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BREAKING BONDS: NEUROBIOLOGICAL CONSEQUENCES OF THE LOSS OF PATERNAL CARE

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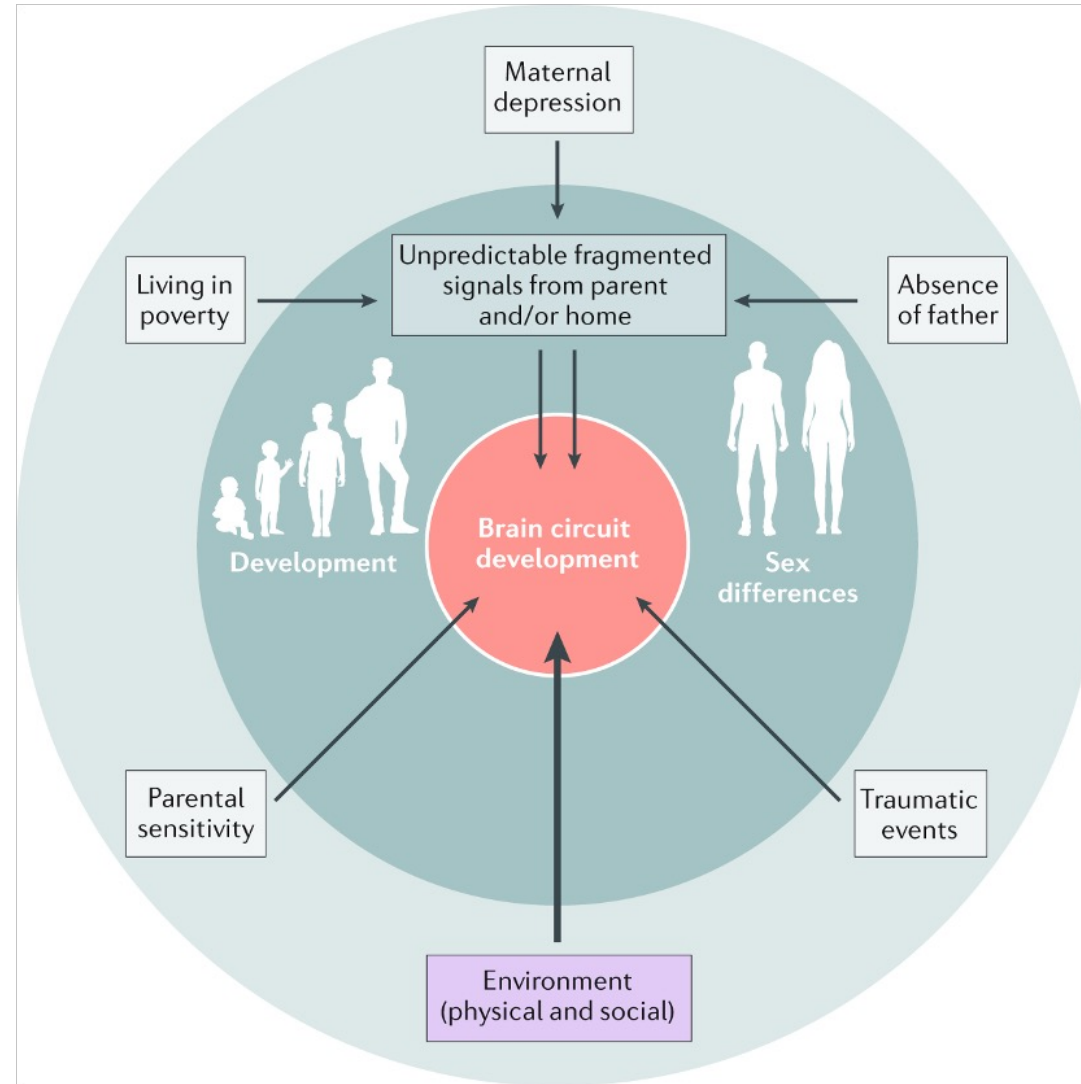
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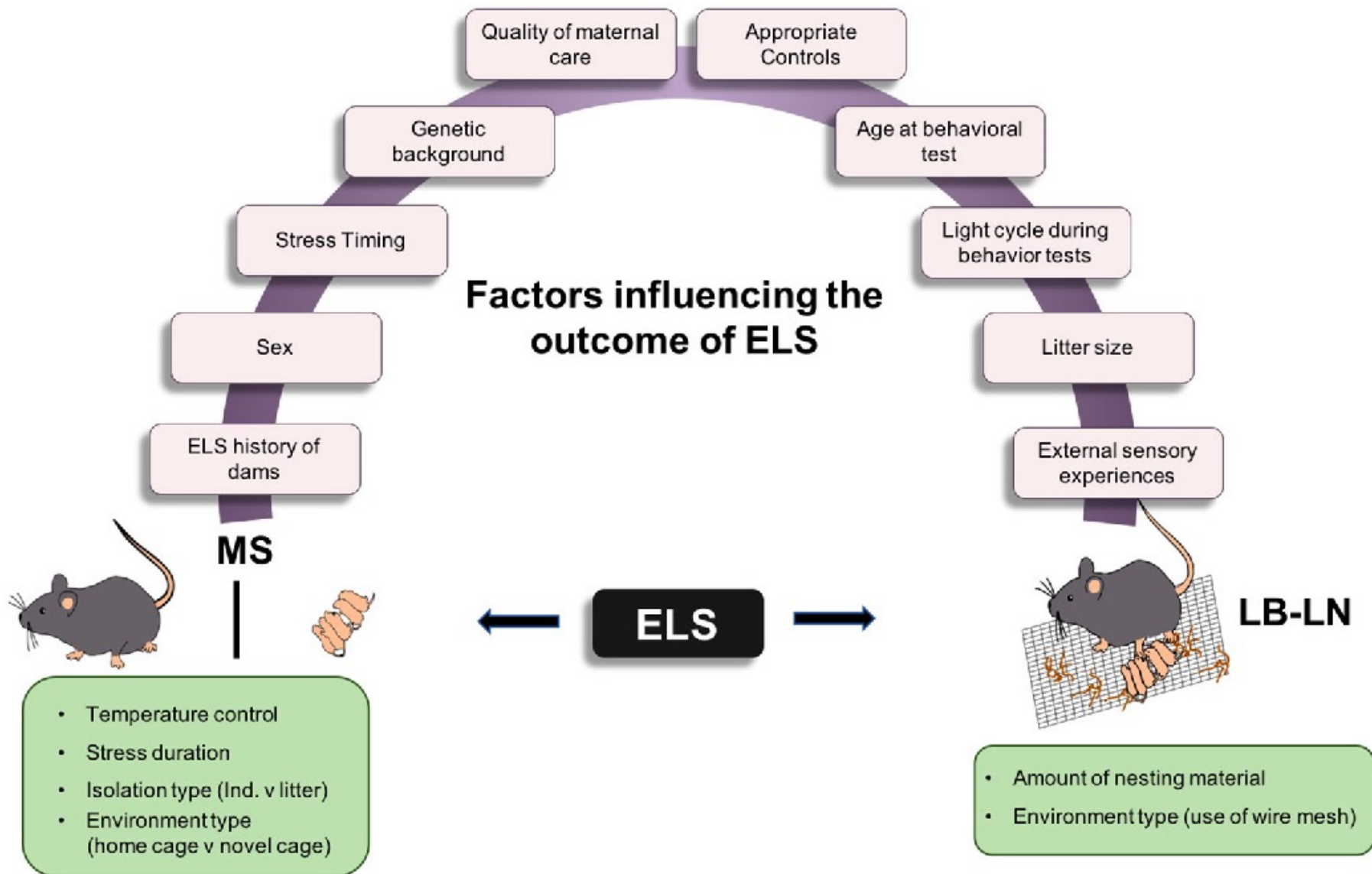
Farrah Madison







Short & Baram, 2019



Childhood psychosocial adversity

Care environment mediates stress

- Prenatal maternal stress, depression
- Postnatal caregiver unavailability/absence (mental illness, substance abuse, death)
- Depriving environments (eg institutional care)
- Child abuse or neglect



Sensitive period effects

Specific to developmental functions/domains



6–12 months
HPA axis (SHRP)

15 months
Language



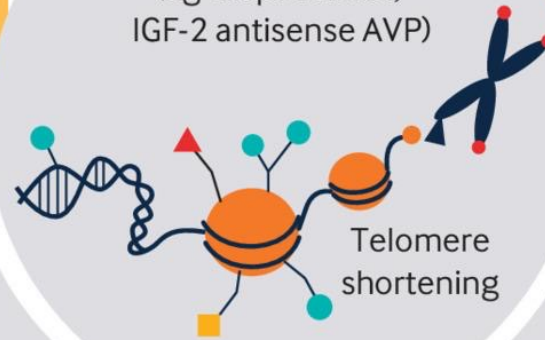
24 months
Attachment, IQ

Biological change

Epigenetic changes

Genetic endowment
Genetic variants alter susceptibility to adversity
• eg 5-HTTLPR, BDNF, FKBP₅, MAOA poly-morphisms

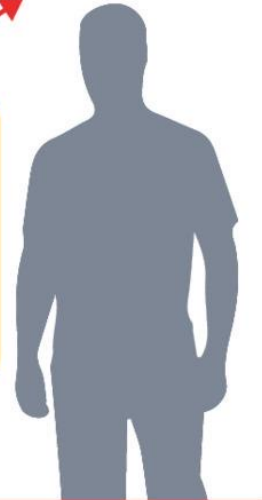
DNA methylation (eg GR promoter, IGF-2 antisense AVP)



Telomere shortening

Developmental trajectory
• Biological change is embedded in behaviour (e.g. substance use, exercise, diet, stress management)

Adult outcomes



Increased risk of:

- Cognitive deficits
- Disease
- Psychopathology
- Social problems, (unemployment, incarceration)

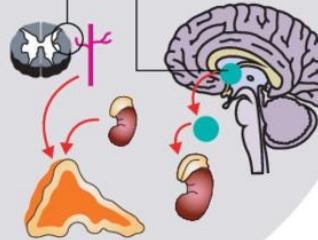
- Reduced volume of key regions
- Neurotransmitter changes
- Altered functional activity, tract connectivity

Neurodevelopmental disruption

Inflammation

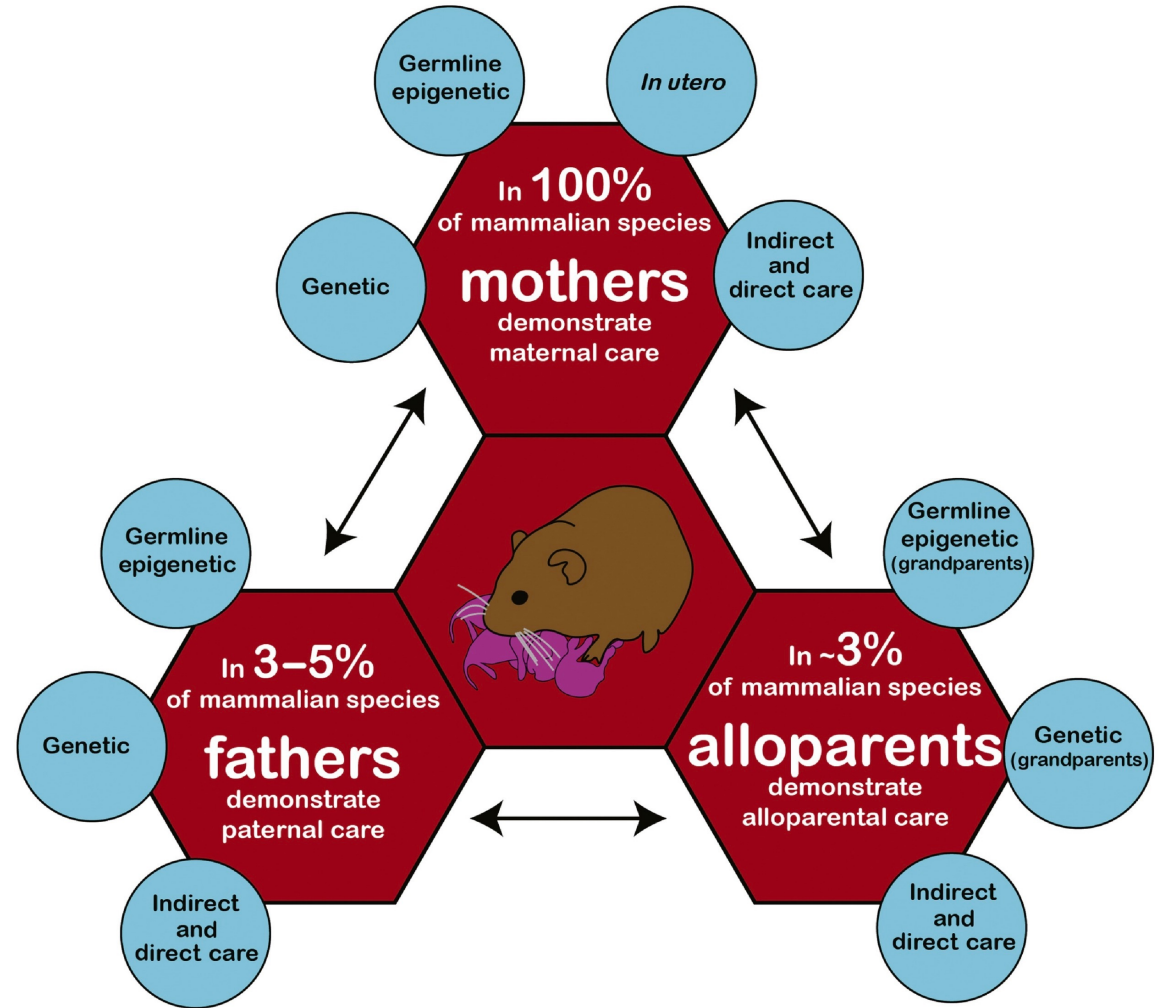


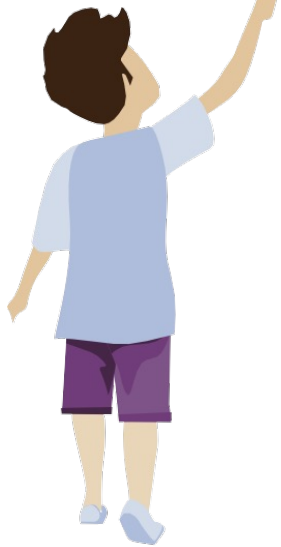
Altered HPA and sympatho-medullary axes



Reprogramming of stress and immune regulatory systems

BIPARENTAL CARE IS RARE IN MAMMALS





Consequences of Father Absence

2x Greater Risk of **Infant Mortality**

More Likely to Have **Behavioral Problems**

More Likely to **Face Abuse** and Neglect

More Likely to **Abuse Drugs** and Alcohol

¹U.S. Census Bureau. (2022). Living arrangements of children under 18 years old: 1960 to present. Washington, D.C.: U.S. Census Bureau.

²National Fatherhood Initiative® 2019. *Father Facts: Eighth Edition*. Germantown, MD: National Fatherhood Initiative®.

MODELING FATHER ABSENCE IN THE LAB

California mouse (*Peromyscus californicus*)

Genetically monogamous

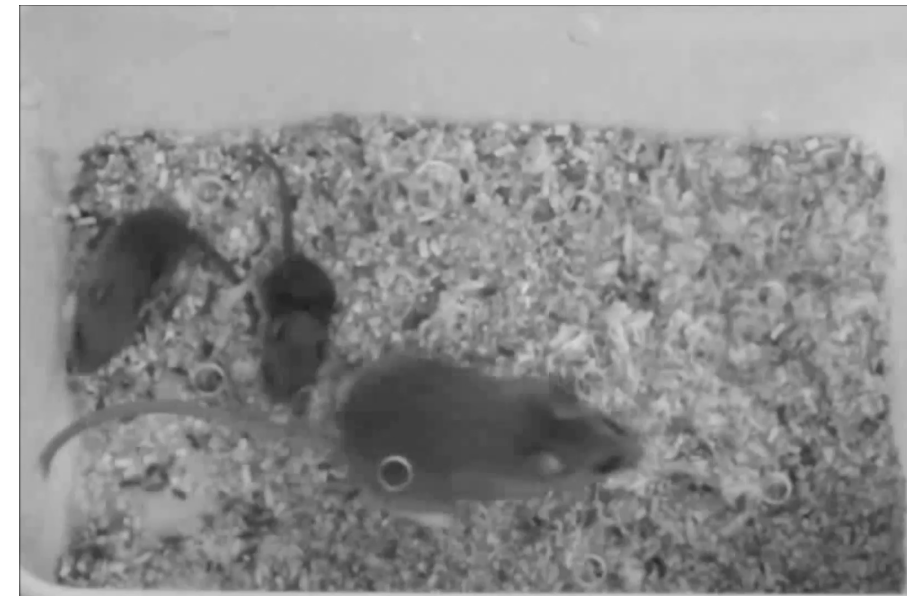
Biparental; father presence necessary for survival in wild

Ethologically-relevant species for studying father absence

Permanently remove the paternal male after birth



Image © Mark A. Chappell

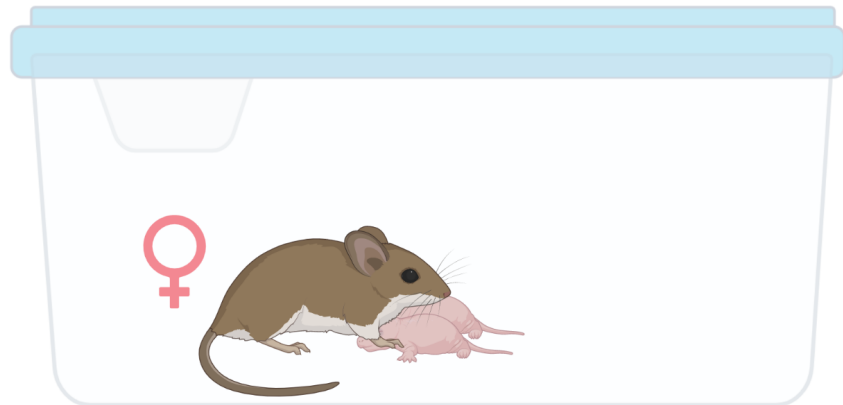


Video: Molly Hyer

Biparental Care

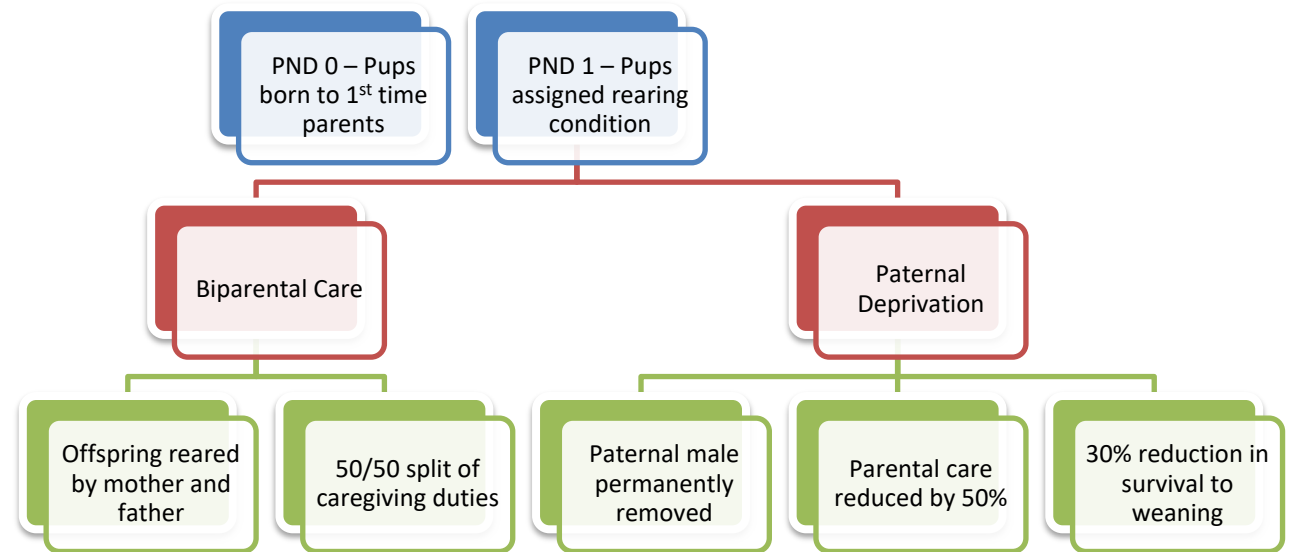


Paternal Deprivation



Created by BioRender

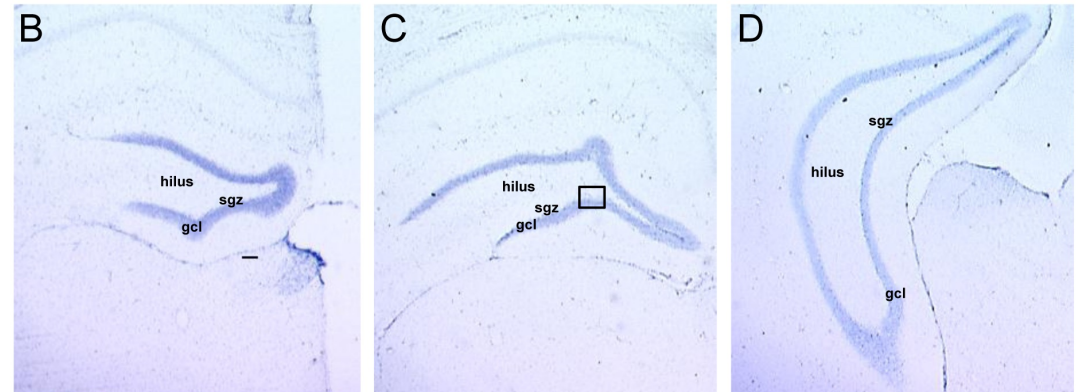
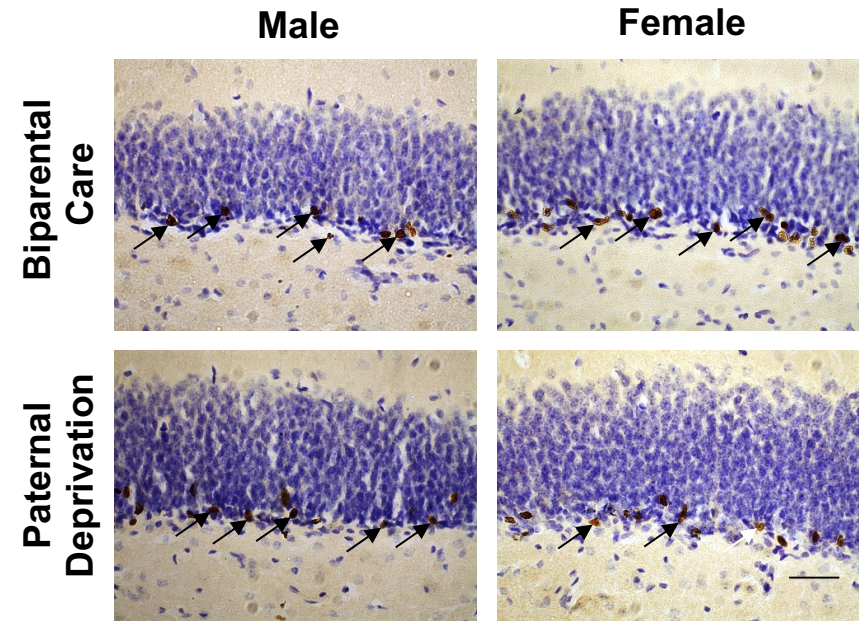
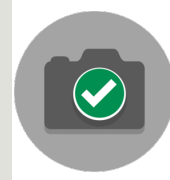
Paternal Deprivation Timeline



EFFECTS OF PATERNAL DEPRIVATION ON HIPPOCAMPAL STRUCTURAL PLASTICITY

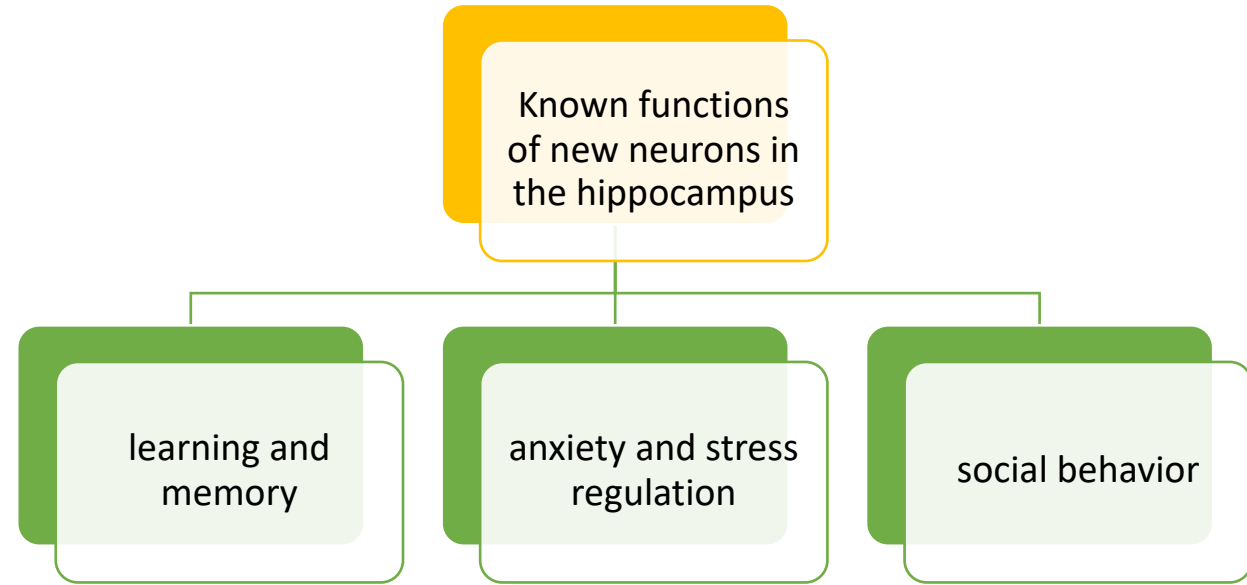
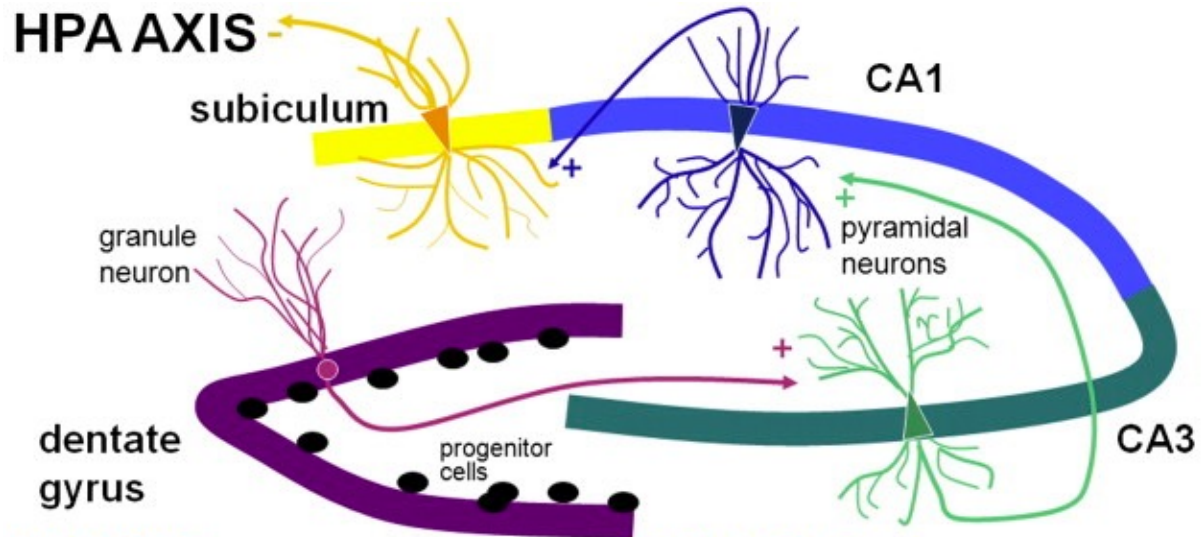
Reduced hippocampal neurogenesis (females only)¹

Reduced volume of hippocampal dentate gyrus²



¹Glasper et al, 2018, PMID: 29487509

²Madison et al., 2022, PMID: 35908654

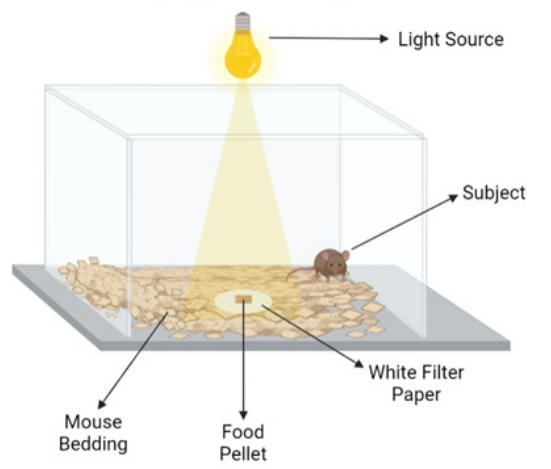
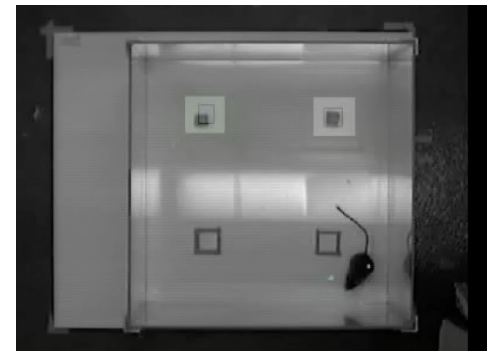




Increased passive-stress coping behavior during forced swim test ¹

Decreased object recognition in chronically-stress females ²

Increased anxiety-like behavior during novelty suppressed feeding testing ³

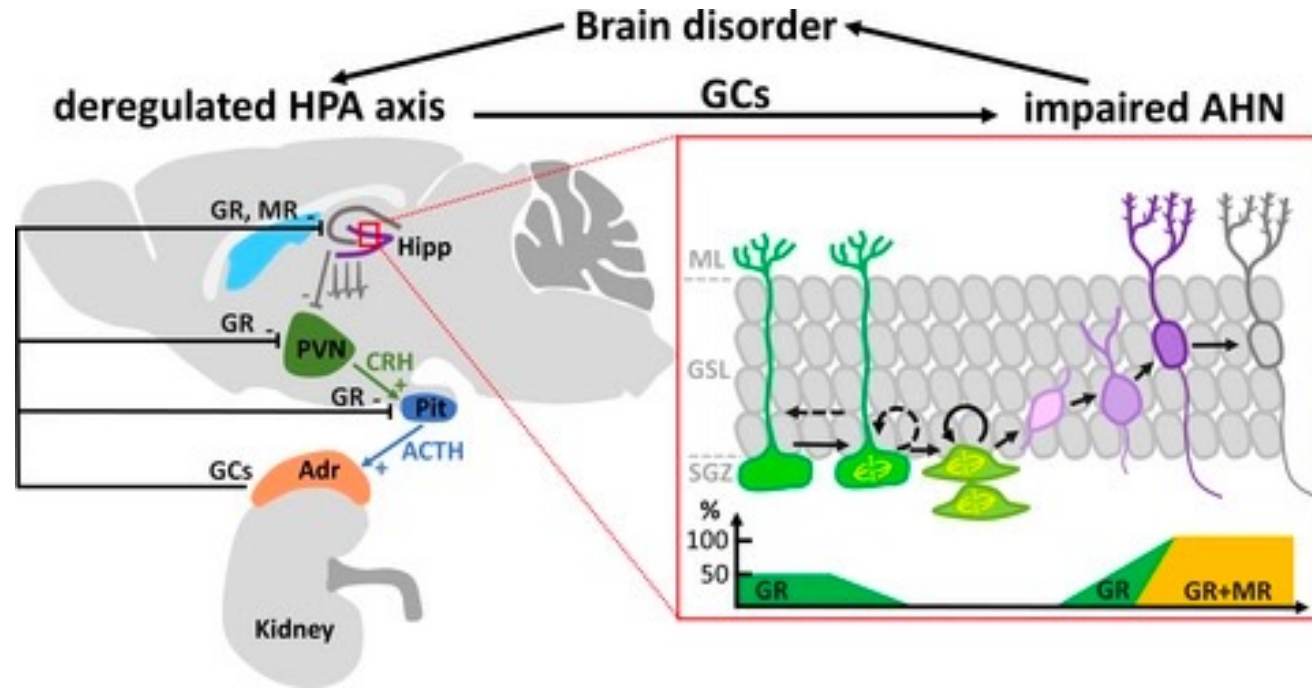


PATERNAL DEPRIVATION IMPAIRS STRESS-RELATED BEHAVIORS

¹Glasper et al, 2018, PMID: 29487509

² Agarwal P et al. 2020 PMID: 31669457

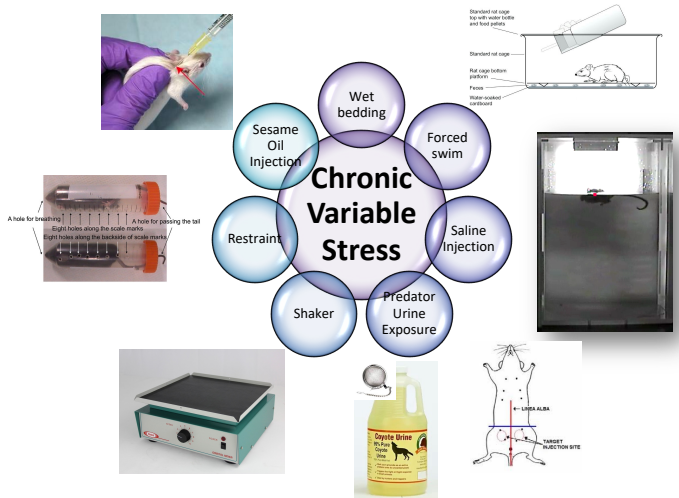
³ Walker et al, in prep



WHAT ROLE DO STRESS HORMONES PLAY IN PATERNAL DEPRIVATION?



PATERNAL DEPRIVATION MAY NOT ALTER CIRCULATING CORT IN ADULTHOOD



Chronic variable stress increased circulating CORT overall

CORT concentrations similar in control-reared and paternally deprived mice without stress

Blunted CORT response in paternally-deprived males after CVS



STRESS-AXIS FOLLOW UP STUDIES

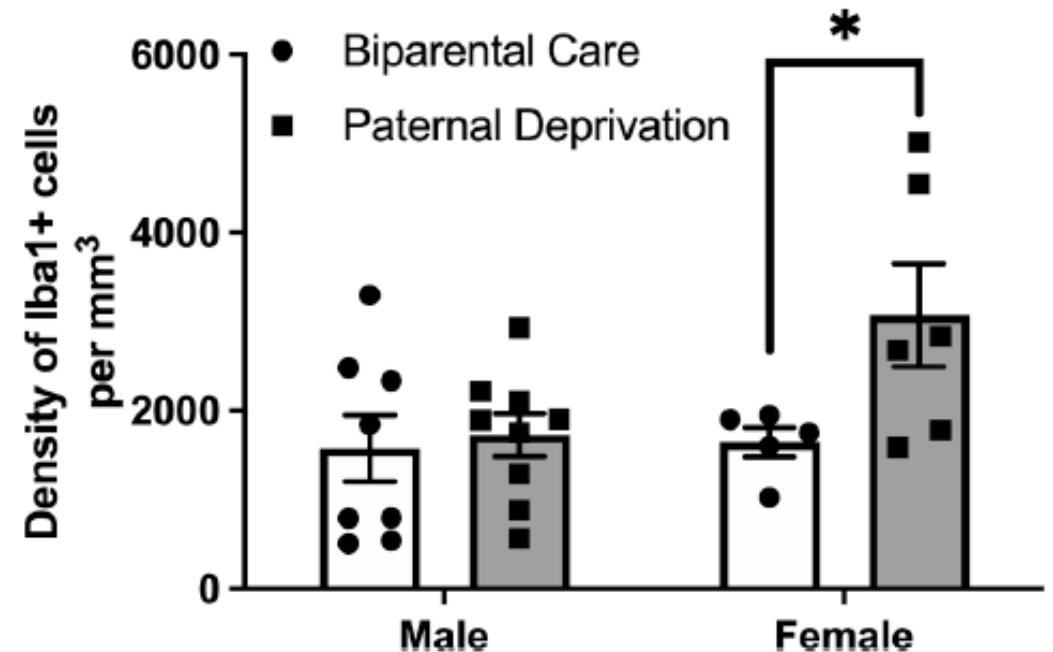
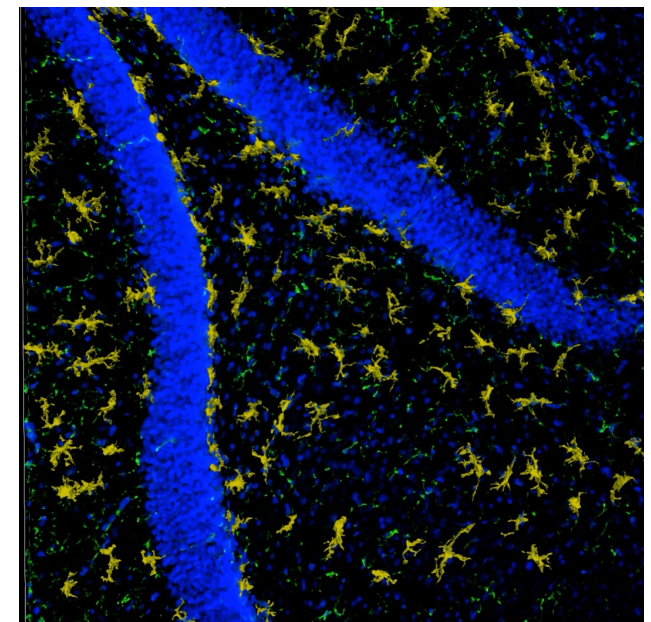
Determine if CORT is altered earlier in development (i.e., early neonatal period; adolescence)

Examine paternal deprivation effects of HPA axis function beyond just the adrenal cortex (i.e., CRH, ACTH)

Paternal deprivation increases density of microglia in dentate gyrus in adult females¹

- No alteration in microglia number
- No alteration in microglia state

Region-specific pro-inflammatory cytokine production similar in control-reared and paternally-deprived mice²



¹ Madison et al., 2022, PMID: 35908654

² Walker et al, revision in prep

EFFECTS OF
PATERNAL
DEPRIVATION
ON ADULT
FEMALES

Reduced adult hippocampal neurogenesis in the dentate gyrus

Decreased novel object recognition following chronic variable stress

Increased microglia density in hippocampal dentate gyrus

Hippocampus
regulates:

learning and
memory

anxiety and
stress
regulation

social
behaviors



What about
social behaviors?

THE CALIFORNIA MOUSE

Genetically monogamous

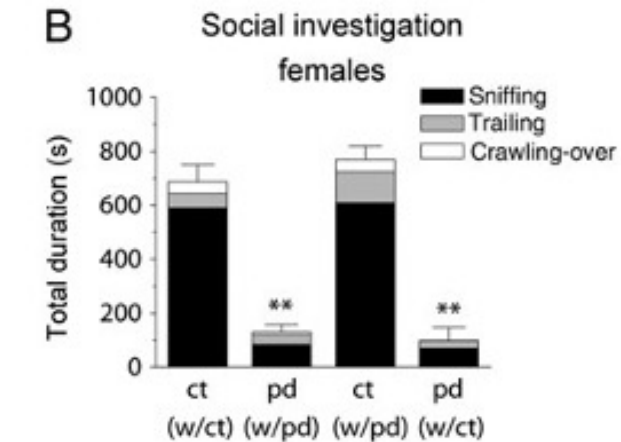
- Form enduring pair bonds
- 24 hrs of cohabitation leads to partner preference

Ethologically-relevant species for studying social behavior disruption



Image © Mark A. Chappell

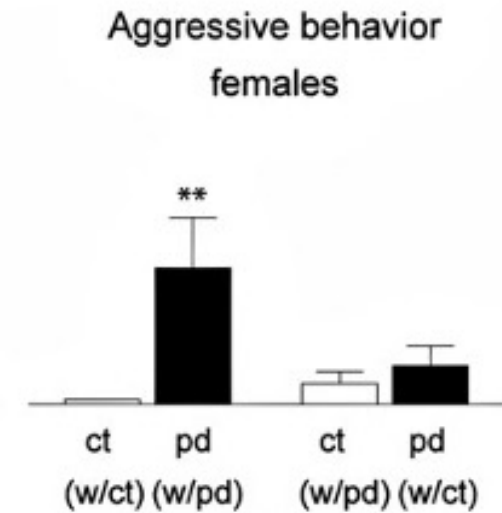
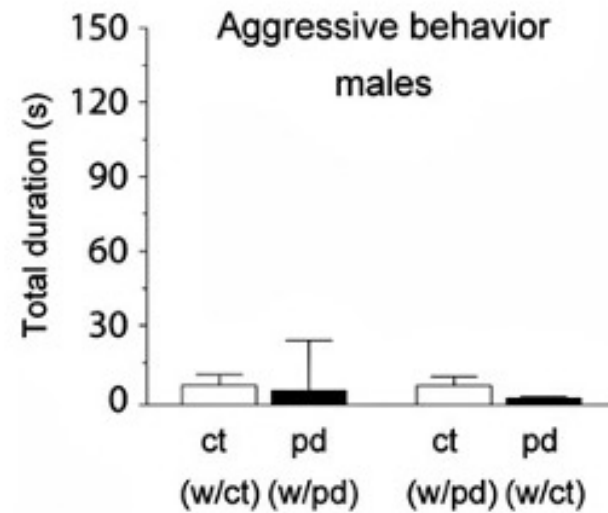
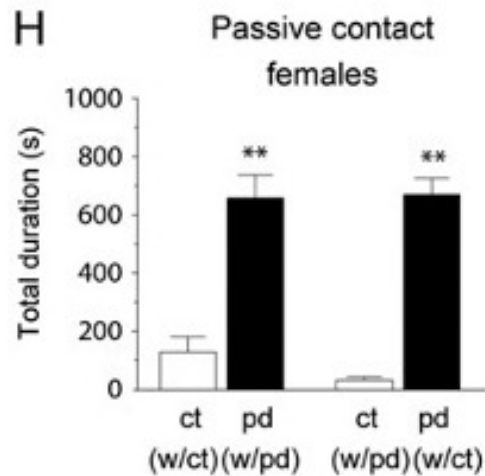
KNOWN CONSEQUENCES OF FATHER ABSENCE ON SOCIAL BEHAVIORS IN CALIFORNIA MICE



Reduced social investigation in females

More passive contact in females

Increased aggression in females



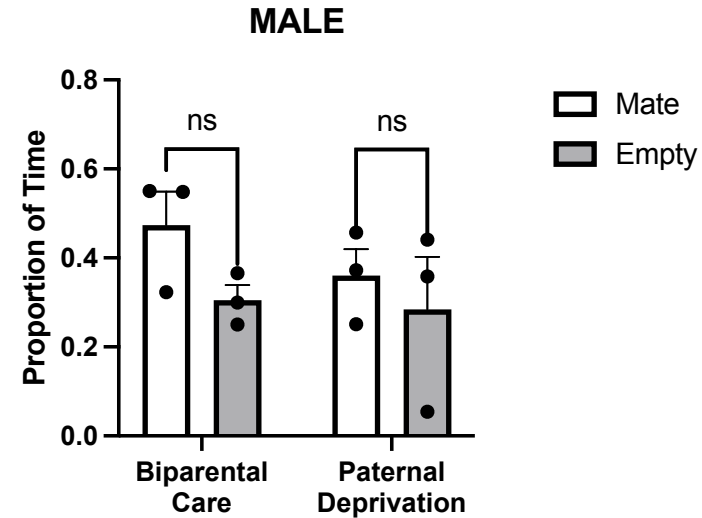
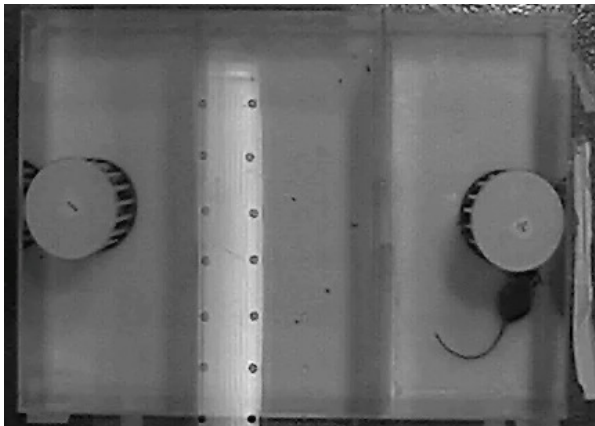
REDUCED PARTNER PREFERENCE IN PATERNALLY-DEPRIVED FEMALES AFTER 24-HR COHABITATION



Control reared and paternally-deprived males explore mate similarly.

Control reared females do NOT show significant partner preference

Paternally-deprived females spend MORE time in empty chamber than with opposite sex partner



CALIFORNIA MICE MAY REQUIRE LONGER SOCIAL INTERACTION TIME



10-minute tests produced inconclusive results

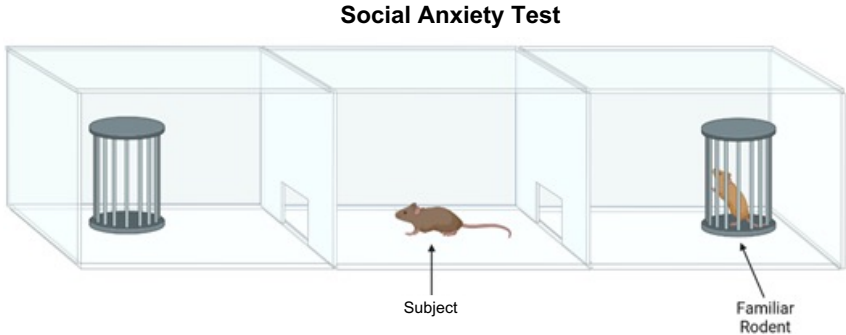
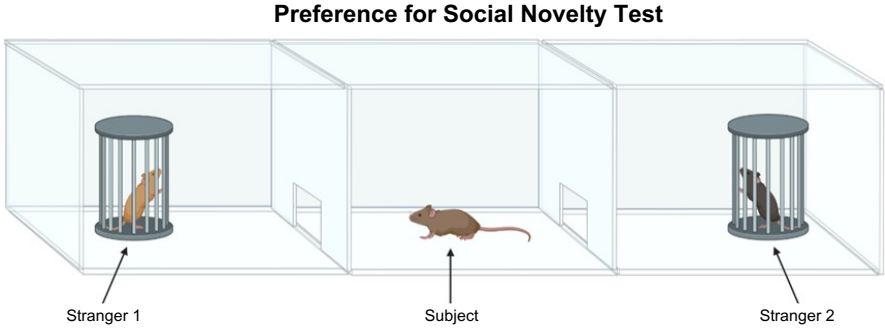
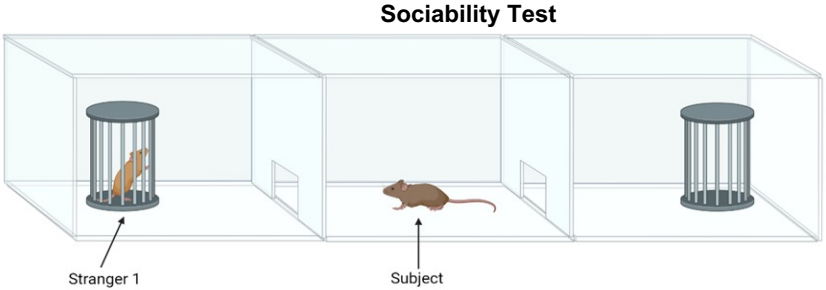


Control-reared mice did not

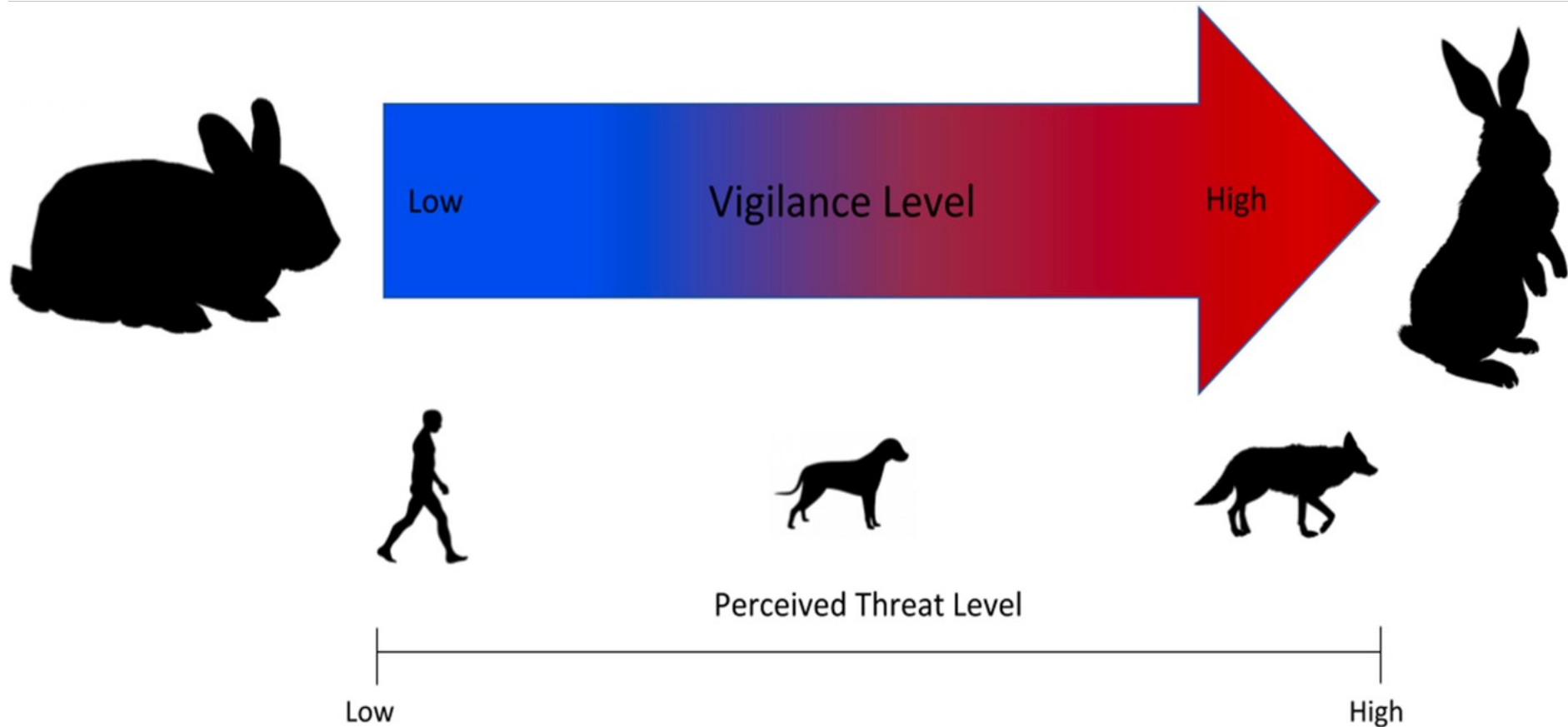
- 1. spend more time with the stranger
- 2. show a preference for social novelty

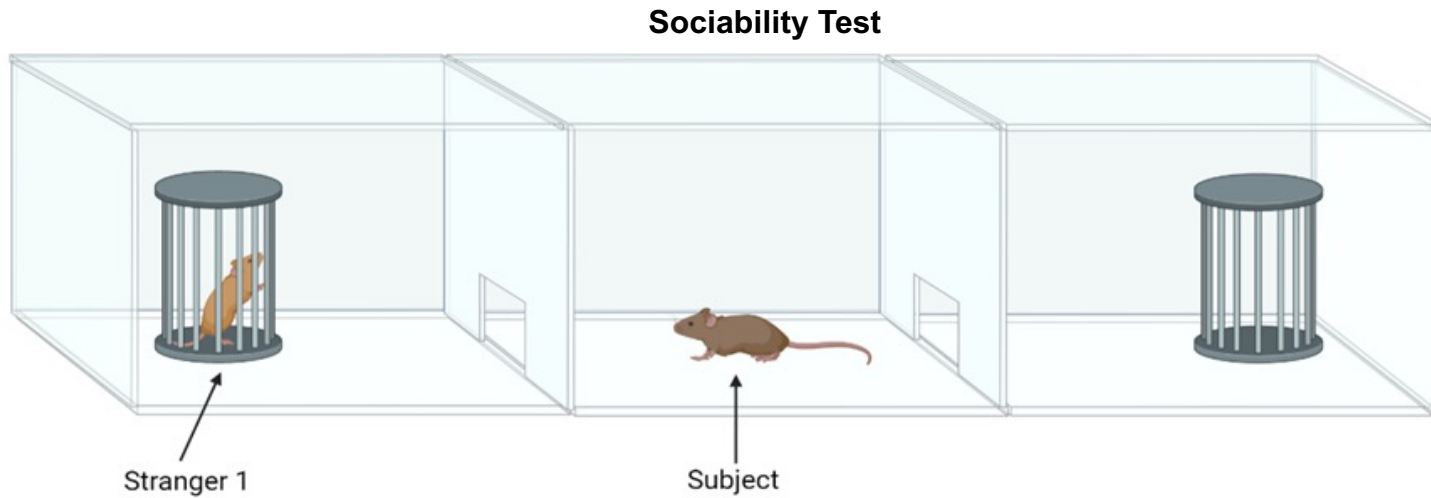


California mice spent more time in empty chamber

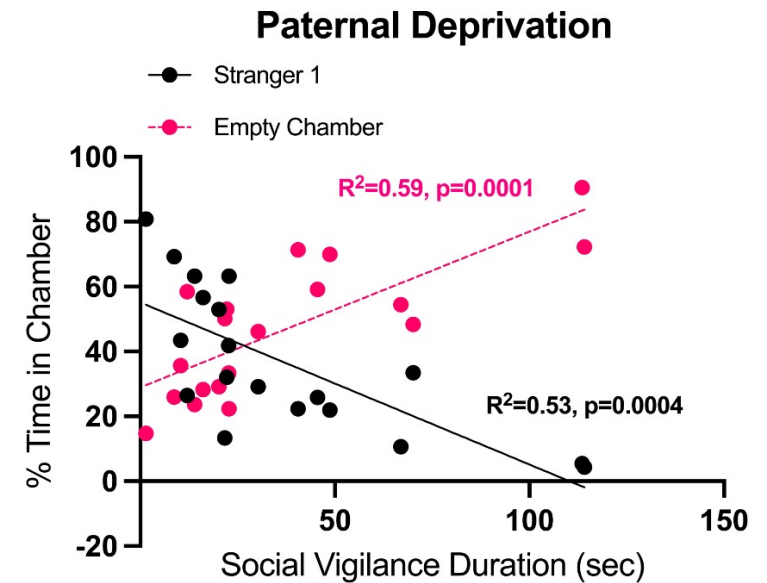
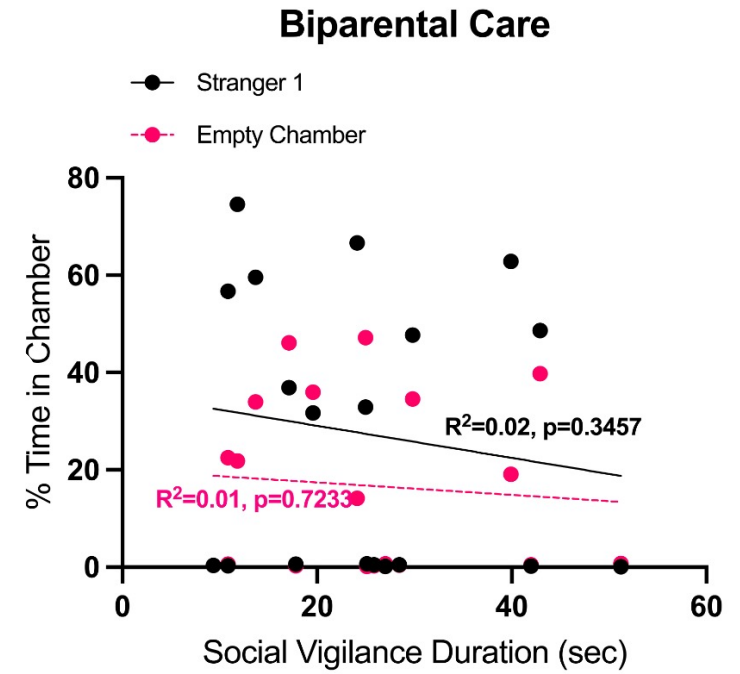


SOCIAL VIGILANCE

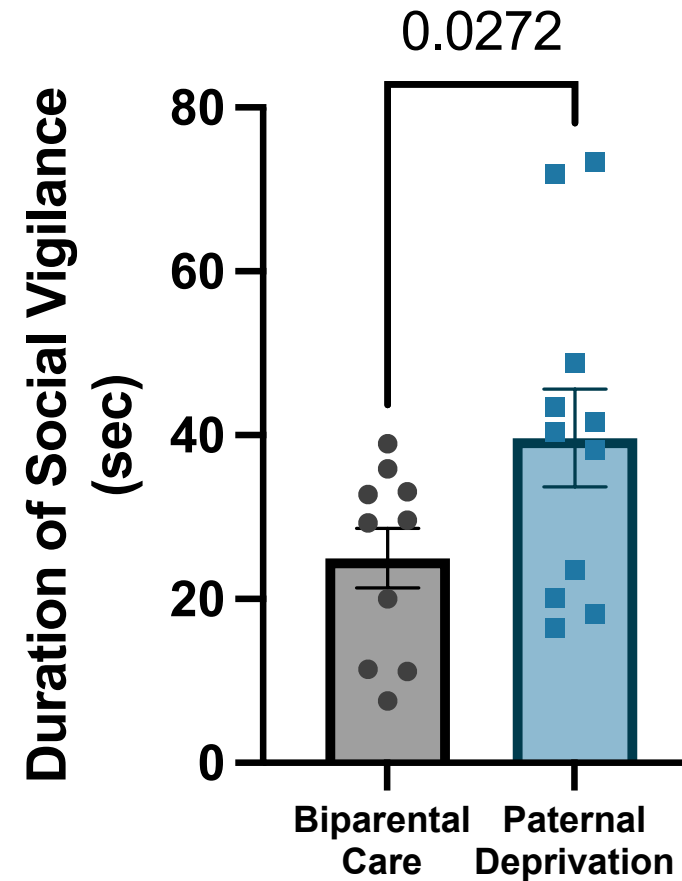
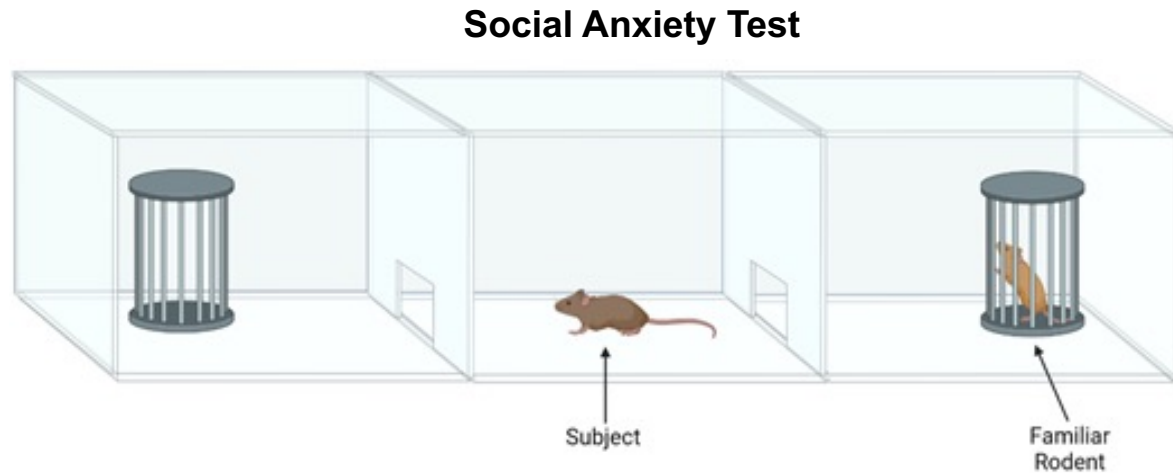




Paternally-deprived mice exhibit more social vigilant behavior while in the empty chamber



SOCIAL VIGILANCE PERSISTS IN PATERNALLY-DEPRIVED FEMALES!



SEX-SPECIFIC
MALADAPTIVE
SOCIAL
BEHAVIORS
FOLLOWING
EARLY-LIFE
PATERNAL
DEPRIVATION

Females fail to show partner preference after 24hr cohabitation.

Social vigilance behavior persists in females.

Overall Conclusion: Loss of paternal care early in life is associated with maladaptive social behaviors and aberrant hippocampal plasticity in females.

FUTURE DIRECTIONS

