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

Víctor Martín-Aguiar, Jose Munoz-Martin, Cristina Ramírez-Pérez, Patricia Chaves-Peña, Alejandro Zea-Doña, María Inmaculada Infantes López, Margarita Pérez-Martín, Carmen Pedraza

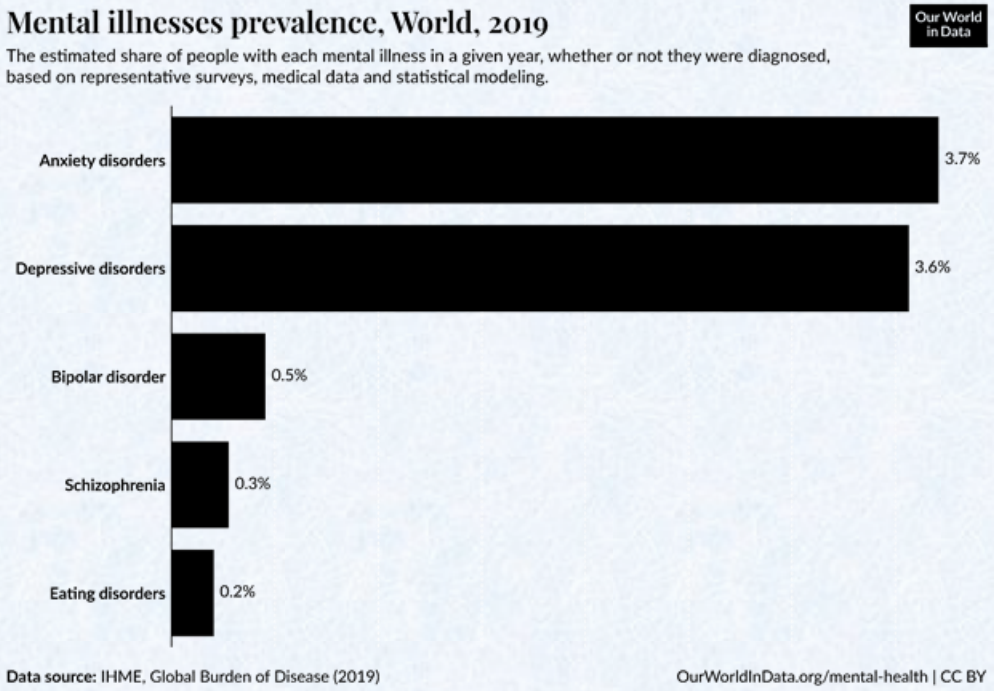
I Congreso de la Red Española de Investigación en Estrés (REIS). Bilbao 29, 30 y 31 de enero de 2025

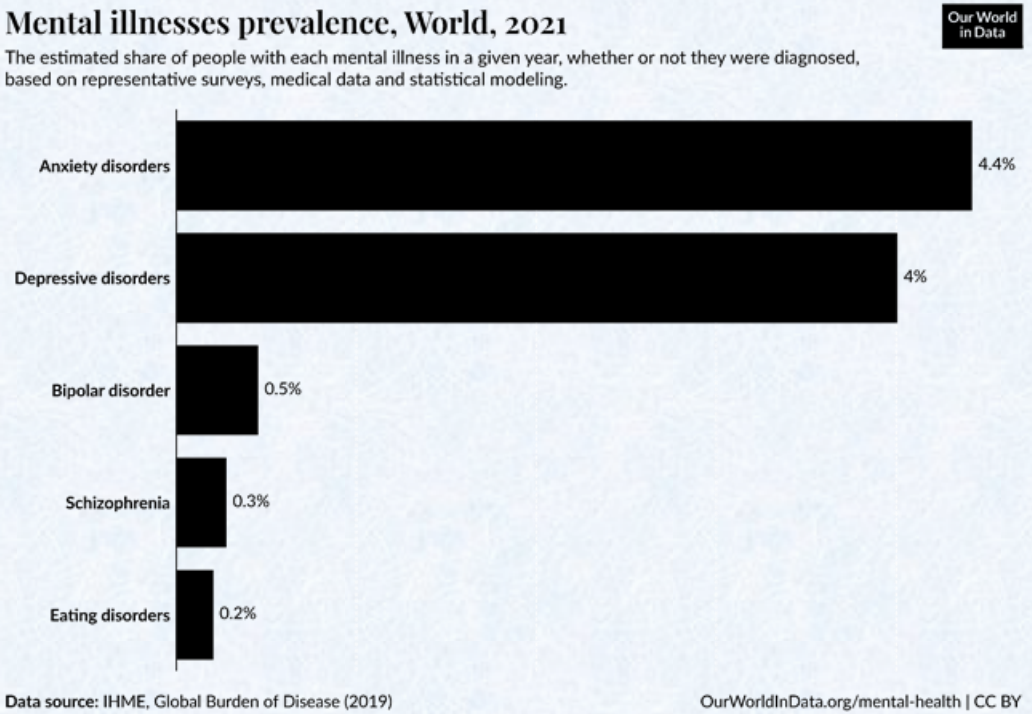
REIS
Red Española de Investigación en Estrés

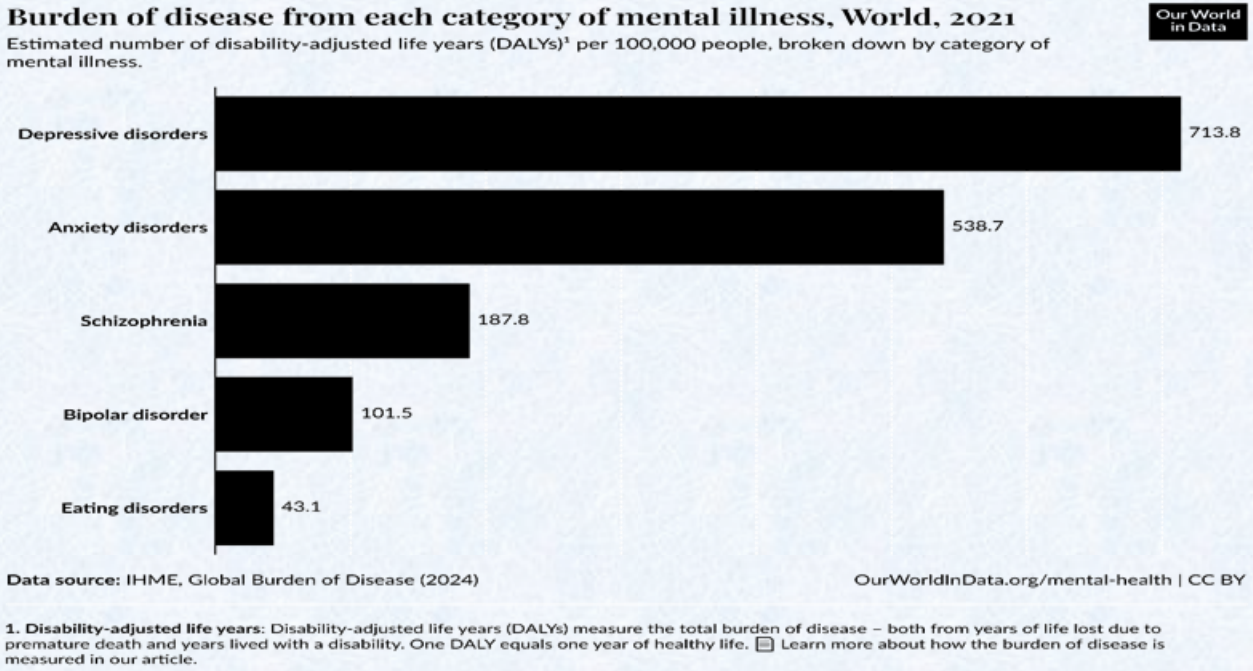
UNIVERSIDAD DE MÁLAGA

FACULTAD DE PSICOLOGÍA Y LOGOPEDIA
Universidad de Málaga

1. INTRODUCTION





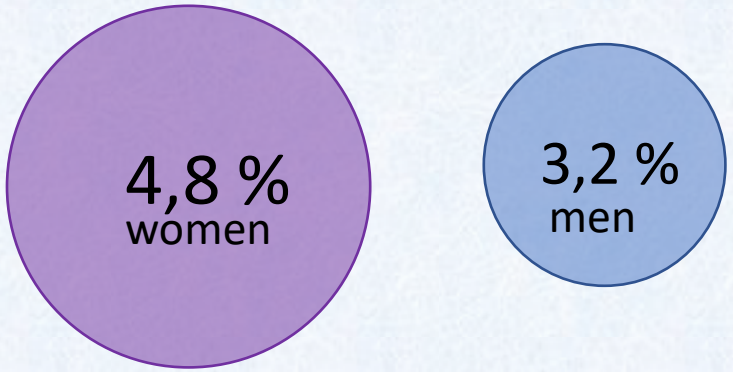


High prevalence

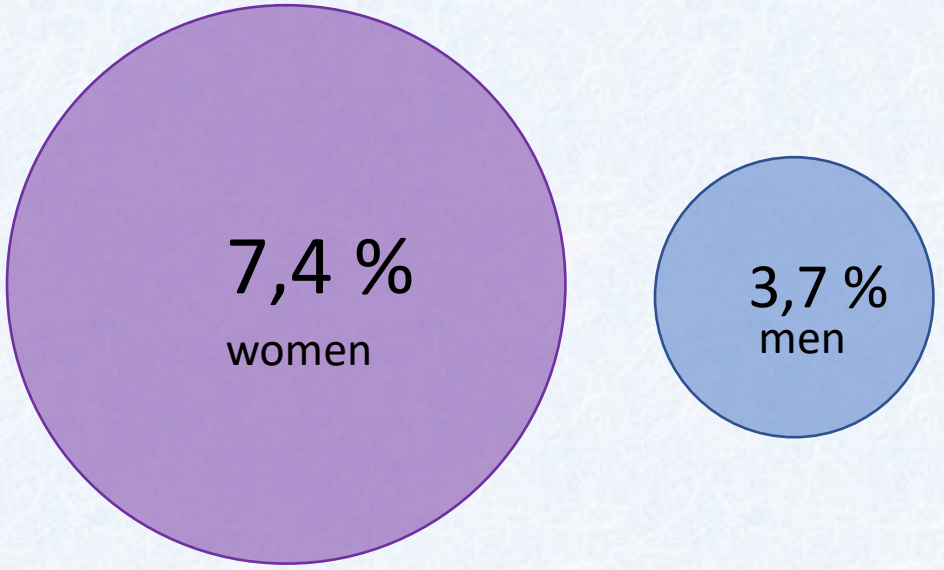
Upward tren in recent years

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)

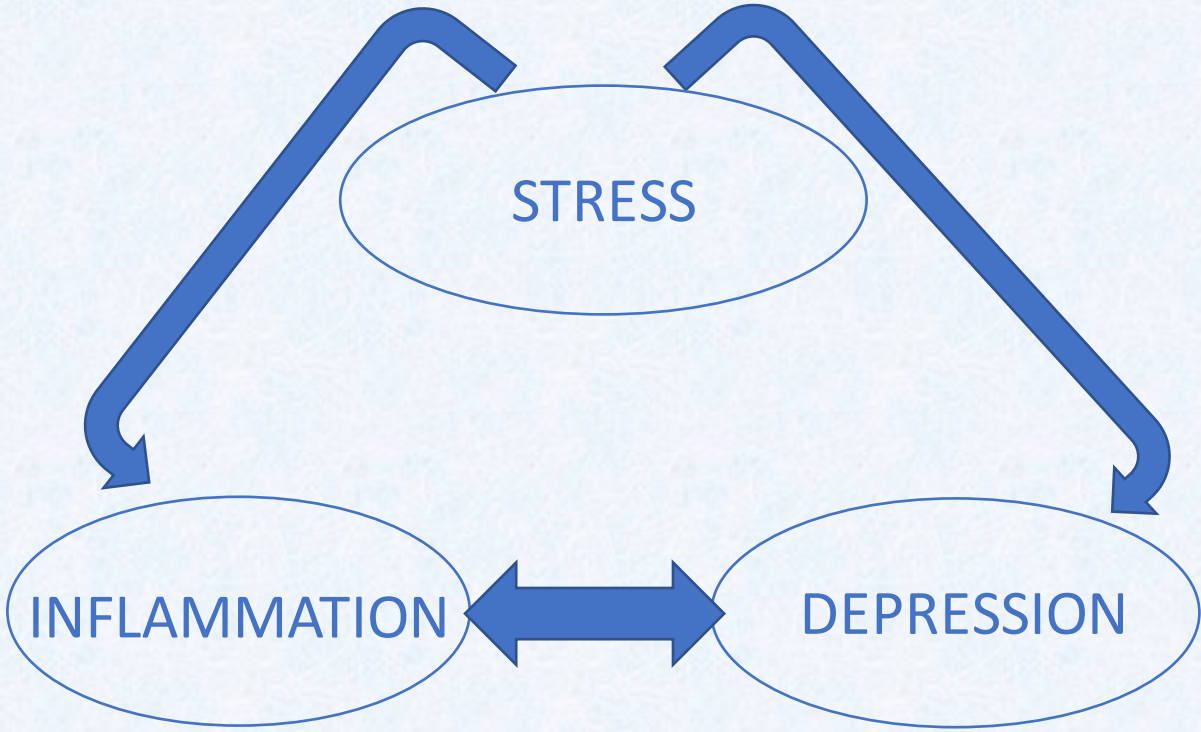
Robust and causal relationship between stress and depression (3)

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	No stress	No stress	
JE	**Juvenile stress**	No stress	
AE	No stress	**Adult stress**	N= 71 (39 F / 32 M)
DE	**Juvenile stress**	**Adult stress**	

Juvenile stress

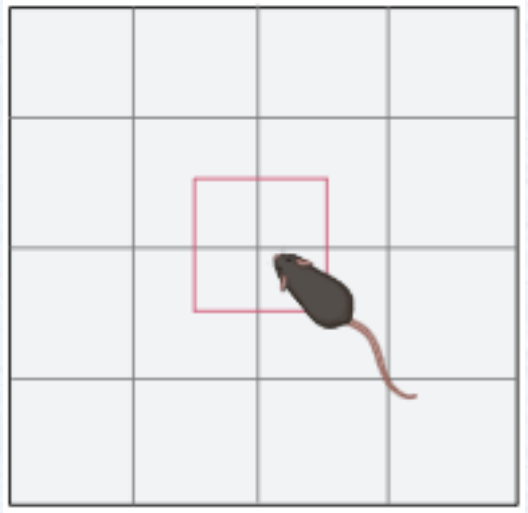
30 min (Day 21)

7 min x2(Day 24, 25)

Adult stress

30 min (Day 86)

OPEN FIELD (10 MINUTES)

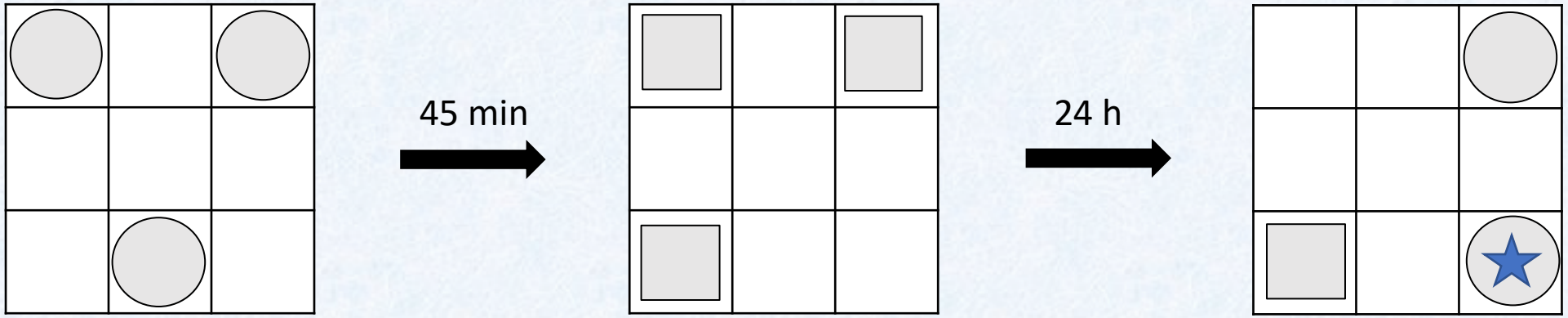


Used to assess **exploratory behavior and anxiety**.

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)



Training 1 (10 min)

Training 2 (10 min)

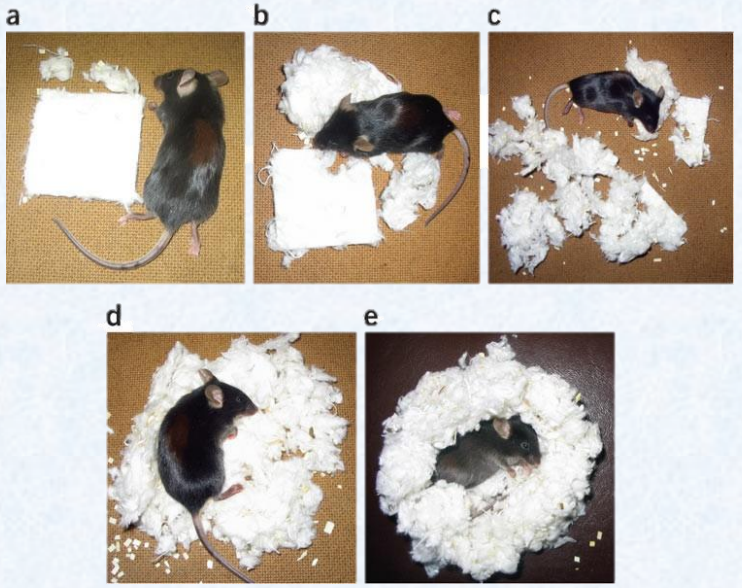
TEST (10 min)

Hippocampus dependent memory (when and where memory)

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

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

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

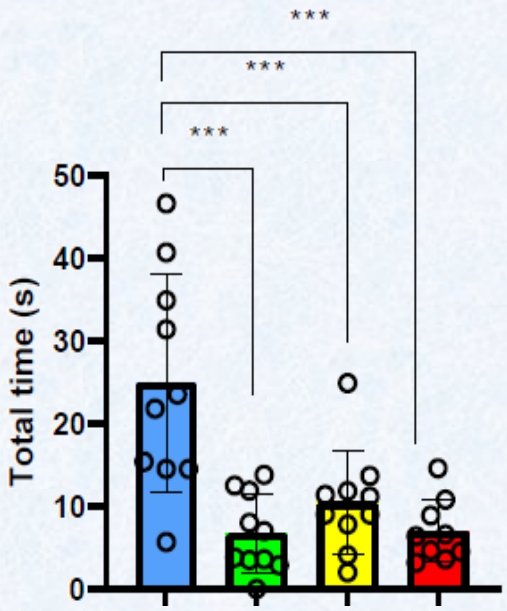
Used to analyze **corticoesterone levels** (**HPA axis** measure)

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

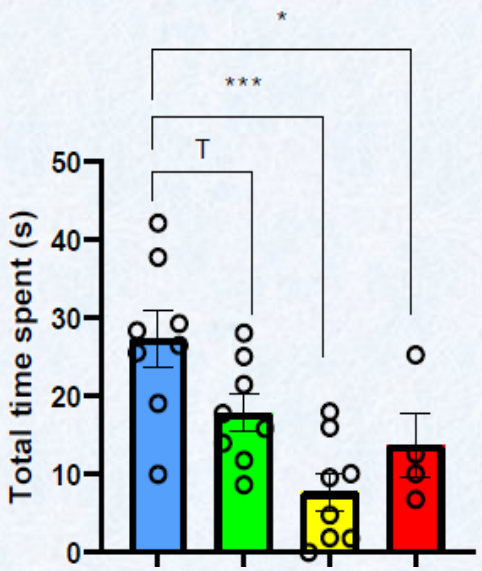
RESULTS

Unsupported rearing total time

Females

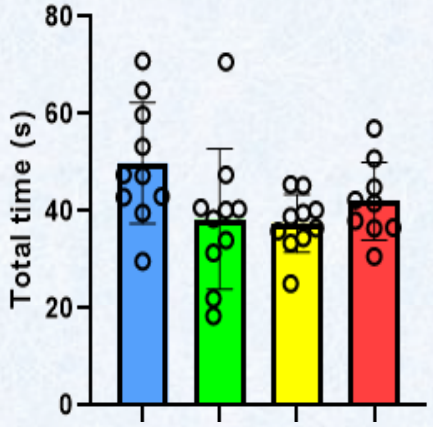


Males

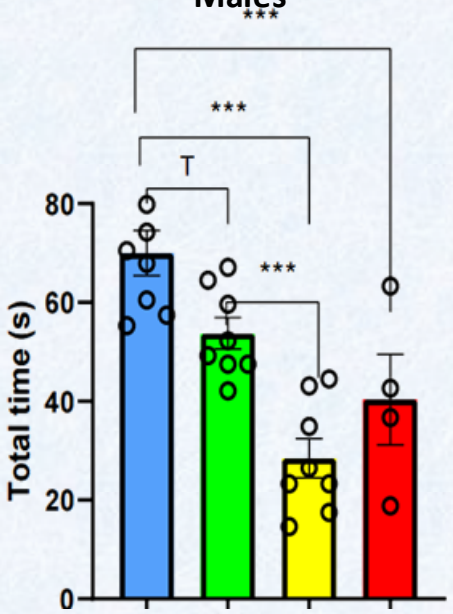


Total time supported rearing

Females

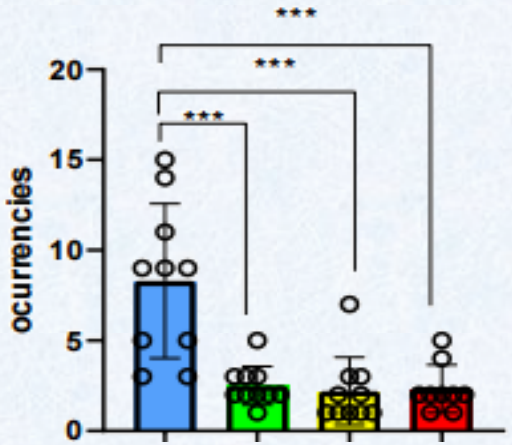


Males

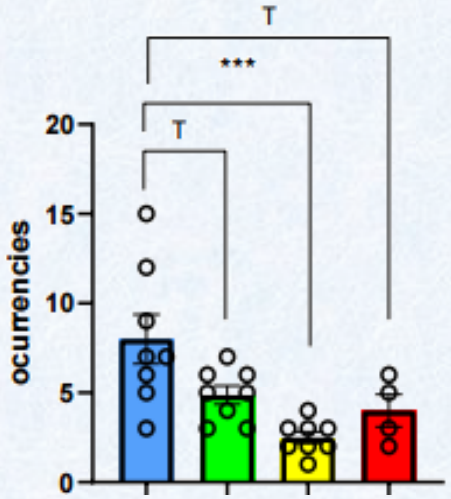


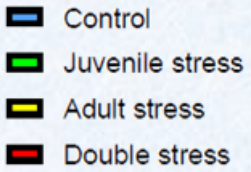
Grooming frequency

Females



Males





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

OPEN FIELD

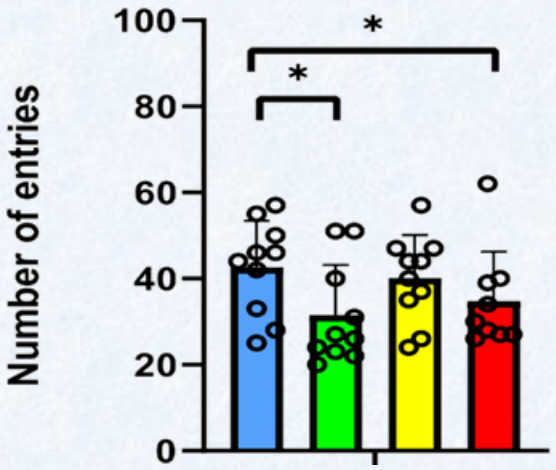
Females stressed during youth (JE and DE) are the most affected within females, showing **reduced exploratory behavior** and an anxious exploratory profile

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

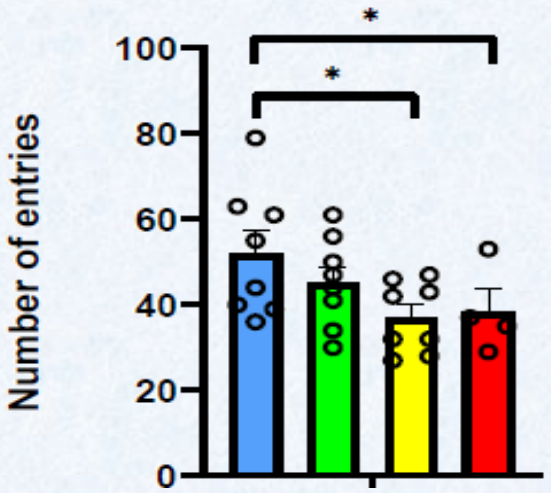
Both sexes are affected by stress

Center entries

Females

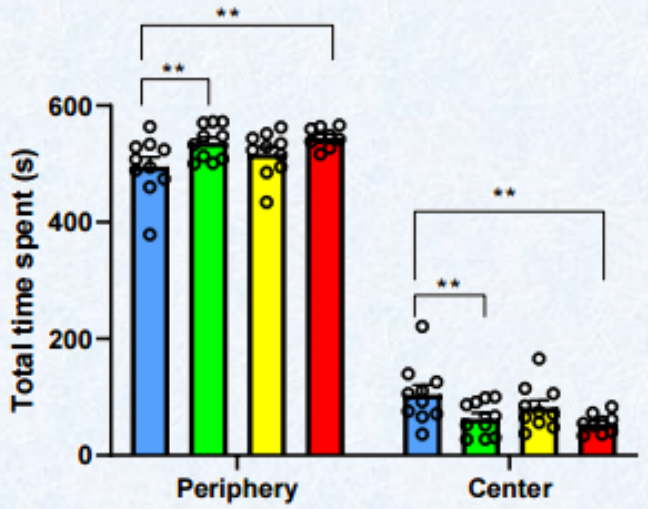


Males

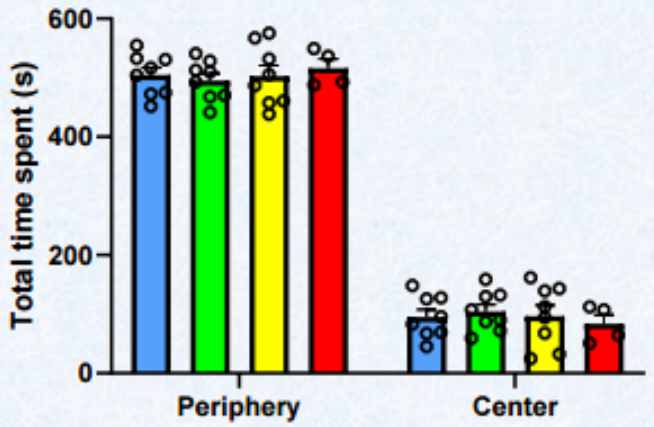


Time spent per zone

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)**

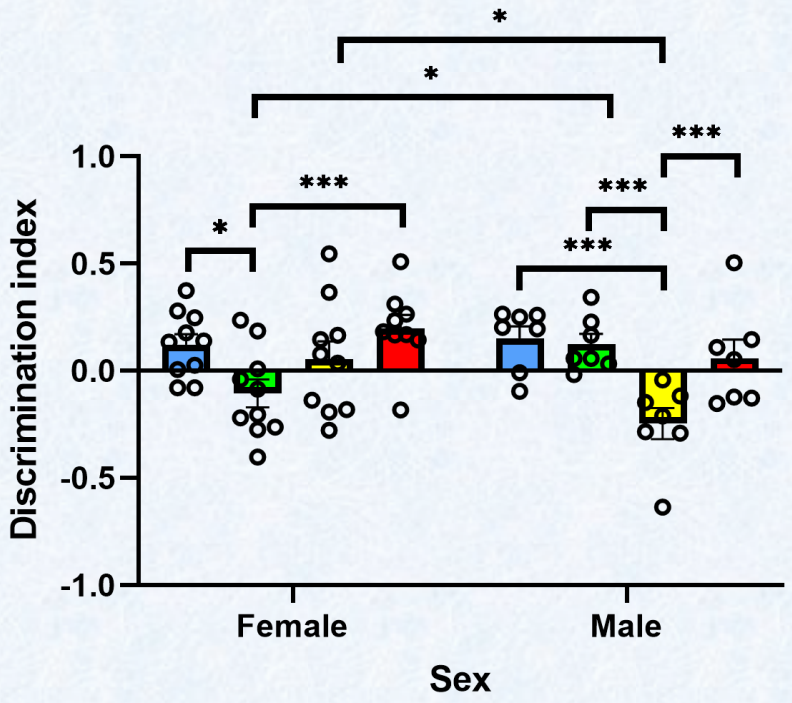
Both sexes are affected by stress, but **females** seem to be **more sensitive**

Control
Juvenile stress
Adult stress
Double stress

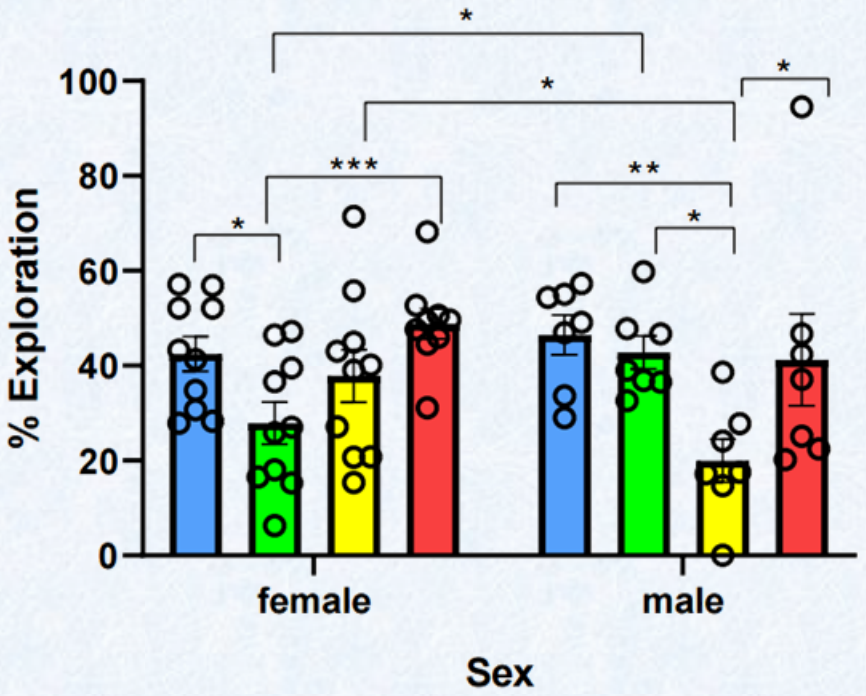
* stands for p < 0,05
** stands for p <0,02
*** stands for p <0,001
T stands for p <0,1

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**

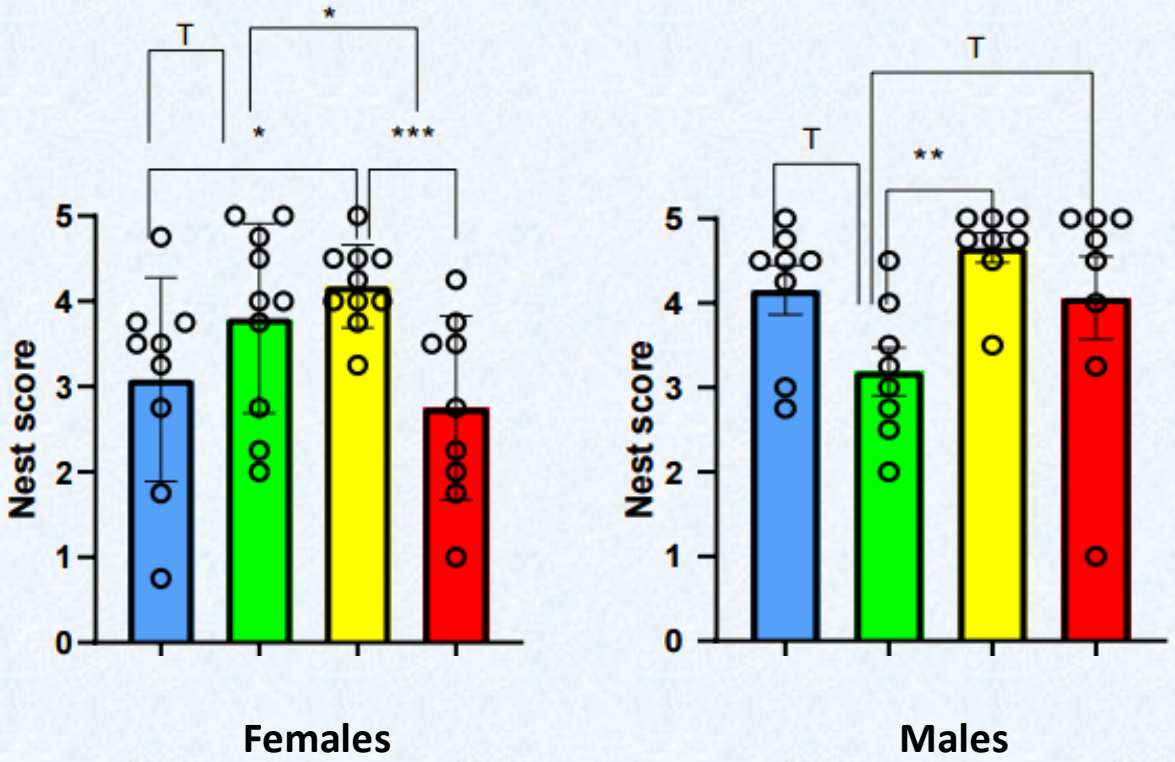
Again, **juvenile-stressed females** and **adult-stressed males** are the **most affected** within their groups

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

Control
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

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

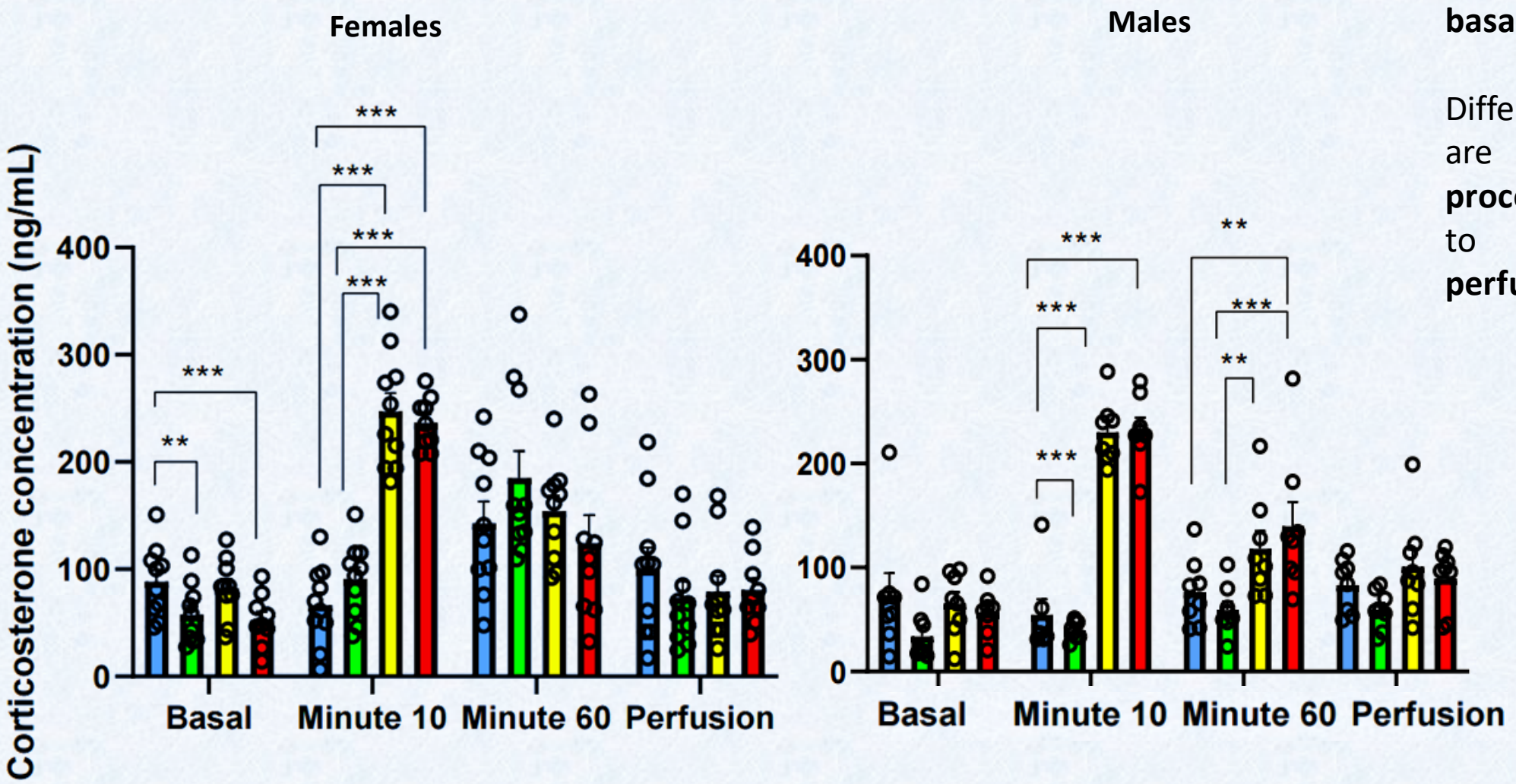
Control
Juvenile stress
Adult stress
Double stress

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

CORTICOSTERONE ELISA

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

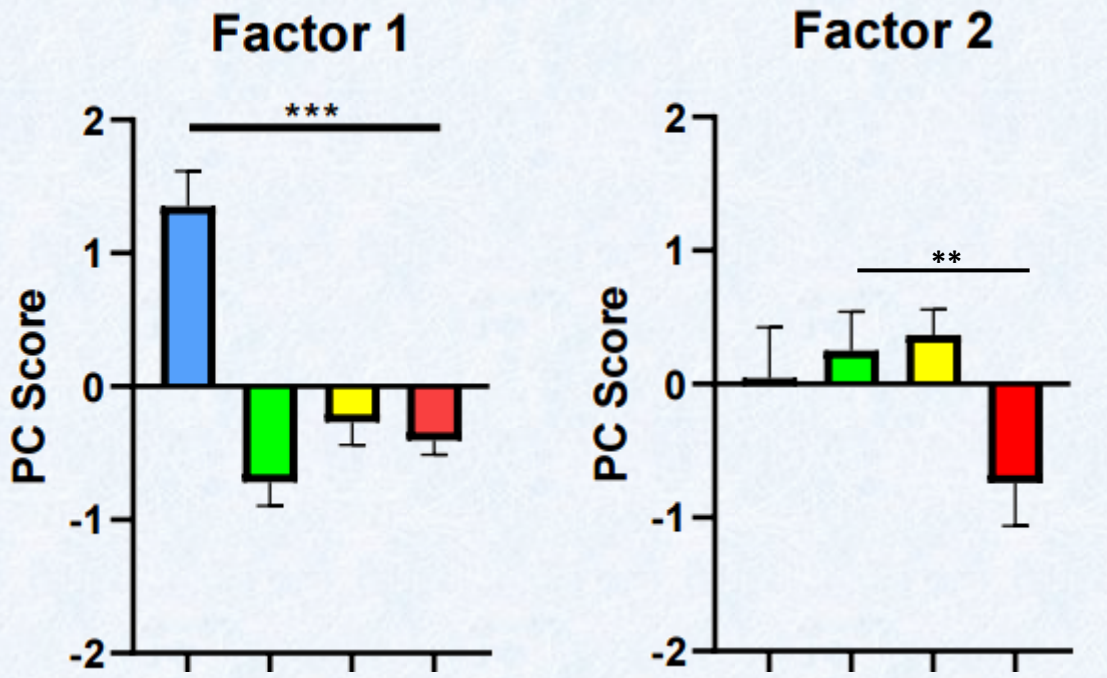
Differences at **10 minutes** are due to the **stress procedure**, and it **returns** to **normal levels** at **perfusion time.**



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

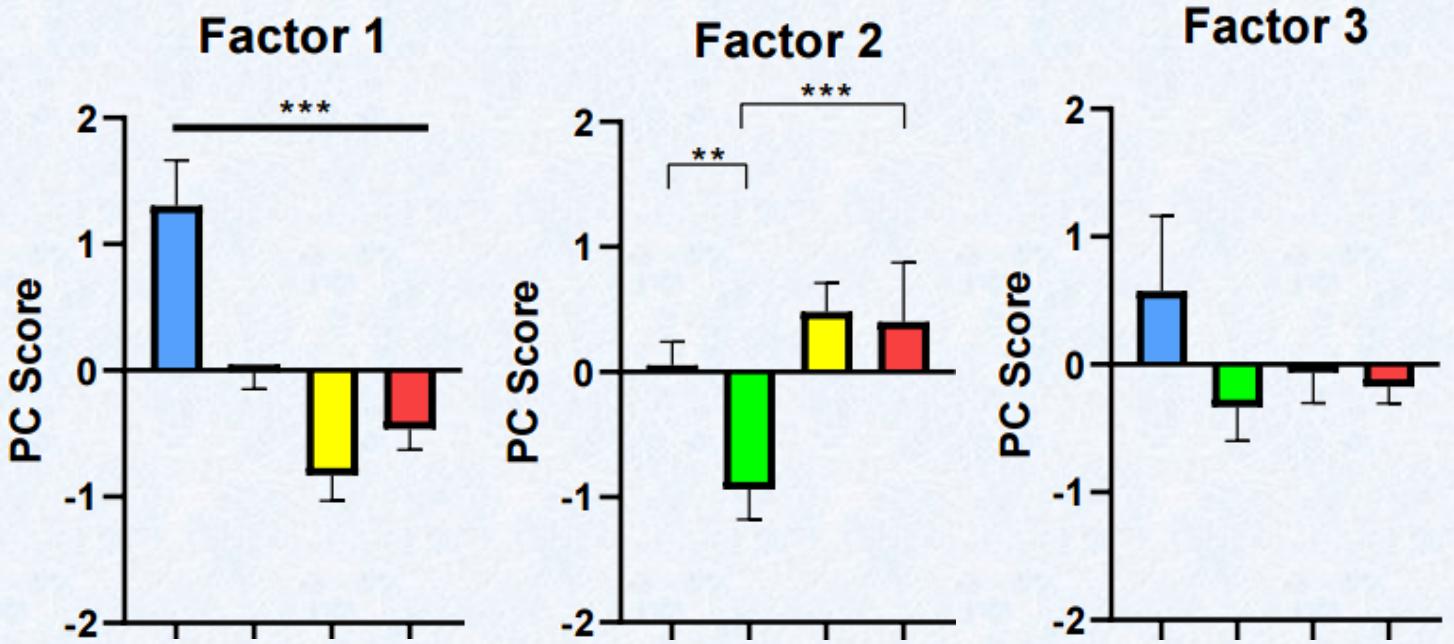
Control
Juvenile stress
Adult stress
Double stress

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

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
** stands for p <0,02
*** 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.

- **Este proyecto ha sido financiado por los siguientes proyectos**

PID2020-117464RB-I00/AEI/10.13039/501100011033

P20_00460 de la Conserjería de Conocimiento, Investigación y Universidades, Junta de Andalucía.

UMA20-FEDERJA-112 of FEDER/Junta de Andalucía-Proyectos I + D + I en el marco del programa operacional FEDER Andalucía 2014-2020.

Víctor Martín Aguiar ha sido financiado por:

- **Programa de Formación de Profesorado Universitario (FPU21/05694)** del Ministerio de Ciencia, Innovación y Universidade
- **II Plan Propio** de Investigación, Transferencia y Divulgación Científica (2022).

Neurobiology of Stress group

Patricia Chaves Peña
Víctor Martín Aguiar
José Muñoz Martín
Carmen Pedraza Benítez
Cristina Ramírez Pérez
Alejandro Zea Doña

vmaragu@uma.es