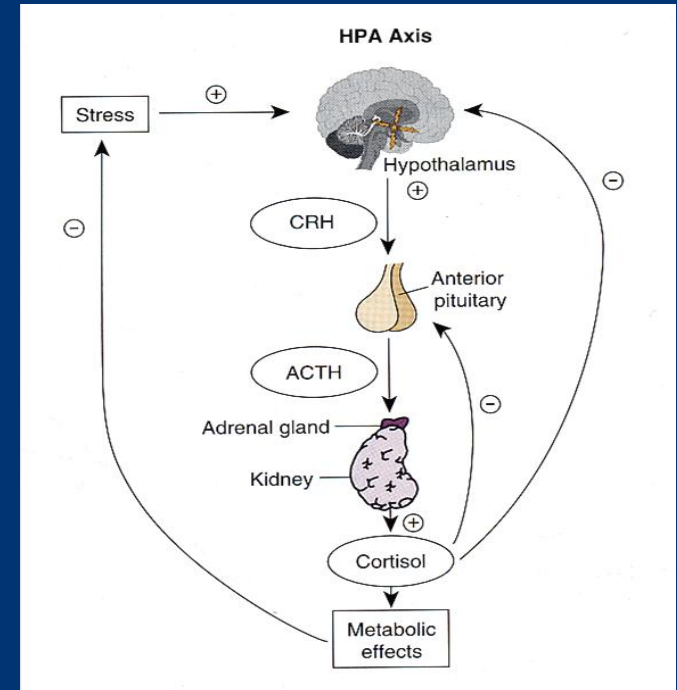
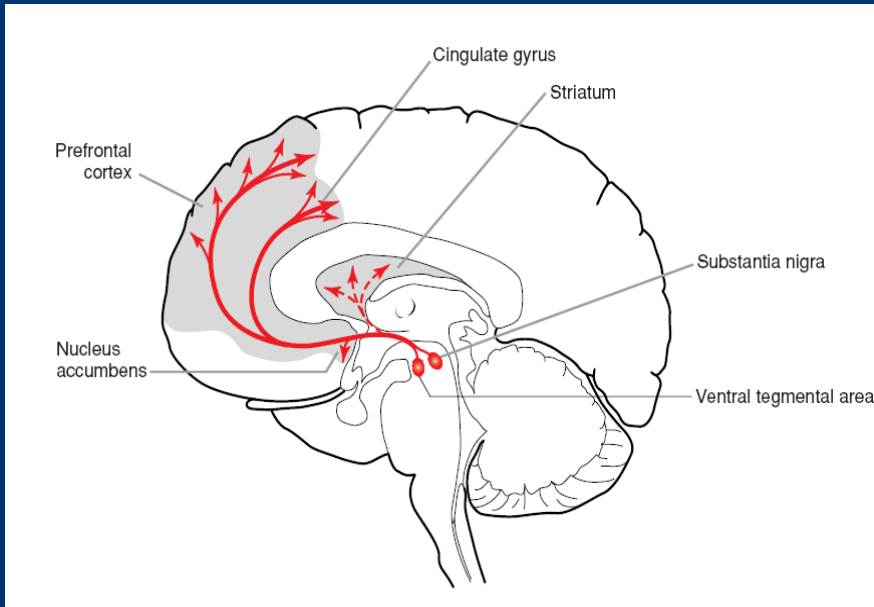




# Neurobiological effects of prenatal alcohol exposure and stress: a potential pathway to increased vulnerability to substance use problems



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Joanne Weinberg<sup>1,2</sup> & Liisa Galea<sup>1</sup>

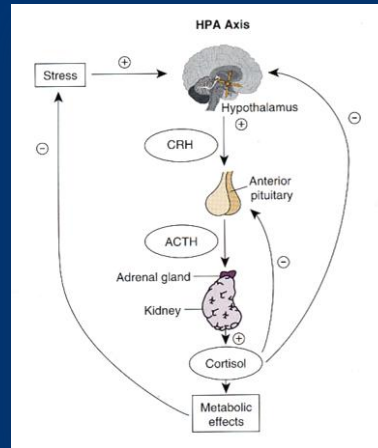
Departments of <sup>2</sup>Cellular and Physiological Sciences and <sup>1</sup>Psychology

# Background and hypotheses

- Children with FASD exhibit cognitive, behavioral, physical abnormalities that can last a lifetime
- “Secondary disabilities”, including mental health problems, alcohol and drug use and trouble with the law, can add challenges
- Increased prevalence of substance use/ addiction problems likely influenced by genetic, neurobiological, environmental and social factors
- **Our focus:** What are the neurobiological mechanisms by which prenatal alcohol exposure influences vulnerability to addiction

# Overview: What is Known

## Stress



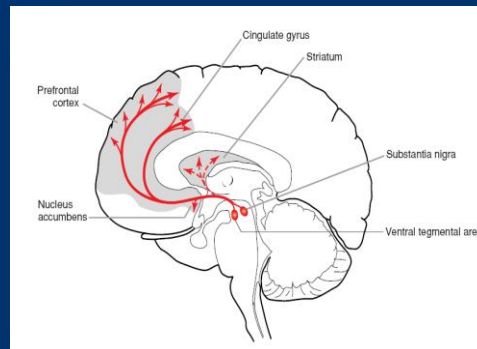
Prenatal Alcohol Exposure

Prenatal Alcohol Exposure

?

## Reward

Prenatal Alcohol Exposure



Vulnerability to Addiction

# What is stress?

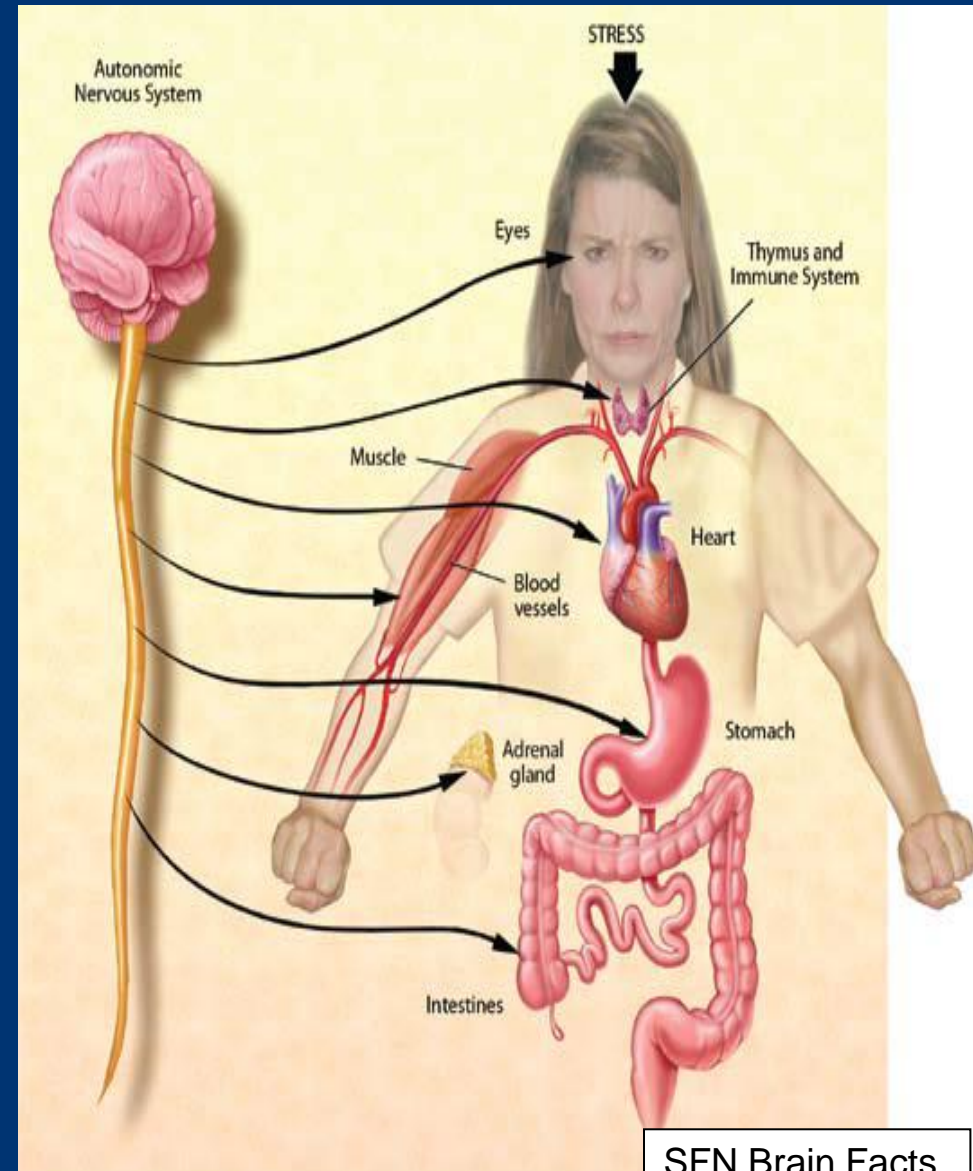
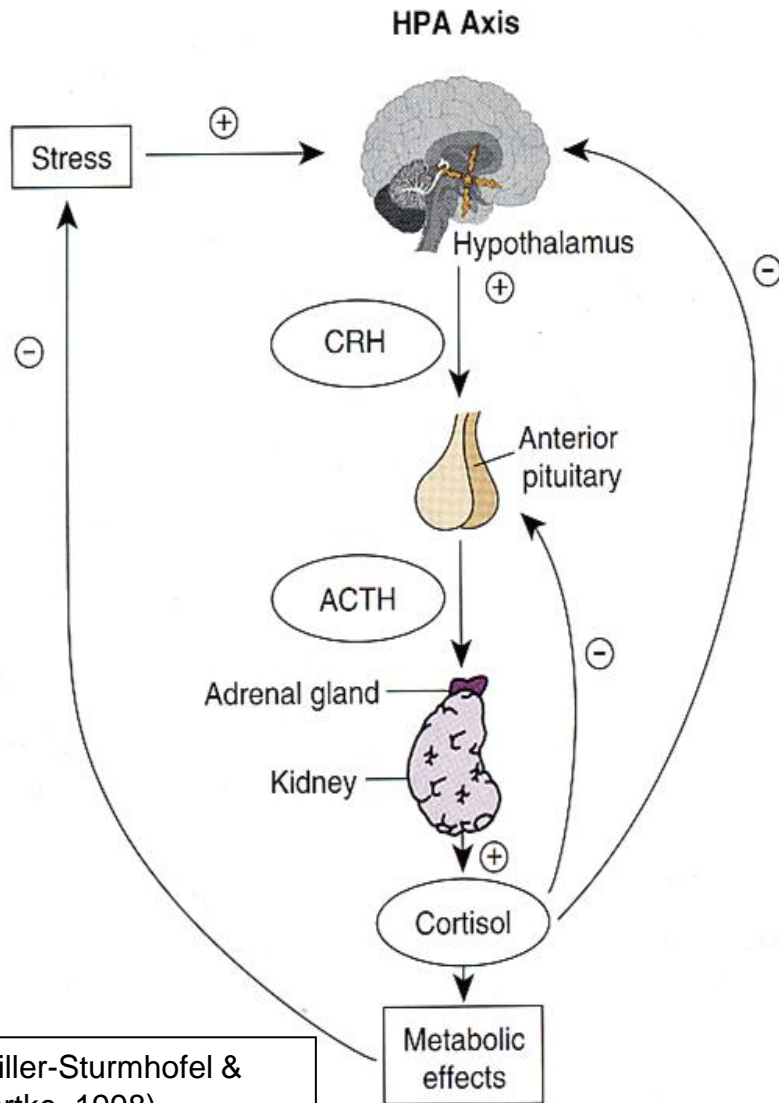
- A constant factor in modern life and a frequent topic of conversation
- Stressors can be physical or psychological
- Stress can be good or bad

**Good stress** – mild and short-term, exciting or novel challenge

**Bad stress** – severe or chronic challenges, negative events, inability to cope – “stressed out”



# The HPA Axis and Sympathetic Nervous System act together to mediate the stress response



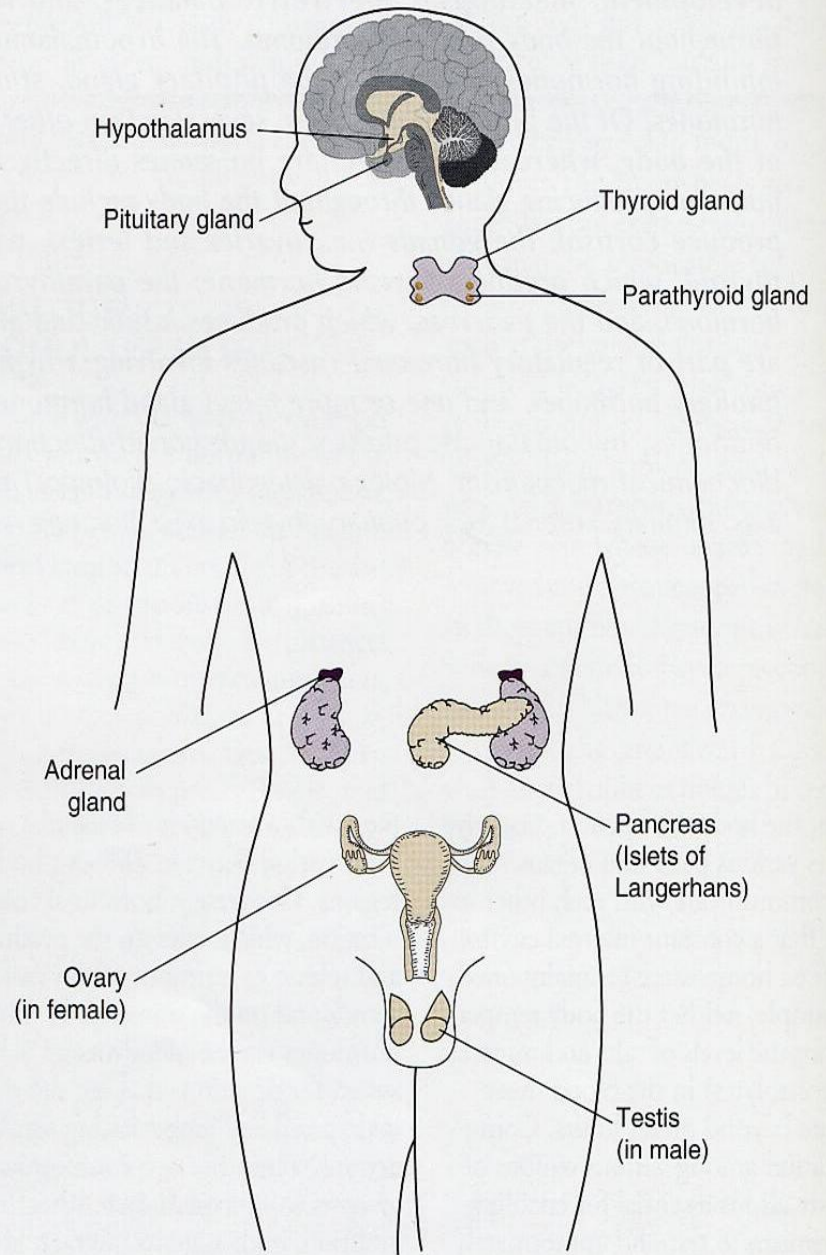
(Hiller-Sturmhofel & Bartke, 1998),  
Alcohol Res & Health

SFN Brain Facts



# Location of the major endocrine (hormone-producing) glands in the body

The stress system involves the hypothalamus, the pituitary and the adrenal glands



# The Hypothalamic-pituitary-adrenal (HPA) or Stress Axis

Stress, circadian changes  
→ activate HPA axis



Cascade of responses

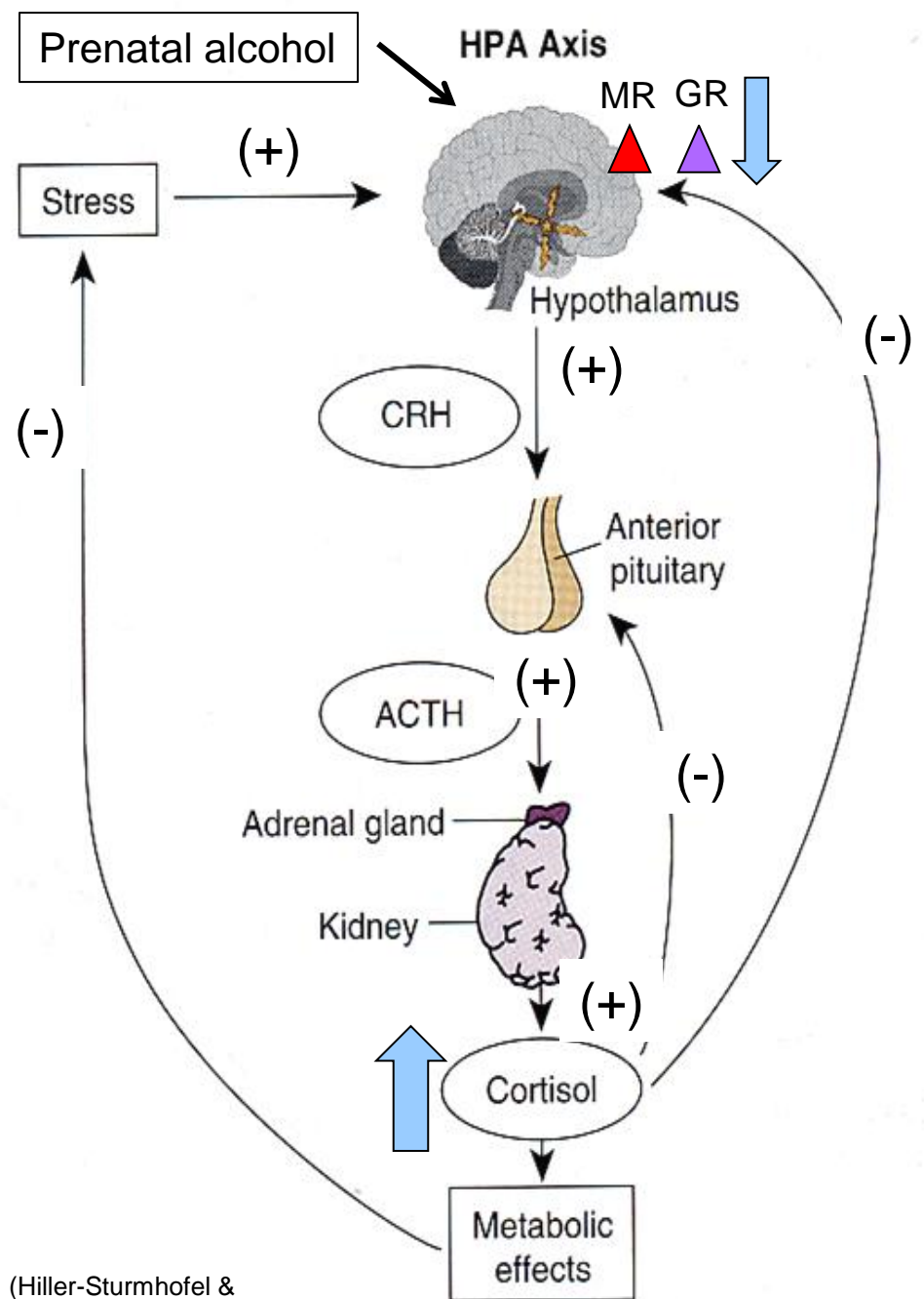


Increased levels of hormones (ACTH, glucocorticoids)



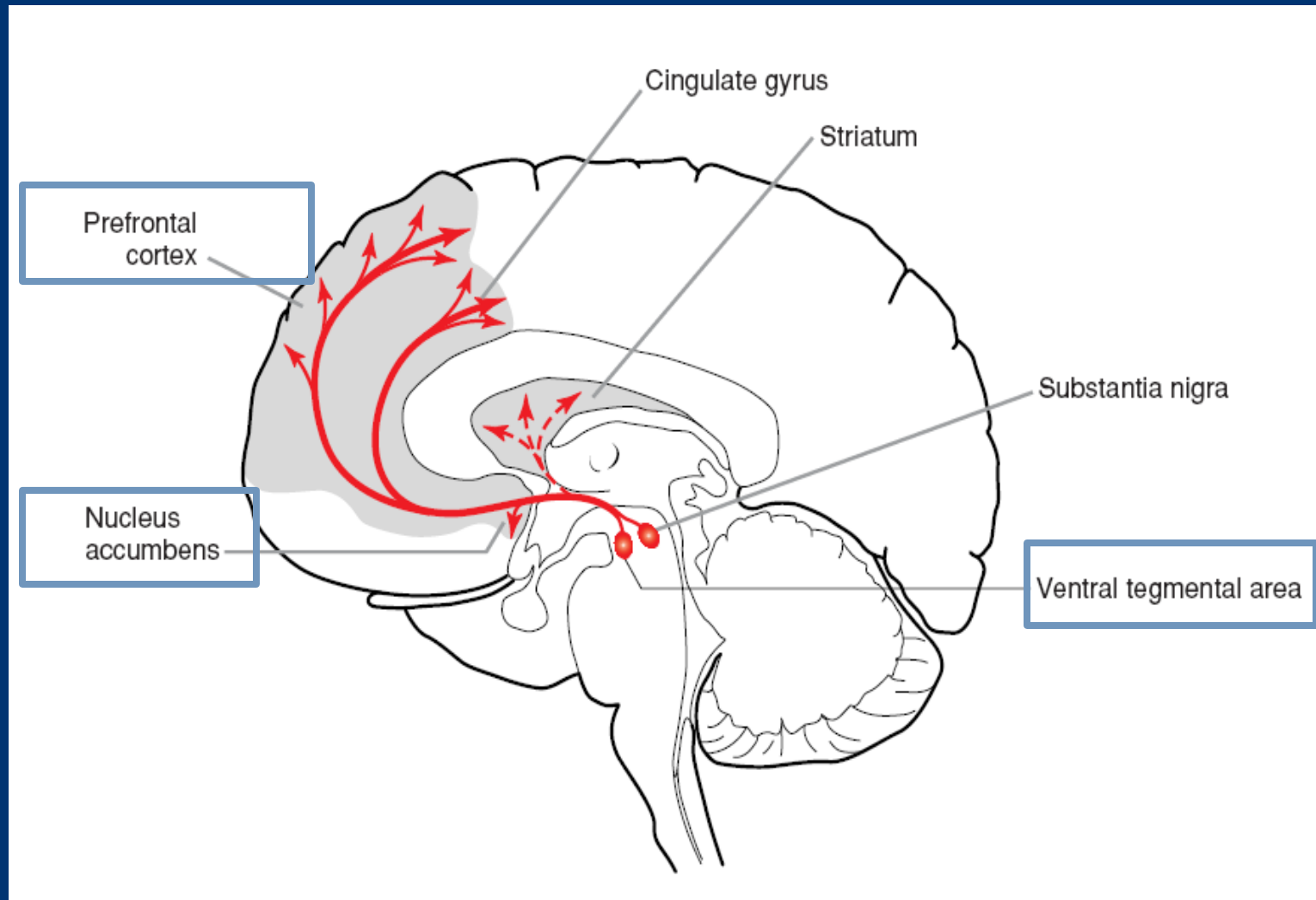
Feedback to reduce activity to normal -

Feedback to pituitary, hypothalamus, hippocampus, PFC and other brain areas



(Hiller-Sturmhofel & Bartke, 1998)

Both natural rewards and addictive drugs influence behaviour by increasing dopamine levels in the nucleus accumbens and PFC.





# Drugs of abuse and dopamine

- The DA system responds to salient stimuli – something that is pleasurable, important, worth paying attention to
- All drugs of abuse increase DA activity
- DA generally stays within the synapse for a very short time, then is removed and recycled by the cell
- Addiction → ↓ in DA receptors → natural rewards less effective
- At the same time, transporter that removes DA from synapse is altered → DA stays around longer → greater and more lasting reward, despite fewer DA receptors
- PAE also → ↓ DA receptor activity

# FASD, stress, dopamine and vulnerability to addiction

- The stress system (HPA axis) and dopamine reward system are key neurobiological pathways in addiction. They interact in numerous ways
- The stress system has a role in initial vulnerability to drugs and in vulnerability to relapse
- Brain areas that mediate stress and reward overlap to a large extent
- Both the stress system and the reward system are altered by prenatal exposure to alcohol

# FASD, stress, dopamine and vulnerability to addiction (cont'd)

- Intimate relationship between stress system (HPA axis) and substance use:
  - Distinct alterations in HPA function with different stages of substance use problems
  - Stress can sensitize healthy individuals to rewarding effects of drugs and can induce relapse after abstinence
  - ↑ stress responsiveness → ↑ propensity for drug self-administration
  - Repeated injections of stress hormones → drug self-administration occurs at a lower dose of drug

# Alterations in stress response correspond with stage of substance use

## Stage of Use

## HPA activity

Acute

↑

Dependence

↓

Withdrawal

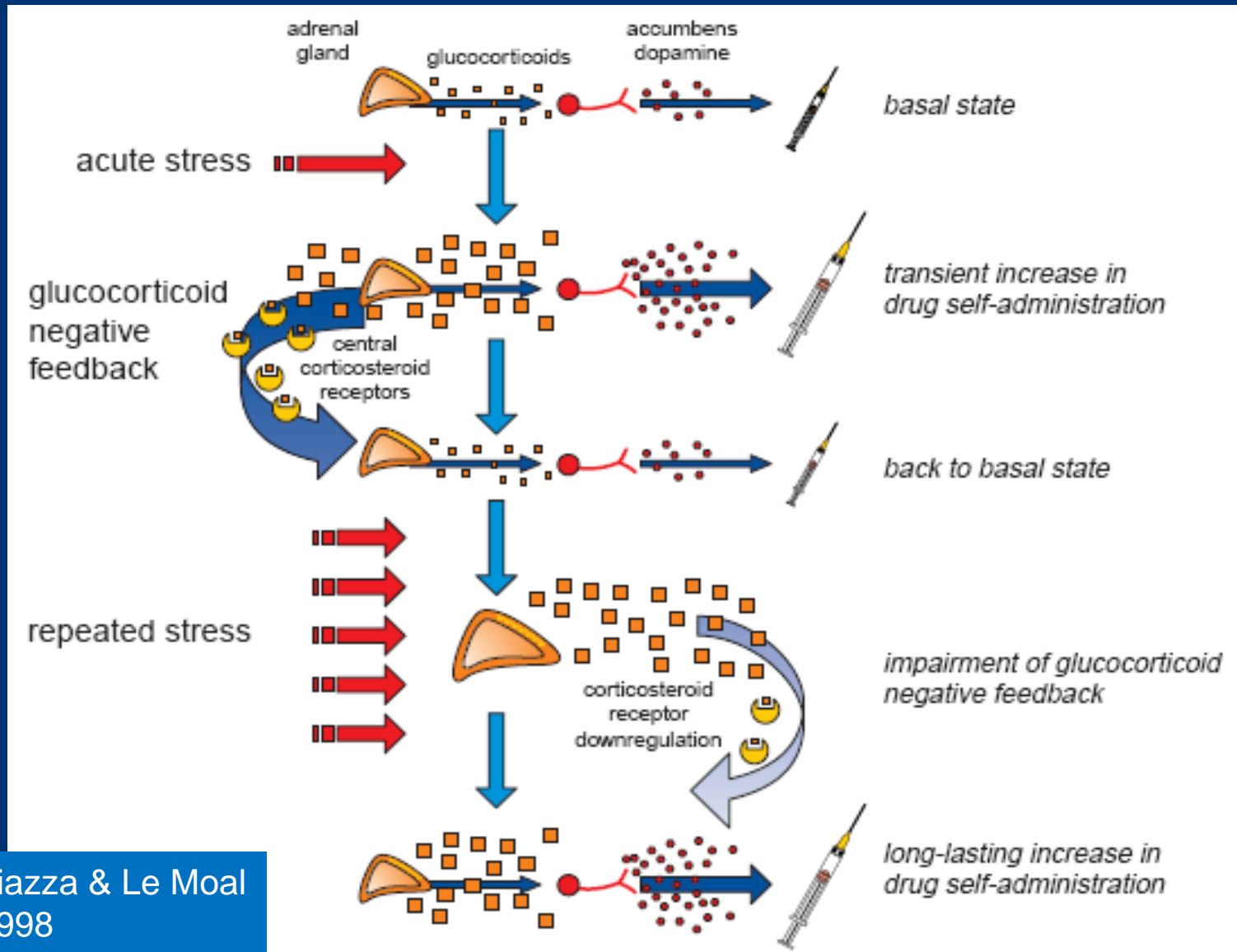
↑

Prolonged  
Abstinence

Returns to baseline

Failure of HPA recovery  
correlated with ↑ risk for  
relapse

# Possible pathophysiological mechanisms mediating the effects of stress on drug intake



From: Piazza & Le Moal  
TIPS, 1998

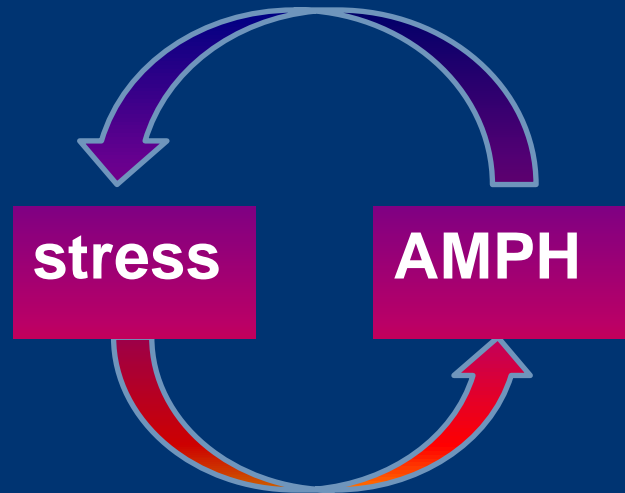


# Current Research

Do prenatal alcohol and stress interact to increase vulnerability to addiction?

- **Objective 1:** Examine the effects of prenatal alcohol exposure and stress in adulthood on the HPA axis and the reward system in males and females
  - Neurobiological mechanisms underlying interactions between these systems and expression of related behaviours
- **Objective 2:** Examine behavioral and HPA cross-sensitization between amphetamine and stress, as a marker of vulnerability to addiction in males and females

# Cross-sensitization: Stress and AMPH



- Bidirectional:
  - Previous exposure to a psychostimulant drug (AMPH) can sensitize the behavioral response to that drug and to another drug or to stress

# Sensitization:

A behavioural marker of neurobiological vulnerability or resilience to addiction

*Some aspects of the sensitization phenomenon may represent a major component of addiction (Robinson and Berridge, 1993).*

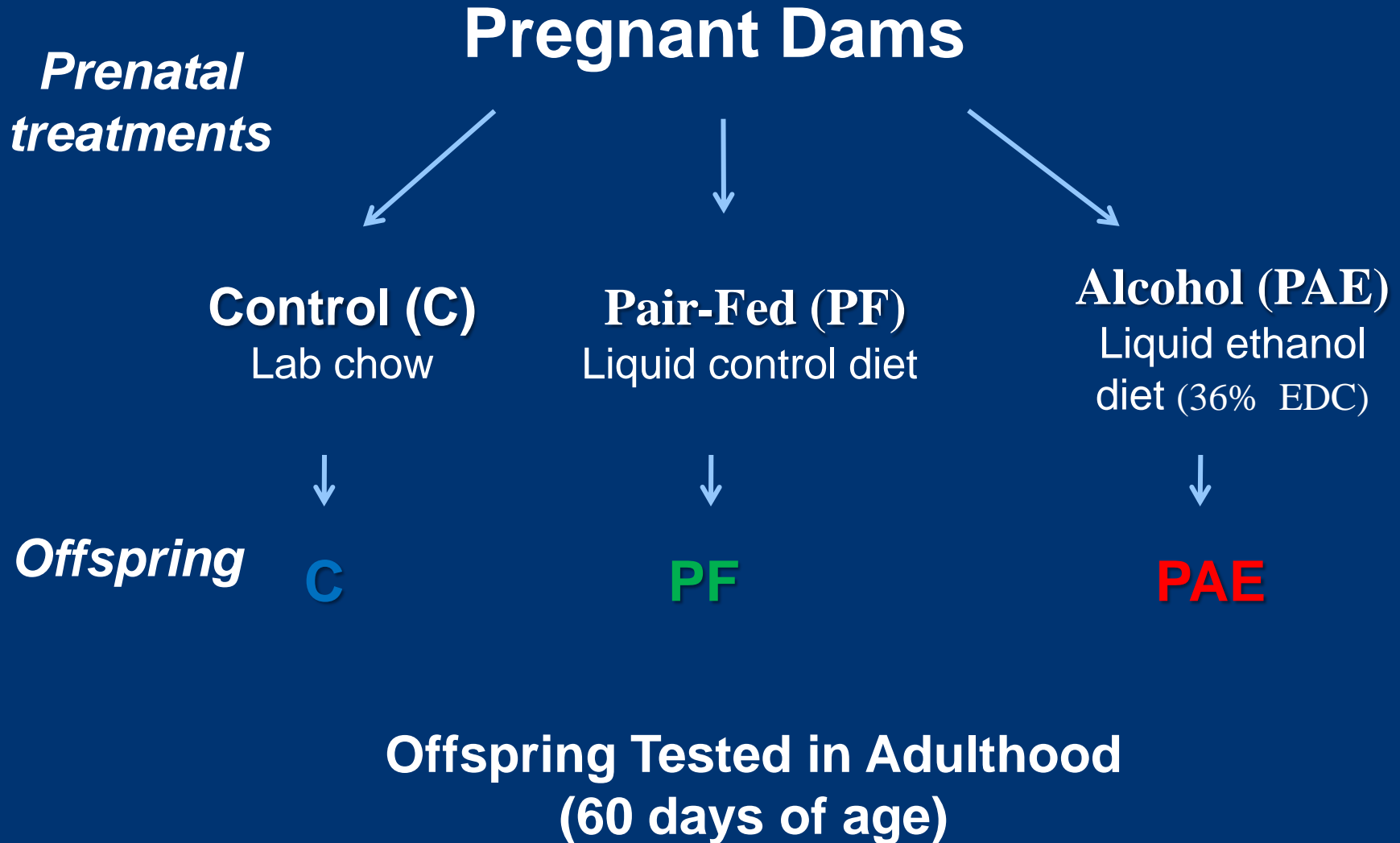
- Differences in behavioral sensitization are predictive of subsequent drug self-administration and relapse
- Once established, the sensitization of dopamine systems can be observed for months and often up to one year later in the rat.
  - Clinical implications
- Sex difference (e.g., effects of estrogen)

# Present Study:

## Cross-sensitization between AMPH and stress in PAE males and females

- How is the interaction between stress and drug use altered by alcohol exposure *in utero*?
- Are males and females differentially affected?

# Study design



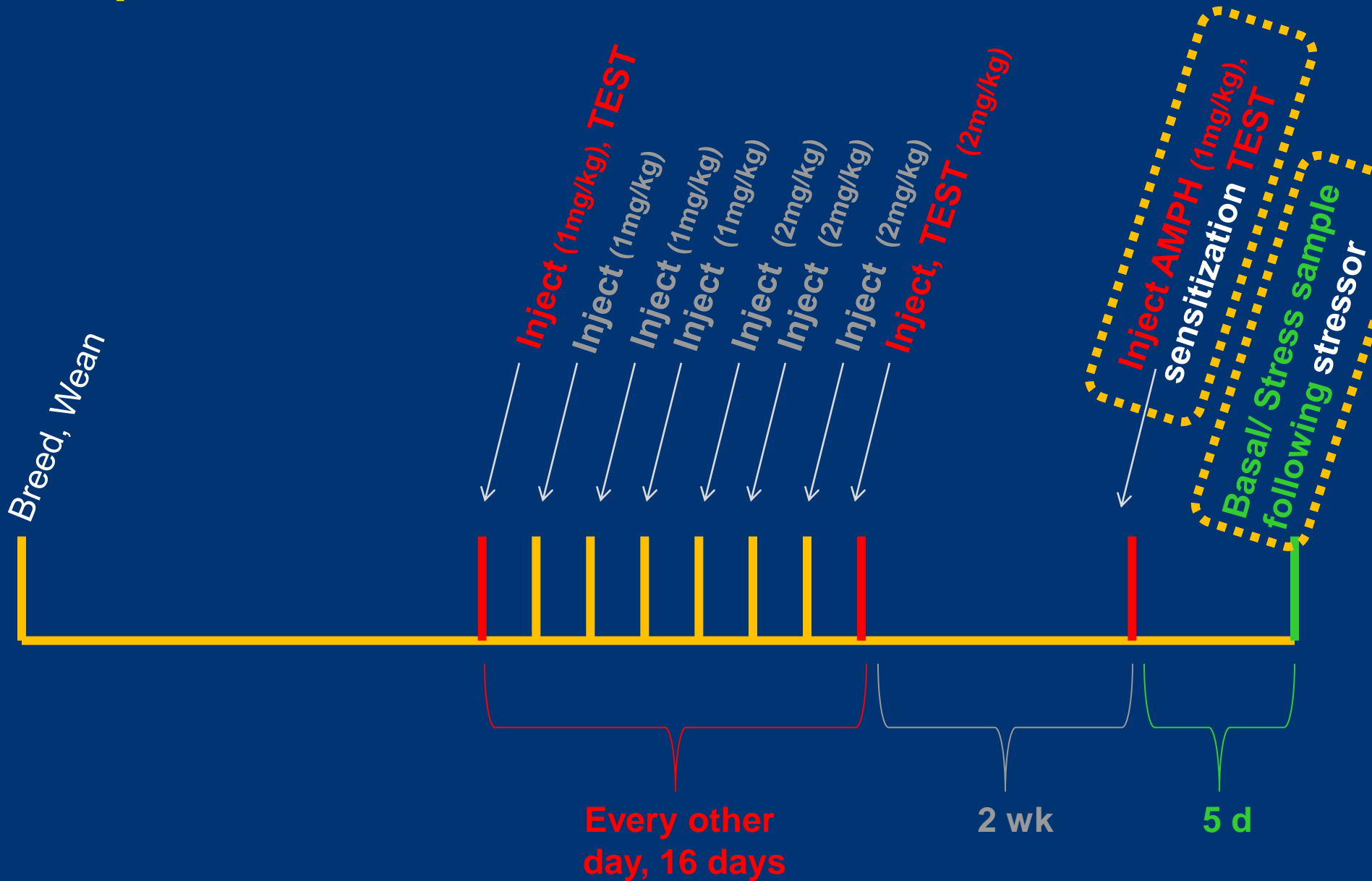


# Experimental Groups and Subjects:

	Saline			AMPH		
Basal	C	PF	PAE	C	PF	PAE
Stress	C	PF	PAE	C	PF	PAE

n=10 per group, males and females

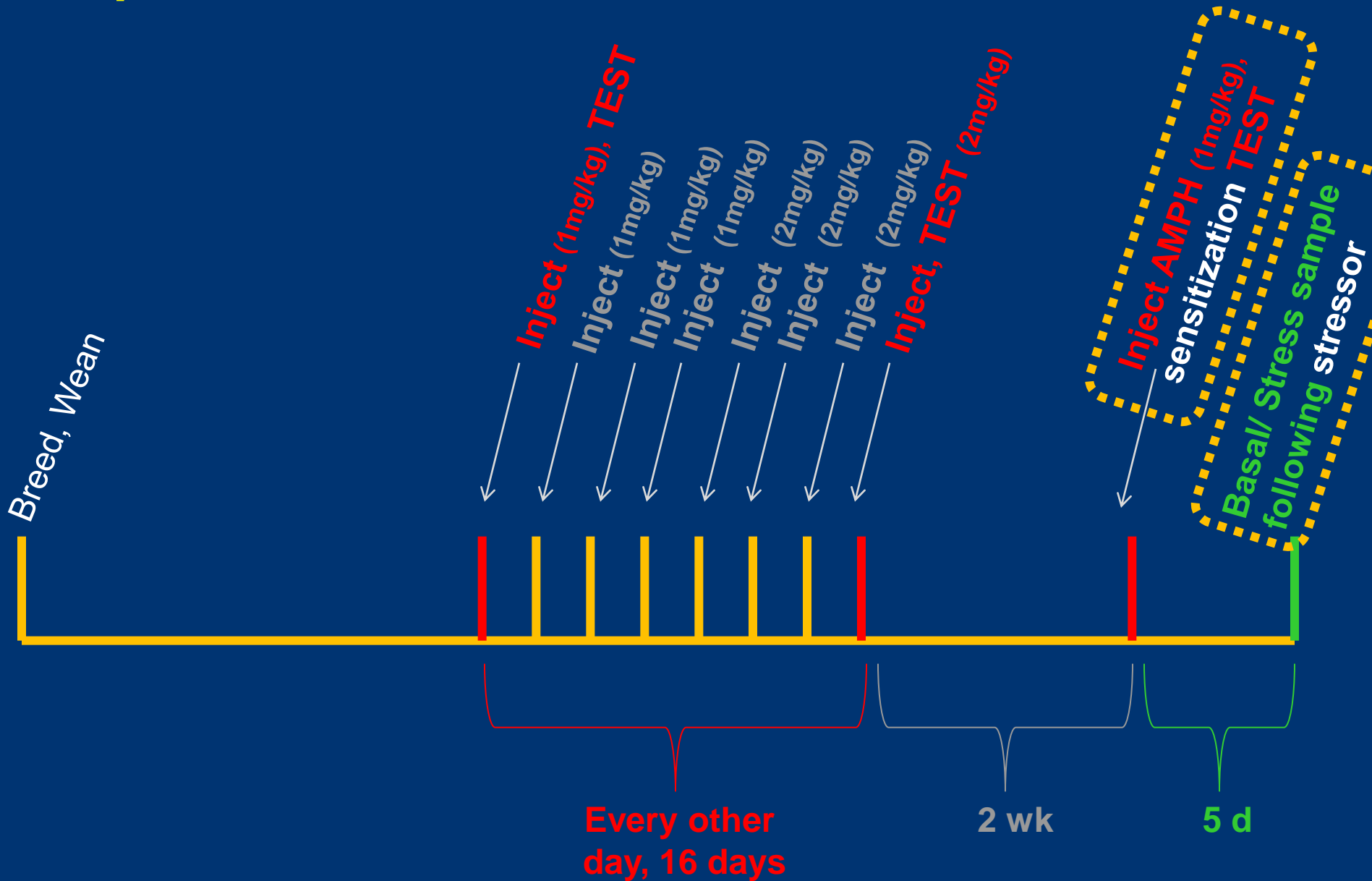
# Experimental Timeline:



# Results to be shown:

- Locomotor activity on the **sensitization test day**
  - Animals previously exposed to AMPH or to Saline
  - 20 min pre-injection exploration → AMPH injection
  - Measure: Distance travelled, speed
- Hormone response to **restraint stress** in animals previously exposed to AMPH or Saline

# Experimental Timeline:



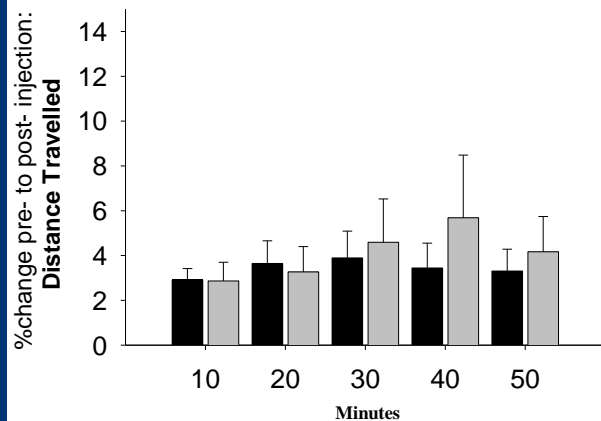
# DISTANCE TRAVELLED - Males

Enhanced response to AMPH challenge in Control and PF males previously treated with AMPH

In contrast, enhanced response to AMPH in PAE males previously treated with Saline

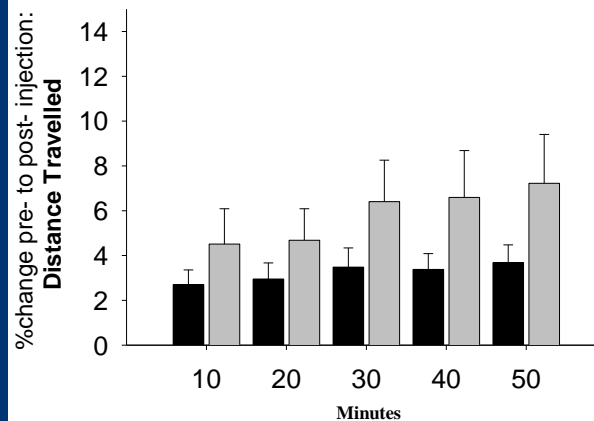
Saline  
AMPH

### Control



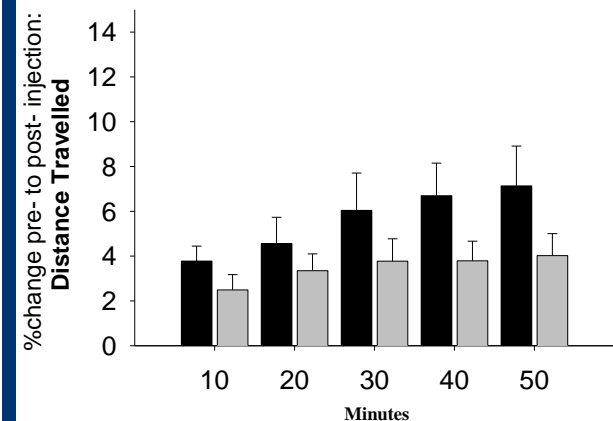
Minutes post-injection

### Pair-fed



Minutes post-injection

### PAE



Minutes post-injection

(%change from pre- to post-injection)

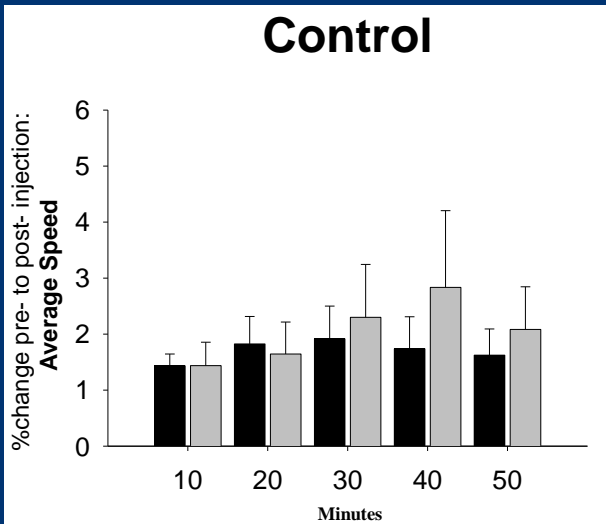


# SPEED – Males

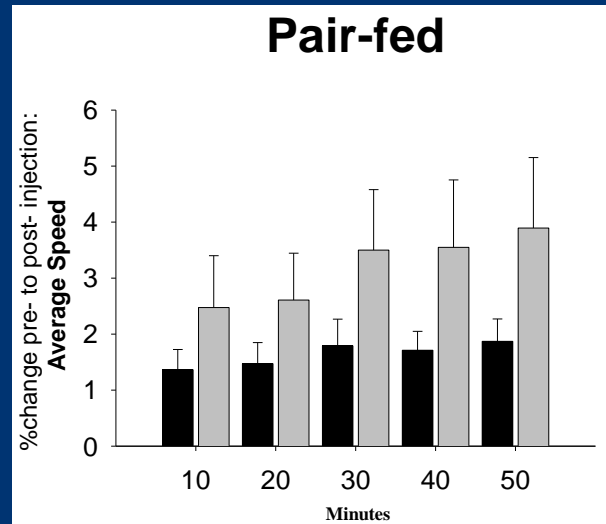
Enhanced response to AMPH challenge in Control and PF males previously exposed to AMPH

Enhanced response to AMPH in PAE males previously treated with Saline

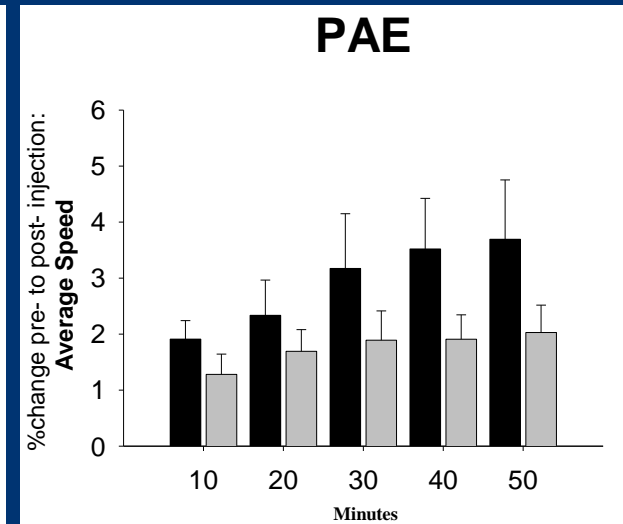
■ Saline  
■ AMPH



Minutes post-injection



Minutes post-injection



Minutes post-injection

(%change from pre- to post- injection)

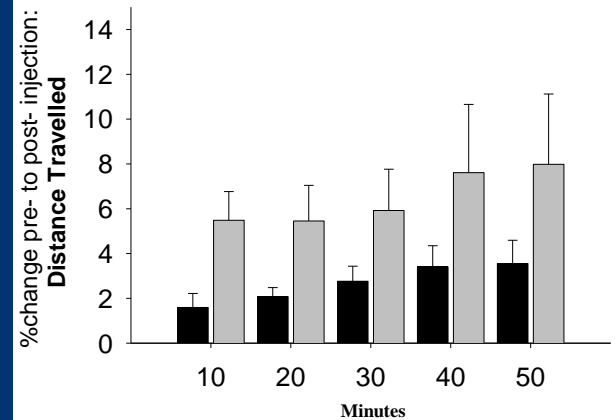
# DISTANCE TRAVELLED - Females

Enhanced response to AMPH challenge in Control females previously treated with AMPH

No significant differences between AMPH and Sal groups for PF and PAE females

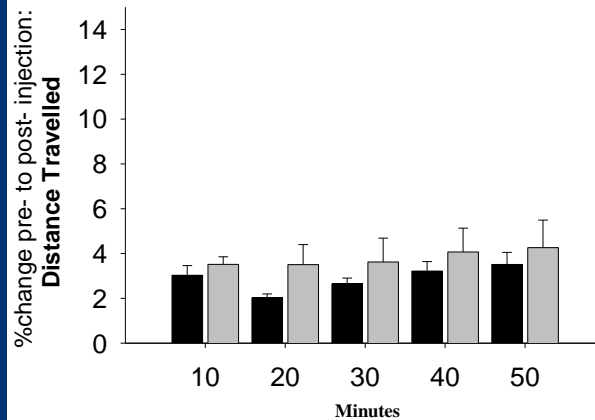


### Control



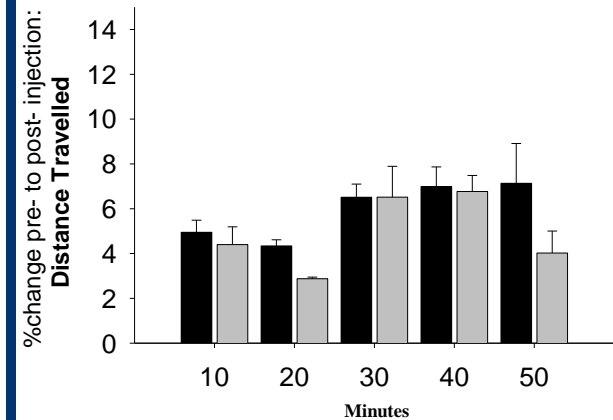
Minutes post-injection

### Pair-fed



Minutes post-injection

### PAE



Minutes post-injection

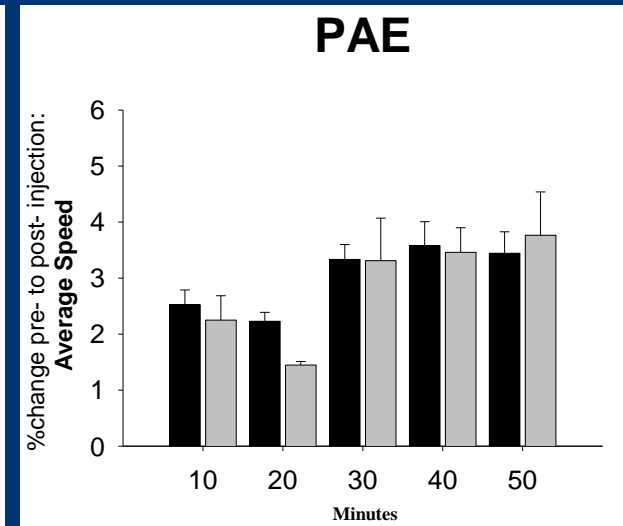
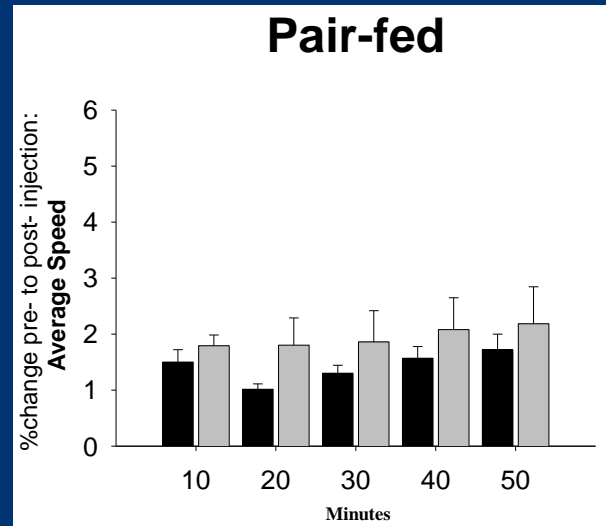
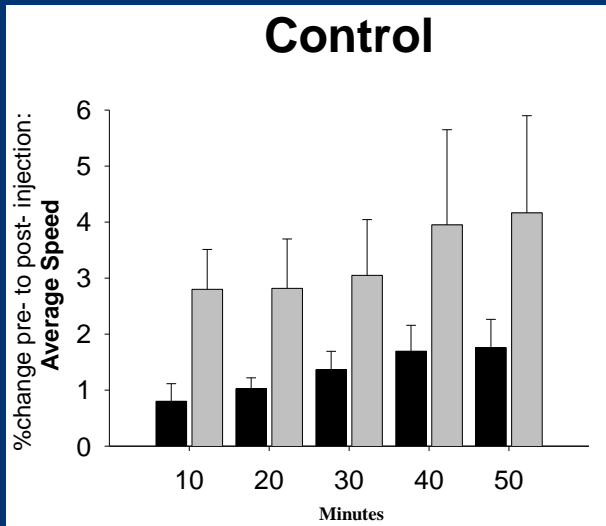
(%change from pre- to post- injection)

# SPEED – Females

Enhanced response to AMPH challenge in Control females previously treated with AMPH

No significant differences between AMPH and Sal groups for PF and PAE females

Saline  
AMPH



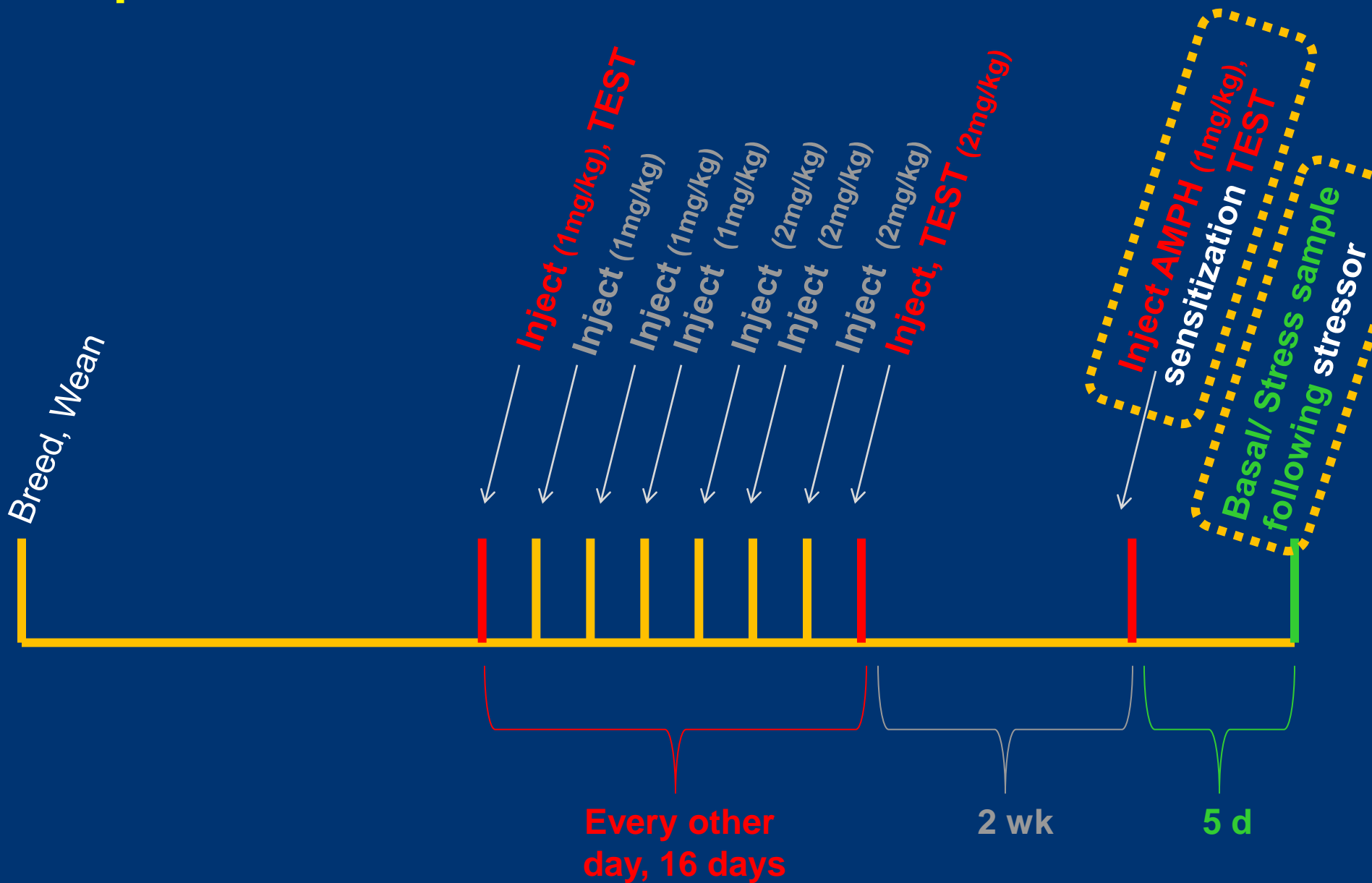
Minutes post-injection

Minutes post-injection

Minutes post-injection

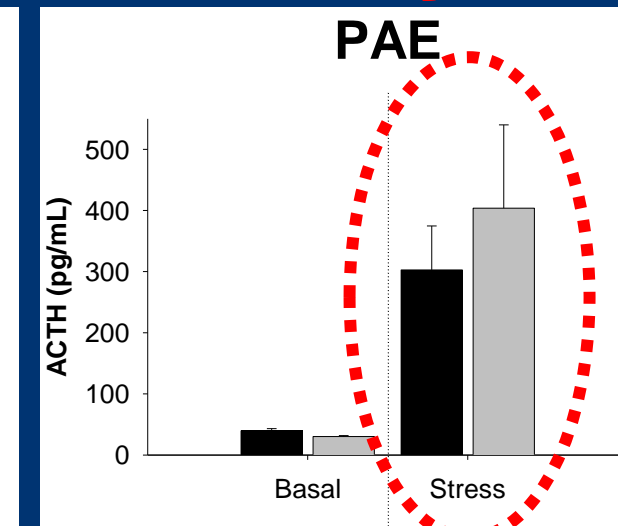
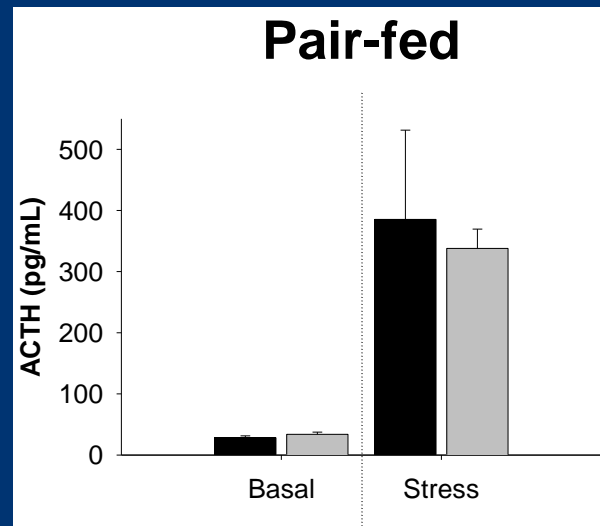
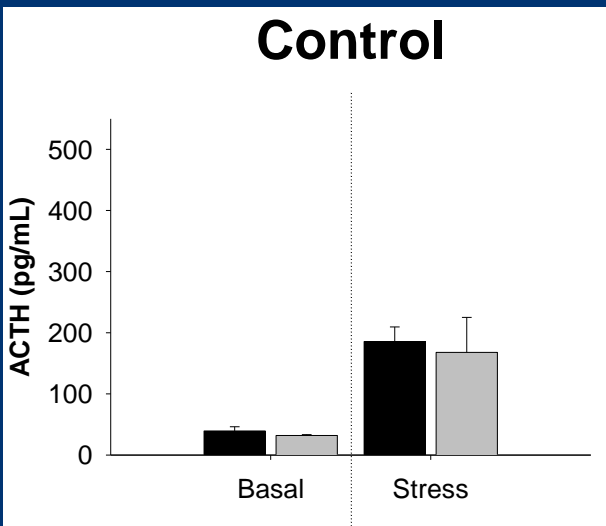
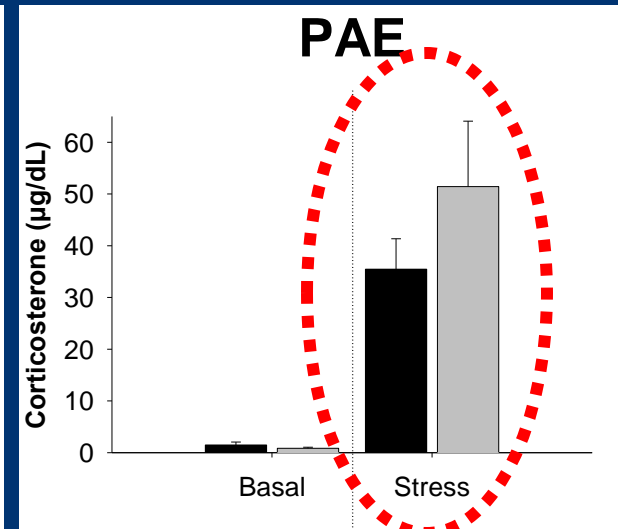
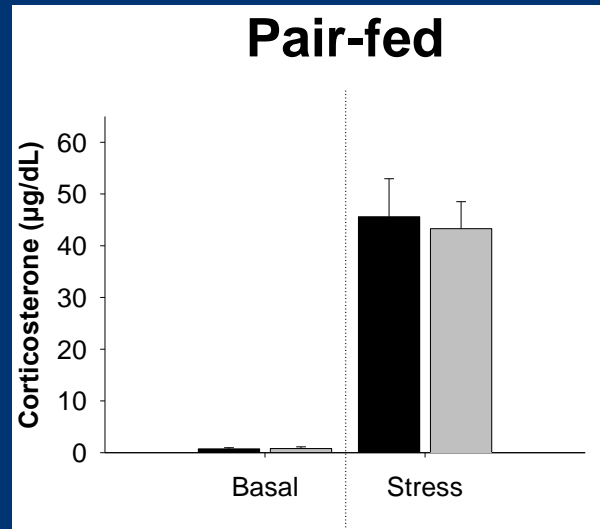
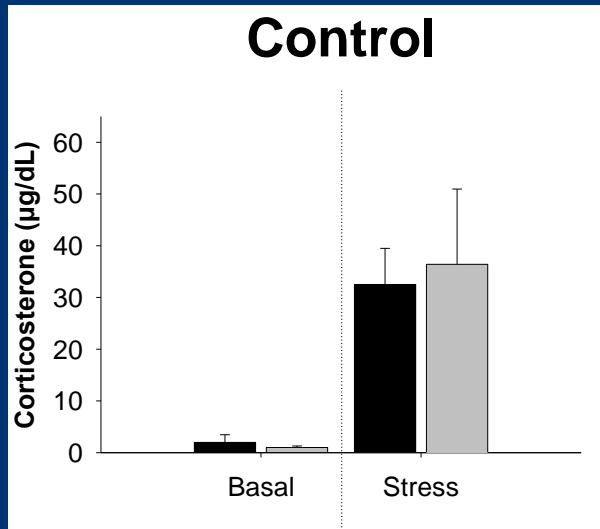
(%change from pre- to post- injection)

# Experimental Timeline:



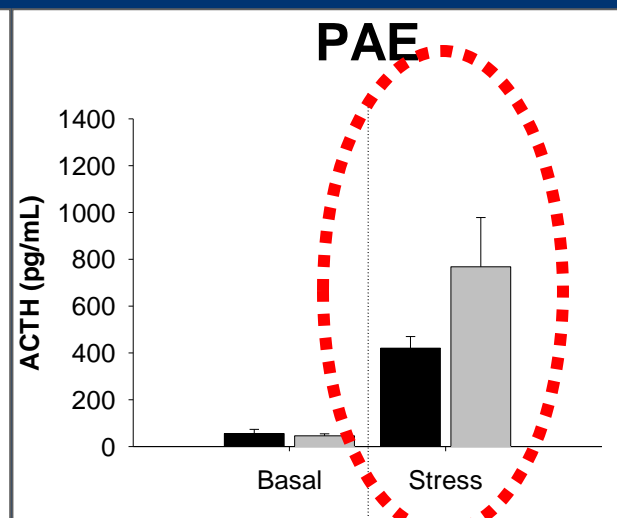
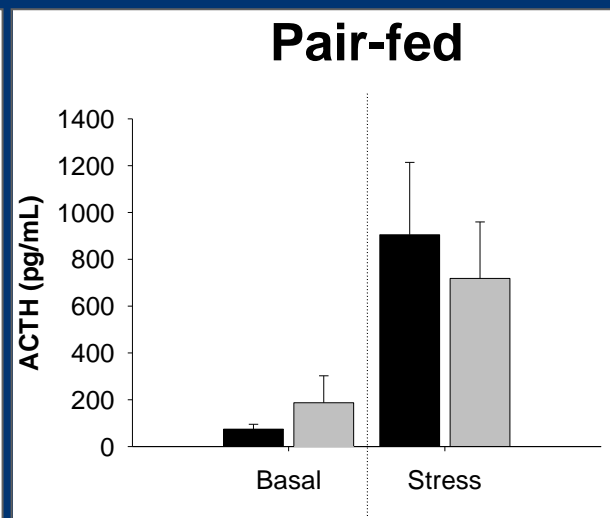
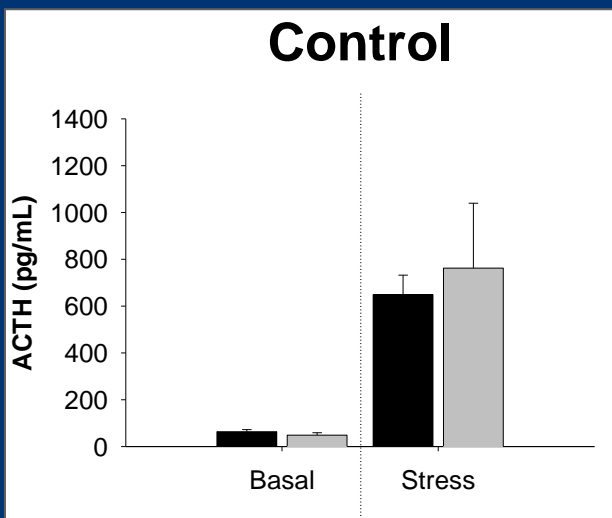
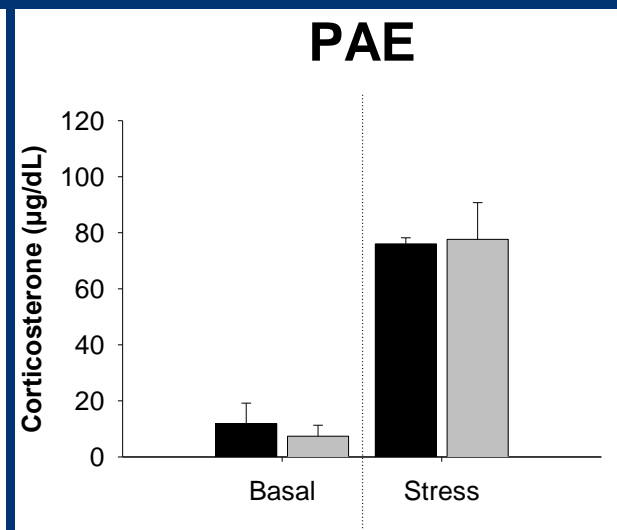
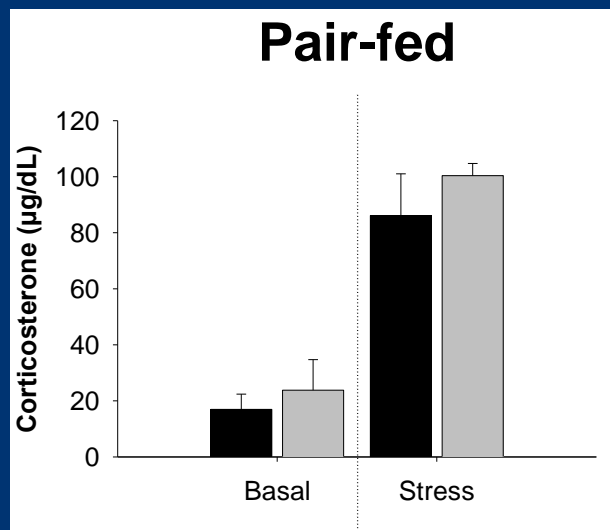
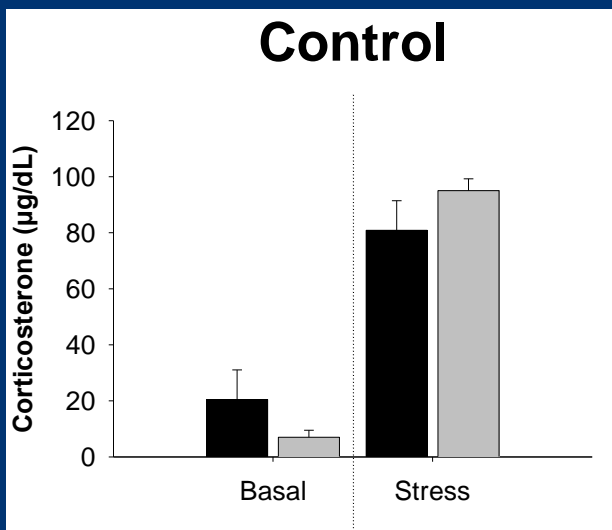
# Increased stress hormone levels (CORT, ACTH) in AMPH-treated PAE males following subsequent stressor challenge

Saline  
AMPH



# Enhanced stress hormone levels (ACTH) in AMPH-treated PAE females following subsequent stressor challenge

Saline  
AMPH



# Conclusions:

- Differential effects of prior AMPH exposure on behavioral and hormonal responses to AMPH challenge in PAE compared to control animals
- Sex differences in both AMPH sensitization and PAE effects on sensitization observed
- HPA response to stress reflects **cross-sensitization between AMPH and stress in PAE but not control animals**
- Altered neurobiological and neurobehavioral responsiveness induced by PAE may increase vulnerability to addiction

# Acknowledgments



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