Physiological and Behavioral Sequelae Induced by a Predator-Based Psychosocial Stress Model of PTSD

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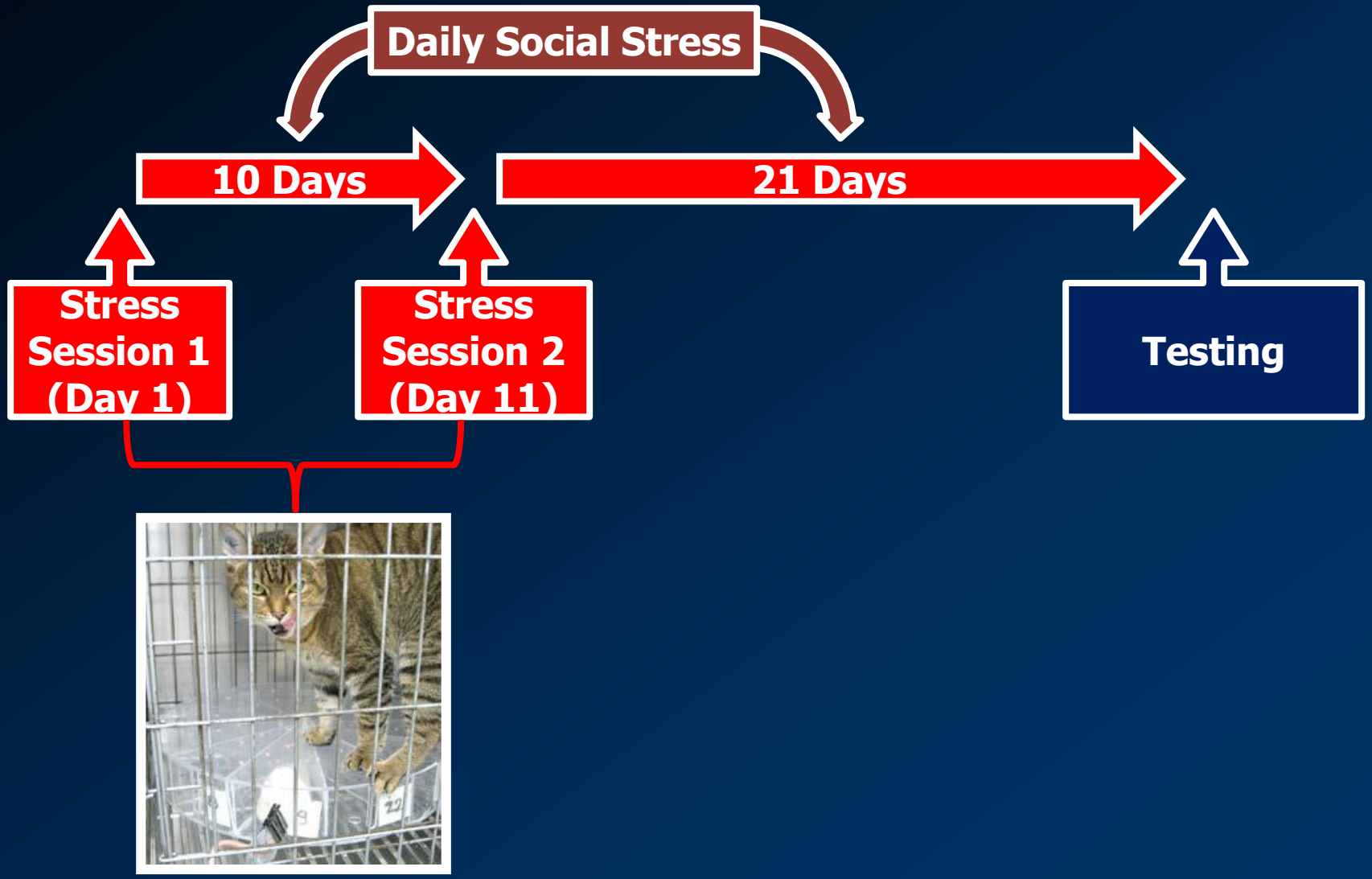
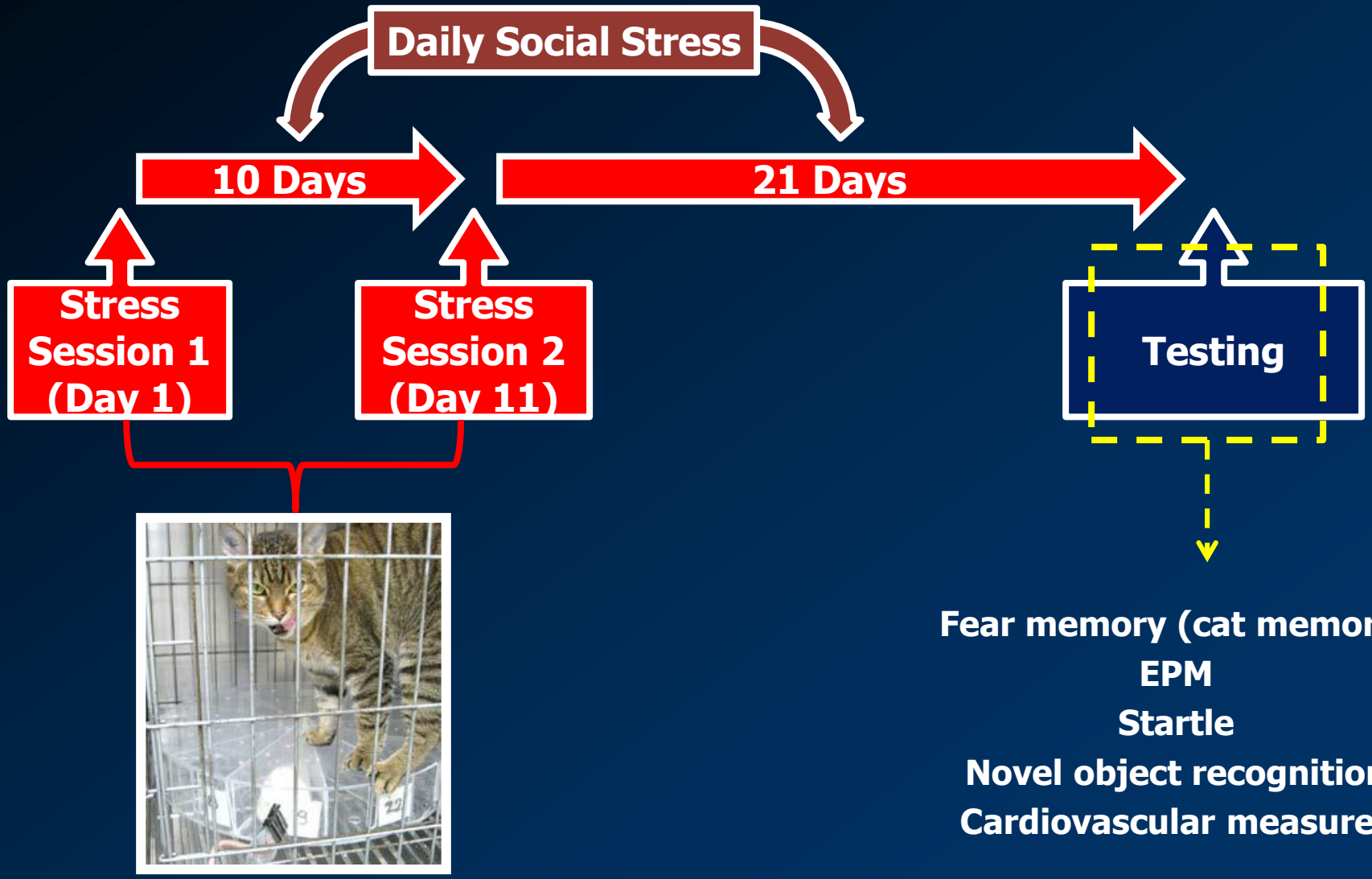
Ohio Northern University

Predator-Based Psychosocial Stress Model



Predator-Based Psychosocial Stress Model



Predator-Based Psychosocial Stress Model

- **Observed Effects that Compare to PTSD Symptoms**
  - **"Traumatic" memory of cat exposures**
  - **Heightened anxiety**
  - **Exaggerated startle response**
  - **Cognitive impairments**
  - **HR/BP abnormalities**
  - **Heightened response to yohimbine**
  - **Social "support" buffering**

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- **Still unknown…**
  - **HPA axis changes**
  - **Pharmacotherapy**
  - **Do HR/BP changes translate to changes in heart?**
  - **Sex differences**

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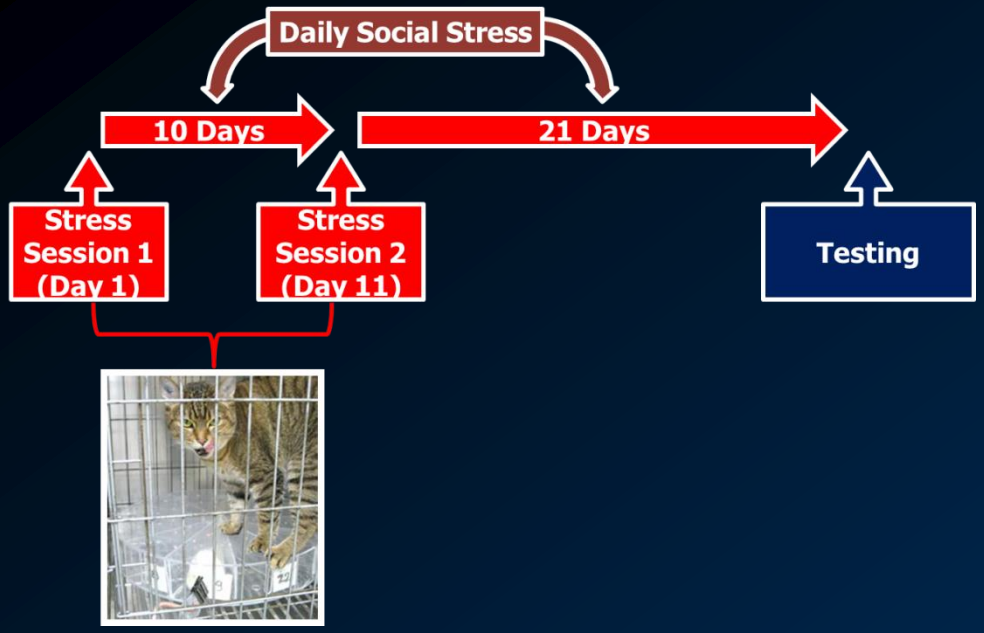
HPA Axis Changes



Zoladz et al., 2012 - *Psychoneuroendocrinol*

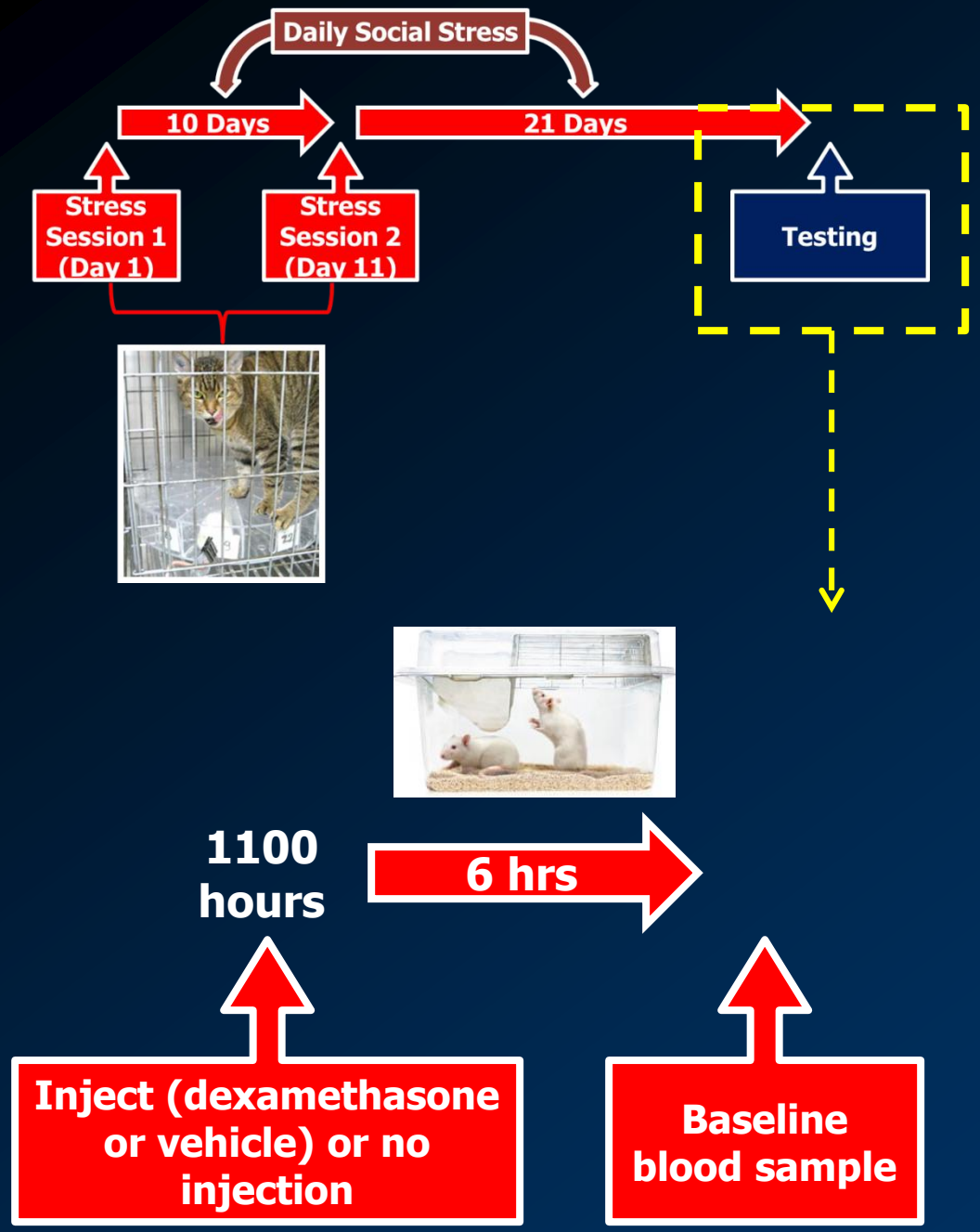
HPA Axis Changes

1100 hours

Inject (dexamethasone or vehicle) or no injection

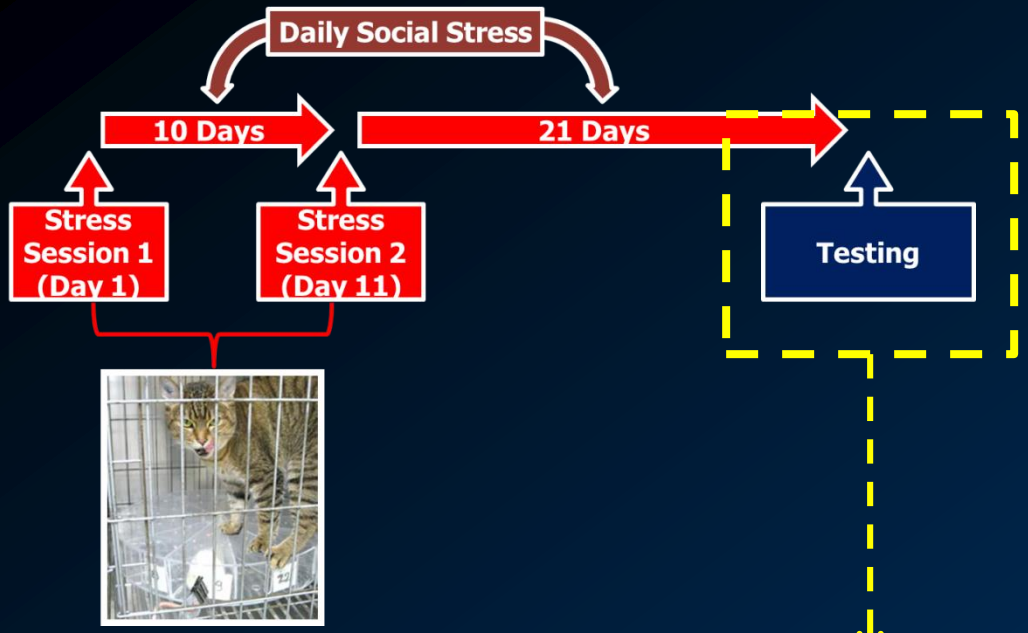
Zoladz et al., 2012 - *Psychoneuroendocrinol*

HPA Axis Changes



Zoladz et al., 2012 - *Psychoneuroendocrinol*

HPA Axis Changes



1100 hours

6 hrs

20 min

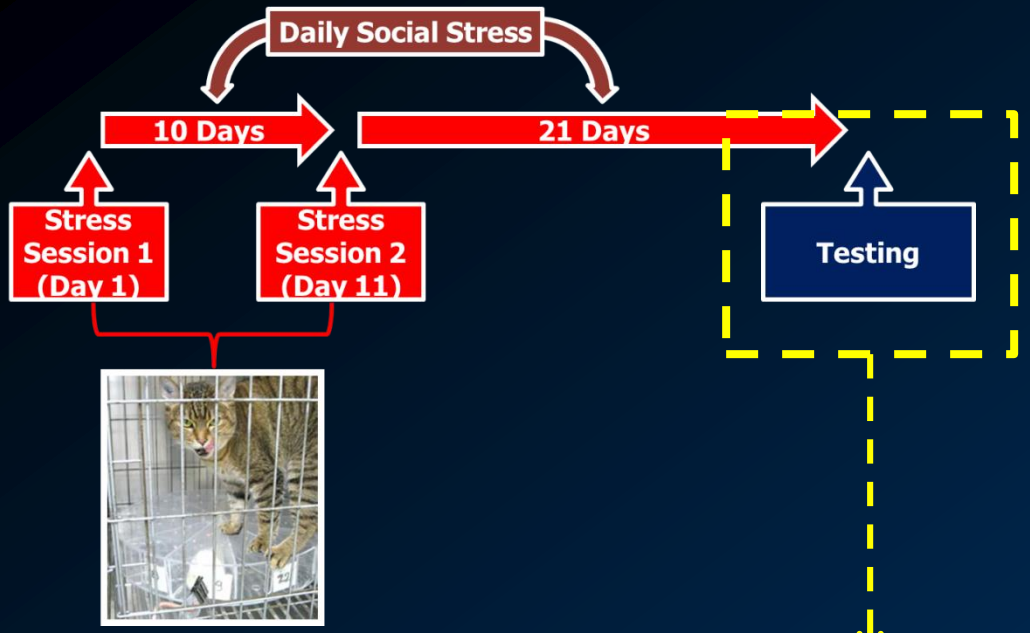
Inject (dexamethasone or vehicle) or no injection

Baseline blood sample

Stress blood sample

Zoladz et al., 2012 - *Psychoneuroendocrinol*

HPA Axis Changes

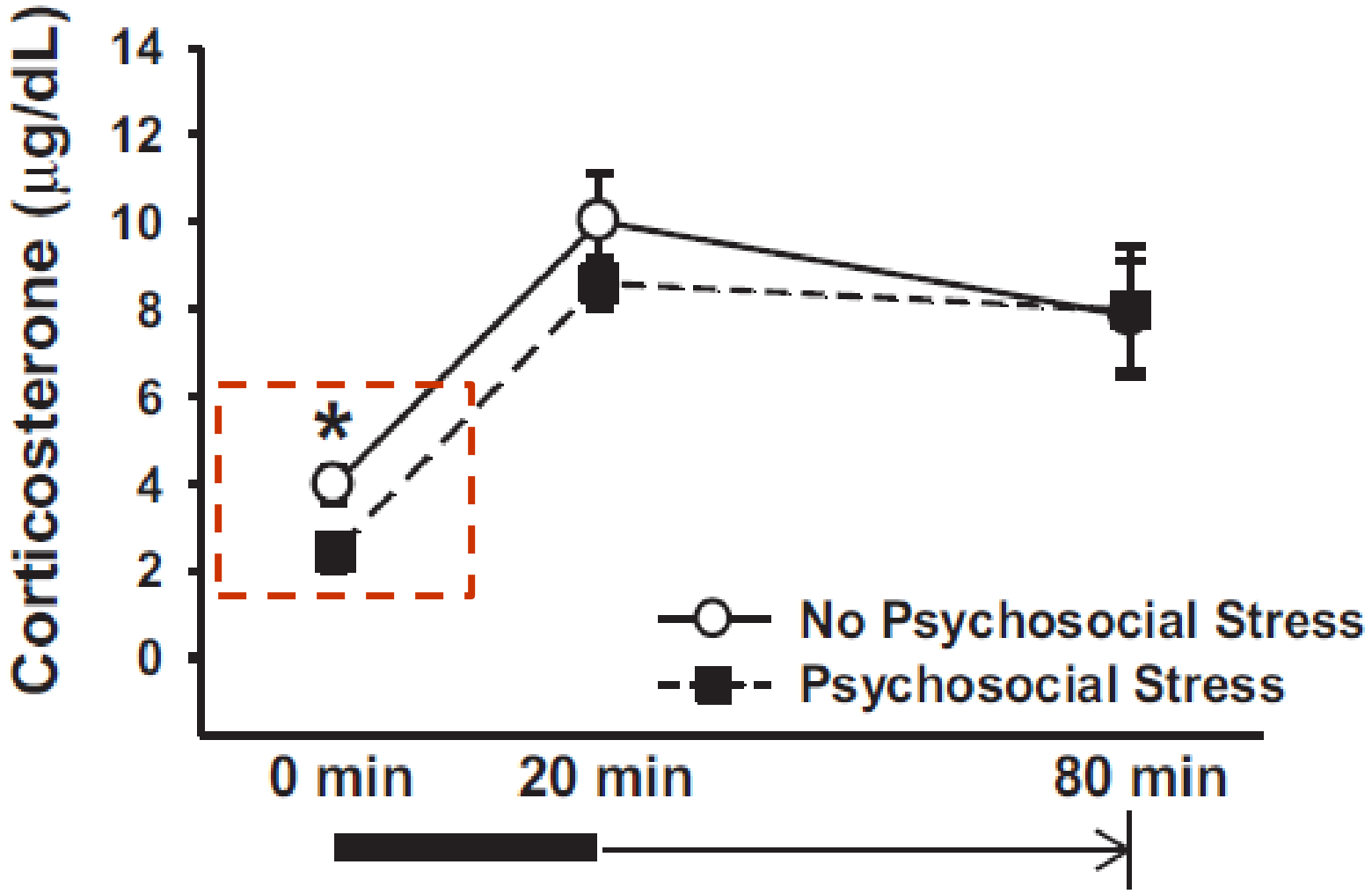


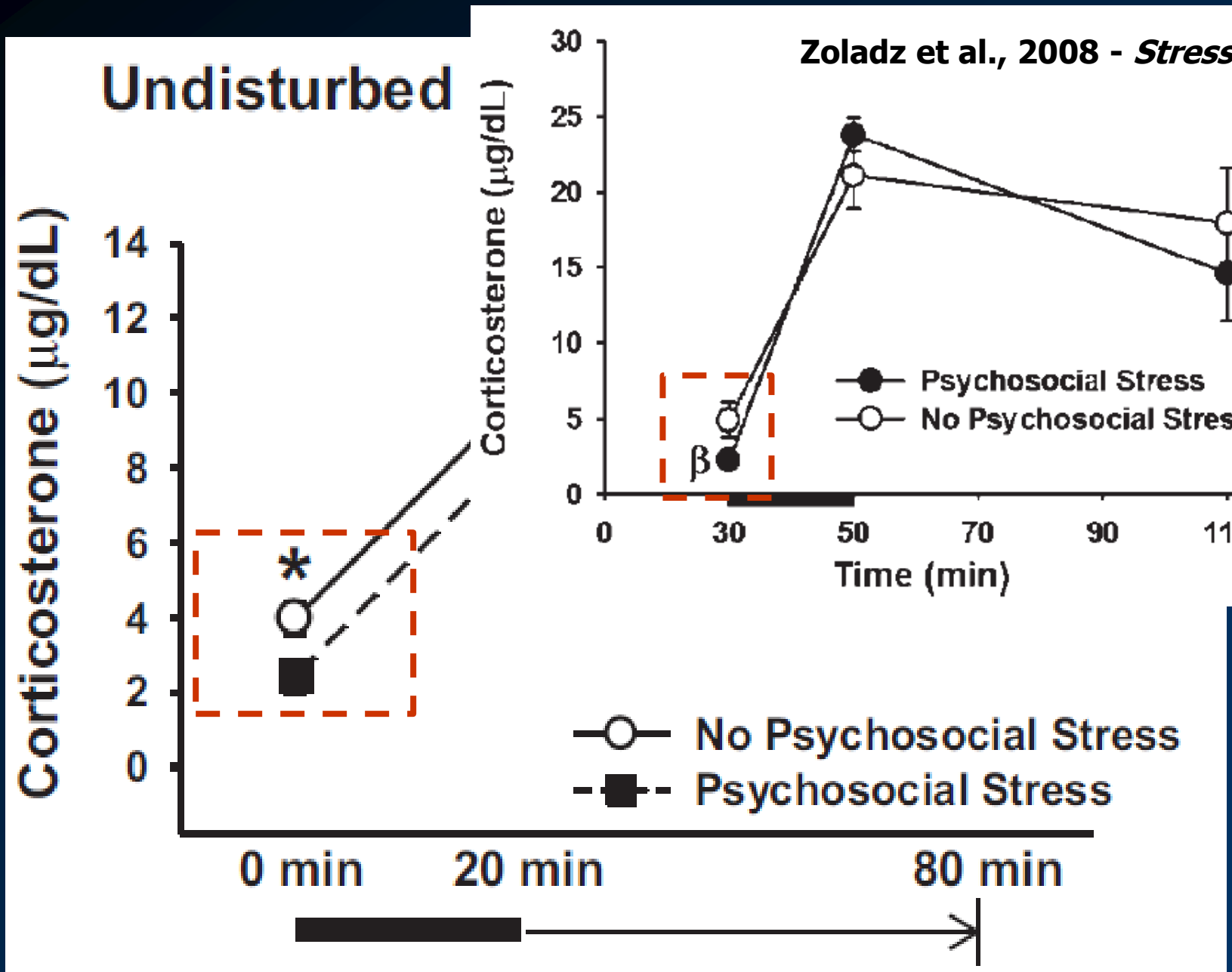
1100 hours → 6 hrs → 20 min → 60 min

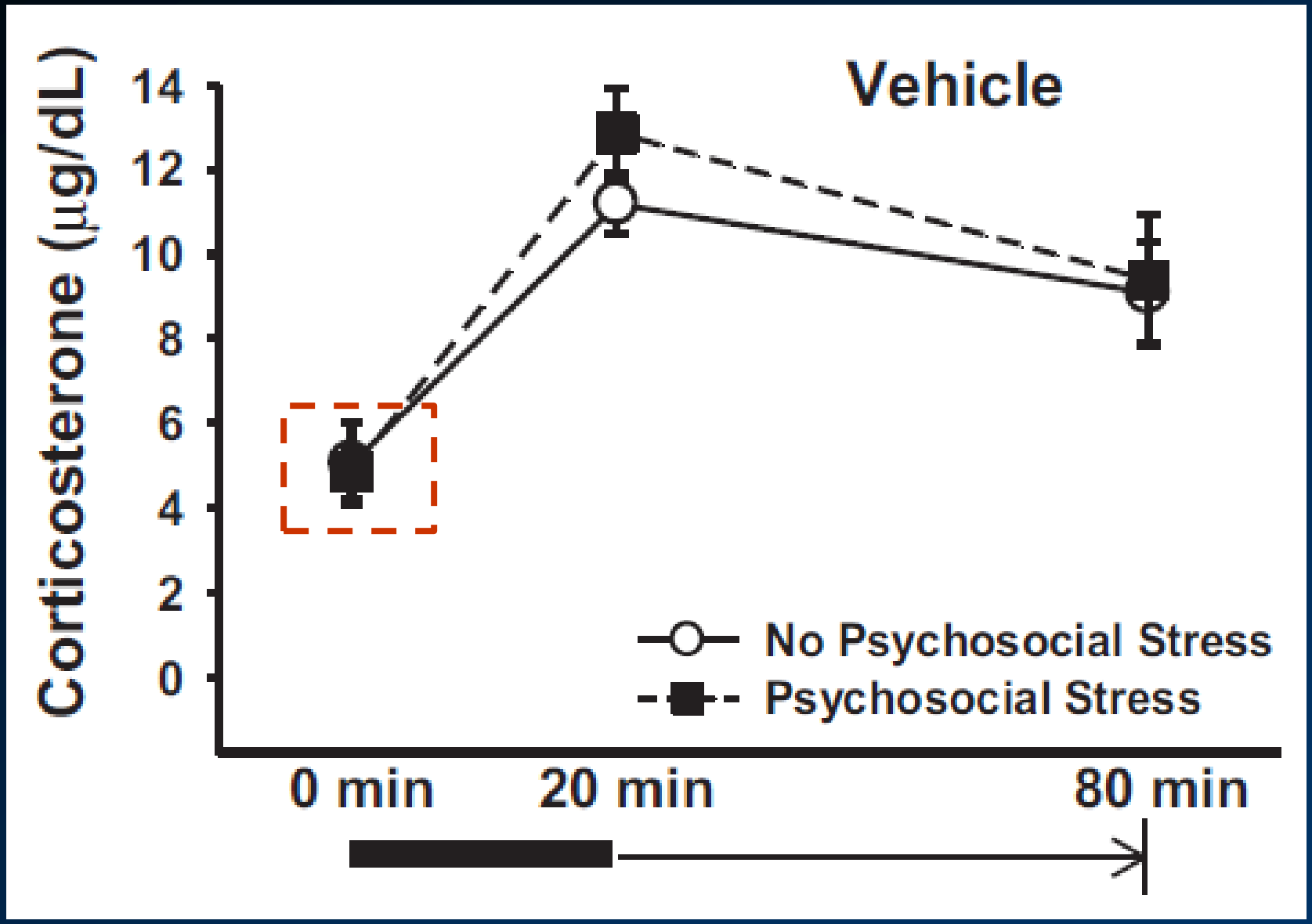
- Inject (dexamethasone or vehicle) or no injection
- Baseline blood sample
- Stress blood sample
- Return-to-baseline blood sample

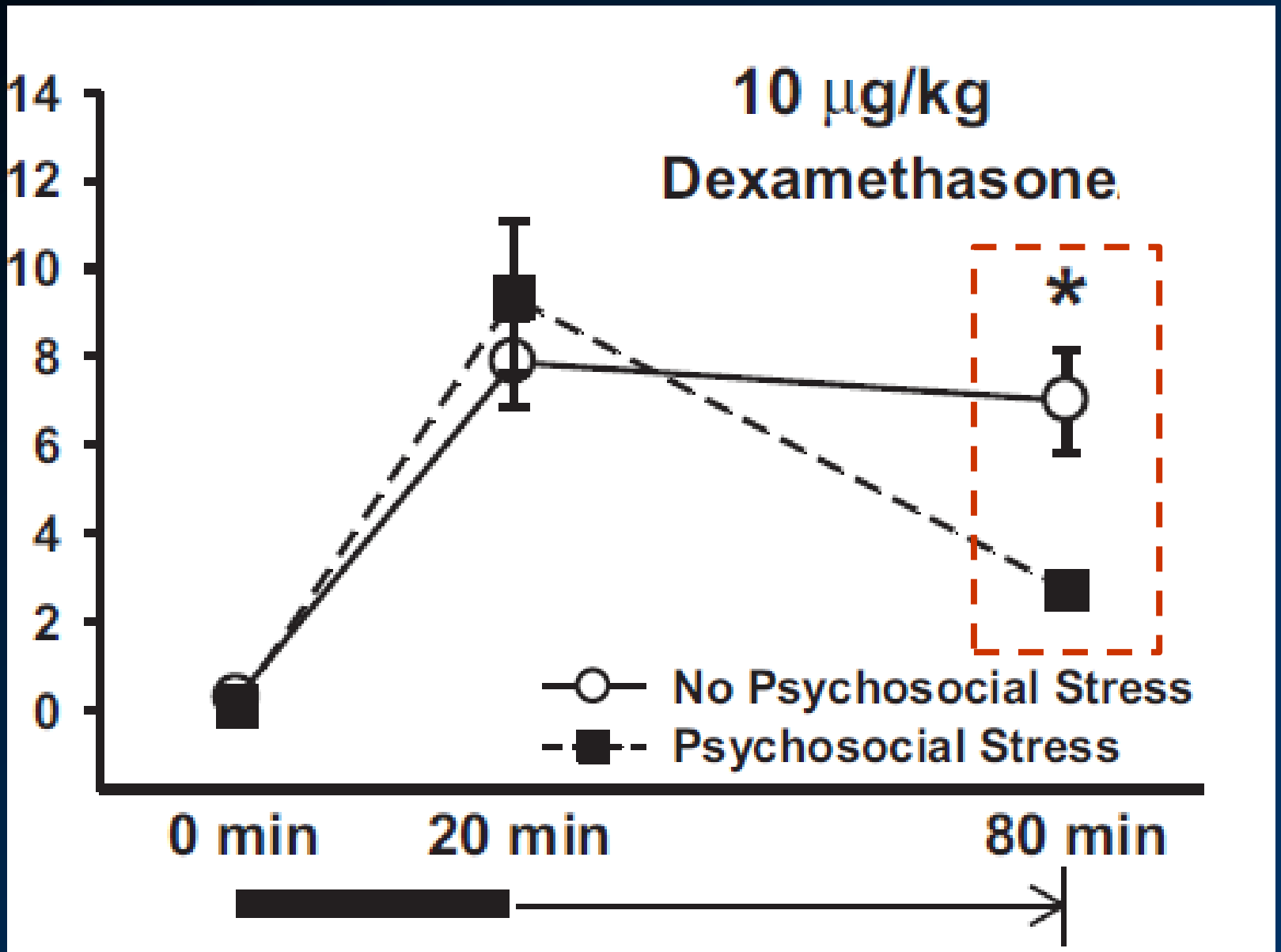
Zoladz et al., 2012 - *Psychoneuroendocrinol*

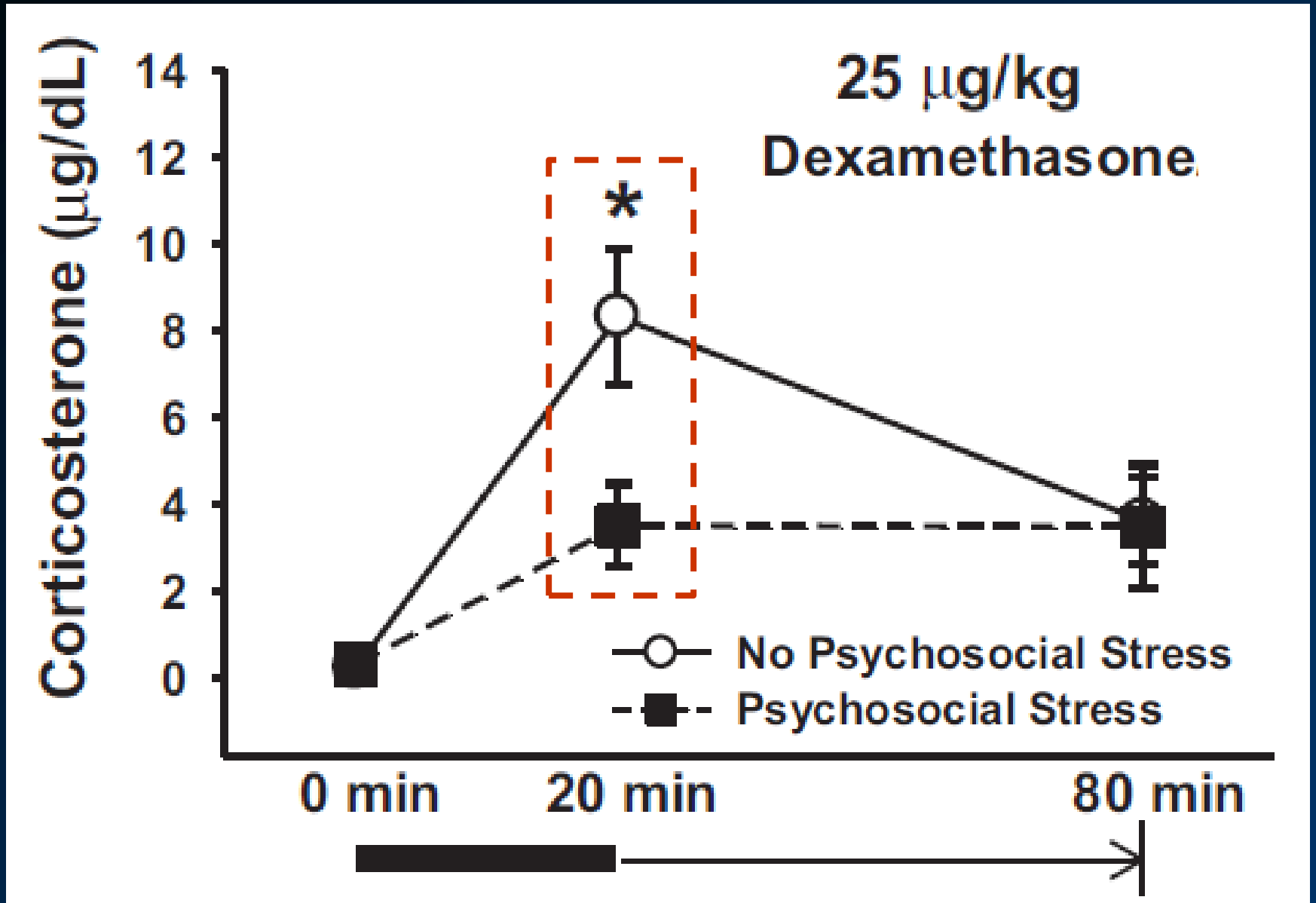
Undisturbed Baseline (No Injection)




Undisturbed
Corticosterone (µg/dL)
14
12
10
8
6
4
2
0
*
0 min
20 min
80 min
No Psychosocial Stress
Psychosocial Stress
Zoladz et al., 2008 - Stress
Corticosterone (µg/dL)
30
25
20
15
10
5
0
α
β
0
30
50
70
90
110
Time (min)
Psychosocial Stress
No Psychosocial Stress


Vehicle
Corticosterone (µg/dL)
14
12
10
8
6
4
2
0
No Psychosocial Stress
Psychosocial Stress
0 min
20 min
80 min


10 µg/kg
Dexamethasone
14
12
10
8
6
4
2
0
*
No Psychosocial Stress
Psychosocial Stress
0 min
20 min
80 min


Corticosterone (µg/dL)
14
12
10
8
6
4
2
0
25 µg/kg
Dexamethasone
*
No Psychosocial Stress
Psychosocial Stress
0 min
20 min
80 min

HPA Axis Changes

- **Findings are consistent with majority of PTSD literature (e.g., Rachel Yehuda's work)**
  - **Lower baseline levels of circulating corticosteroids**

Yehuda, 2009 – *Ann NY Acad Sci*

HPA Axis Changes

Finding in PTSD	Enhanced negative feedback
Lower ambient cortisol levels[12,56,57,60,63,64,70,71,80–84]	yes
Normal or variable cortisol levels[20,35,54,62,65–67,72]	yes
Higher cortisol levels[51,53,55,59,79]	yes[a]
Increased circadian rhythm of cortisol[48,58,60,69]	yes
Decreased circadian rhythm of cortisol[86]	no
Normal ACTH levels[51,62,70,71,76]	yes
Low β-endorphin levels[69]	yes[b]
Increased corticotropin-releasing factor(CRF) levels in cerebrospinal fluid[19,20]	yes
Increased glucocorticoid receptor number[57,68]	yes
Increased glucocorticoid receptor responsiveness[46]	yes
Normal cortisol levels following 1 mg dexamethasone (DEX)[33,54,73,74]	yes
Decreased cortisol levels following 0.5 mg DEX[28,35,37,39]	yes
Increased cortisol levels following 1 mg DEX[60,75]	no
Decreased number of cytosolic glucocorticoid receptors following DEX compared to baseline receptors[35]	yes
Increased ACTH suppression following DEX administration[30,36,38]	yes
Increased ACTH levels to high dose metyrapone[58]	yes
Decreased ACTH levels to low dose metyrapone[71]	no
Decreased ACTH levels following CRF[61,72]	yes
Increased ACTH levels following CRF[26,62,77,78]	no
Decreased ACTH levels following cholecystokinin (CCK)-4[70]	yes
Increased ACTH levels following naloxone[76]	no
Increased ACTH levels following stress[51,76]	yes
Increased cortisol response to ACTH[62]	no
Decreased cortisol response to ACTH[70]	yes

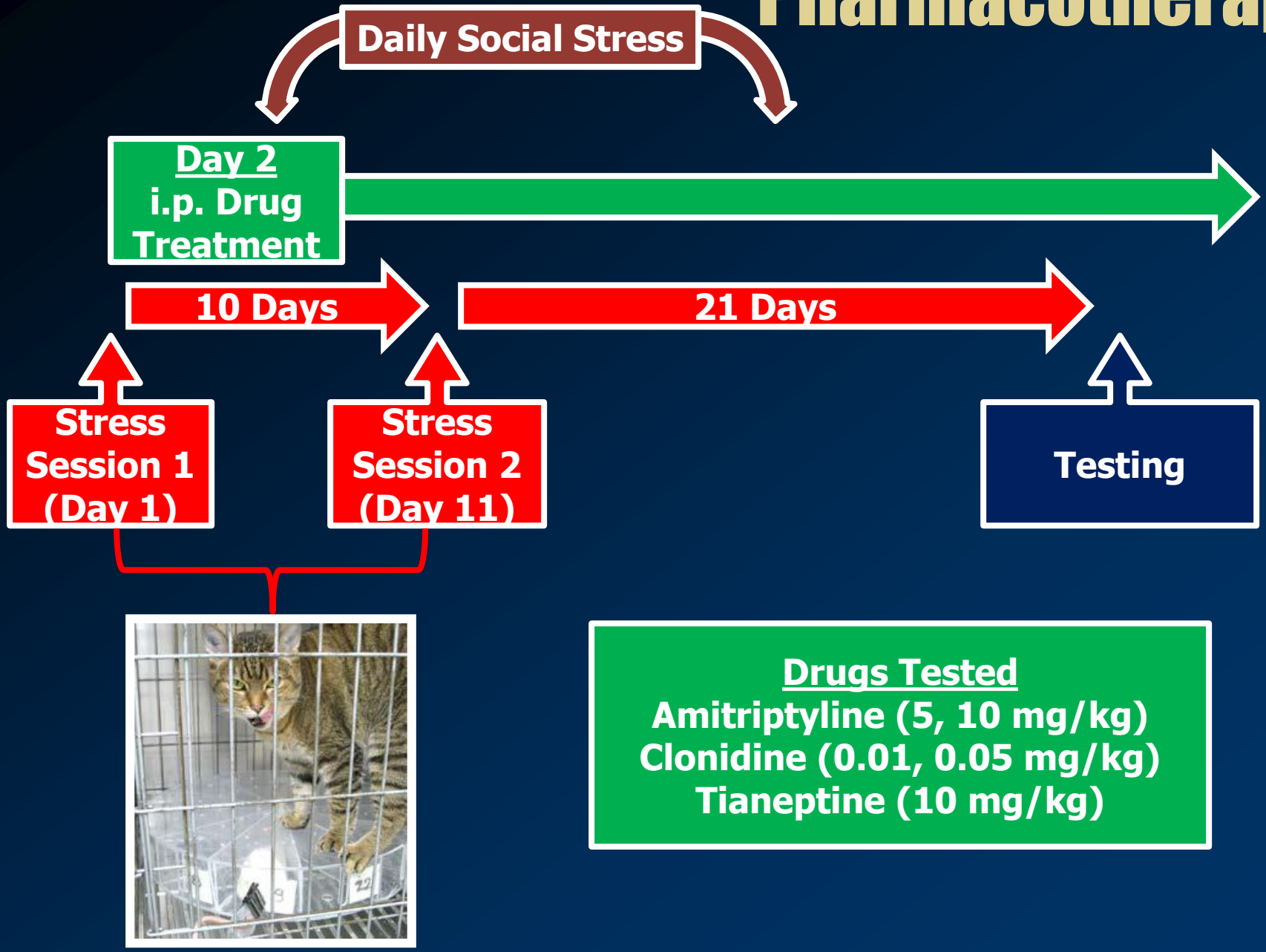
- **Findings are consistent with majority of PTSD literature (e.g., Rachel Yehuda's work)**
  - **Lower baseline levels of circulating corticosteroids**
  - **Enhanced negative feedback of the HPA axis**
    - **Blunted response to acute stress (comparable to DEX-CRH challenges)**
    - **Faster return-to-baseline**

Yehuda, 2009 – *Ann NY Acad Sci*

Pharmacotherapy

Zoladz et al., 2013 – *Prog Neuropsychopharm Biol Psychiatry*

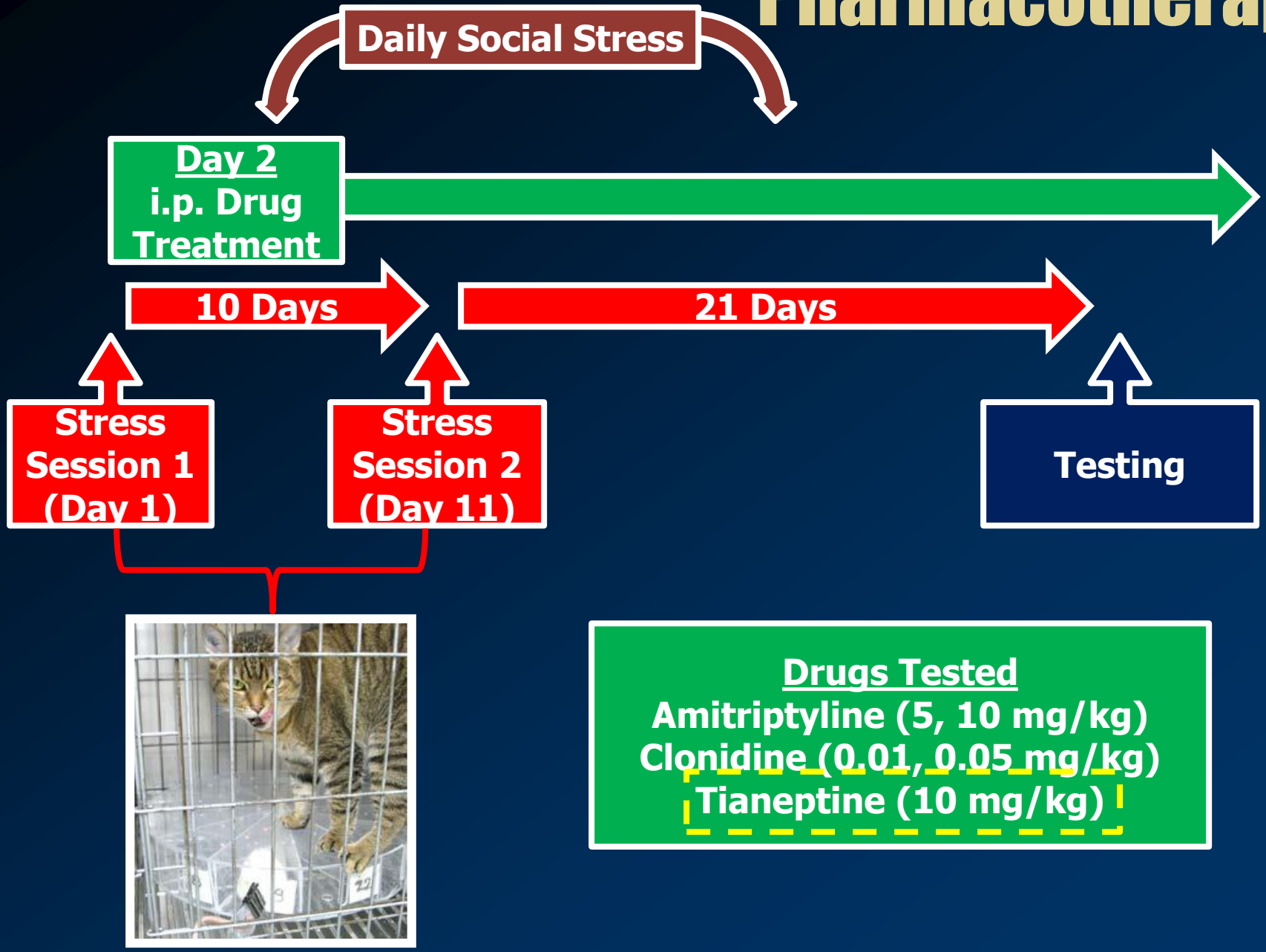
Pharmacotherapy



Drugs Tested
Amitriptyline (5, 10 mg/kg)
Clonidine (0.01, 0.05 mg/kg)
Tianeptine (10 mg/kg)

Zoladz et al., 2013 – *Prog Neuropsychopharm Biol Psychiatry*

Pharmacotherapy



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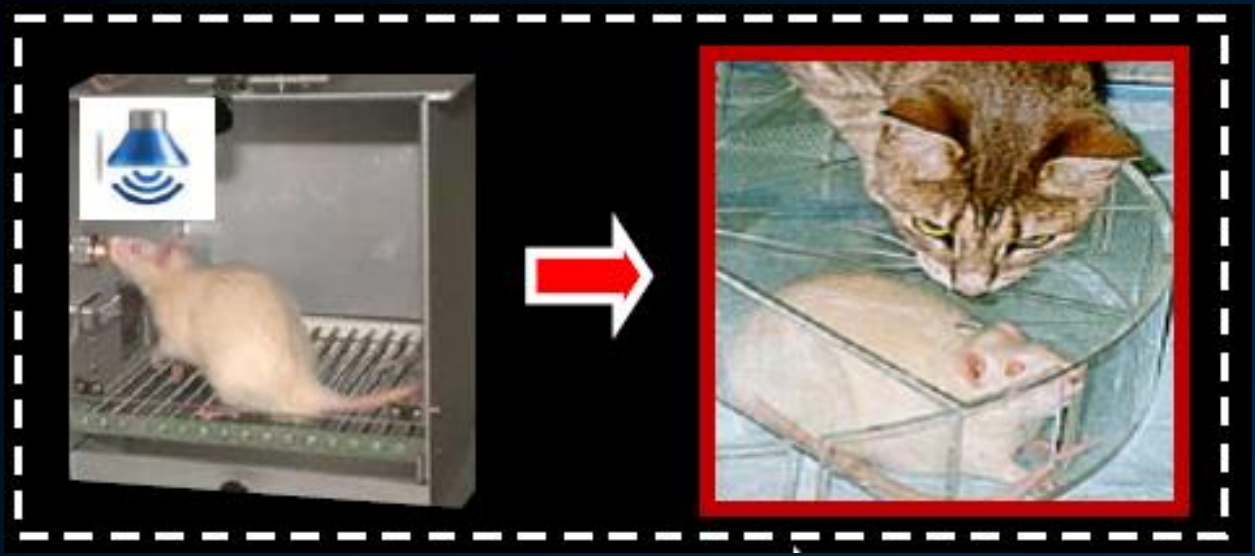
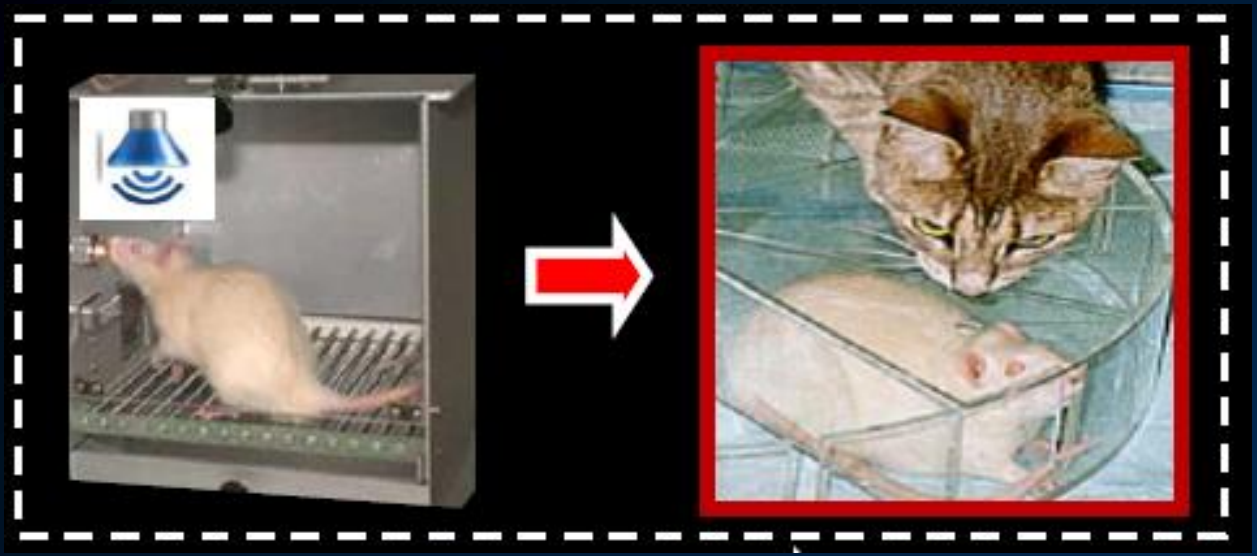
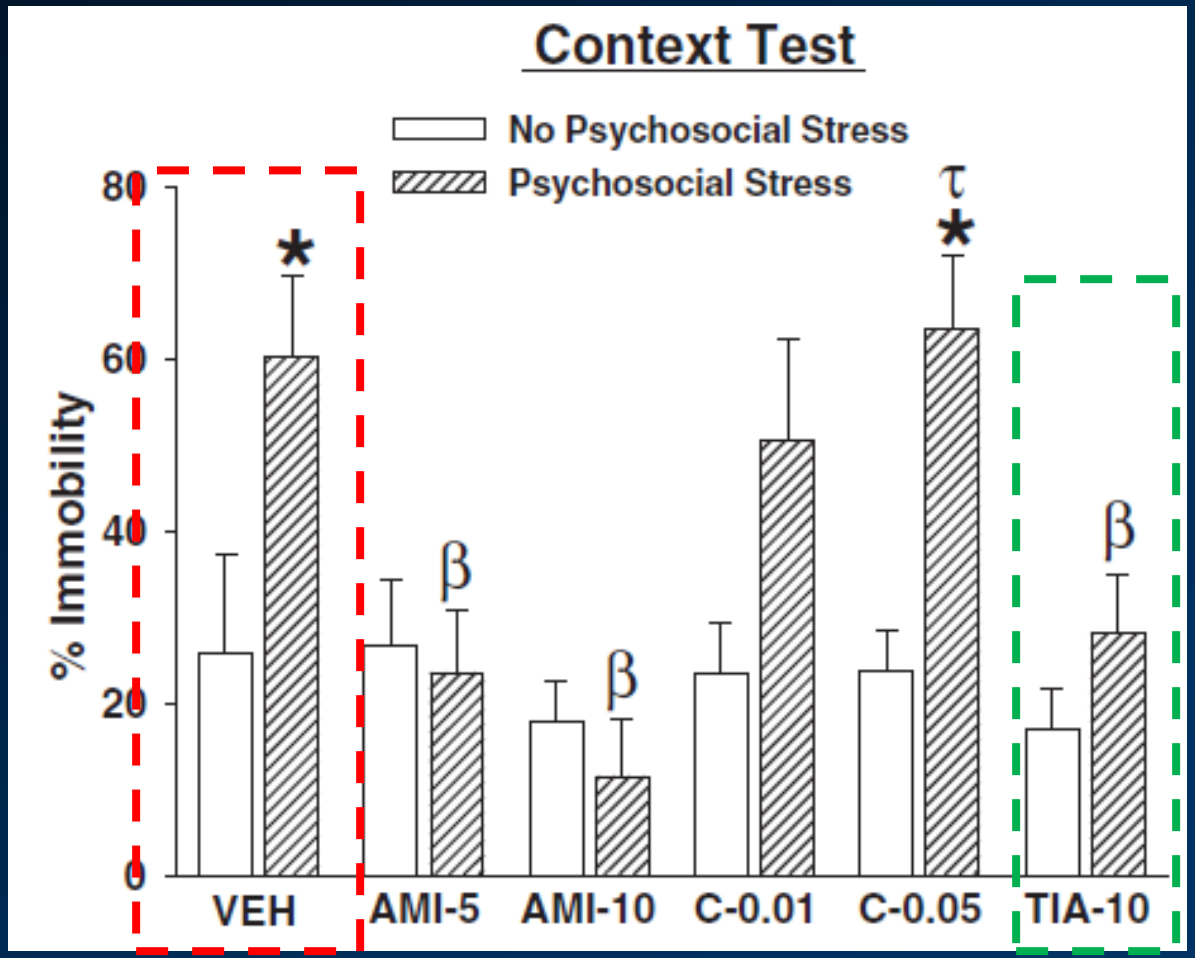


Each stress session



Each stress session

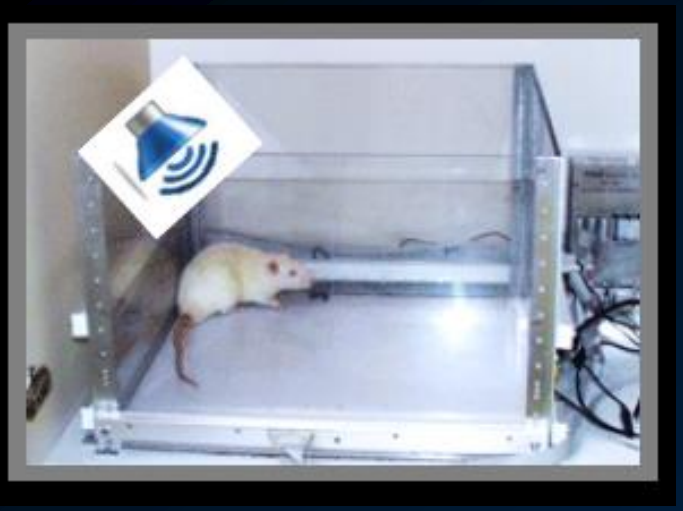
Testing

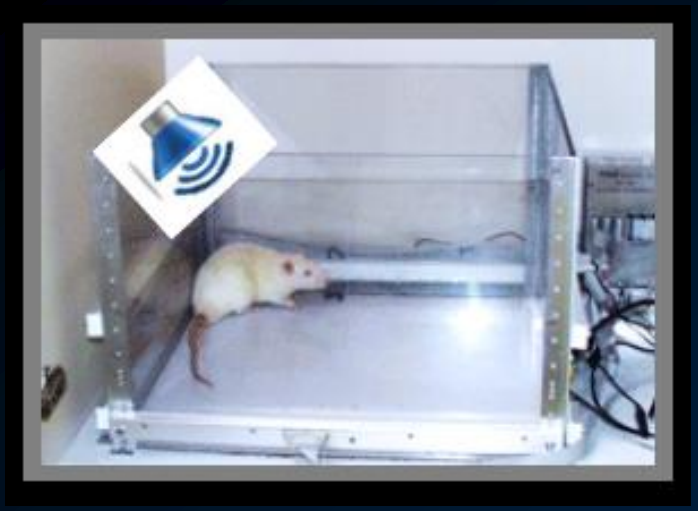


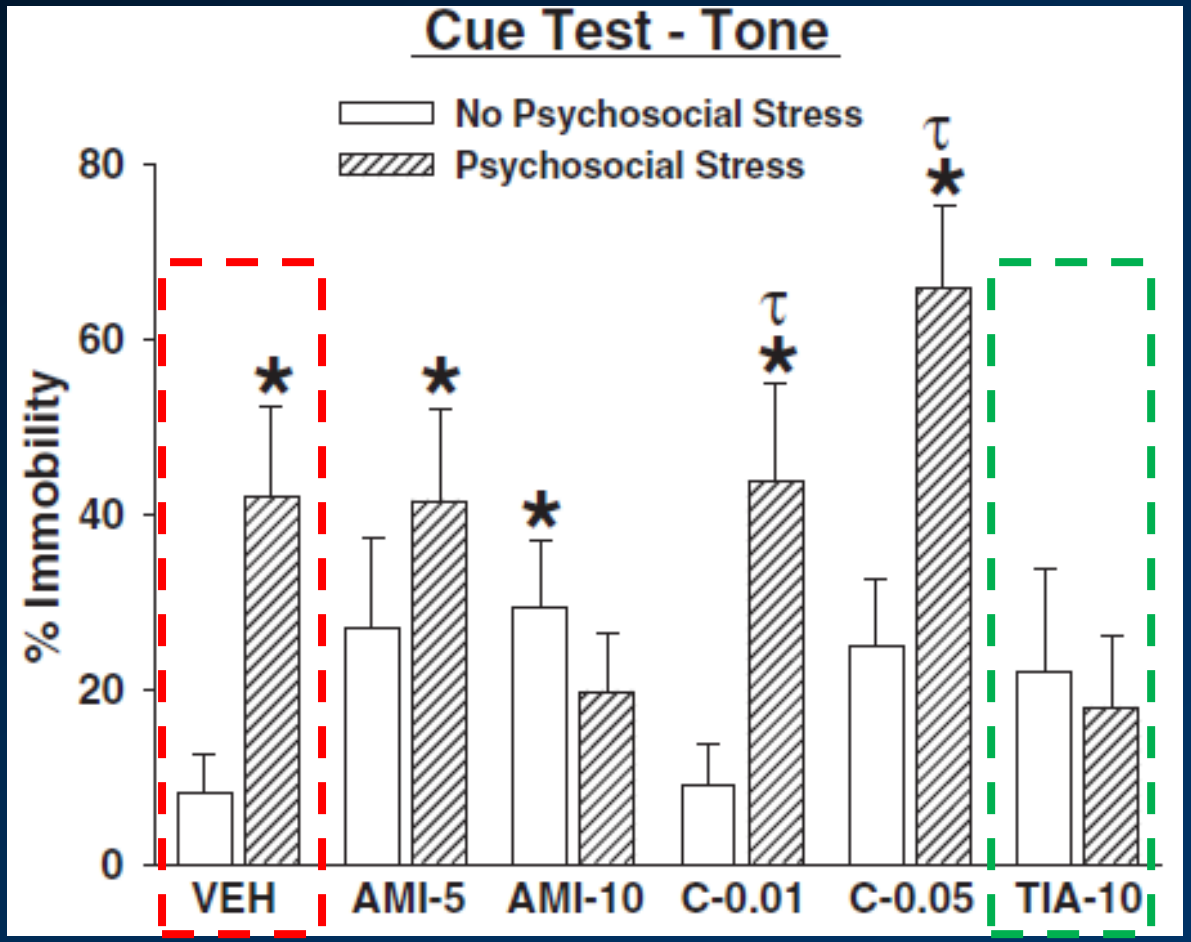
* $p < 0.05$ relative to vehicle no stress

β $p < 0.05$ relative to vehicle stress

τ $p < 0.05$ relative to respective no stress group







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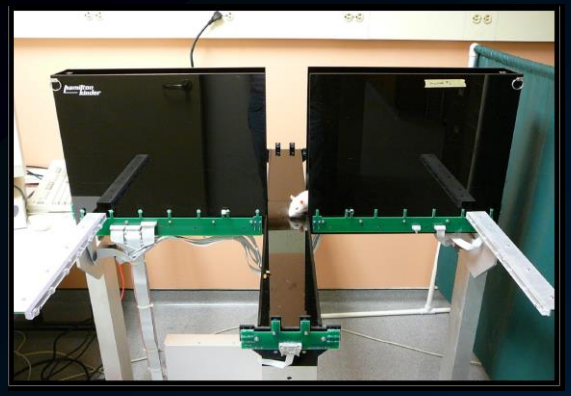

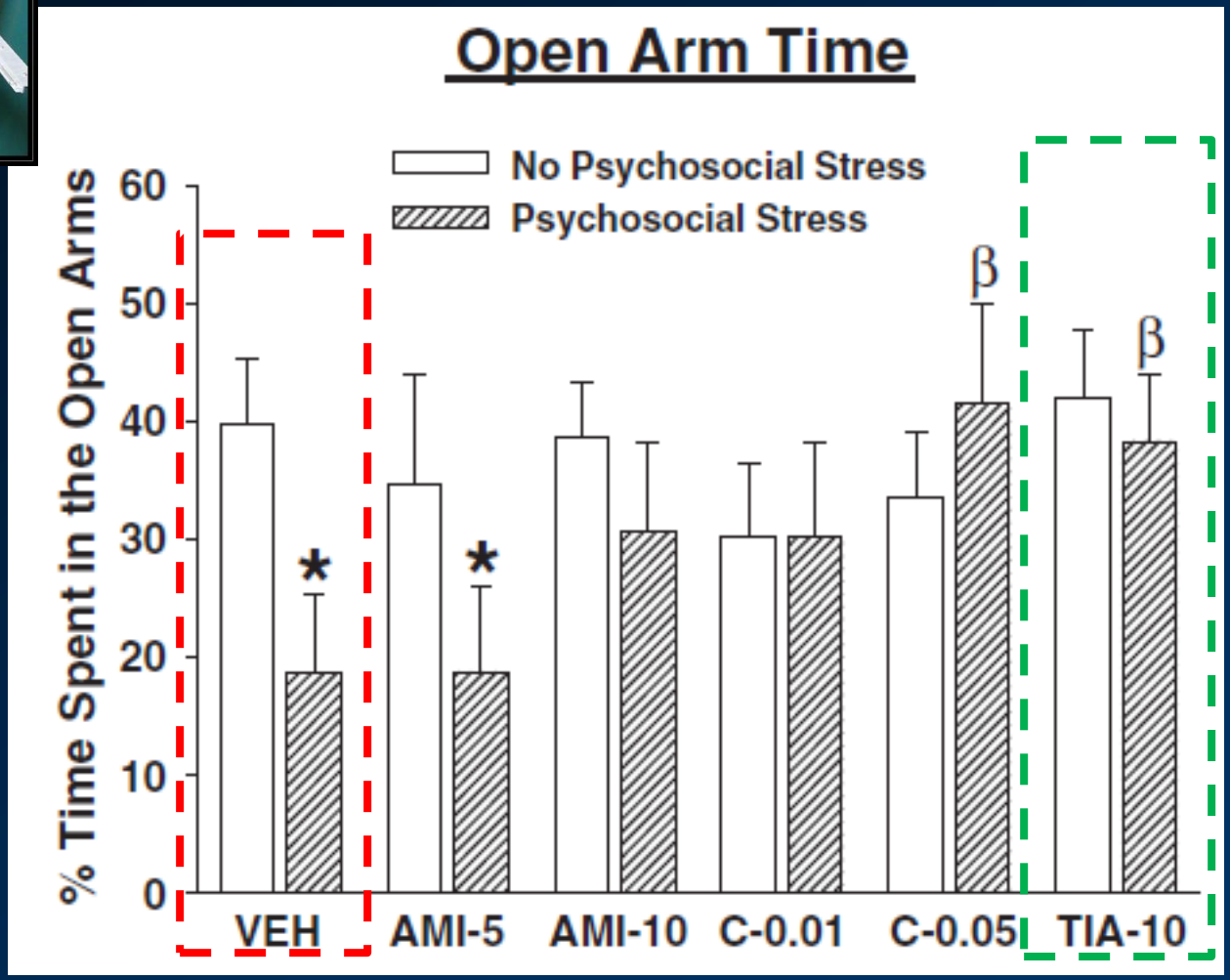

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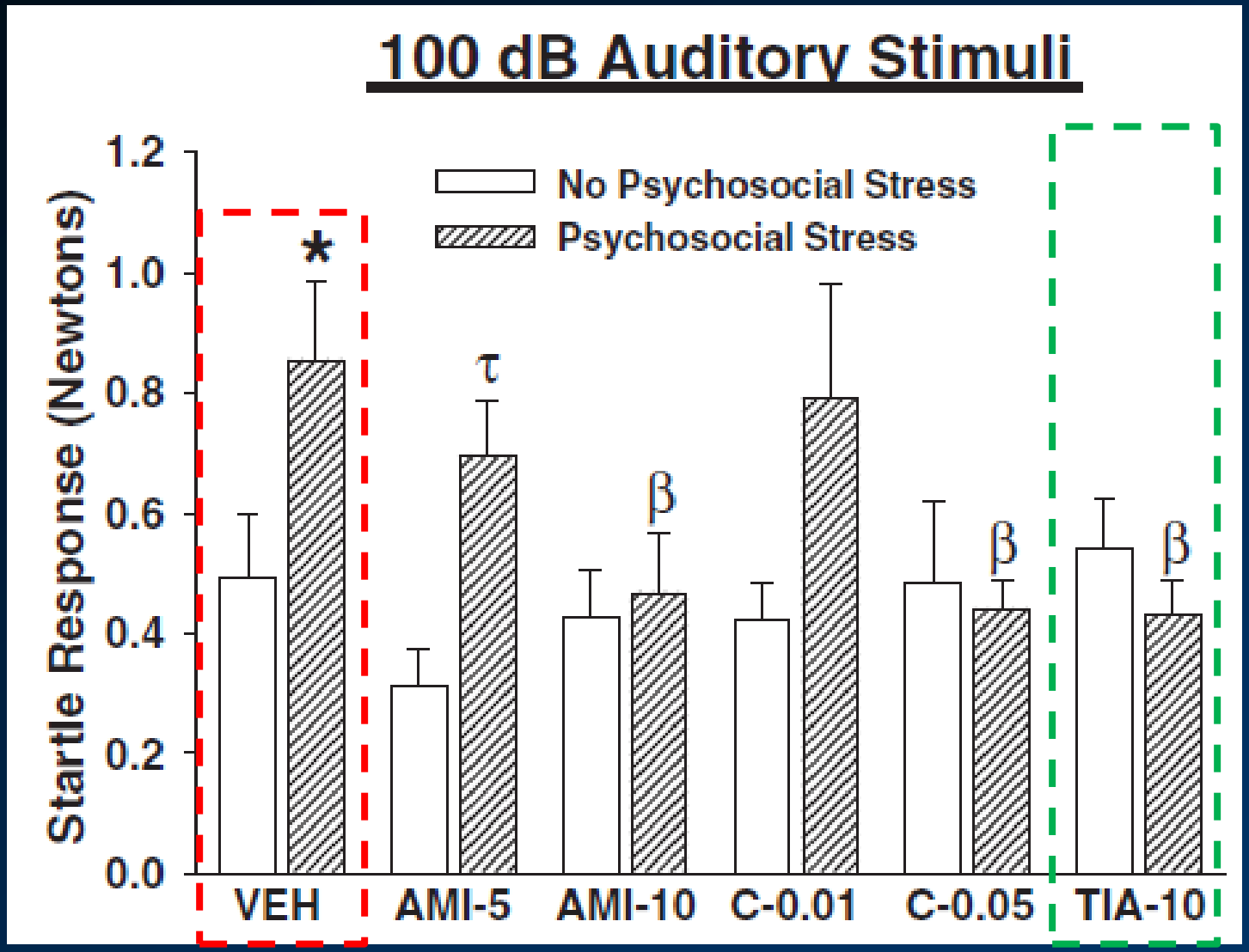

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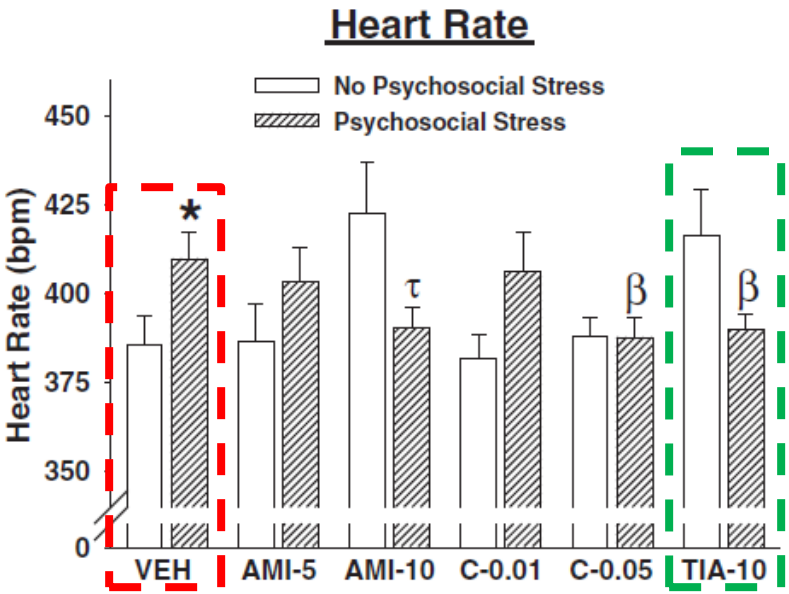

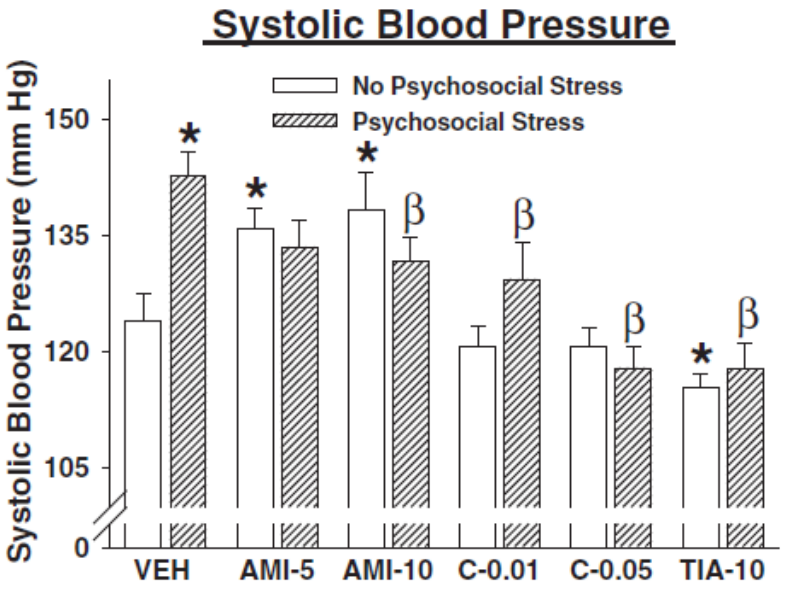

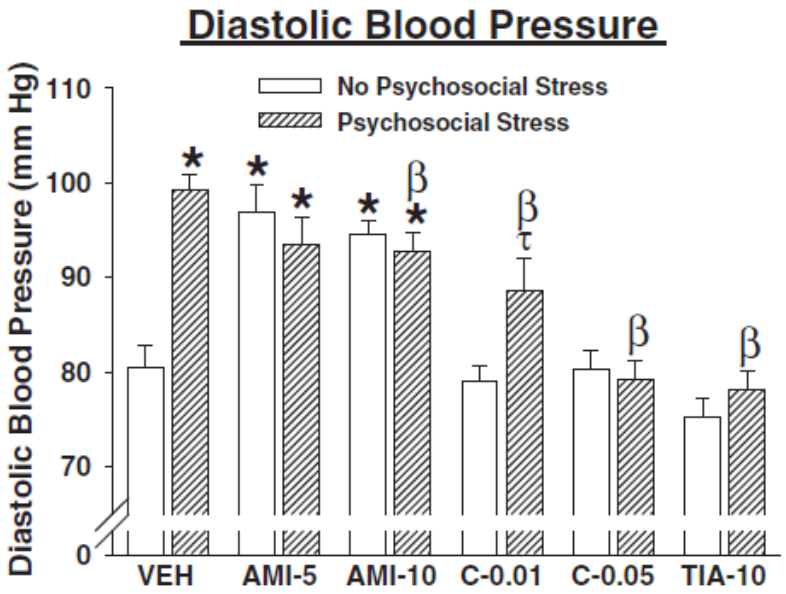

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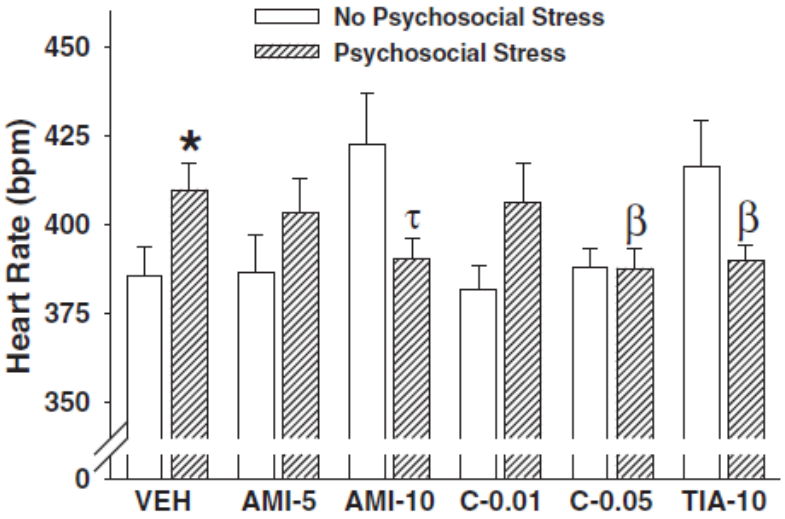

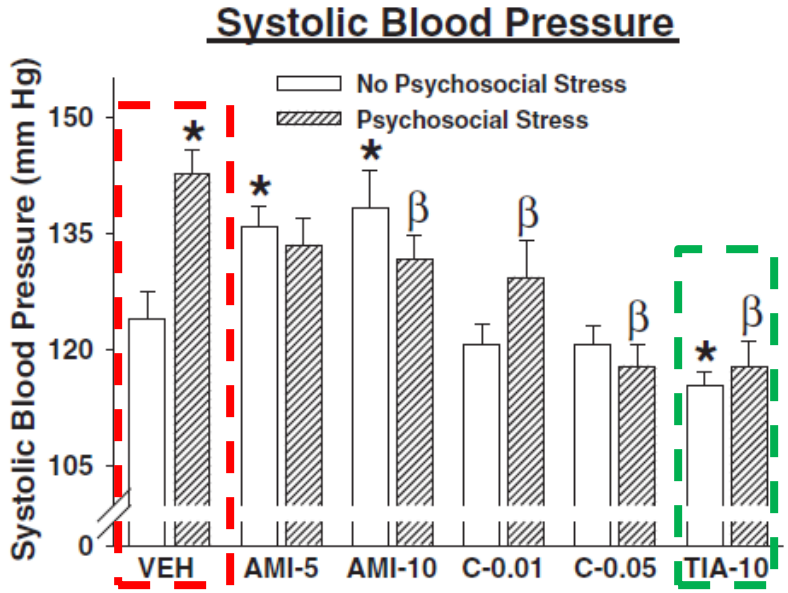

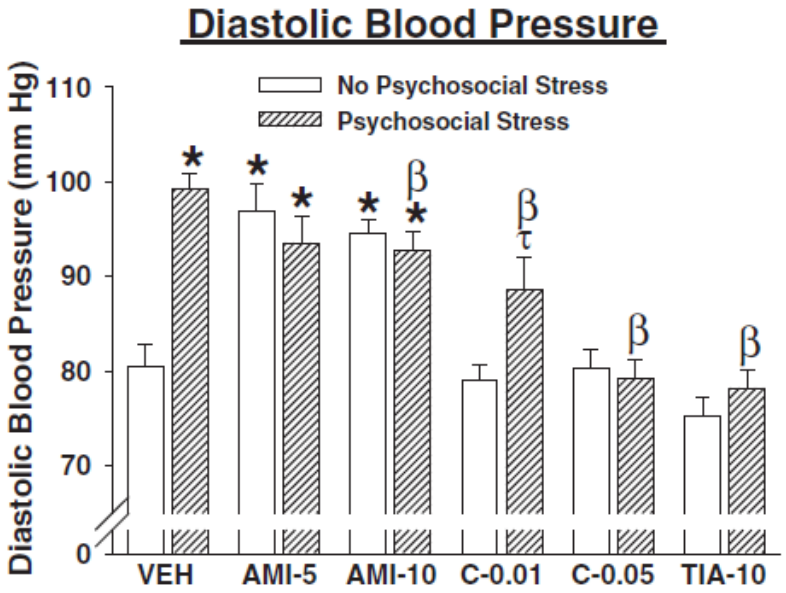

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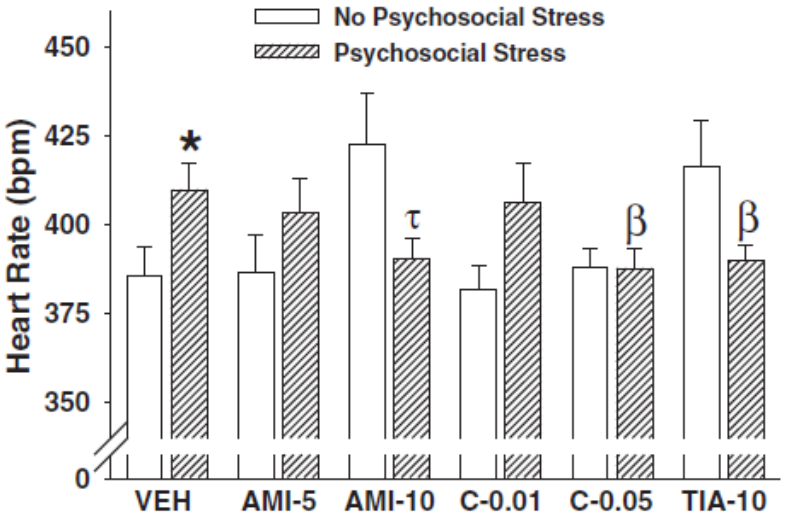

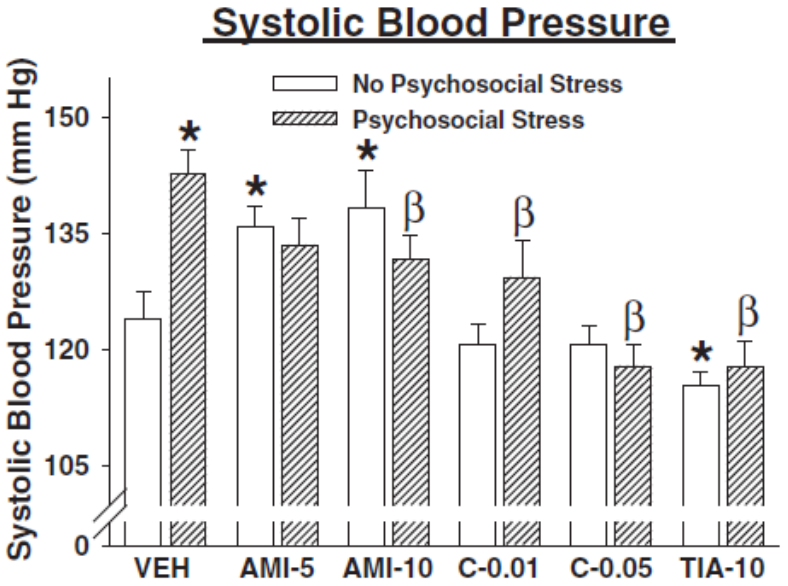

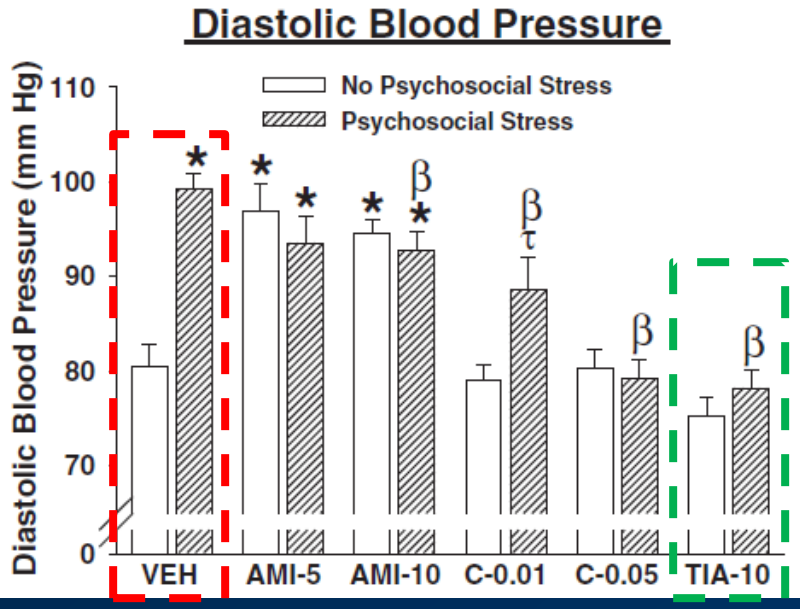

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Pharmacotherapy

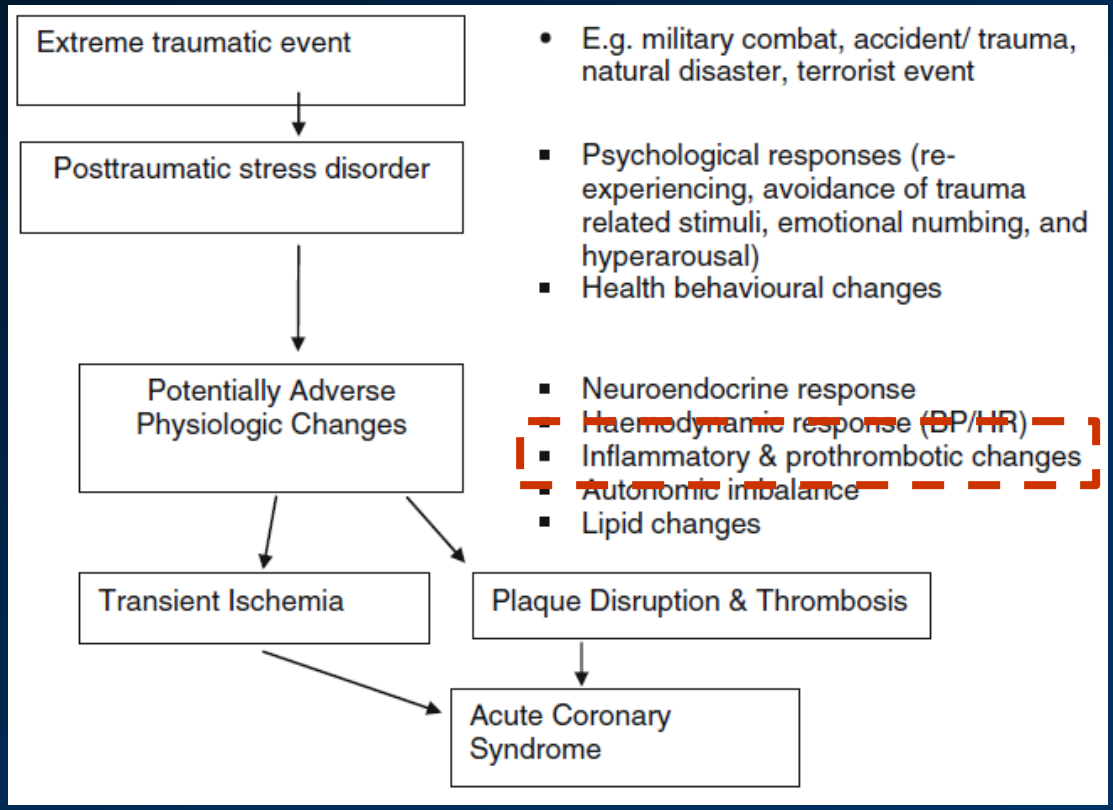
- **Tianeptine was most efficacious agent**
  - **Clonidine, amitriptyline effects varied**

Pharmacotherapy

- **Tianeptine was most efficacious agent**
  - **Clonidine, amitriptyline effects varied**
- **Other pharmacological agents shown to be effective in model (Wilson et al., 2013, 2014)**
  - **Valproic acid**
  - **Sertraline (only *some* effects blocked)**

Cardiovascular Abnormalities in PTSD

- **PTSD heart/SNS issues**
  - **Increased risk of CVD**
  - **Lower HRV**
  - **Increased QT variability**
  - **Reduced baroreflex sensitivity**
  - **Elevated HR/BP**
  - **Increased NE**



Buckley et al., 2013 – *Curr Cardiovasc Risk Rep*

Myocardial Sensitivity to Ischemic Injury

Rorabaugh et al., 2015 – *Stress*

Myocardial Sensitivity to Ischemic Injury

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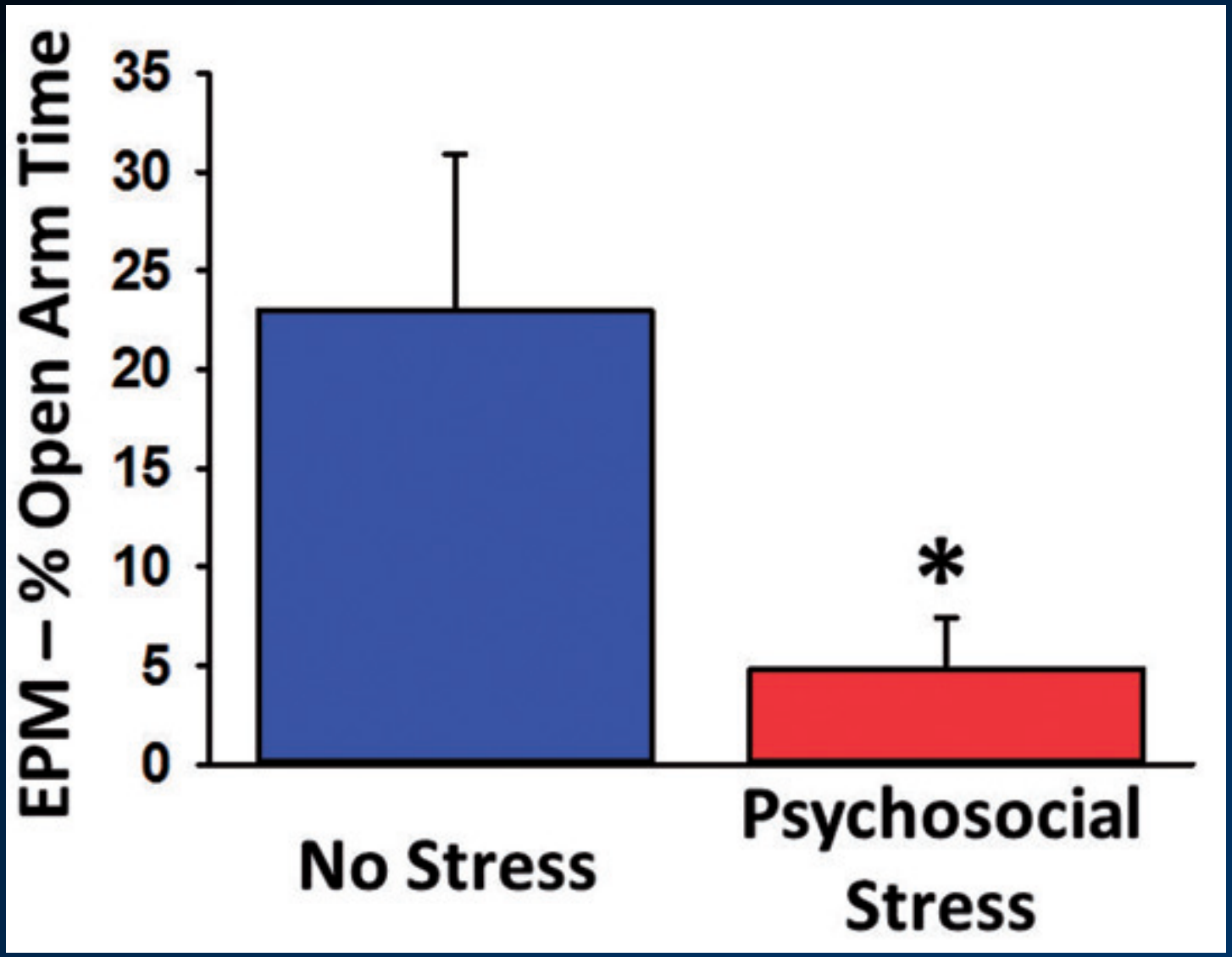
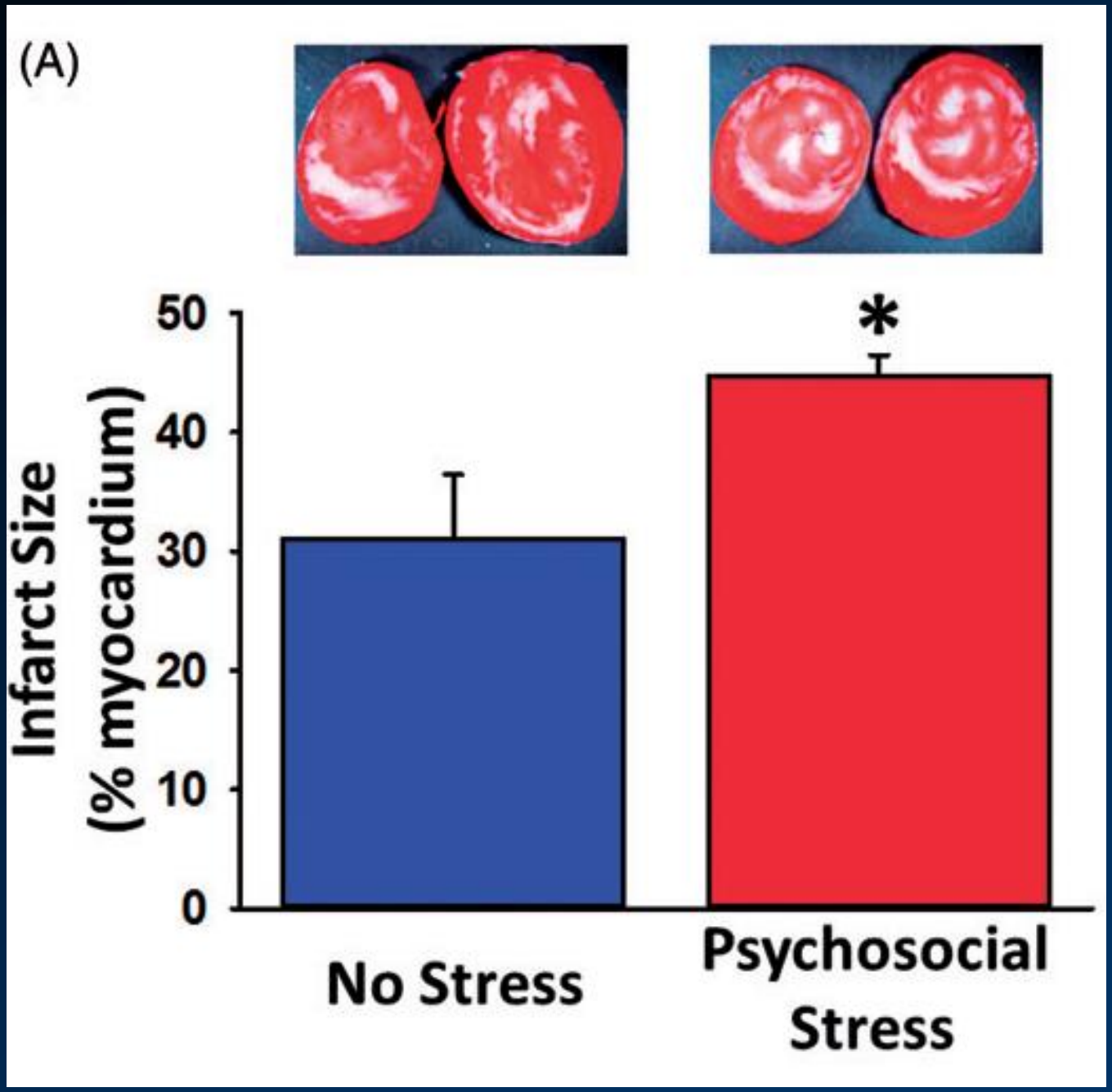
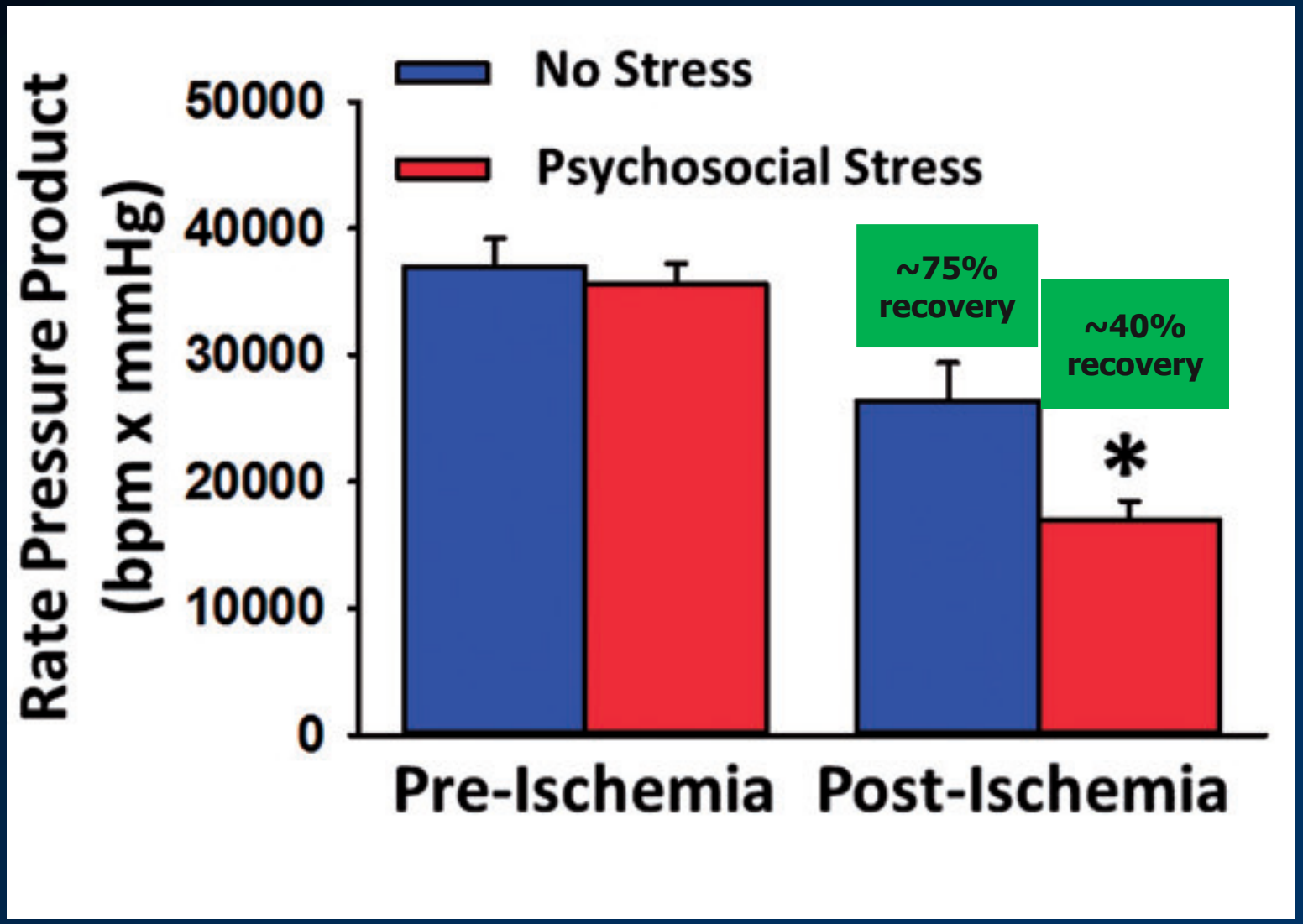

EPM – % Open Arm Time
35
30
25
20
15
10
5
0
*
No Stress
Psychosocial Stress


(A)
Infarct Size
(% myocardium)
50
40
30
20
10
0
*
No Stress
Psychosocial
Stress


No Stress
Psychosocial Stress
Rate Pressure Product
(bpm x mmHg)
50000
40000
30000
20000
10000
0
~75% recovery
~40% recovery
*
Pre-Ischemia
Post-Ischemia

Pharmacological Blockade of Increased Myocardial Sensitivity to Ischemic Injury

Daily Social Stress

10 Days

21 Days

1 Day

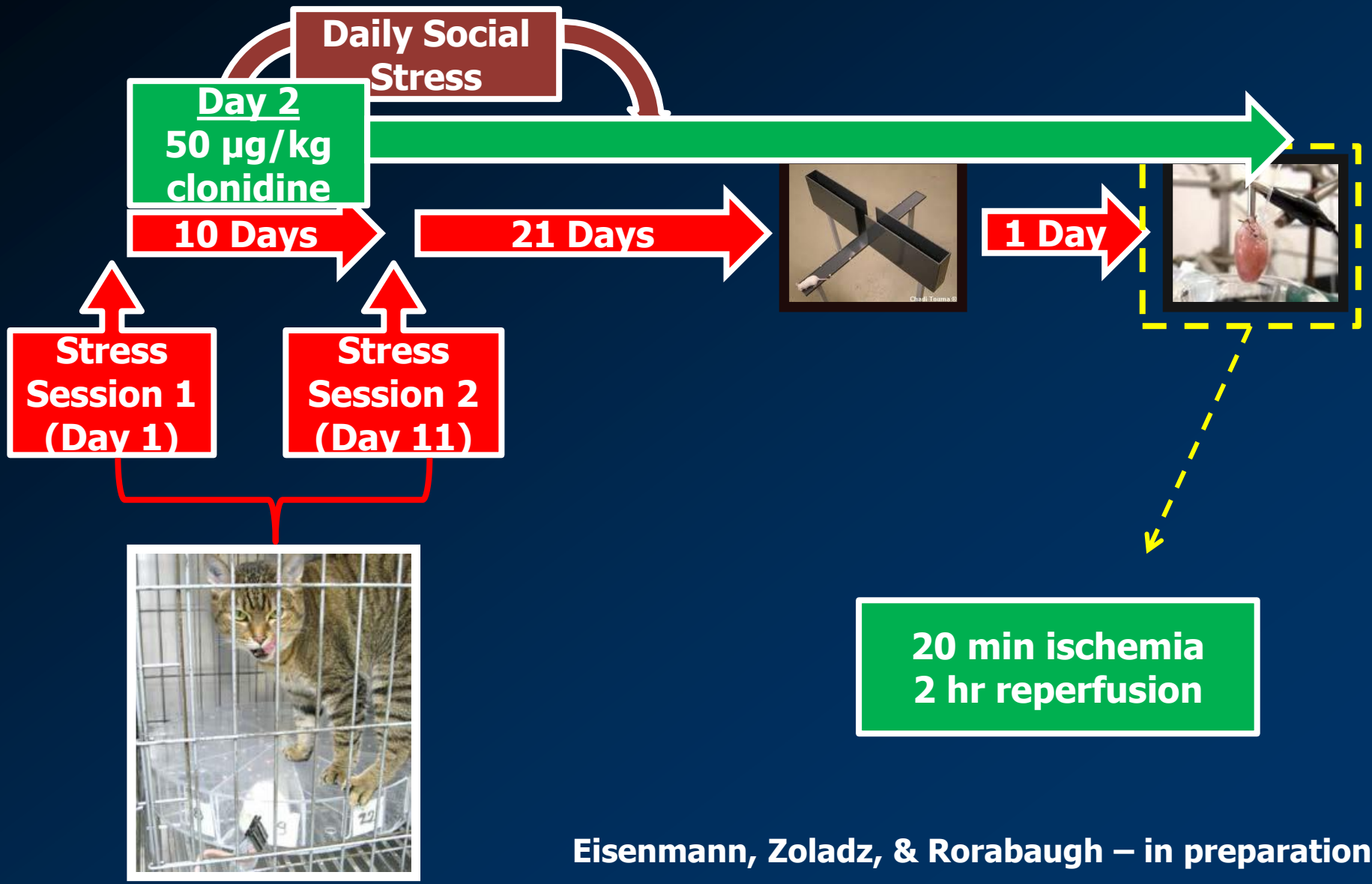
Stress Session 1 (Day 1)

Stress Session 2 (Day 11)

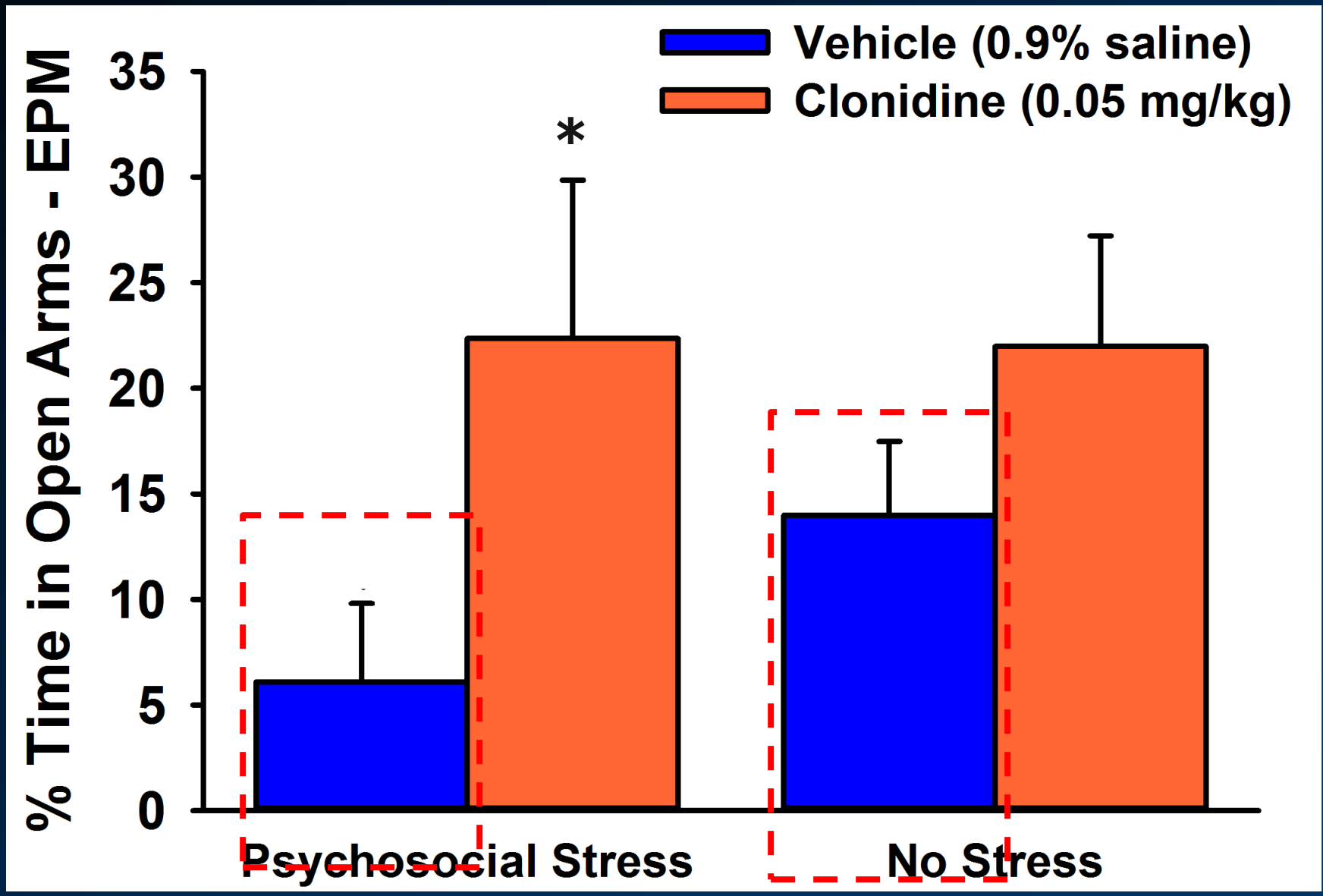
20 min ischemia
2 hr reperfusion

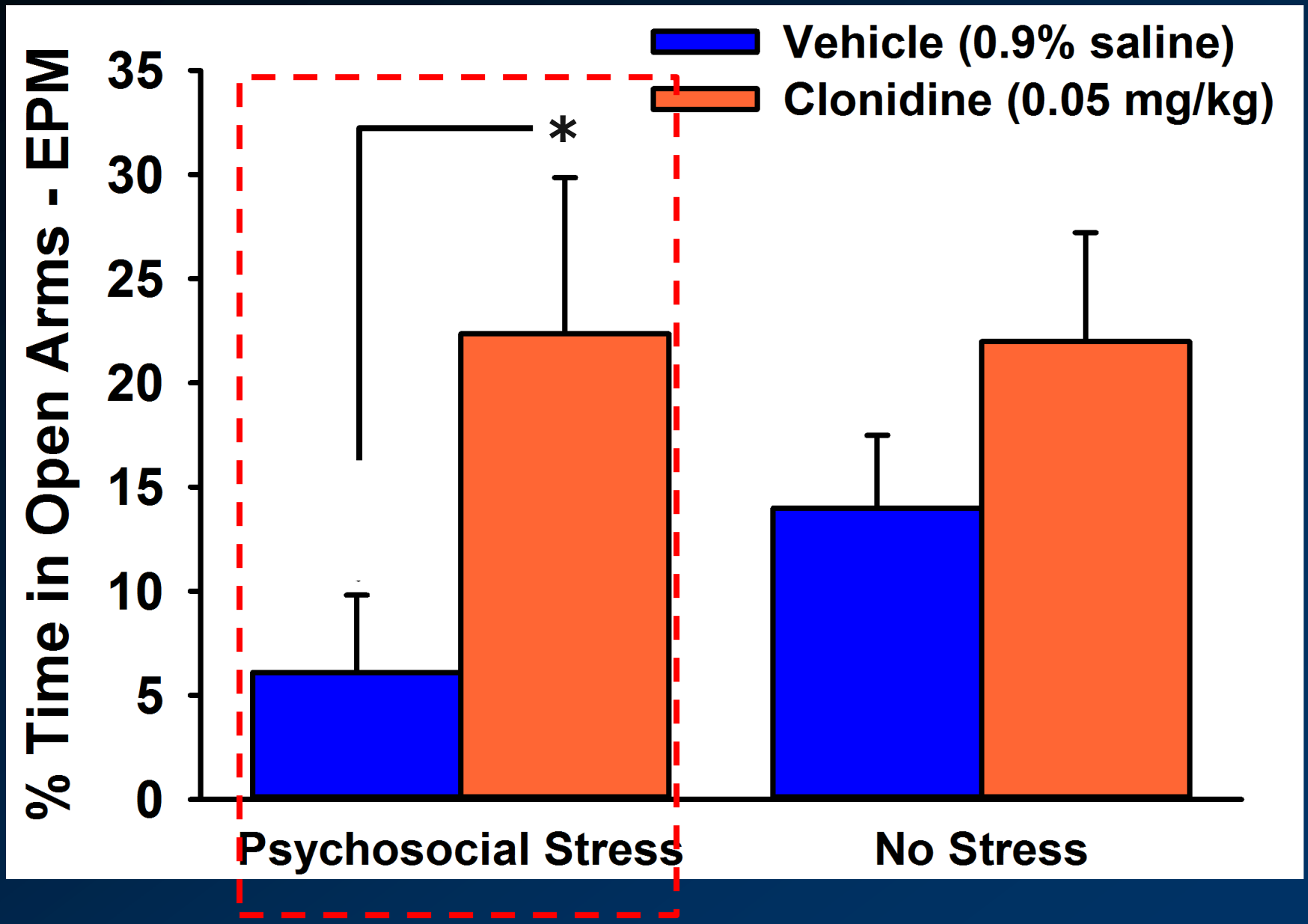
Eisenmann, Zoladz, & Rorabaugh – in preparation

Pharmacological Blockade of Increased Myocardial Sensitivity to Ischemic Injury



Eisenmann, Zoladz, & Rorabaugh – in preparation


Vehicle (0.9% saline)
Clonidine (0.05 mg/kg)
% Time in Open Arms - EPM
35
30
25
20
15
10
5
0
*
Psychosocial Stress
No Stress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35
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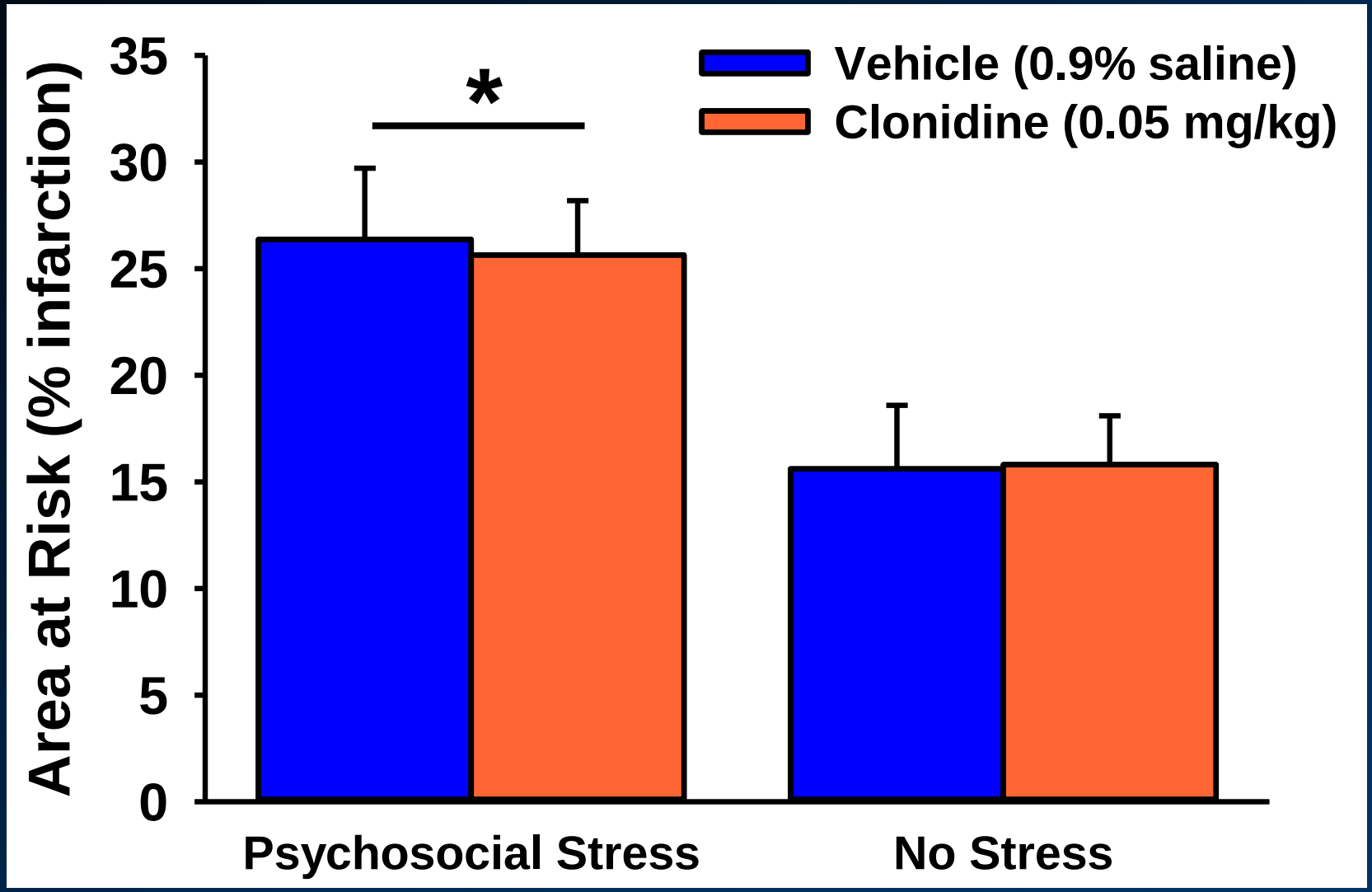
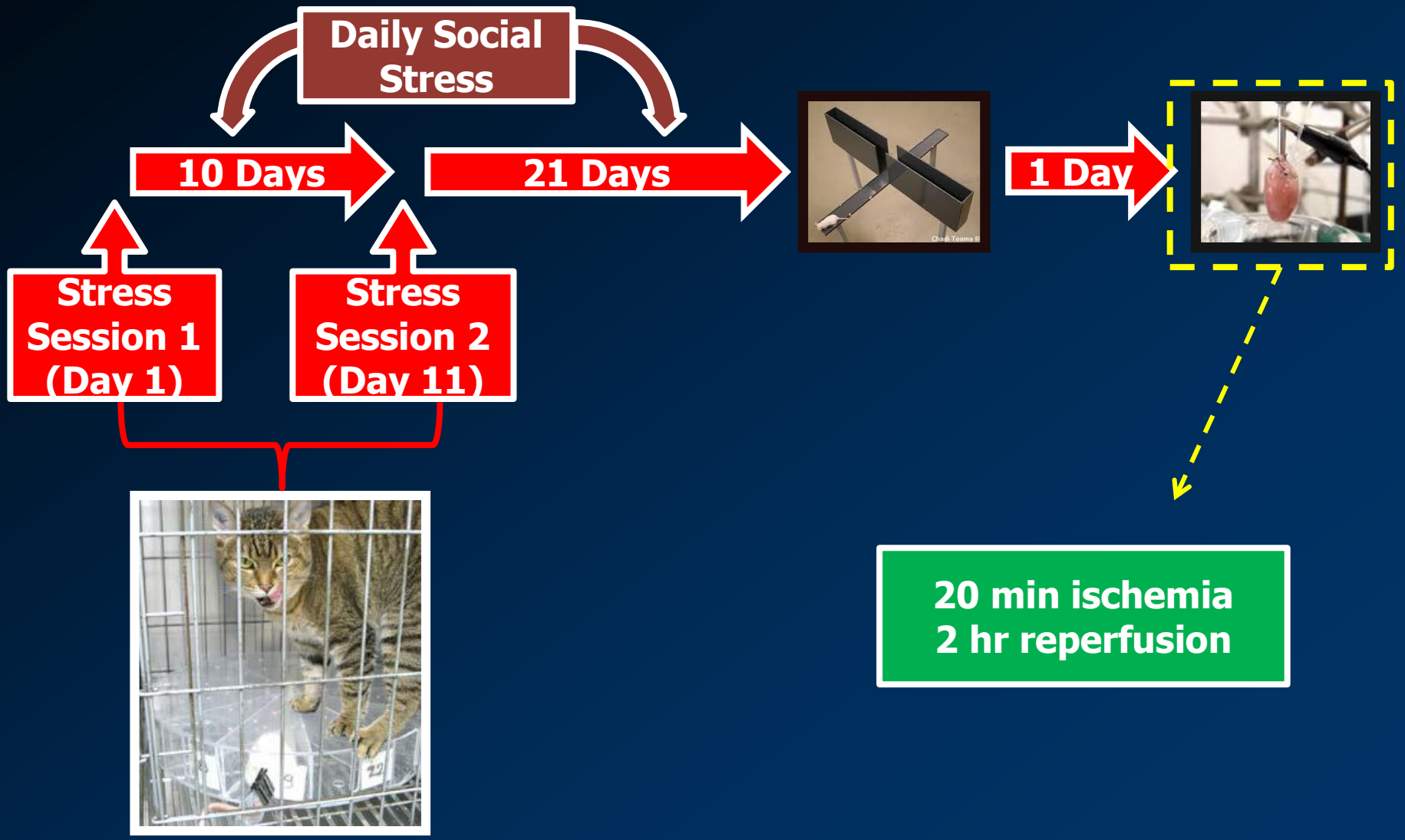
Psychosocial Stress
No Stress

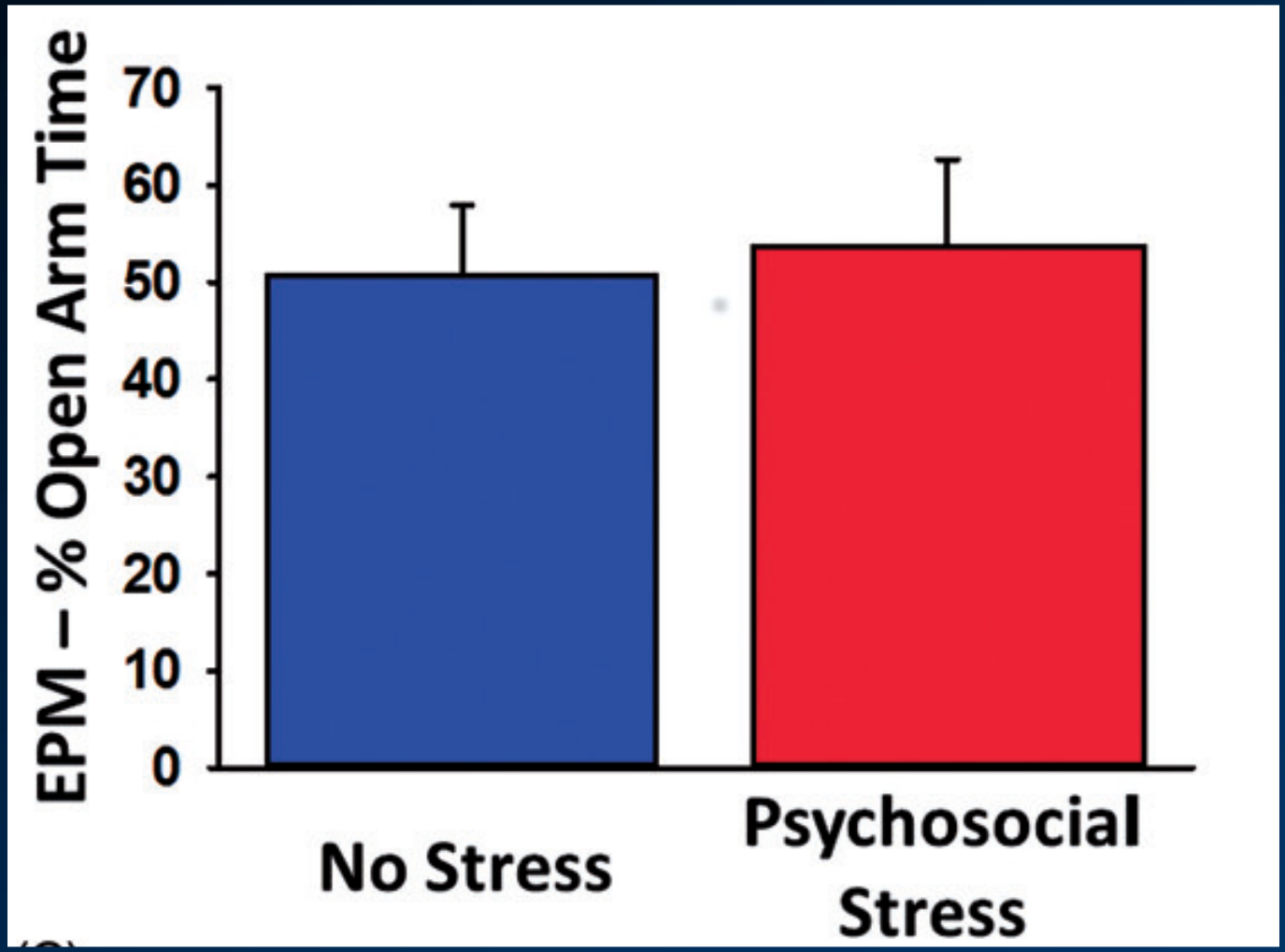

Area at Risk (% infarction)
35
30
25
20
15
10
5
0
*
Vehicle (0.9% saline)
Clonidine (0.05 mg/kg)
Psychosocial Stress
No Stress

Would Same Effects be Observed in Females?



Zoladz & Rorabaugh – *unpublished observations*

Would Same Effects be Observed in Females?



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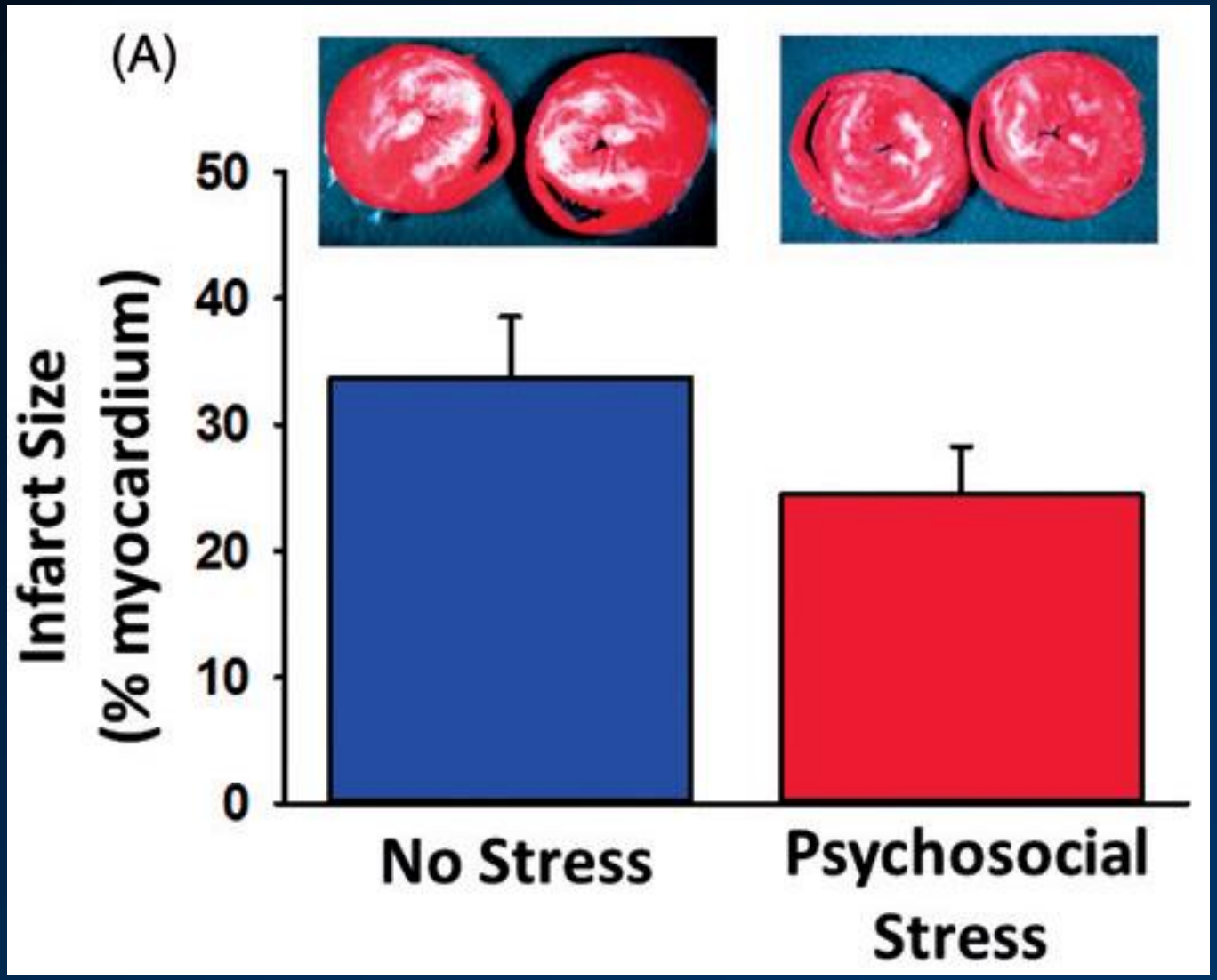

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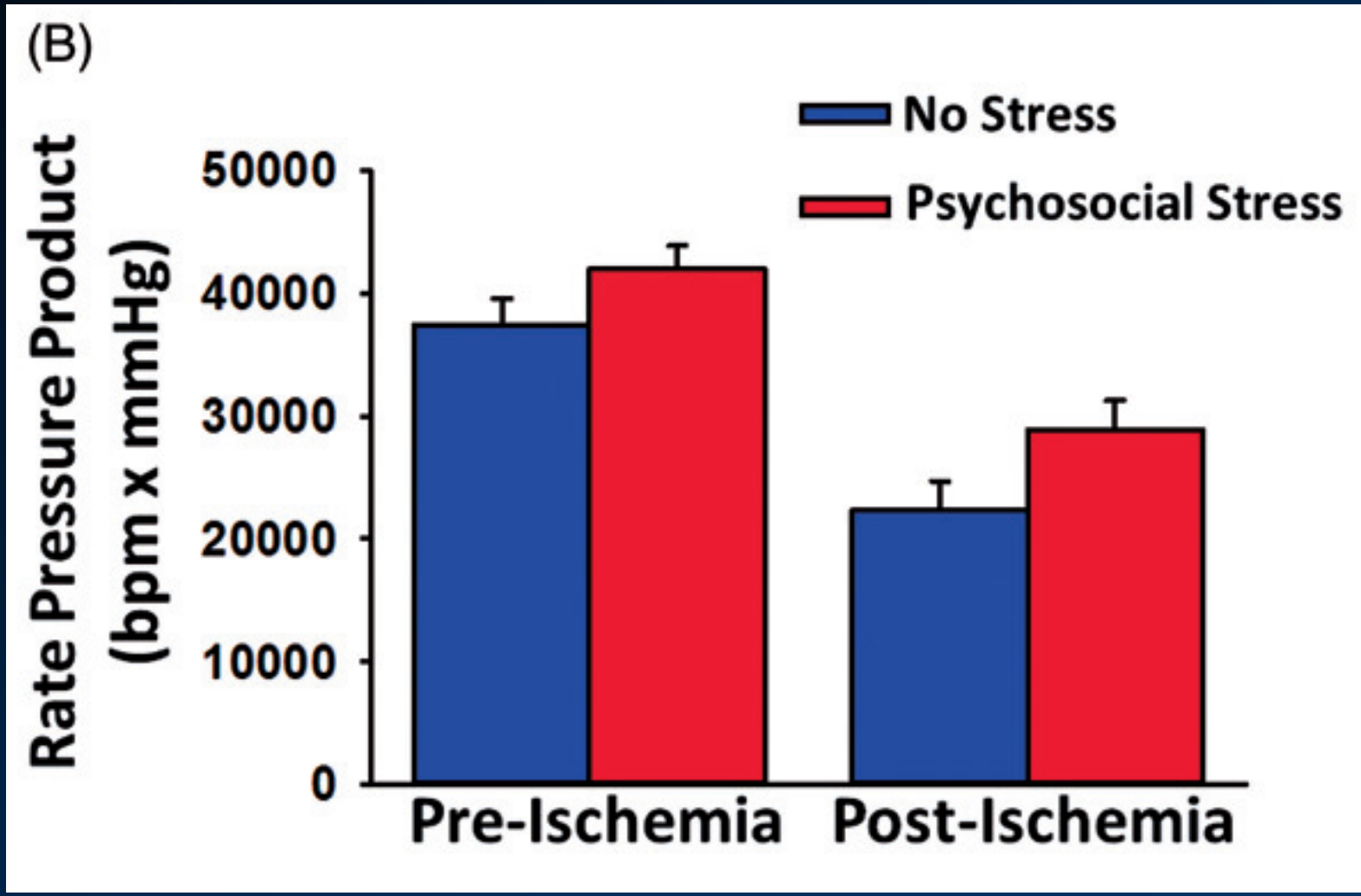
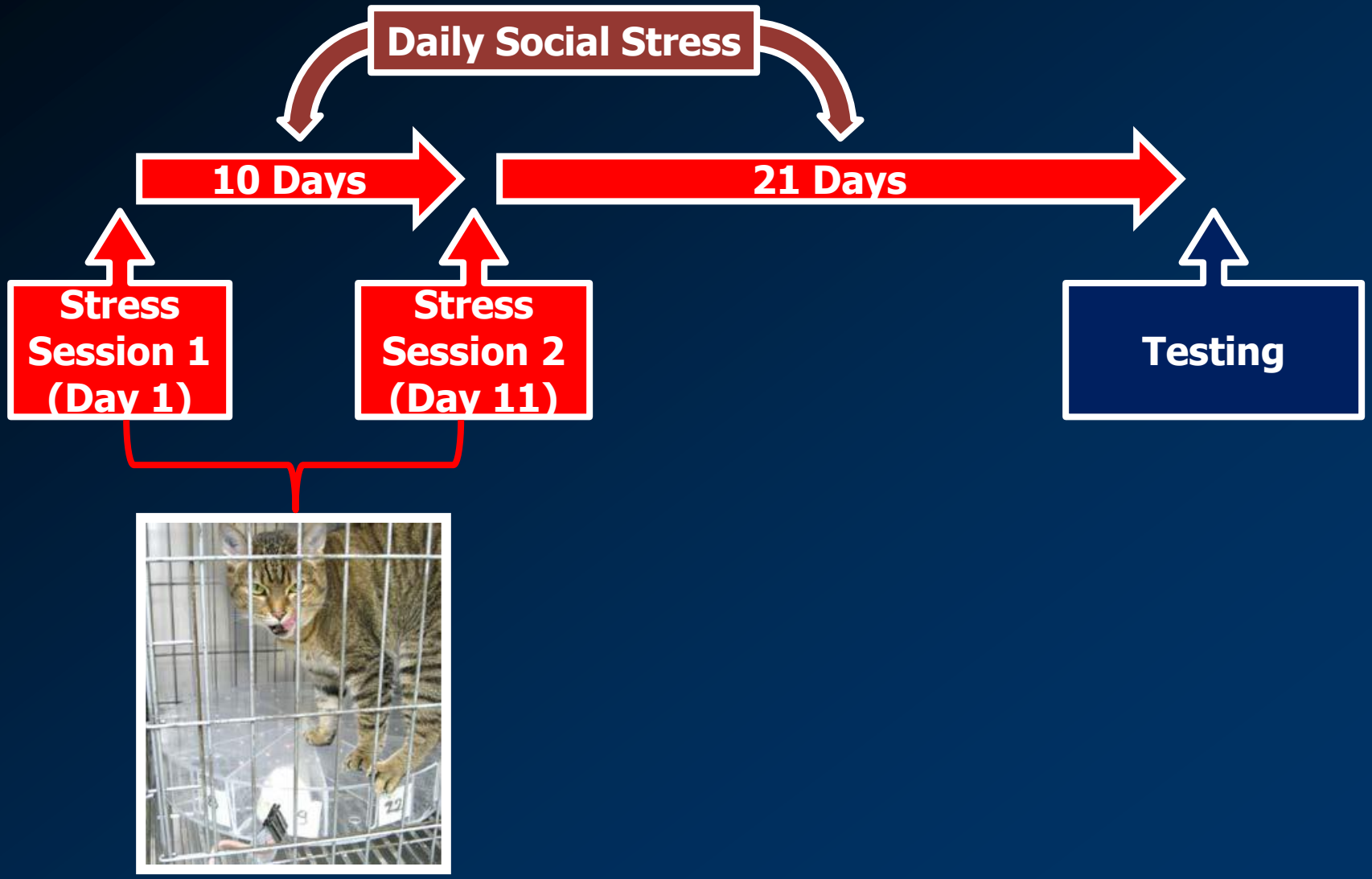


Animal Model of PTSD in Females?



Zoladz – unpublished observations

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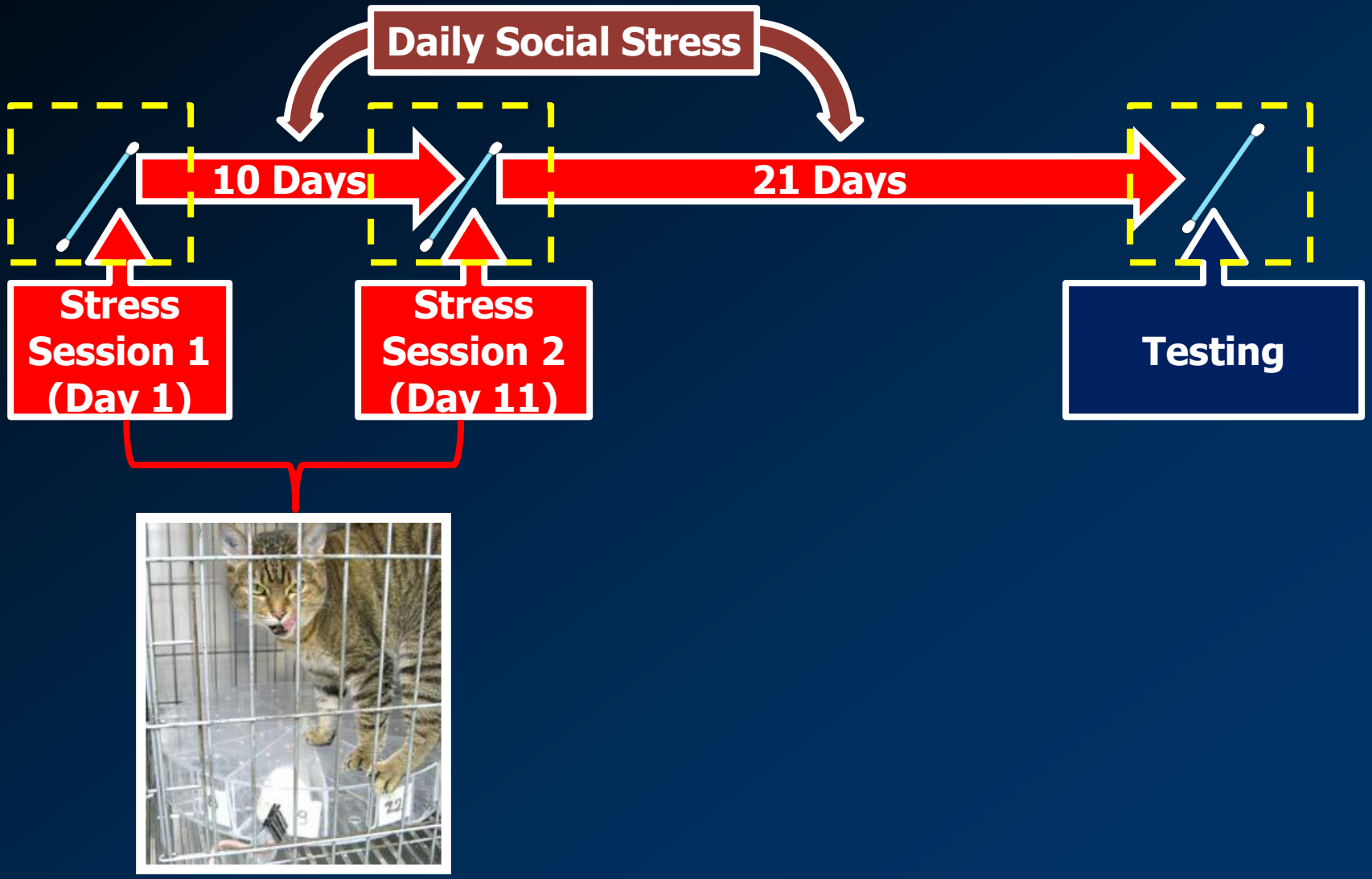
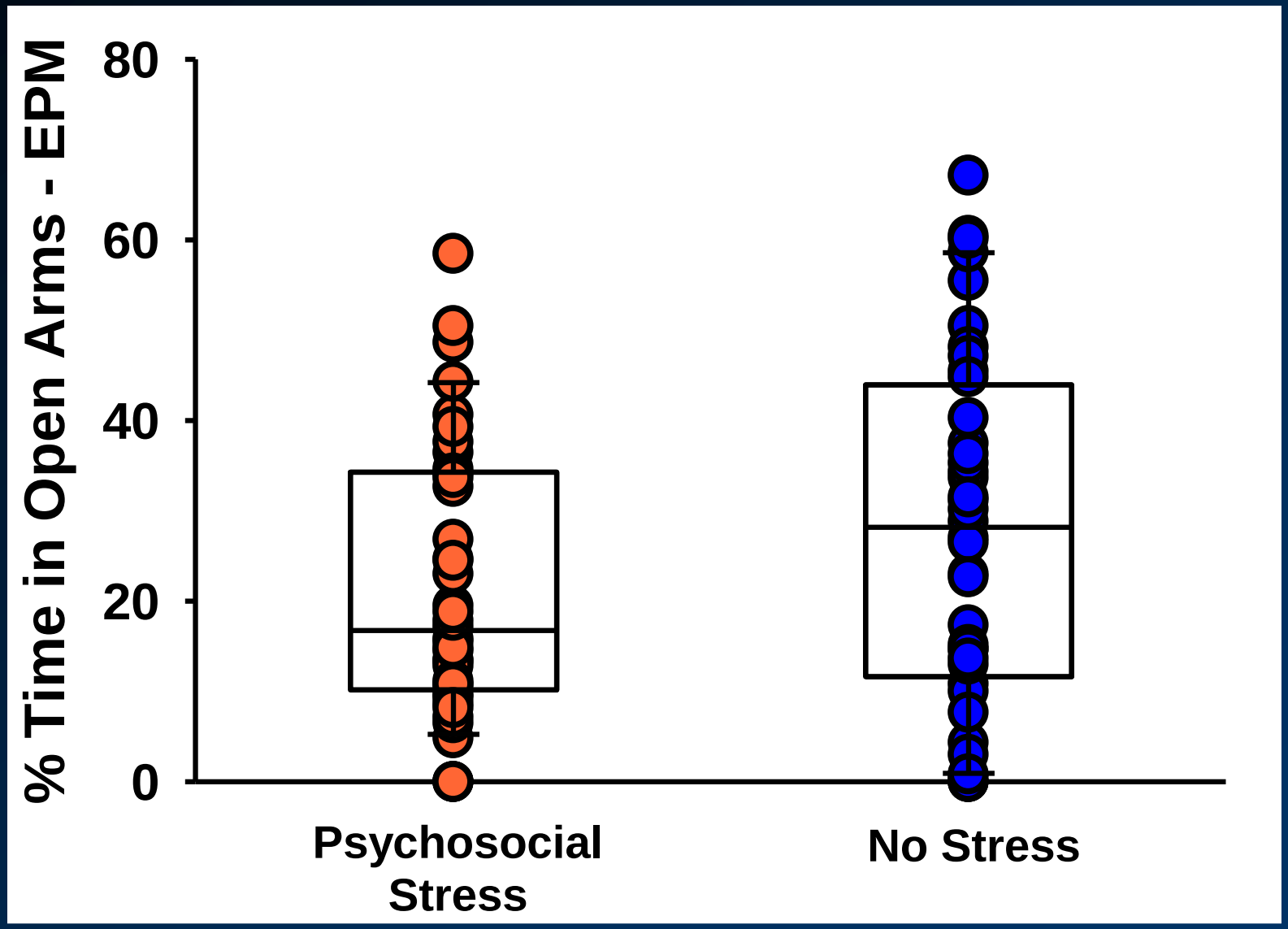
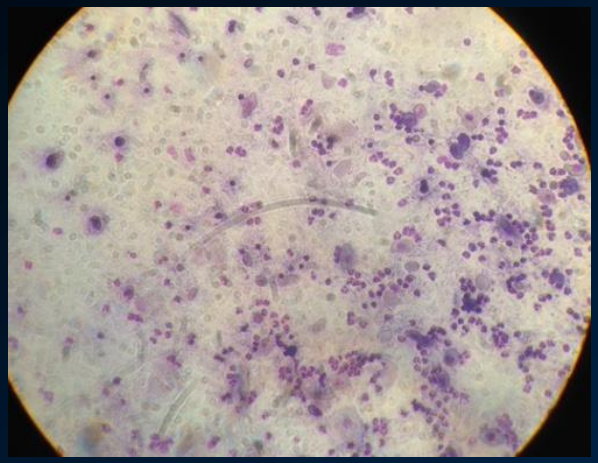


Zoladz – unpublished observations

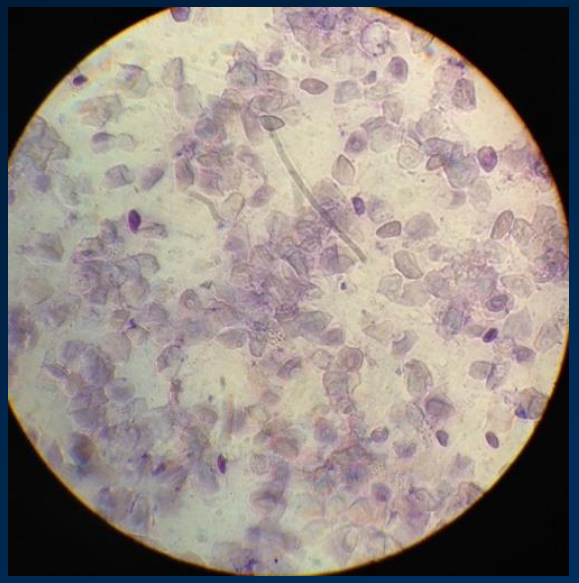
EPM Behavior Showed Significant Variability



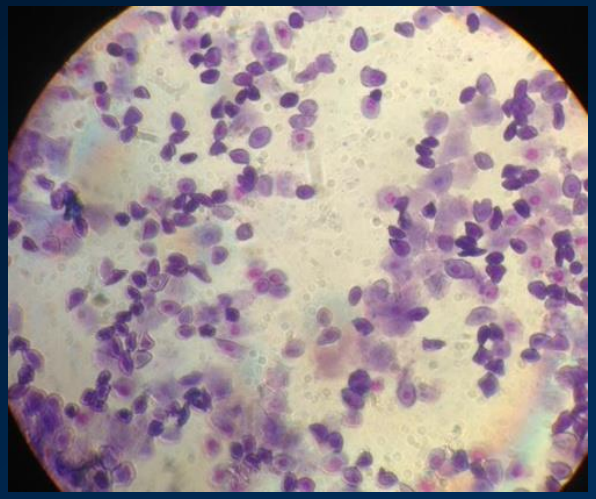
Estrous Stages based on Vaginal Cell Cytology



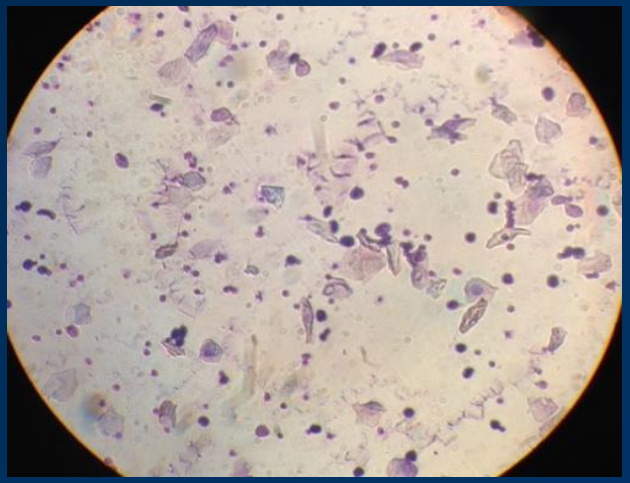
Diestrus



Estrus

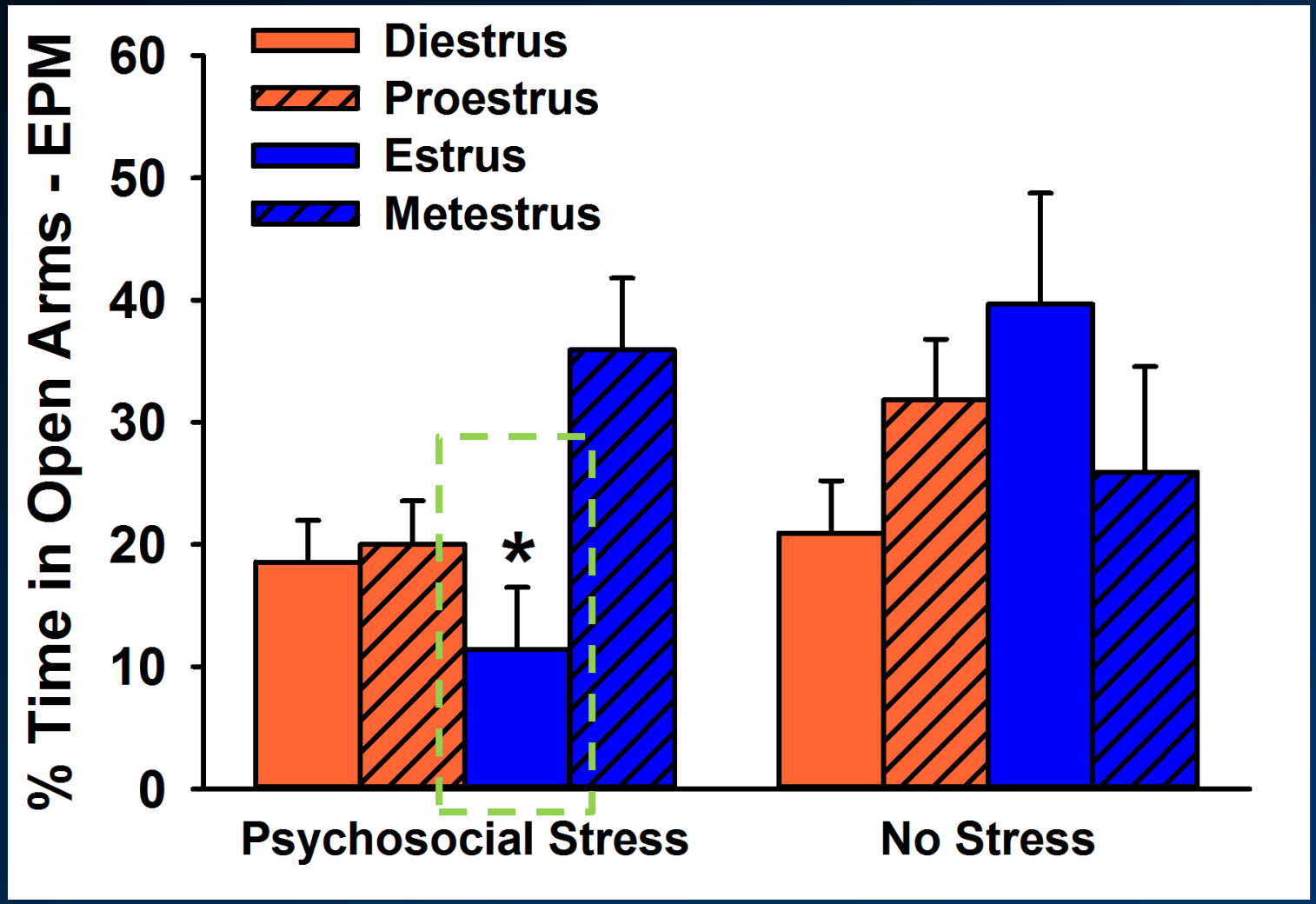


Proestrus

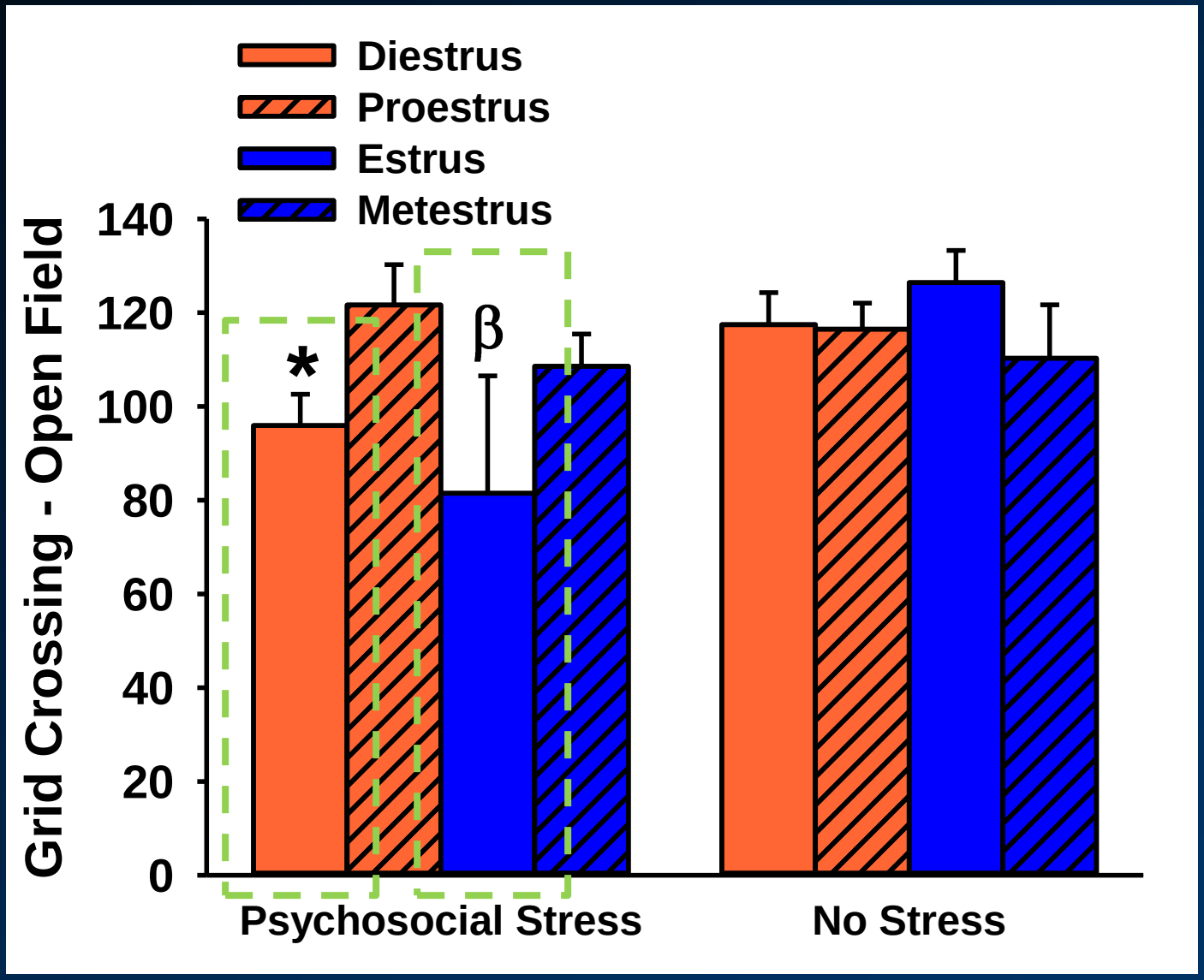


Metestrus

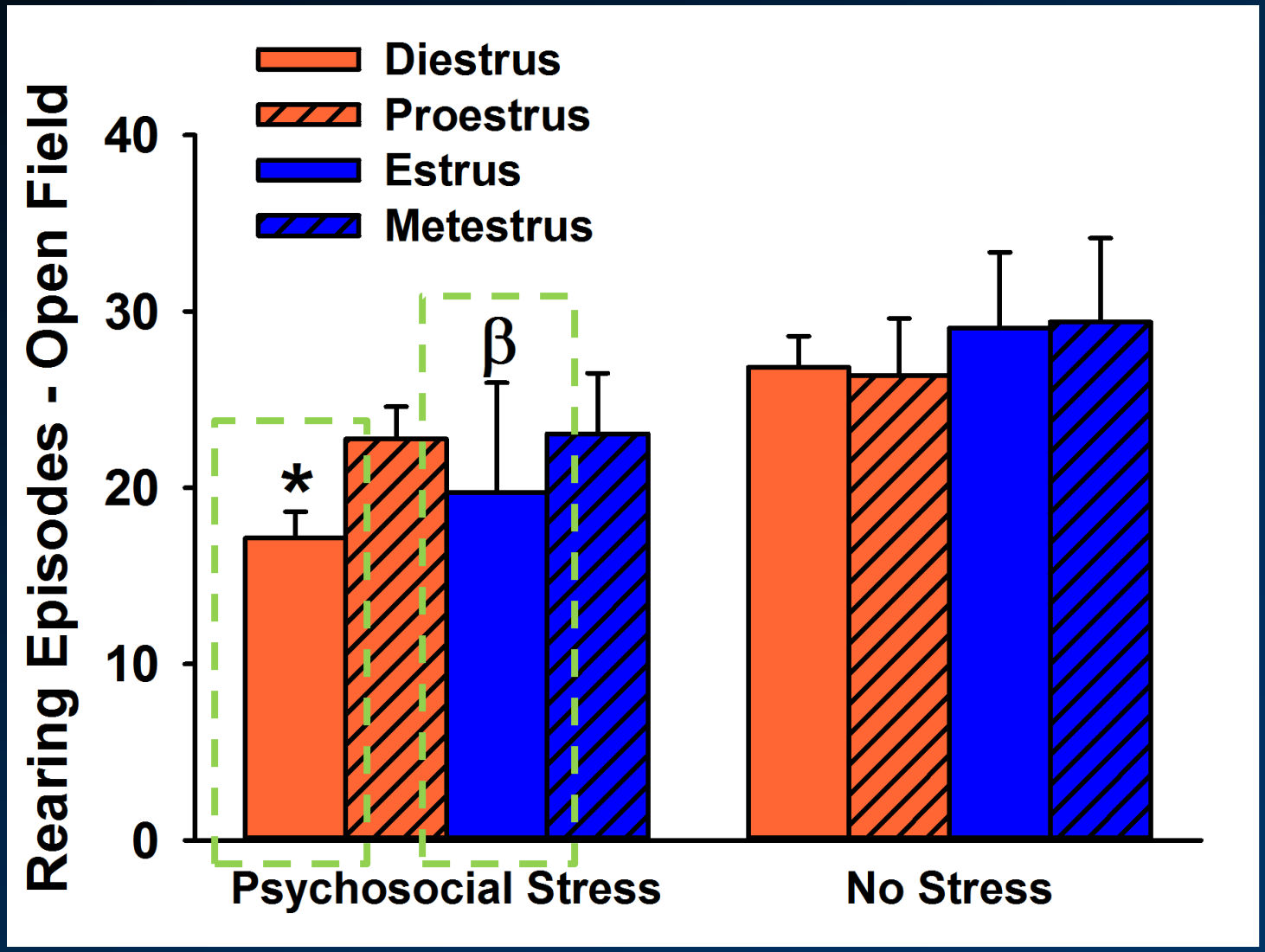
EPM Behavior based on Estrous Stage at Testing



OF Behavior based on Estrous Stage at Testing



OF Behavior based on Estrous Stage at Testing



Females

- **Effects of PTSD model may depend on estrous stage at testing**
  - **Need more samples for estrous stage during SS1 and SS2**

Females

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  - **Need more samples for estrous stage during SS1 and SS2**
- **To our knowledge, no animal model of PTSD in females**
  - **Must consider an issue if PTSD risk really is greater in females**

Conclusions & Future Directions

- **Female studies looking at estrous stage**
  - **General behavioral effects (anxiety, startle)**
  - **HPA axis changes**
  - **Myocardial sensitivity to ischemic injury**

Conclusions & Future Directions

- **Female studies looking at estrous stage**
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  - **Myocardial sensitivity to ischemic injury**

- **Mechanisms of increased myocardial sensitivity to ischemic injury in males**
  - **Pharmacological prevention**
  - **Measures of ROS and inflammation in heart tissue**

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