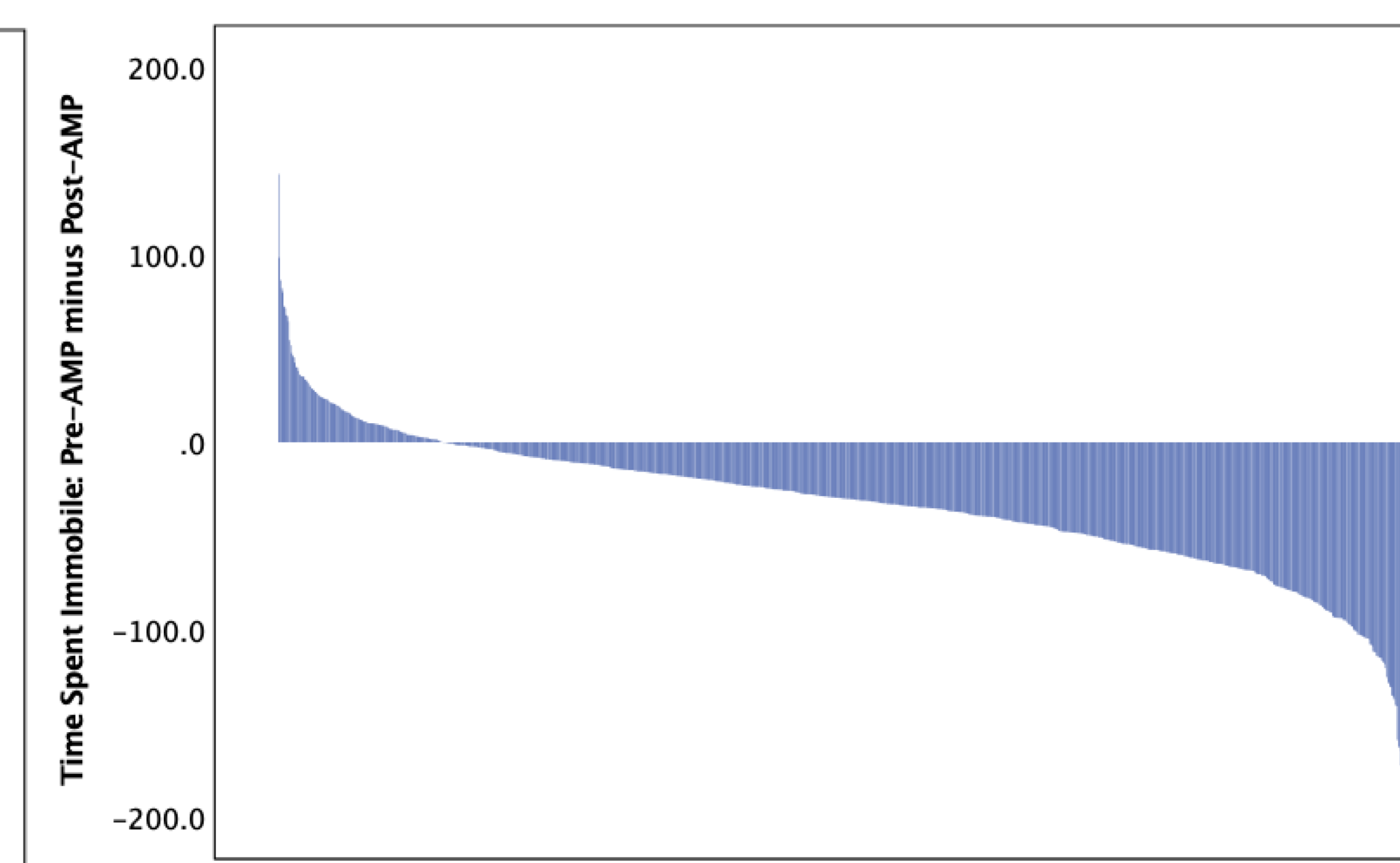

Figure 8. Distribution of AMP Withdrawal-Induced Changes in Time Immobile during FST (N = 1015).
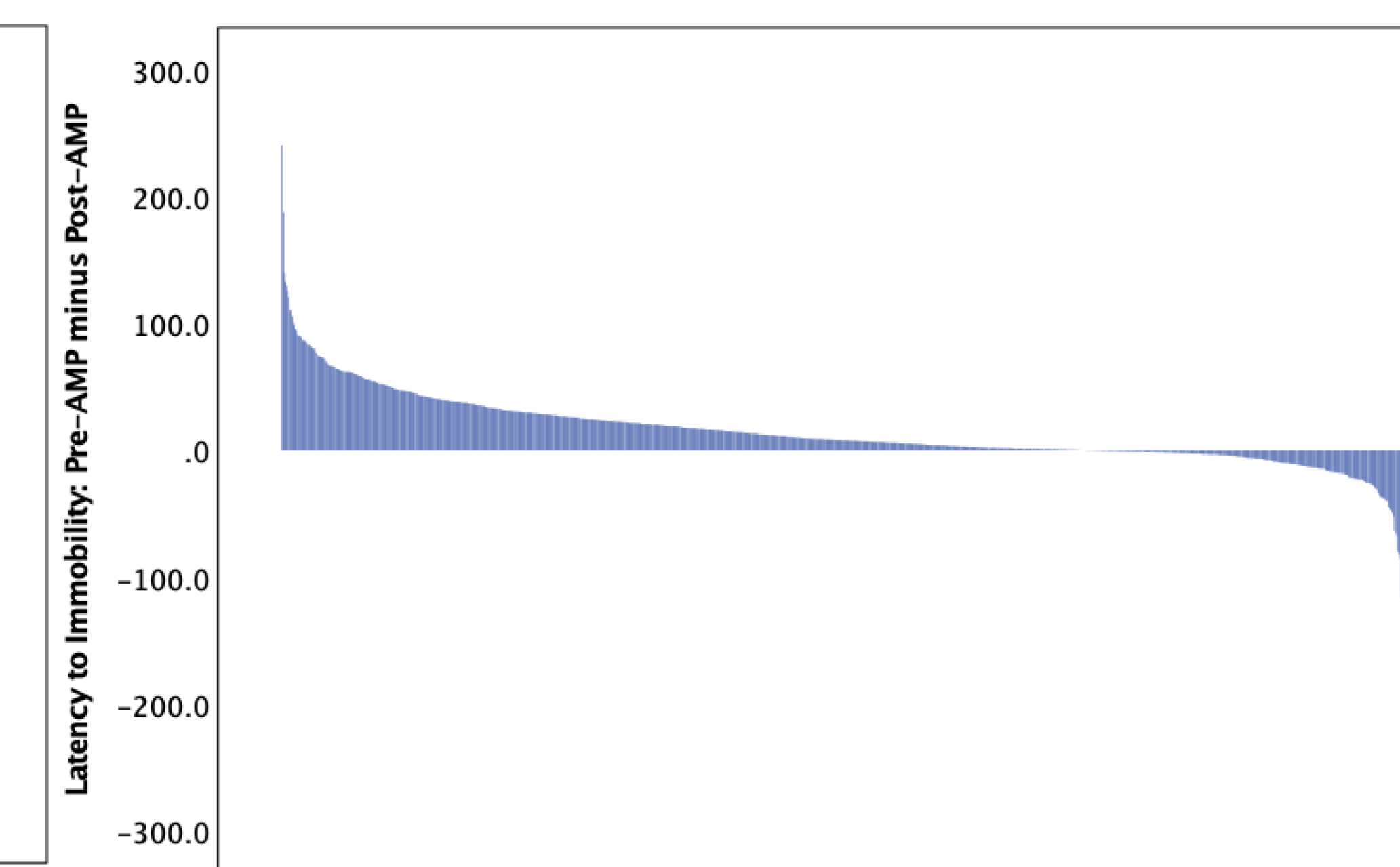

Figure 10. Distribution of AMP Withdrawal-Induced Changes in Latency to Immobility during FST (N = 1011).

CONCLUSIONS AND FUTURE DIRECTIONS

- On average, CFW mice exhibited increased anxiety-like behavior and dysphoria, but not anhedonia during acute withdrawal from d-amphetamine.

- Importantly, we observed a wide range of values for these traits, which is essential for the success of QTL mapping studies.

- By exploiting the higher number of recombinations in CFW mice, we hope to map behavioral and gene expression QTLs with high precision.

- This approach will allow for the identification of plausible biological explanations for how alleles influence behavior and thereby implicate specific genes.