Sex differences in the neural and behavioral effects of acute high-dose edible cannabis consumption in rats

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Running Title: Sex differences in high-dose edible cannabis consumption effects

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Supplementary Information

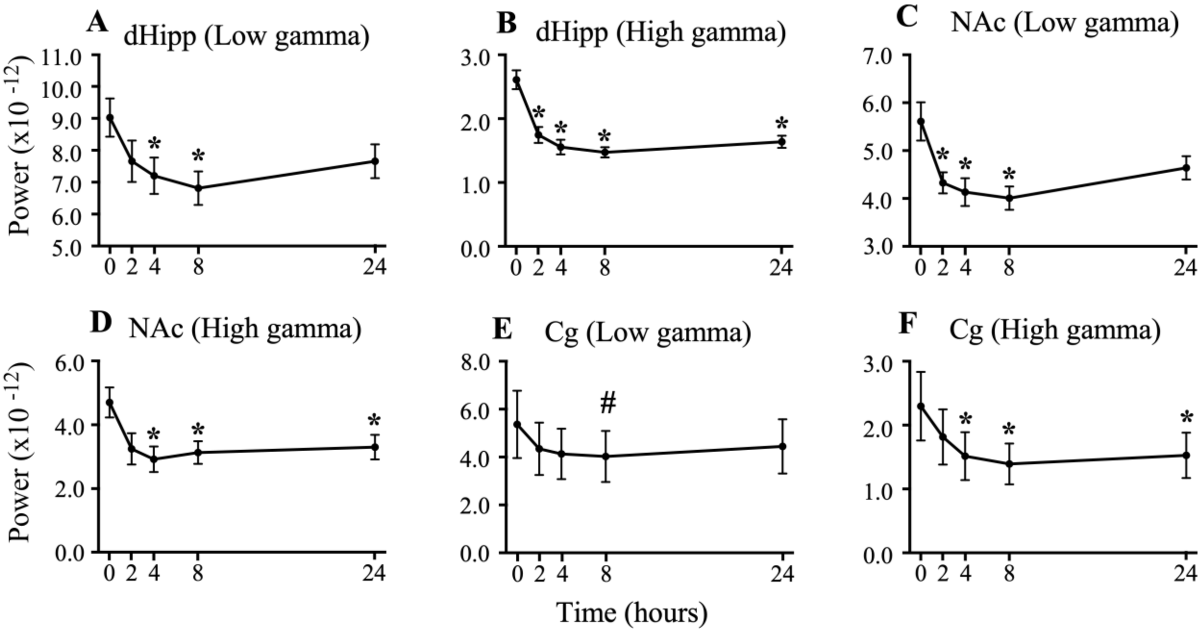

Fig. S1

S1 Fig. Comparison of low and high gamma power at other time points with baseline in male rats using one-way repeated measures analysis of variance. A and B. Graphs comparing low and high gamma power spectral densities, respectively, in the dorsal hippocampus (dHipp) at the 2, 4, 8, and 24-h time-points with that at baseline. C and D. Graphs comparing low and high gamma power spectral densities, respectively, in the cingulate cortex (Cg) at the 2, 4, 8, and 24-h time-points with that at baseline. D and E. Graphs comparing low and high gamma power spectral densities, respectively, in the nucleus accumbens (NAc) at the 2, 4, 8, and 24-h time-points with that at baseline. *: significantly different compared to baseline, #: tending towards significance compared to baseline.

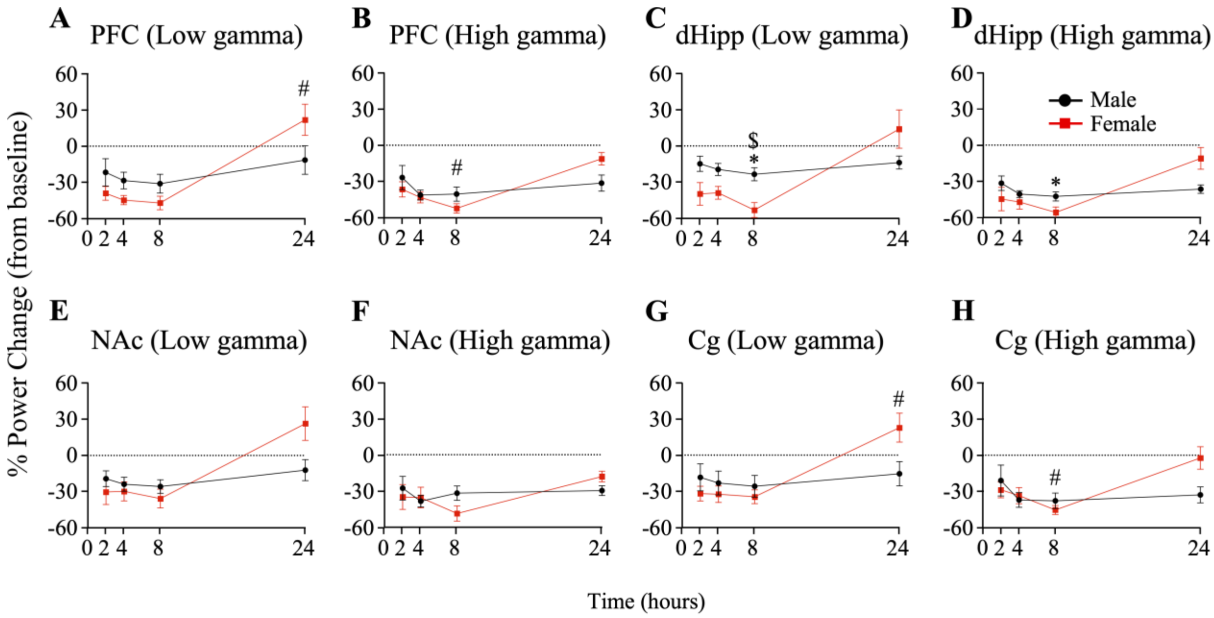

Fig. S2

S2 Fig. Power spectral density (PSD) plotted as percentage change from baseline for male and female rats after acute high-dose edible cannabis consumption. A and B. Low and high gamma power percentage change, respectively, in the PFC between males and females at different time-points. C and D. Low and high gamma power percentage change, respectively, in the dorsal hippocampus (dHipp) of males and female rats at different time-points. E and F. Low and high gamma power percentage change, respectively, in the nucleus accumbens (NAc) of males and female rats at different time-points. G and H. Low and high gamma power percentage change, respectively, in the cingulate cortex (Cg) between males and females at different time-points. $: comparison of time-points between sexes with $p<0.05$, *: comparison of power at other time-points with that at the 2-h time-point in males with $p<0.05$, #: comparison of power at other time-points with that at the 2-h time-point in females with $p<0.05$.

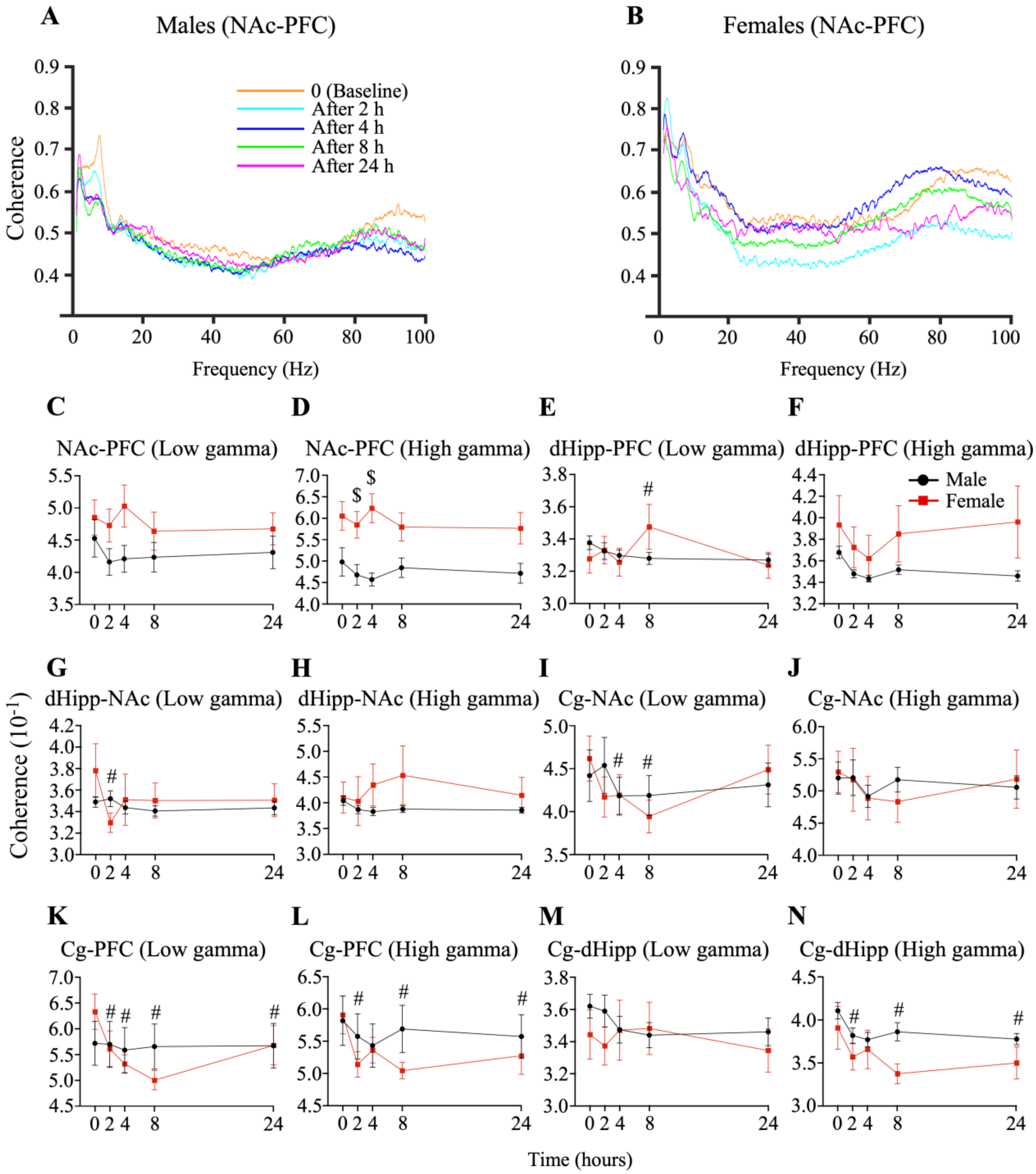

Fig. S3

S3 Fig. Coherence plots for male and female rats after acute high-dose edible cannabis consumption. Representative coherence plots for male rats (A) and female rats (B) showing the coherence between the nucleus accumbens and prefrontal cortex (NAc-PFC) for each time-point of interest. Orange plot: Baseline, cyan plot: 2-h time-point, blue plot: 4-h time-point, green plot: 8-h time-point, and pink plot: 24-h time-point. C. Graph comparing NAc-

PFC low gamma coherence between male and female rats at different time-points. D. Graph comparing NAc-PFC high gamma coherence between male and female rats at different time-points. E. Graph comparing dorsal hippocampus and prefrontal cortex (dHipp-PFC) low gamma coherence between male and female rats at different time-points. F. Graph comparing dHipp-PFC high gamma coherence between male and female rats at different time-points. G. Graph comparing dorsal hippocampus and nucleus accumbens (dHipp-NAc) low gamma coherence between male and female rats at different time-points. H. Graph comparing dHipp-NAc high gamma coherence between male and female rats at different time-points I. Graph comparing cingulate cortex and nucleus accumbens (Cg-NAc) low gamma coherence between male and female rats at different time-points. J. Graph comparing Cg-NAc high gamma coherence between male and female rats at different time-points. K. Graph comparing cingulate cortex and prefrontal cortex (Cg-PFC) low gamma coherence between male and female rats at different time-points. L. Graph comparing Cg-PFC high gamma coherence between male and female rats at different time-points. M. Graph comparing cingulate cortex and dorsal hippocampus (Cg-dHipp) low gamma coherence between male and female rats at different time-points. N. Graph comparing Cg-dHipp high gamma coherence between male and female rats at different time-points. $: comparison of different time-points between sexes, #: comparison of other time-points with baseline in female rats.

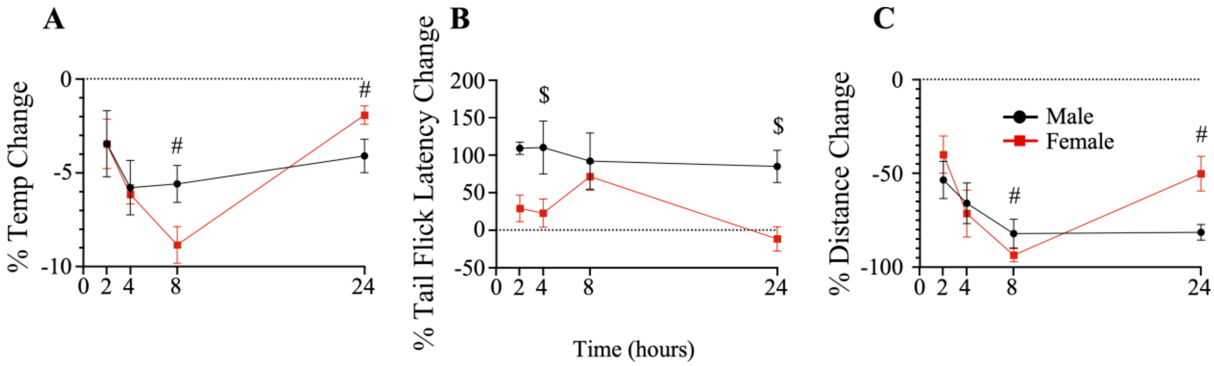

Fig. S4

S4 Fig. Acute edible cannabis-induced effects on body temperature, anti-nociception, and locomotion percentage change in male and female rats. A. Percentage change in rectal temperatures of males and females measured following acute high-dose edible cannabis consumption. B. Percentage change in latency to tail flick of males and females at the time-points of interest following acute high-dose edible cannabis consumption. C. Percentage change in total distance traveled by males and females in the open field box at the time-points of interest following acute high-dose edible cannabis consumption. $: comparison of outcome at different time-points between sexes with p<0.05, *: comparison of outcome at other time-points with that at the 2-h time-point in males with p<0.05, #: comparison of outcome at other time-points with that at the 2-h time-point in females with p<0.05.

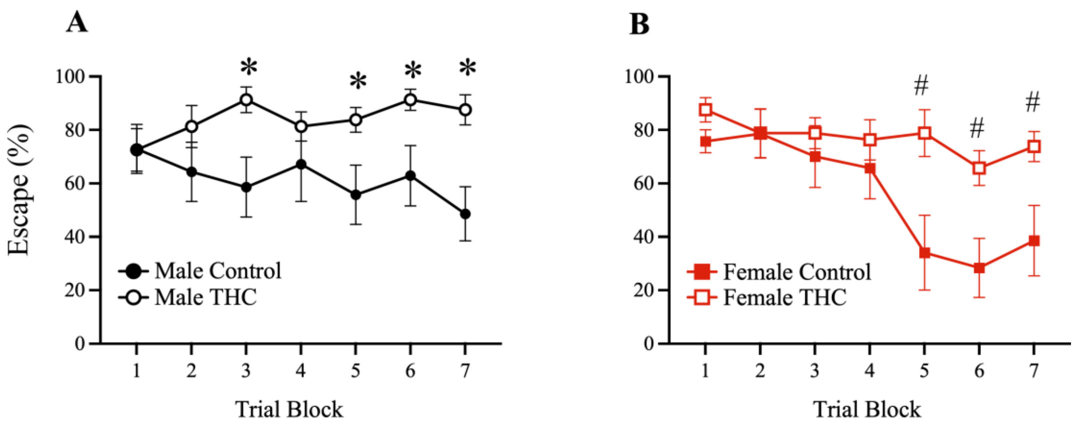

Fig. S5

S5 Fig. Active avoidance is disrupted by acute high-dose edible cannabis consumption. A. Graph comparing the percentage escape among male control and THC rats. Filled black circle: male control rats, empty black circle: male THC rats. B. Graph comparing the percentage escape among female control and THC rats. Filled red square: female control rats, empty red square: female THC rats. *: comparison of percentage avoidance for different trials between male control rats and male THC rats with $p<0.05$, #: comparison of percentage avoidance for different trials between female control rats and female THC rats with $p<0.05$.

Rat Equivalent Dose Calculation

We assumed a situation where a child with an average weight of 20 kg, consumes an entire pack of cannabis edibles containing 100 mg THC. This will lead to a human equivalent dose of 5 mg/kg. To calculate the animal (rat) equivalent dose, we used the formula below (Reagan-Shaw, Nihal, and Ahmad 2008):

$$\text{Animal equivalent dose} = \frac{\text{human equivalent dose}}{\text{animal } \mathrm{k_m} \text{ factor} / \text{human } \mathrm{k_m} \text{ factor}}$$

where $\mathrm{k_m} = \frac{\text{body weight}}{\text{body surface area}}$

$\mathrm{k_m}$ factor (6-year-old child) ≈ 25, $\mathrm{k_m}$ factor (rats, 150 g) = 6.

Using this formula, the animal equivalent dose = $\frac{5}{6/25} = \frac{5}{0.24} = 20.83\ mg/kg$

References

Reagan-Shaw, S., M. Nihal, and N. Ahmad. 2008. 'Dose translation from animal to human studies revisited', *Faseb j*, 22: 659-61.