

Sexual differences in depressive-like behaviours after juvenile and adult stress



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Background

Depression is a highly prevalent disorder. Its diagnosis has alarmingly increased in recent years. There is great symptomatic variability, being differently manifested in women and men. Exposure to adversity and stress during early life may affect and increase vulnerability to mental health problems such as depression, with possible differential manifestation depending on sex. We propose the use of an animal two-hit model (juvenile stress + adult stress) to investigate the behavioral changes in depressive-like behaviors related to both the developmental stage and sex.

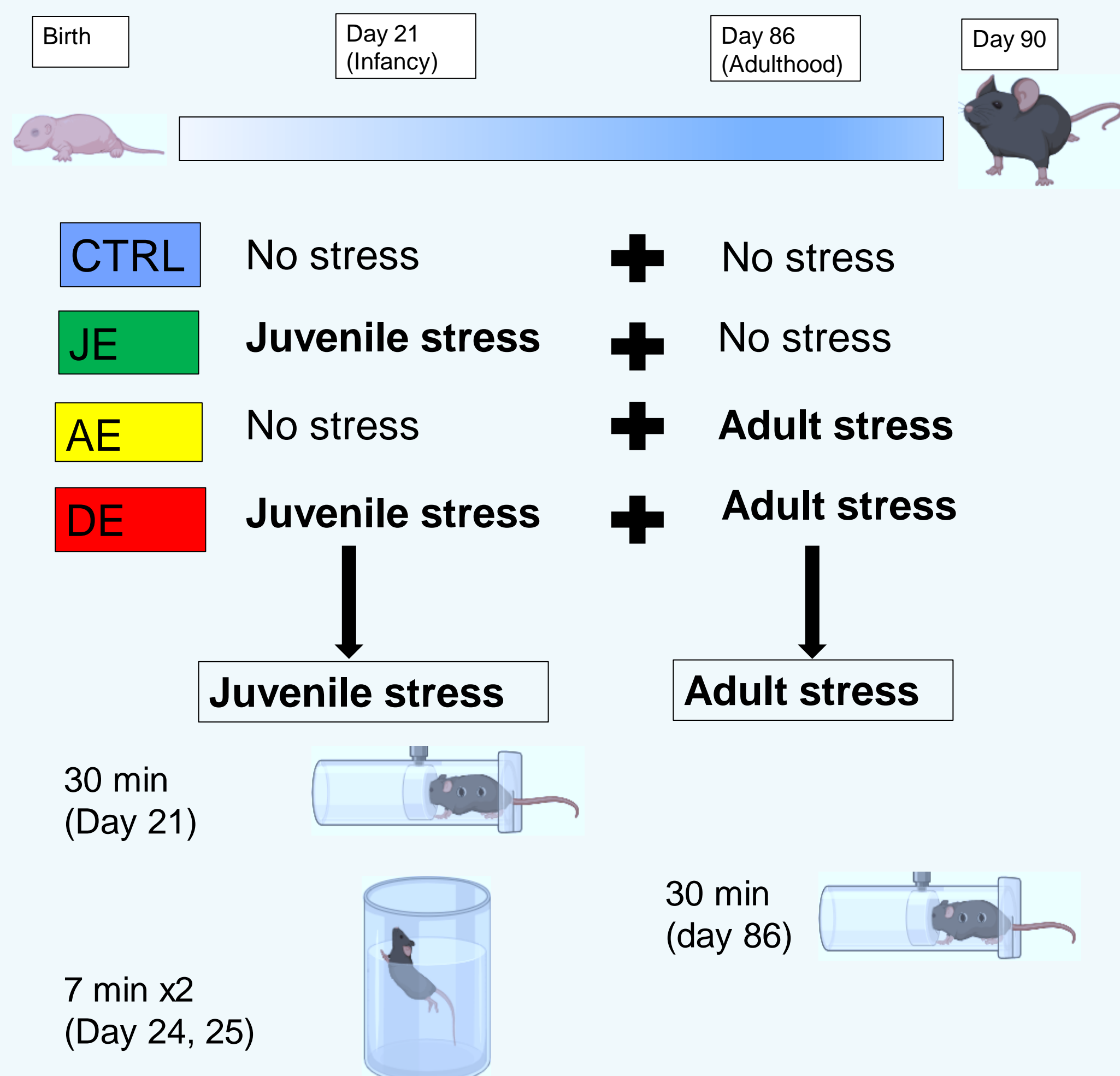
Objectives

The analysis of depressive-like behavior in male and female mice subjected to a two-hit model.

Methods

1. Two-hit experimental model

An N=72 of C56BLJ/6J mice was employed for the study (8 male and 10 females per experimental group) using the following experimental design:



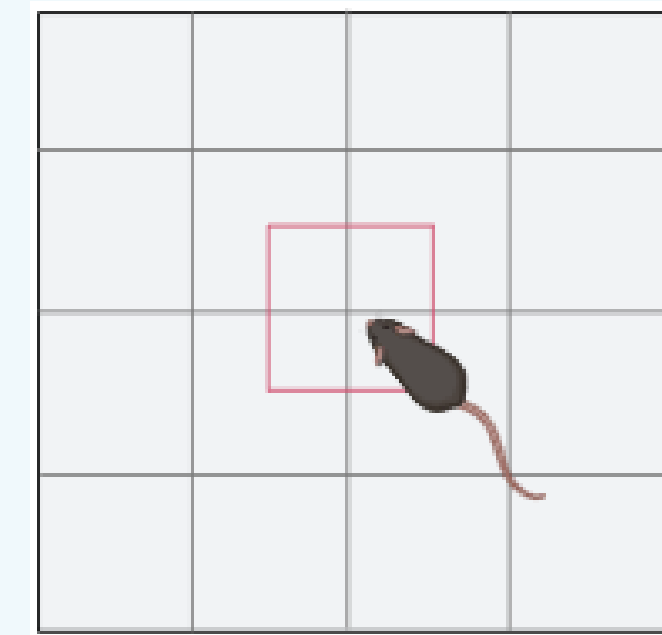
2. Behavioral tests

2.1 Open field (10 minutes)

Used to assess exploratory behavior and anxiety. Ethological and spatiotemporal measures were taken using Ethovision XT v12 (Noldus).

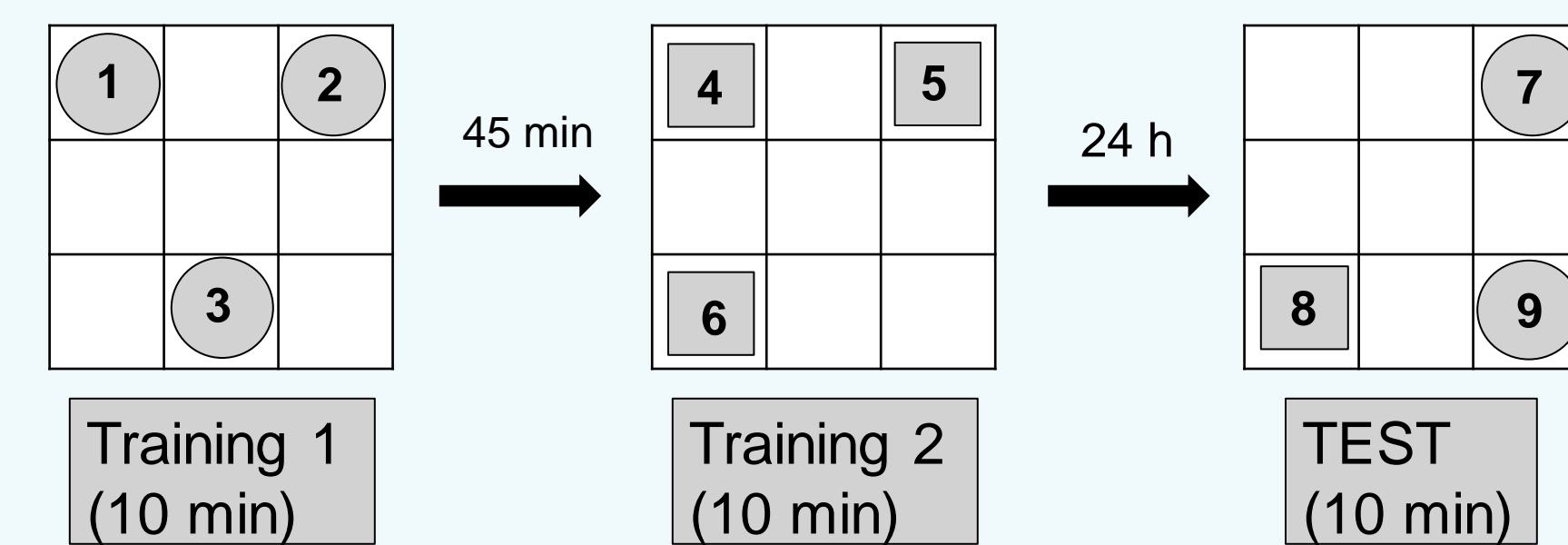
Ethological measures: supported rearing, unsupported rearing, grooming, freezing and risk behavior.

Exploration measurements: time in periphery and center, distance traveled and speed.



2.2 Object based memory test (OBMT)

Hippocampus dependent memory (when and where memory) was tested using the following design:



$$\text{Discrimination index} = \frac{\text{time spent in new object} - \text{mean of time spent in familiar objects}}{\text{total time spent in objects}}$$

$$\text{Recognition index} = \frac{\% \text{ exploration in training} - \% \text{ exploration in test}}{\% \text{ exploration in training}}$$

2.3 Tail suspension test (TST) (5 minutes)

Used to assess coping mechanisms to face an unscapable stress

Behavioral measures: total time of immobility, total time of mobility, latency to first immobility episode (<2 seconds).



Results

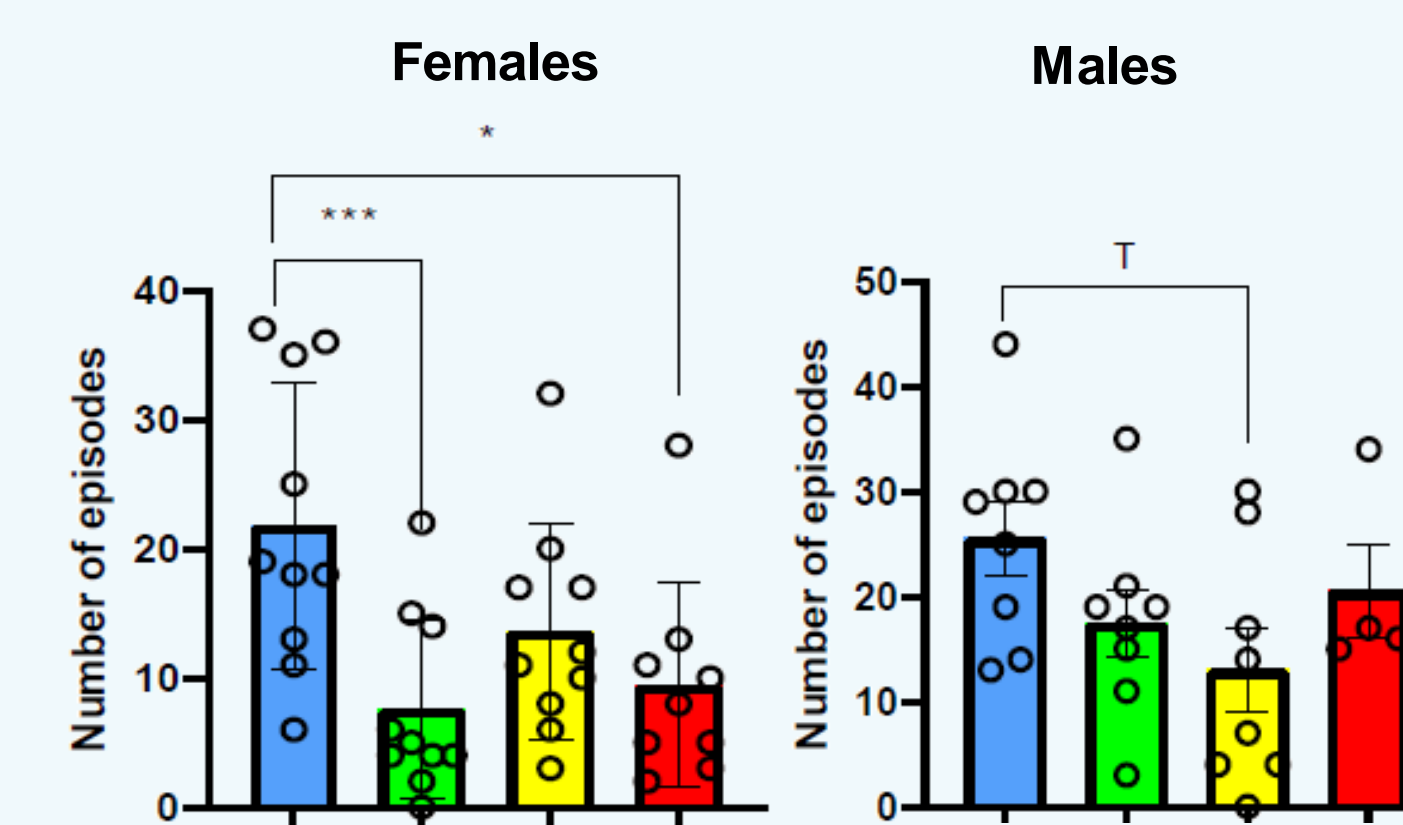
1. Open field

In females, juvenile stress (JE and DB) are more affected, and show reduced unsupported rearing and a more anxious exploration, based both in the number of center entries and the distribution of periphery and center time.

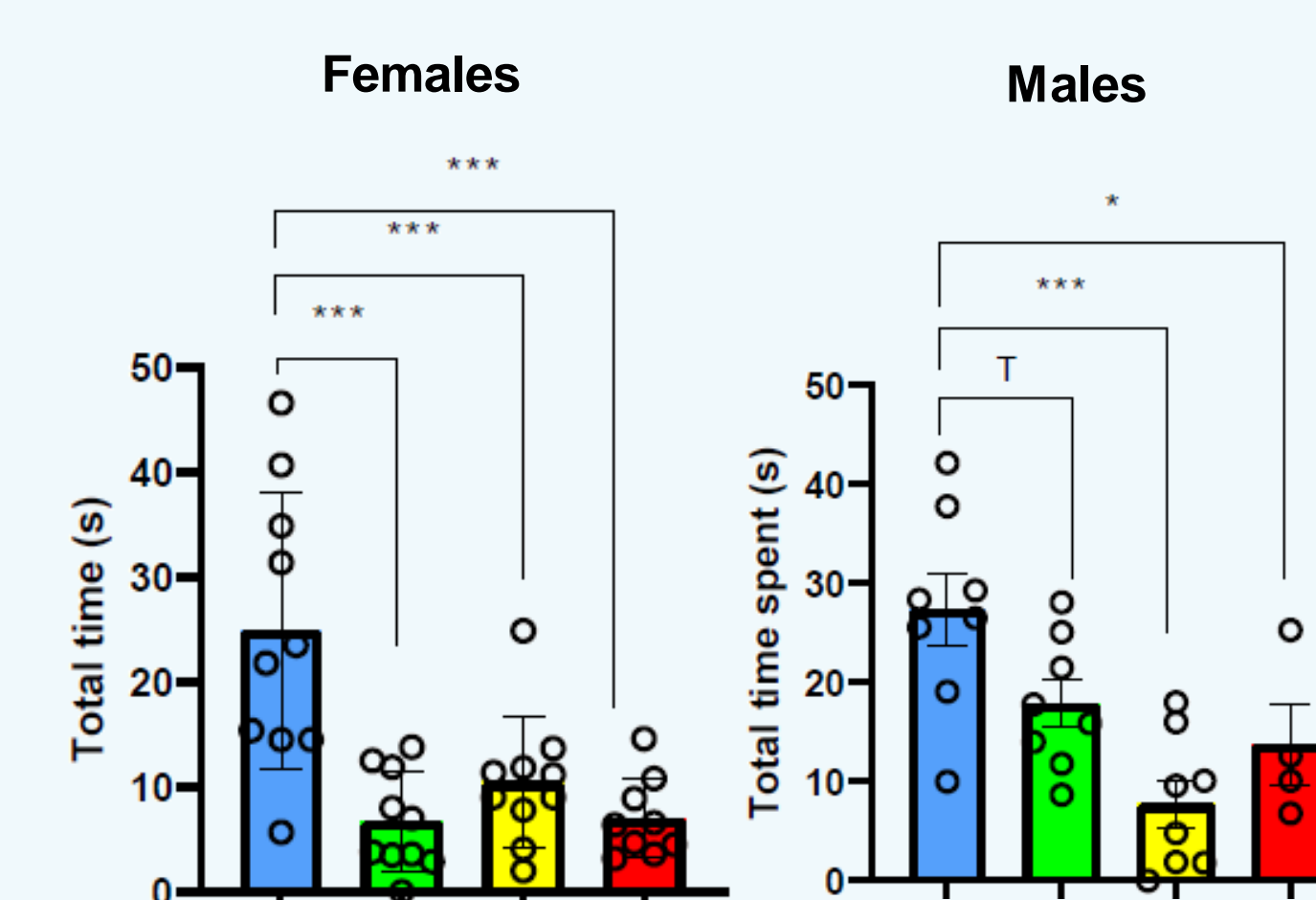
However, in male mice, adult stress groups (AE and DE) are more affected, with reduced unsupported rearing and less center entries.

Both male and female exploratory behavior is affected by stress. However, female exploration and anxiety behavior seem to be more affected by overall stress.

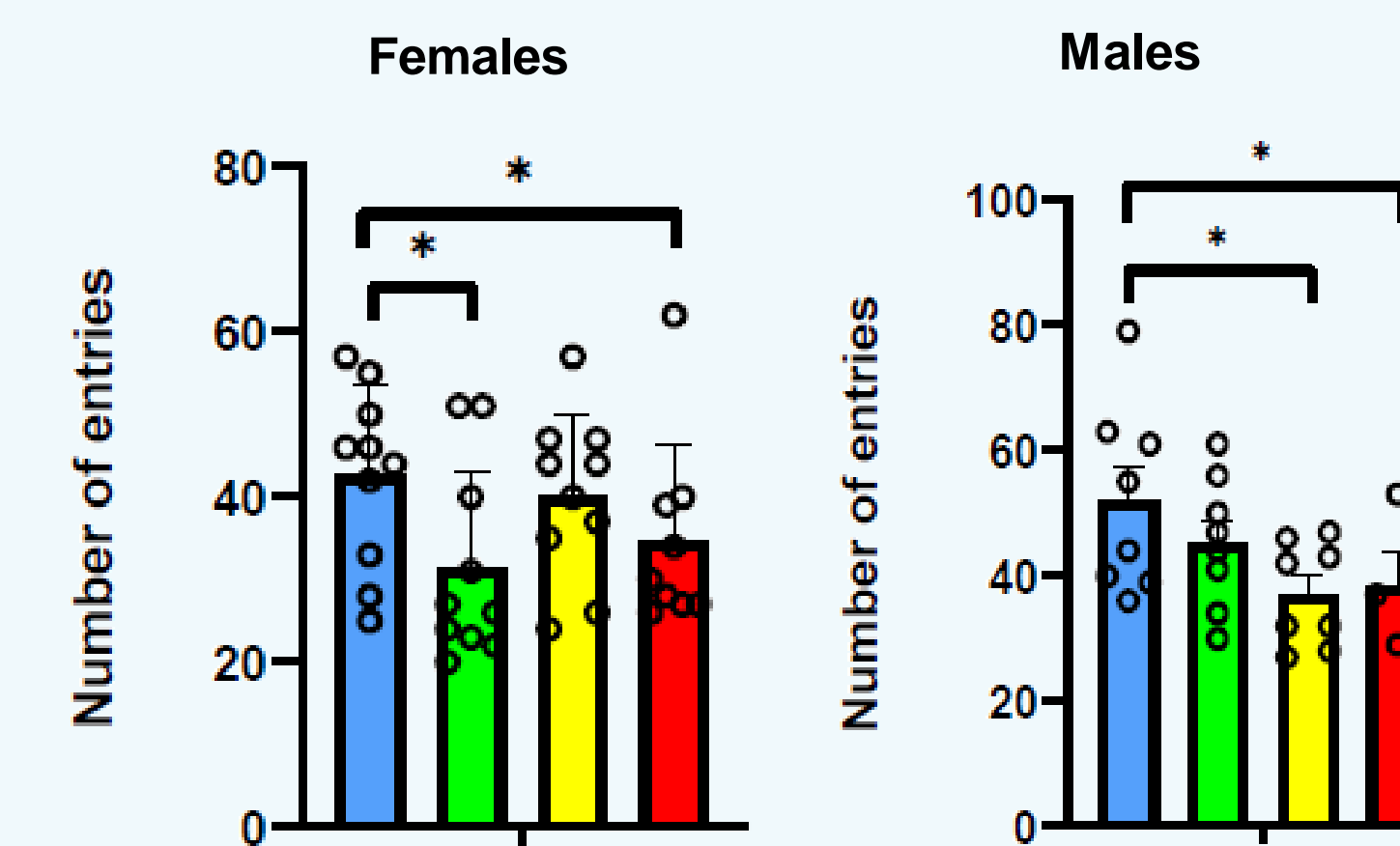
Unsupported rearing occurrences



Unsupported rearing total time



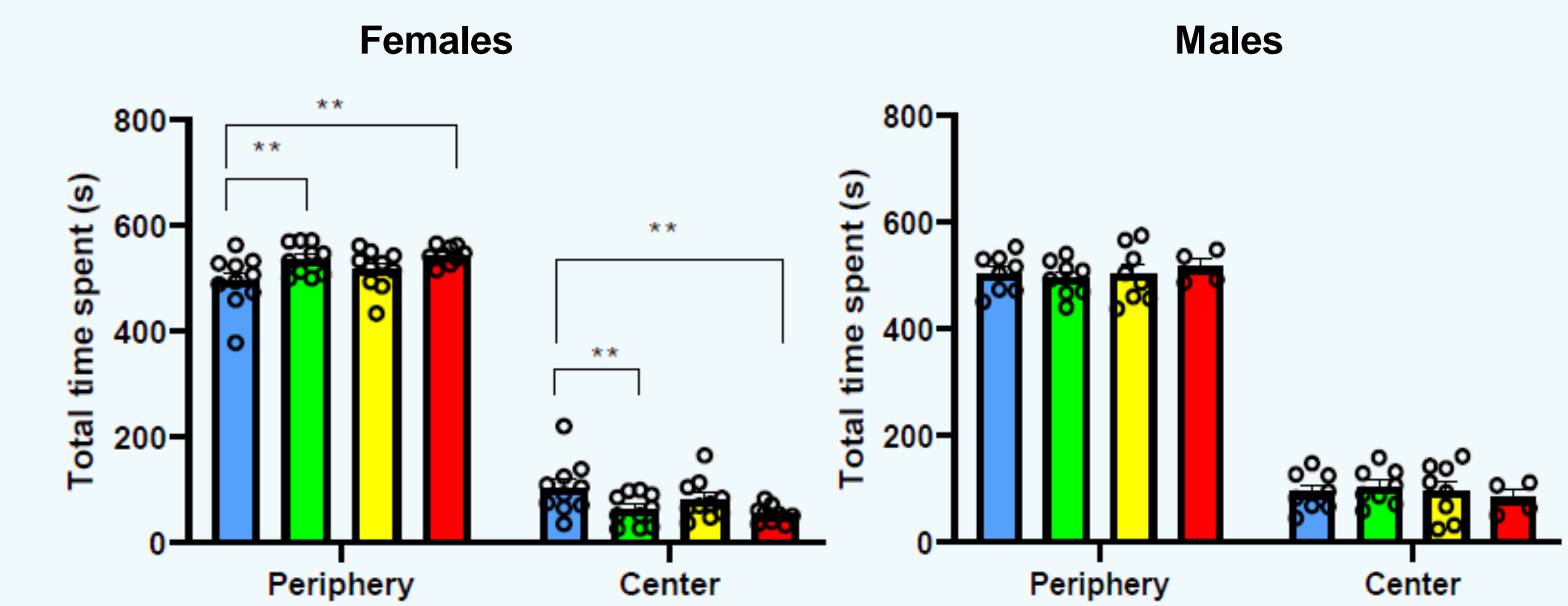
Center entries



Control
Juvenile stress
Adult stress
Double stress

* stands for p < 0,05
** stands for p < 0,02
*** stands for p < 0,001
T stands for p < 0,1

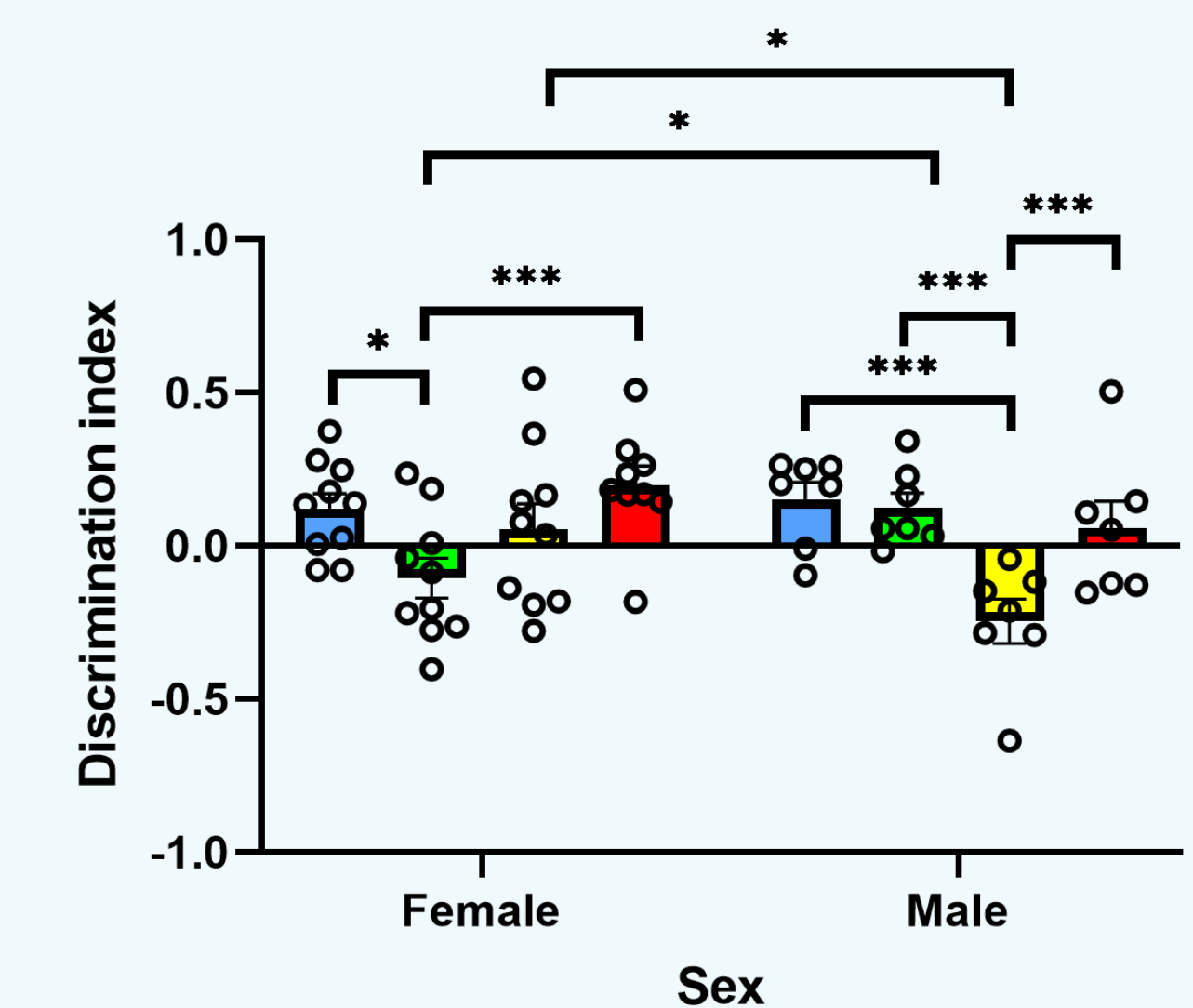
Time spent per zone



2. OBMT

Stress affected memory, measured by the discrimination index. Again, JE mice were more affected in the female group and adult stress in males. However, the DE groups behave closer to the control, with no significant differences with their controls.

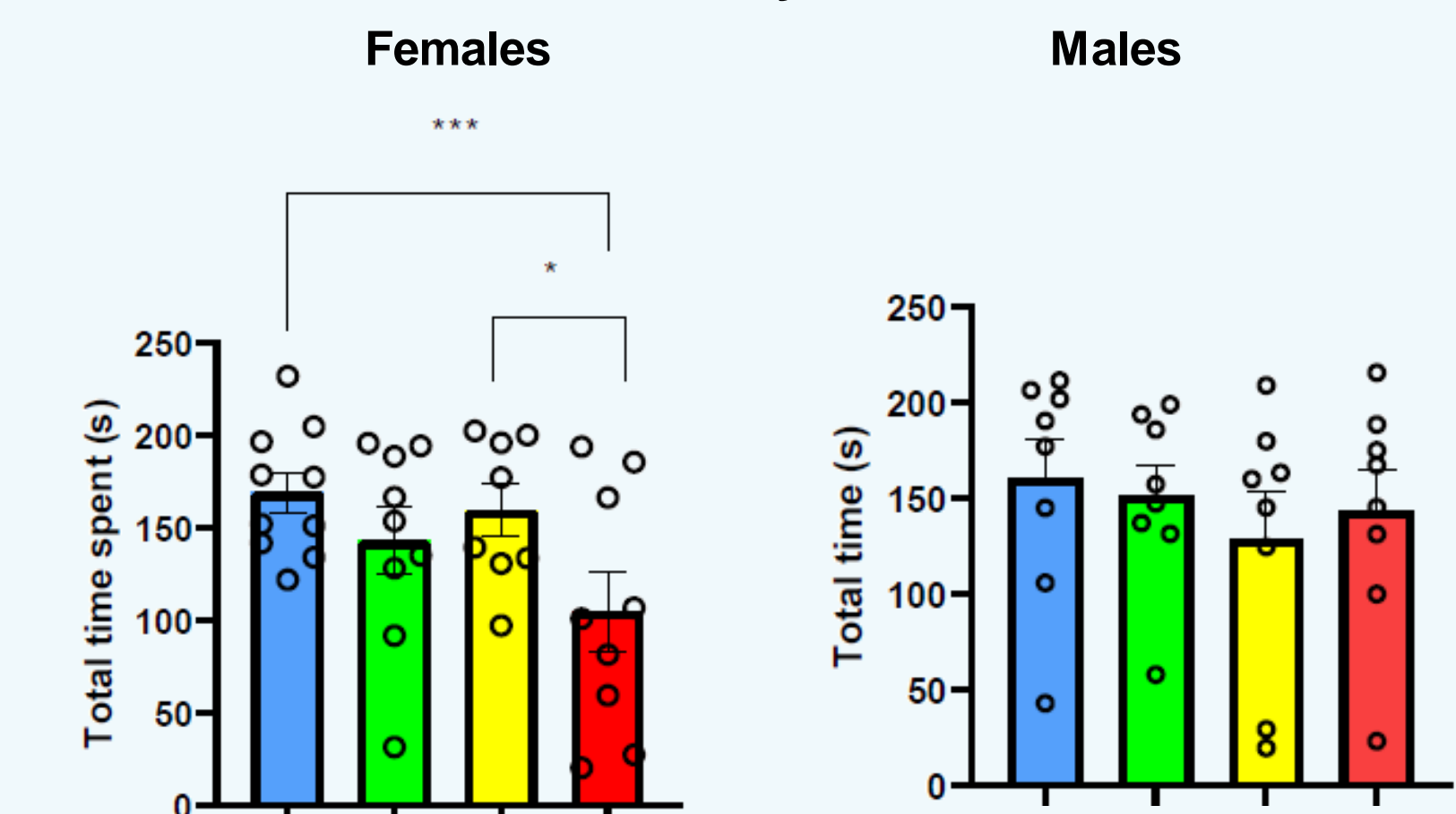
Discrimination index in Test



3. TST

Stress affects the behaviour in female mice. Double stress group takes significantly longer for the first immobility episode, trying to scape the situation for a longer time. No differences in male mice.

Immobility total time



Conclusions

Our results show that there are differences in depressive-like behaviours (exploration, anxiety, memory impairment and despair) in both male and female mice. However, there are specific differences related to the developmental stage of the stress episode and sex, being female mice more affected.

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