

SEX MATTERS: HOW STRESS AT DIFFERENT LIFE STAGES AFFECTS MALES AND FEMALES DIFFERENTLY

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UNIVERSIDAD DE MÁLAGA



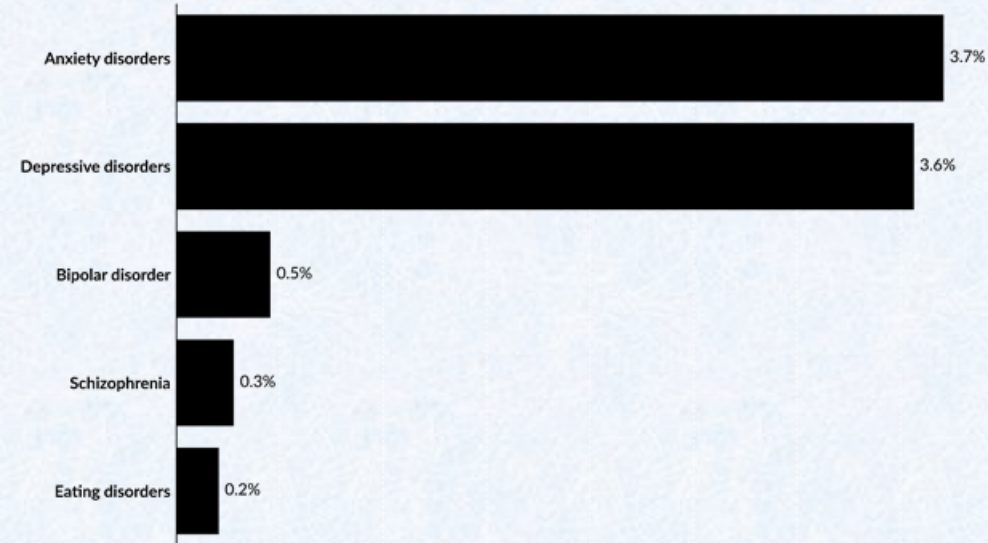
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1. INTRODUCTION

Mental illnesses prevalence, World, 2019

The estimated share of people with each mental illness in a given year, whether or not they were diagnosed, based on representative surveys, medical data and statistical modeling.

Our World
in Data



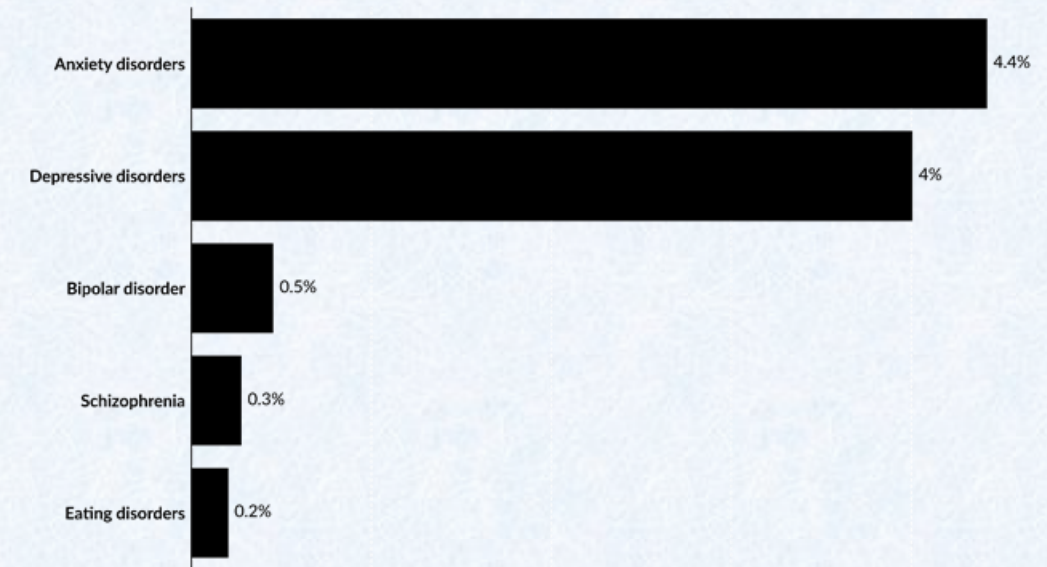
Data source: IHME, Global Burden of Disease (2019)

OurWorldInData.org/mental-health | CC BY

Mental illnesses prevalence, World, 2021

The estimated share of people with each mental illness in a given year, whether or not they were diagnosed, based on representative surveys, medical data and statistical modeling.

Our World
in Data



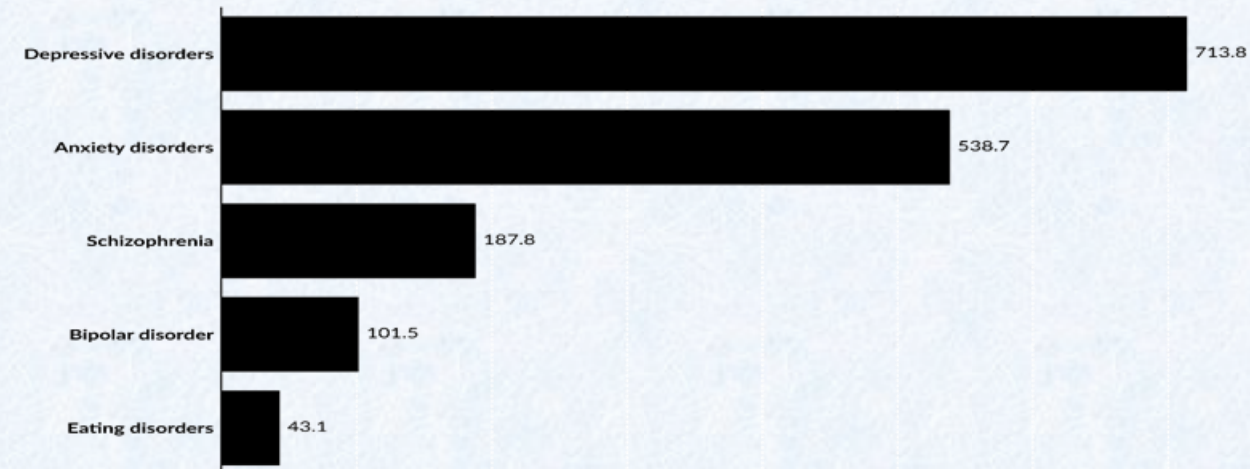
Data source: IHME, Global Burden of Disease (2019)

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Burden of disease from each category of mental illness, World, 2021

Estimated number of disability-adjusted life years (DALYs)¹ per 100,000 people, broken down by category of mental illness.

Our World
in Data



Data source: IHME, Global Burden of Disease (2024)

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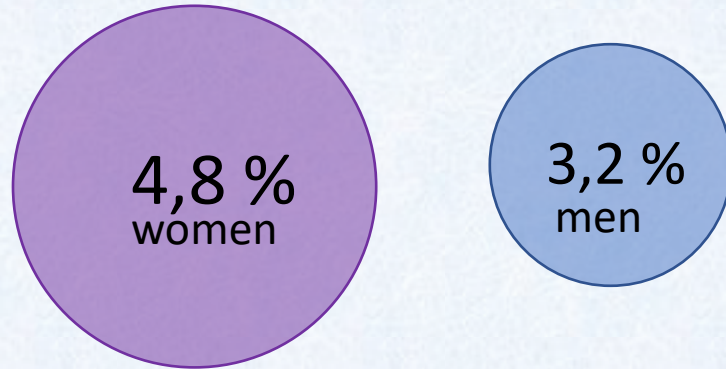
1. **Disability-adjusted life years:** Disability-adjusted life years (DALYs) measure the total burden of disease – both from years of life lost due to premature death and years lived with a disability. One DALY equals one year of healthy life. [Learn more about how the burden of disease is measured in our article.](#)

High prevalence

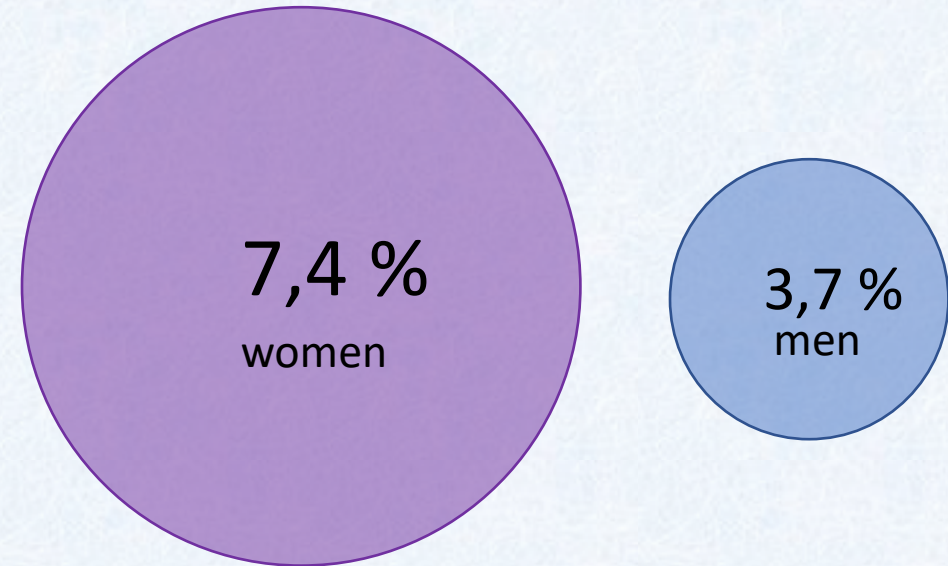
Upward trend in recent years

Leading cause of disability worldwide (1)

Global prevalence of depression



Spanish prevalence of depression



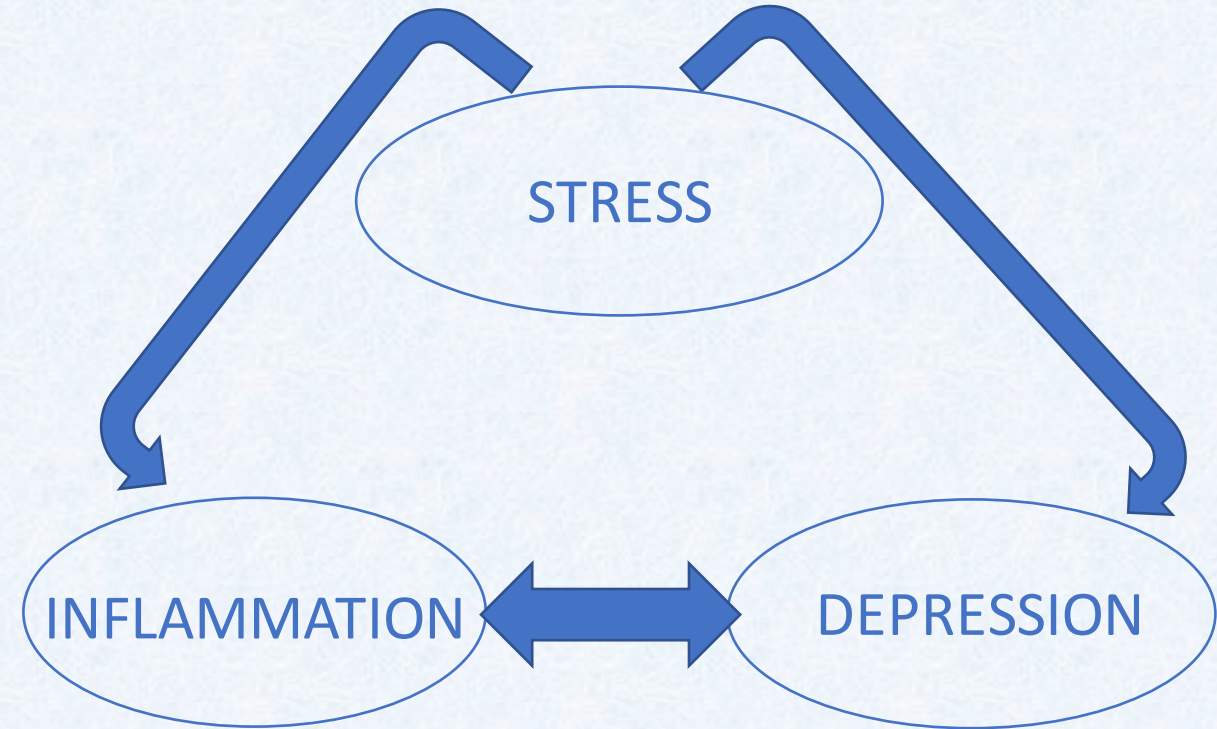
(1)

Depressive symptomatology varies between **sexes**, reflecting **potential sex-specific differences** (2)

Robust and causal relationship between stress and depression (3)

STRESS, MICROGLIA AND DEPRESSION

- Adolescent stress is a **robust predictor** of the **onset, maintenance** and **severity** of **MDD** (4)
- **Juvenile stress** can induce **microglial sensitization**. This **sensitization** may lead to an **exaggerated response** to a **subsequent adult stressor** (5)
- Microglia orchestrate the inflammatory response, and a growing body of evidence has implicated their role in the pathophysiology of depression (6,7)



Our goal is to **characterize changes** induced by **early-life stress** and exposure to a **second stressor** in **adulthood** in **behaviors** that **model depression**

Does sex matter? Does it differ?



METHODS

P0



Day 21 (Juvenile)

Día 86 (Adulthood)

Day 90



CTRL

JE

AE

DE

No stress

Juvenile stress

No stress

Juvenile stress



Juvenile stress

30 min (Day 21)



7 min x2 (Day 24, 25)



No stress

No stress

Adult stress

Adult stress



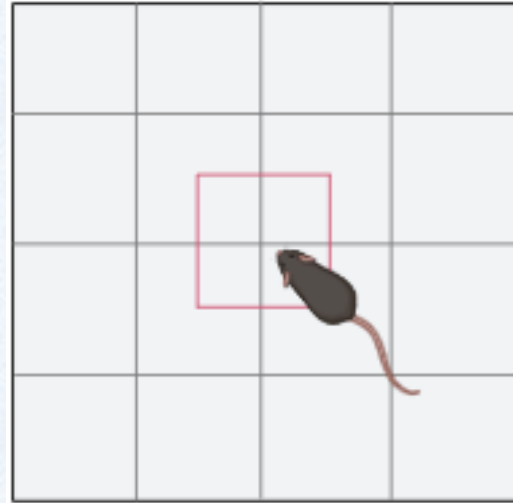
Adult stress



30 min (Day 86)

N= 71 (39 F / 32 M)

OPEN FIELD (10 MINUTES)

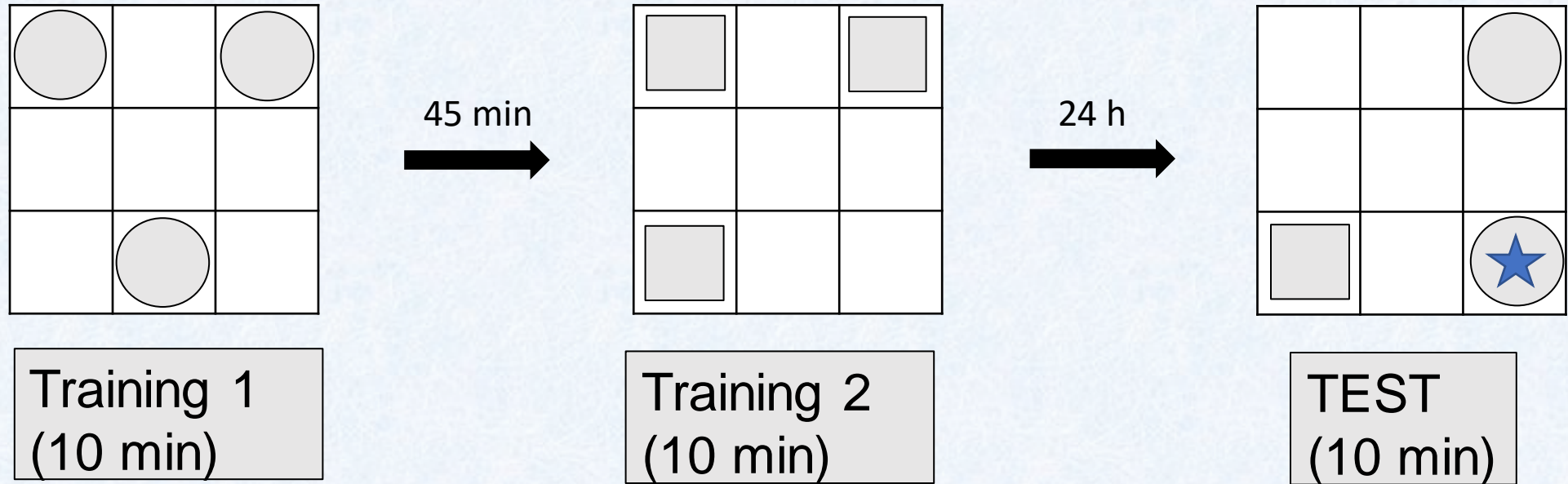


Used to assess **exploratory behavior and anxiety**.

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

Spatio-temporal measures: time in periphery and center, number of center entries, distance traveled and speed.

OBJECT BASED MEMORY TEST (OBMT)

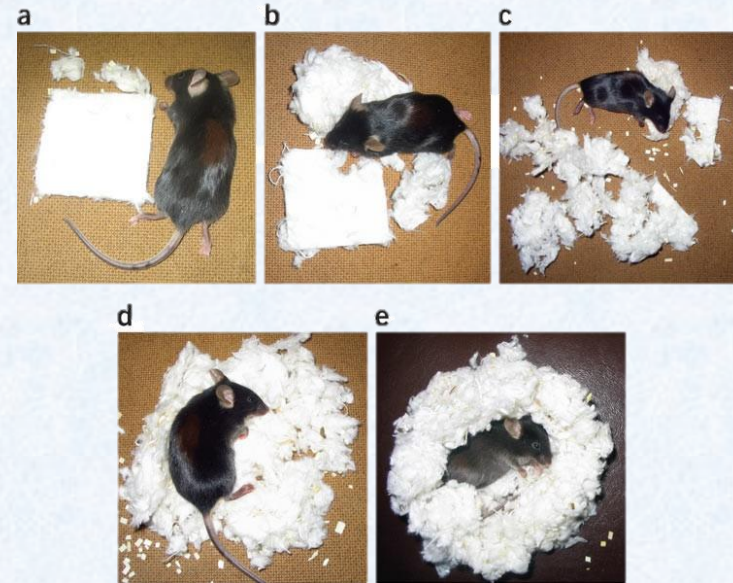


Hippocampus dependent memory (when and where memory)

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

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

NEST BUILDING TEST



Used to analyze **stress effect** on **self-reflected activity, motivation and anhedonia**

Generally used as screening for pharmacological treatments

Measures: Nest score after 18 hours

CORTICOSTERONE ELISA



Used to analyze **corticoesterone levels (HPA axis measure)**

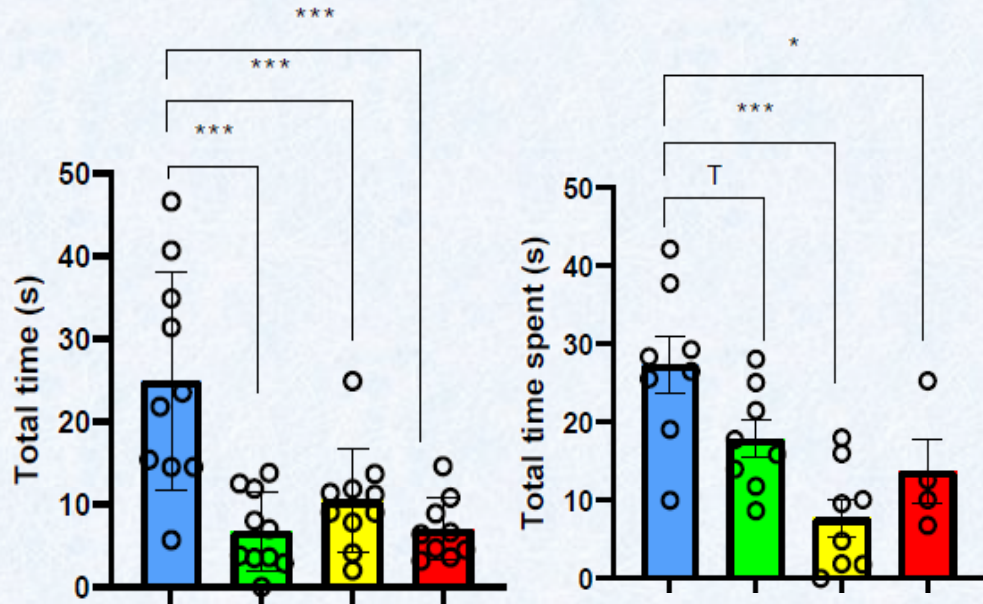
Measure points: Basal, 10 minutes after adult stress, 60 minutes after adult stress, perfusion

RESULTS

Unsupported rearing total time

Females

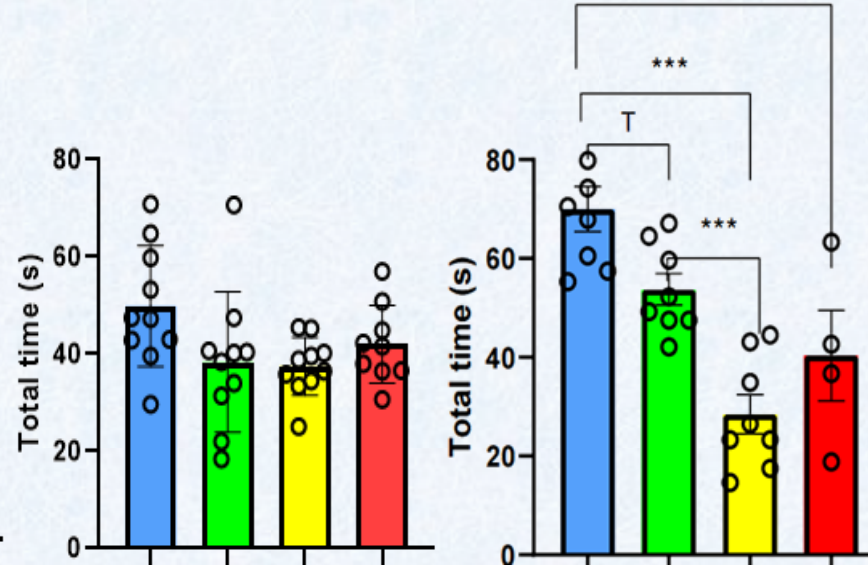
Males



Total time supported rearing

Females

Males



OPEN FIELD

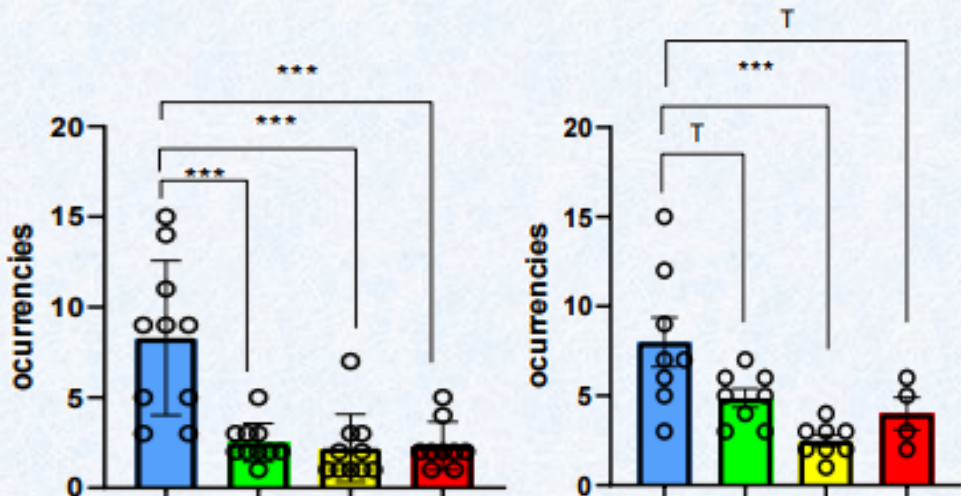
Females stressed during youth (JE and DE) are the most affected within females, showing **reduced exploratory behavior** and an anxious exploratory profile

In **contrast**, in **males**, the differences are observed in those **stressed during adulthood (AE and DE)**

Grooming frequency

Females

Males

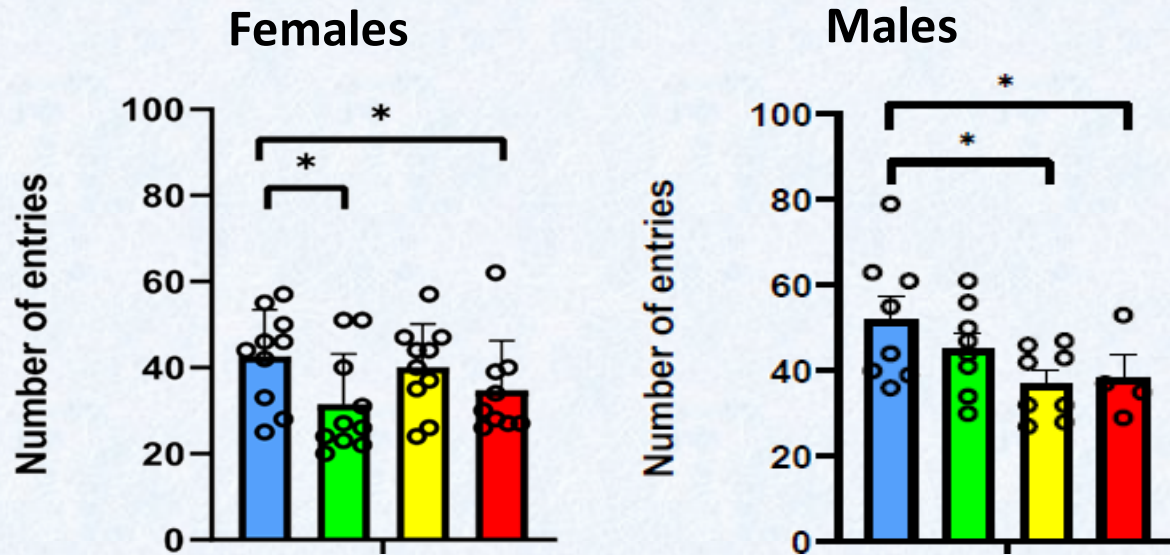


- Control
- Juvenile stress
- Adult stress
- Double stress

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

Both sexes are affected by stress

Center entries

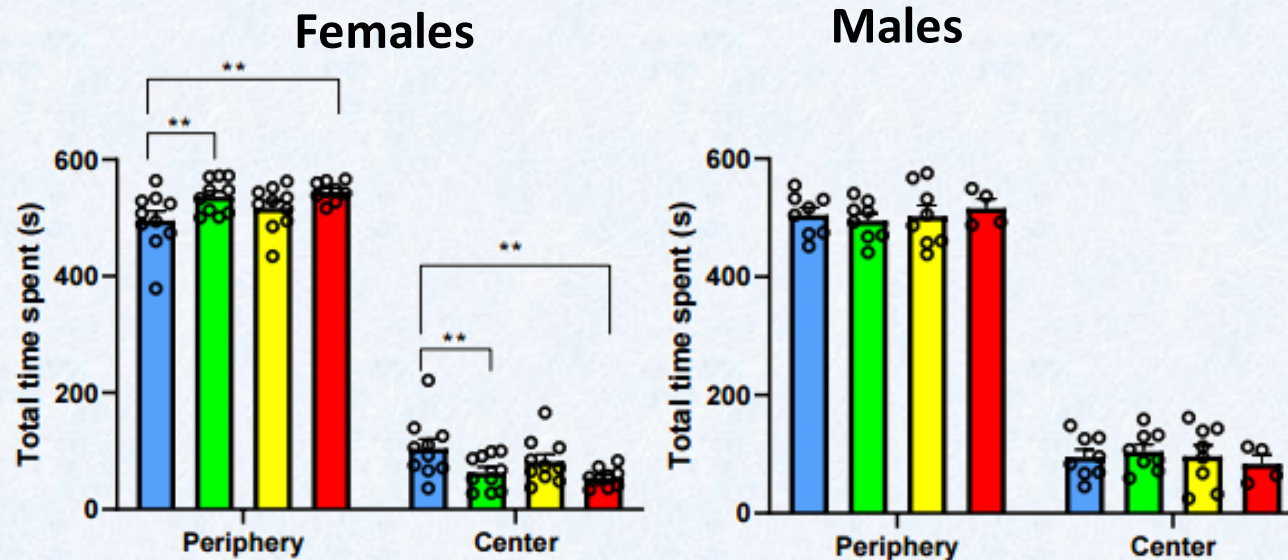


OPEN FIELD

Females stressed during youth (JE and DE) are the most affected within females, showing reduced exploratory behavior and an **anxious exploratory profile**

In contrast, in males, the differences are observed in those stressed during adulthood (AE and DE)

Time spent per zone



Both sexes are affected by stress, but females seem to be **more sensitive**

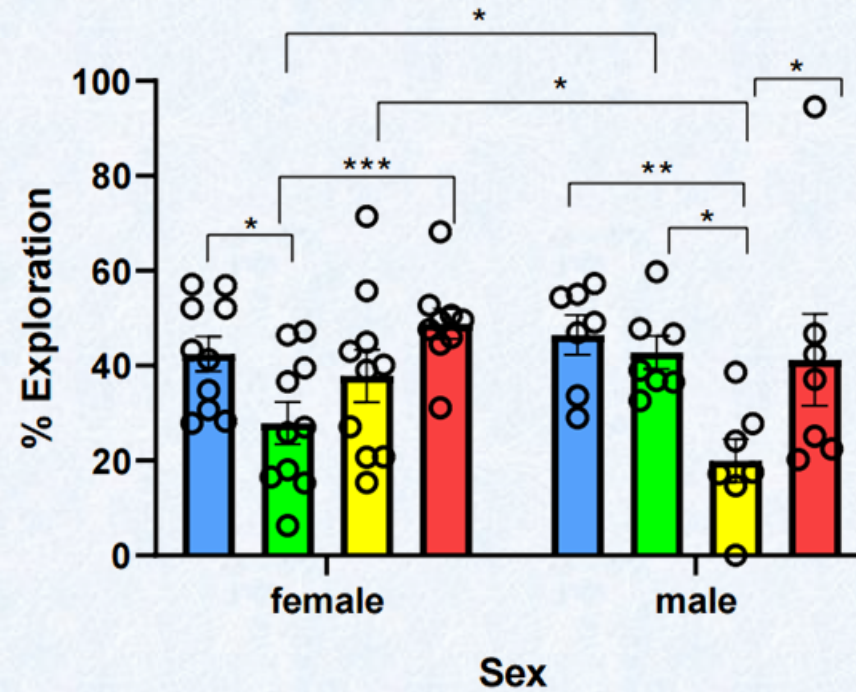
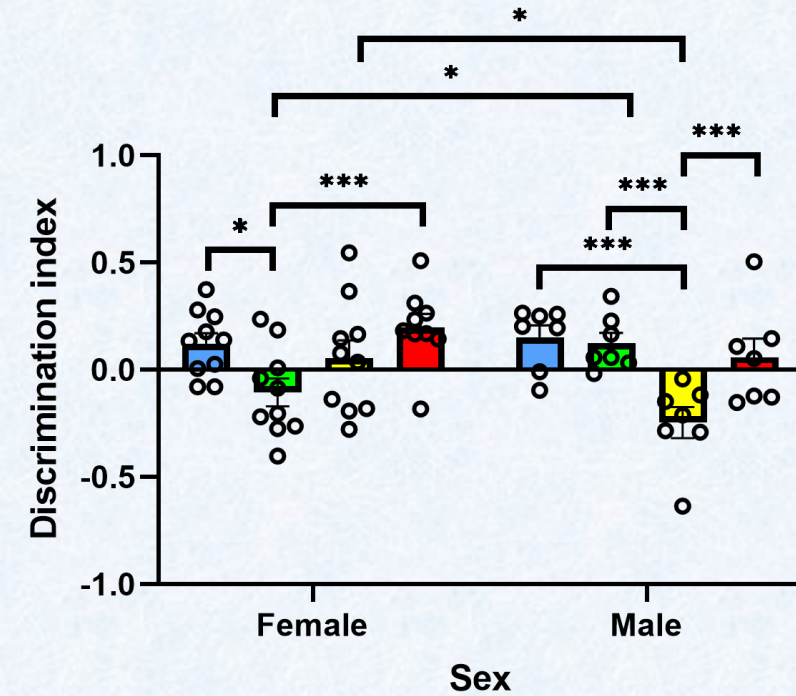
- █ Control
- █ Juvenile stress
- █ Adult stress
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MEMORY TEST

Discrimination index in Test

Relative time in new object during test



Stress **affects memory**, as measured by the **discrimination index** and the **relative time** spent on **new object**

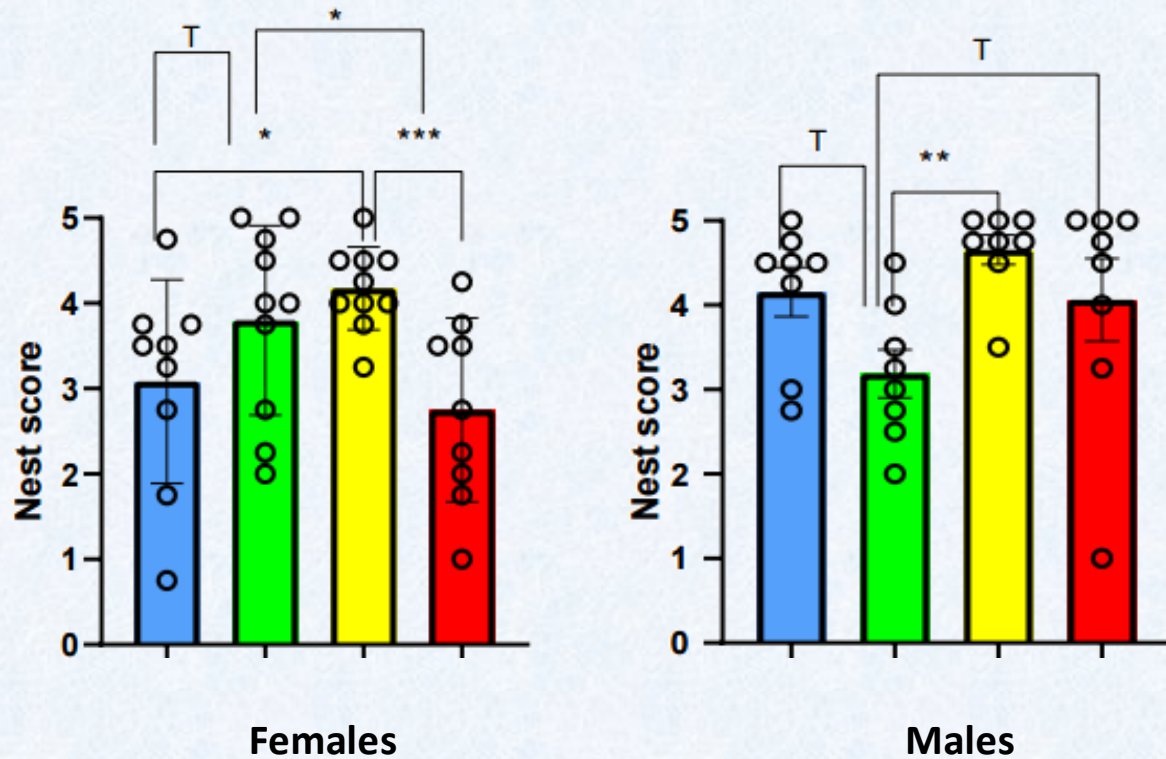
Again, **juvenile-stressed females** and **adult-stressed males** are the **most affected** within their groups

However, in memory, the **DE** group **behaves similarly** to the **control** group in both sexes

- Control
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- Adult stress
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NEST SCORES 18 H



Stress (especially adult stress) seems to be related with better scoring in both males and females.

However, DE is detrimental in females

- Control
- Juvenile stress
- Adult stress
- Double stress

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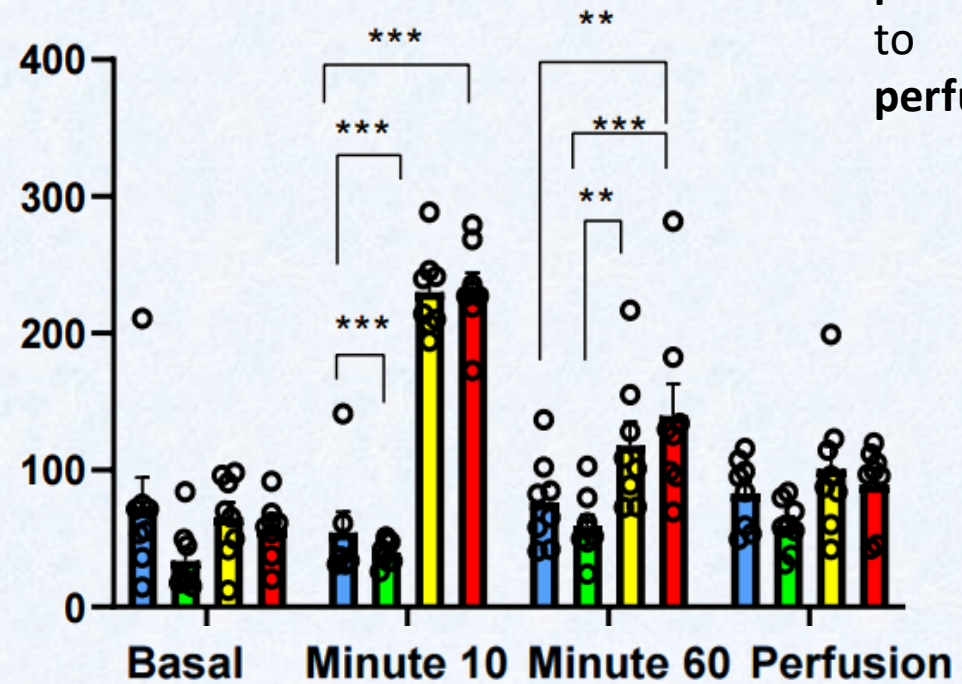
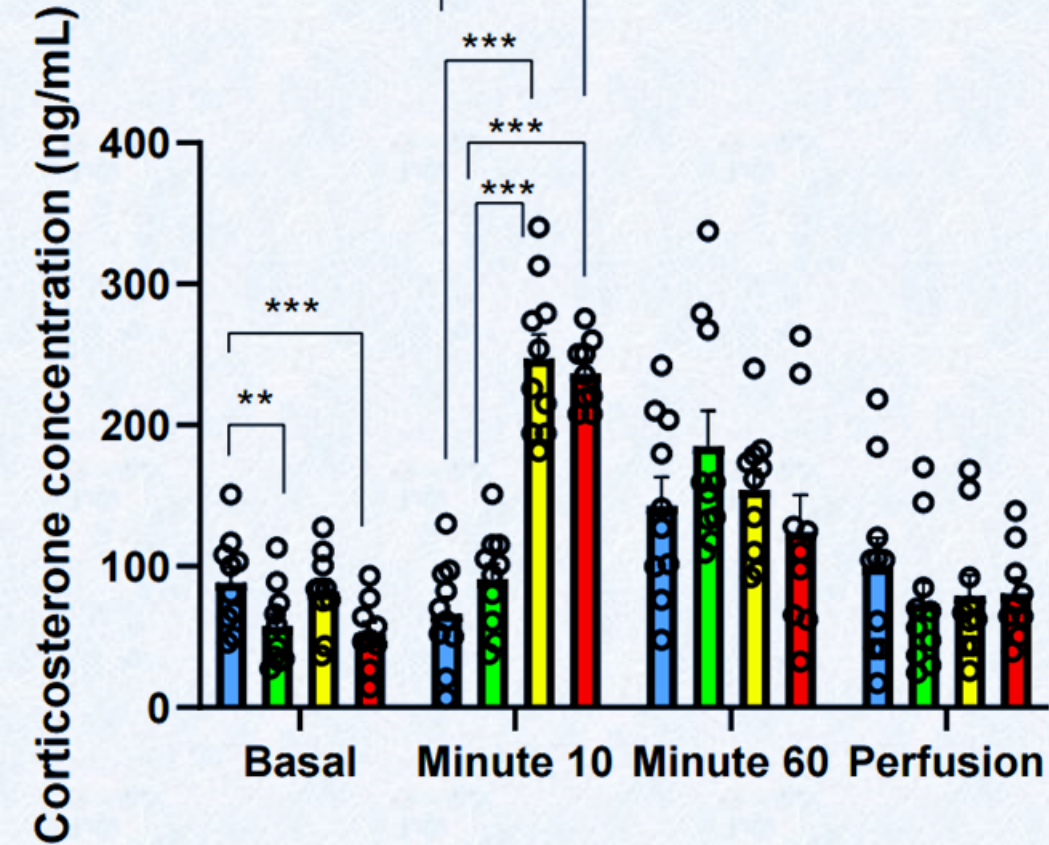
CORTICOSTERONE ELISA

Juvenile-stressed females (JE and DE) show reduced basal levels.

Females

Males

Differences at **10 minutes** are due to the **stress procedure**, and it **returns to normal levels** at perfusion time.



- █ Control
- █ Juvenile stress
- █ Adult stress
- █ Double stress

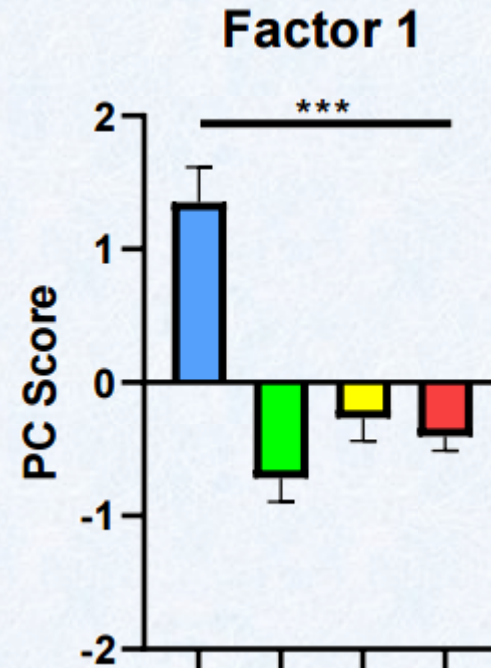
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PRINCIPAL COMPONENT ANALYSIS FEMALES

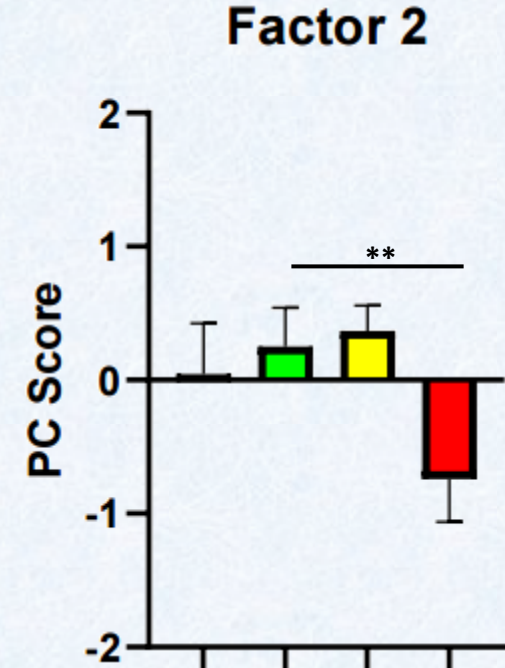
MEASURES	Factor 1	Factor 2
Relative time in object 9	0,793	
Center entries	0,550	
Basal corticosterone		0,698
Min 60 corticosterone		0,659
Nest score		0,687
Grooming frequency	0,628	
Unsupported rearing time	0,840	
Eigenvalue	2,231	1,504
% Variance (cumulative)	31,877	53,358

KMO= 0,537

p<0,001



Treatment p value <0,001



Treatment p value p=0,065

- █ Control
- █ Juvenile stress
- █ Adult stress
- █ Double stress

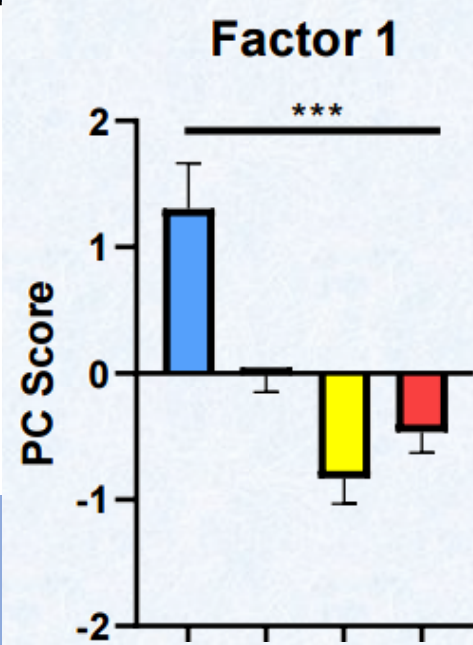
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PRINCIPAL COMPONENT ANALYSIS MALES

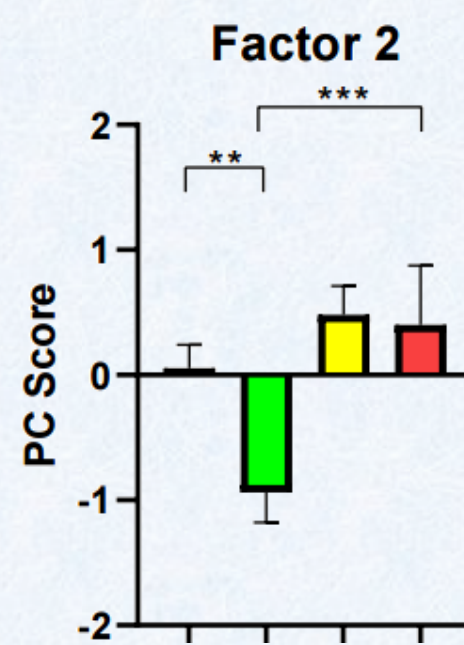
MEASURES	Factor 1	Factor 2	Factor 3
Relative time in object 9	0,672	-0,417	
Center entries			0,767
Basal corticosterone			0,896
Min 60 corticosterone		0,750	
Nest score		0,864	
Grooming frequency	0,910		
Unsupported rearing time	0,718		
Eigenvalue	2,644	1,485	1,084
% Variance (cumulative)	37,77	58,98	74,46

KMO= 0,625

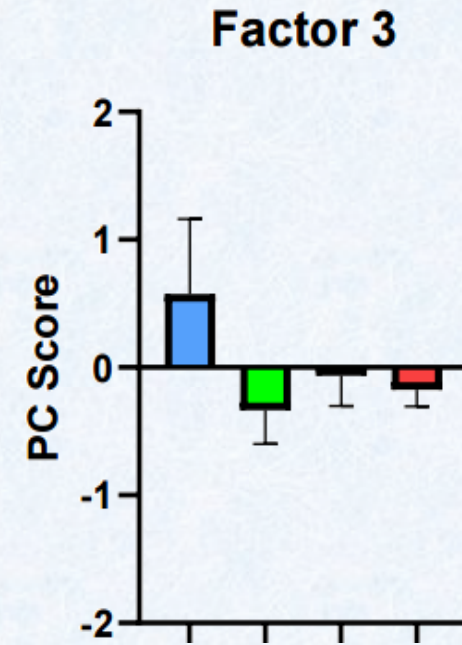
p<0,001



Treatment p value p<0,001



Treatment p value p<0,002



Treatment p value p>0,05

- █ Control
- █ Juvenile stress
- █ Adult stress
- █ Double stress

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

CONCLUSIONS

Conclusions

- (1) **Stress affects behaviors that model depression**
- (2) There are **specific differences** depending on the **developmental stage** at which **stress** occurs and the **sex** of the **mouse**
- (3) There are **specific differences** depending on the **analyzed behavior**
- (4) **Juvenile-stressed females** and **adult-stressed males** are the **most affected** within their **groups**

References

- (1) Dattani, S., Rodés-Guirao, L., Ritchie, H., & Roser, M. (2023). *Mental health*. Our World in Data. Retrieved from <https://ourworldindata.org/mental-health>
- (2) Parker, G., & Brotchie, H. (2010). Gender differences in depression. *International review of psychiatry*, 22(5), 429-436.
- (3) Hammen, C. (2005). Stress and depression. *Annu. Rev. Clin. Psychol.*, 1(1), 293-319.
- (4) Grant, K. E., Compas, B. E., Thurm, A. E., McMahon, S. D., & Gipson, P. Y. (2004). Stressors and child and adolescent psychopathology: Measurement issues and prospective effects. *Journal of Clinical Child and Adolescent Psychology*, 33(2), 412-425.
- (5) Li, B., Yang, W., Ge, T., Wang, Y., & Cui, R. (2022). Stress induced microglial activation contributes to depression. *Pharmacological research*, 179, 106145.
- (6) Nimmerjahn, A., Kirchhoff, F., & Helmchen, F. (2005). Resting microglial cells are highly dynamic surveillants of brain parenchyma in vivo. *Science*, 308(5726), 1314-1318.
- (7) Nusslock, R., & Miller, G. E. (2016). Early-life adversity and physical and emotional health across the lifespan: A neuroimmune network hypothesis. *Biological psychiatry*, 80(1), 23-32.



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