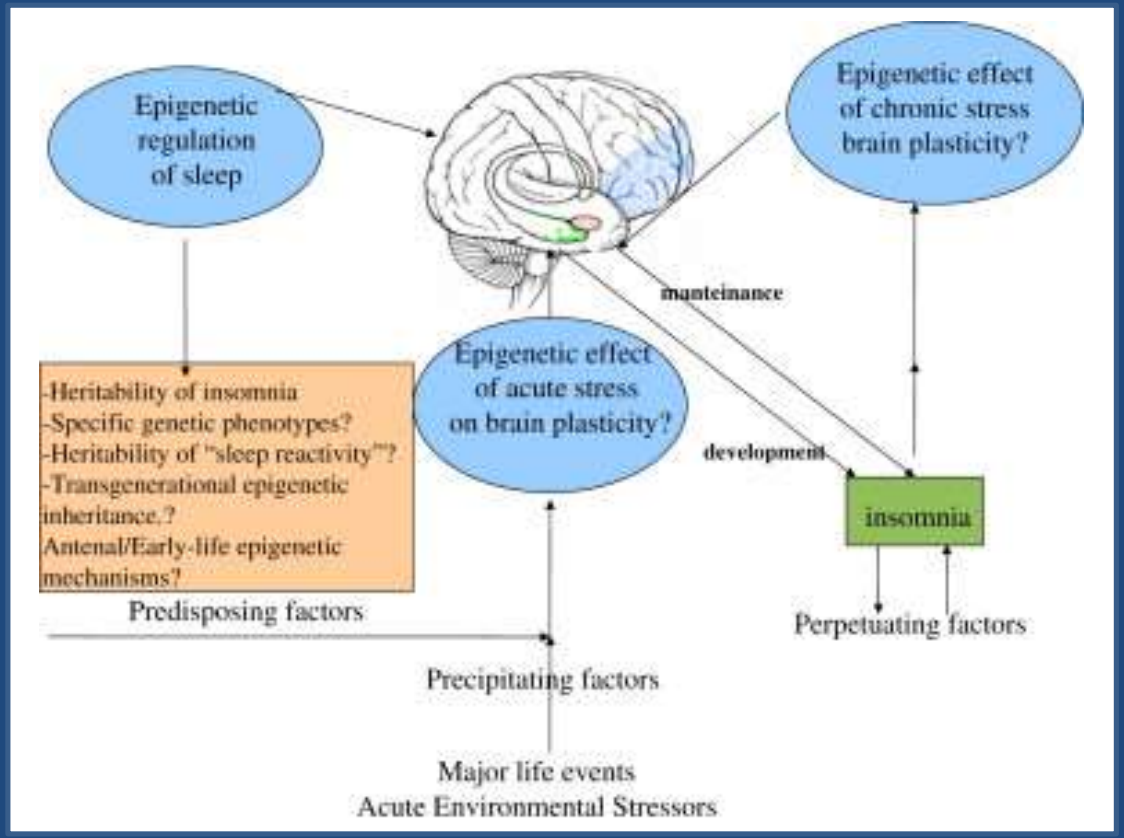
Impact of Sleep Deprivation Stress in Promoting Sensitization of the Trigeminal System

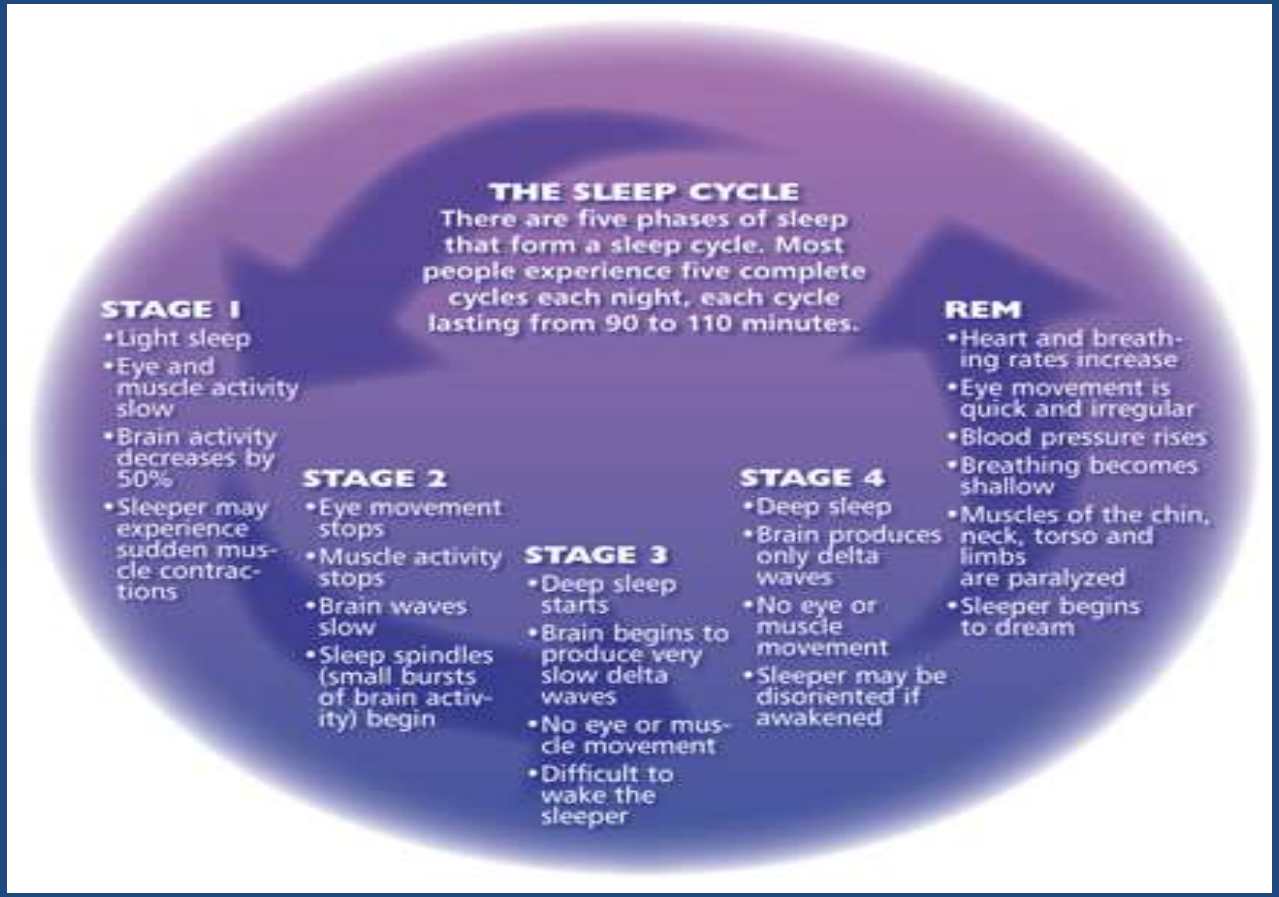


Functions of Sleep

- Fatigue reversal
  - allows individual to recover and reenergize
- Biochemical refreshment
  - promotes synaptic efficiency, protein synthesis, neurogenesis, metabolic restoration
- Immune function
  - reset or protection

- Memory
  - memory consolidation, facilitates encoding new information
- Psychologic well-being
  - lack of sleep: risk of mood alteration to depression

Basic Sleep Cycle



As the night progresses, the length of REM stages increases and the length of time spent in deep sleep decreases. By morning, nearly all sleep is stage one, two or REM.

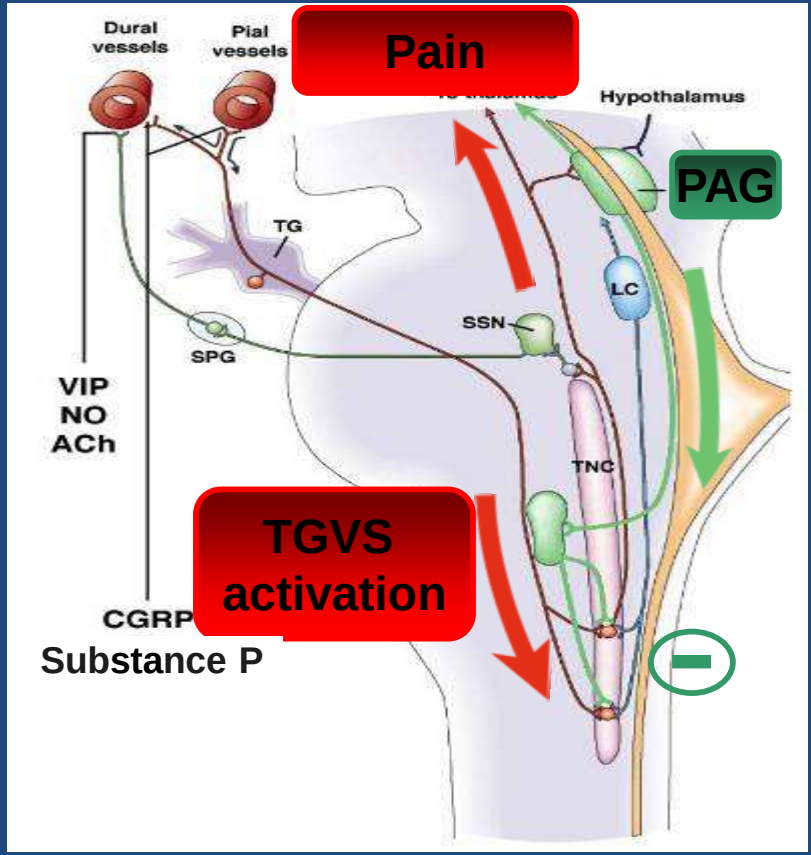
Typical cycle:
7 1/2 - 9 hrs

Sleep Deprivation: Major Epidemic

- Significant impact on public health
- 20%-60% hospitalized patients
- 20% general population
- Incidence and prevalence
  increasing in youth and young adults
- Triggers:
  - mood alteration
  - sociability dysfunction
  - complaints of bodily pain

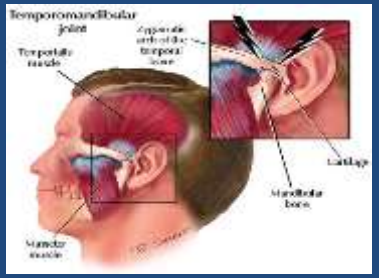
Sleep Quality/Quantity and Pain – Vicious Cycle

- Bad night's sleep enhances pain – but pain disrupts sleep creating vicious cycle
- Sleep loss increases hyperalgesia and spontaneous pain
- Pain perception - dependent on activity of ascending (stimulatory) and descending (inhibitory) pathways
- Potential mechanisms contributing to sleep loss-induced pain enhancement :
  - opioid, monoaminergic, HPA , melatonin, and immune (inflammatory) systems
- Sleep loss – increased levels of proinflammatory cytokines (IL-1β, IL-6, TNF-α) – potent pain inducing and facilitating factors



TMD (Migraine) - Sleep - Pain

- TMD patients exhibit enhanced responses to painful stimuli
- Genetic polymorphorphisms predict development of new onset TMD
- Peripheral and central contributions early - but as progresses, changes in central pain processing (central sensitivity syndromes)
- Evidence that sleep disturbance – factor that directly contributes to central sensitization and pain amplification
- 77% of orofacial pain patients report reduced sleep quality and quantity of sleep
- 75% ICSD self-reported sleep bruxism; 17% met RDC PSG criteria for active
- 43% diagnosed with 2 or more sleep disturbances
  - primary insomnia (36%), obstructive sleep apnea (28.4%)

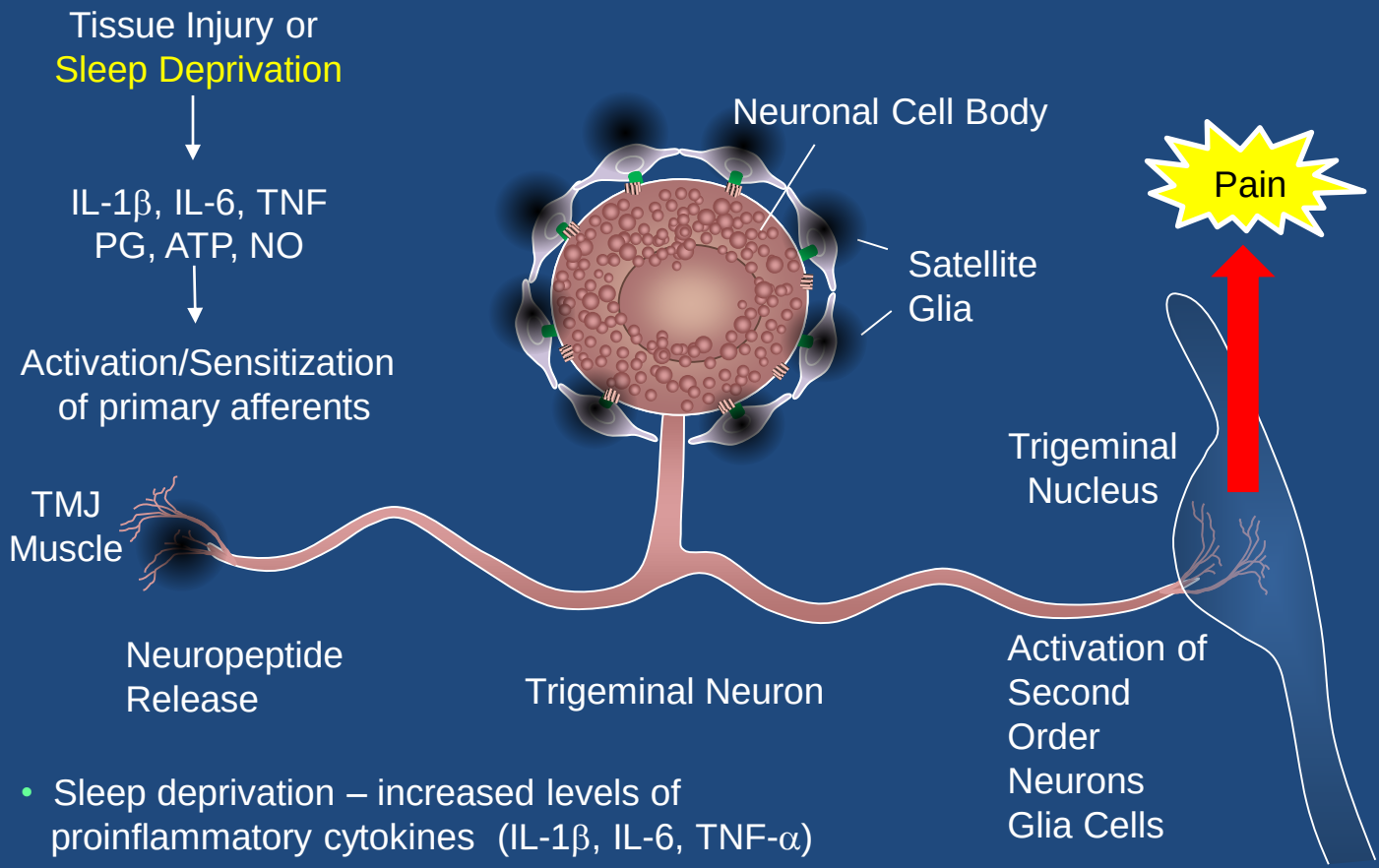


Smith et al., *SLEEP*, 2009

REM Sleep Deprivation Suppresses Phosphatase Levels in Trigeminal Neurons and Glia

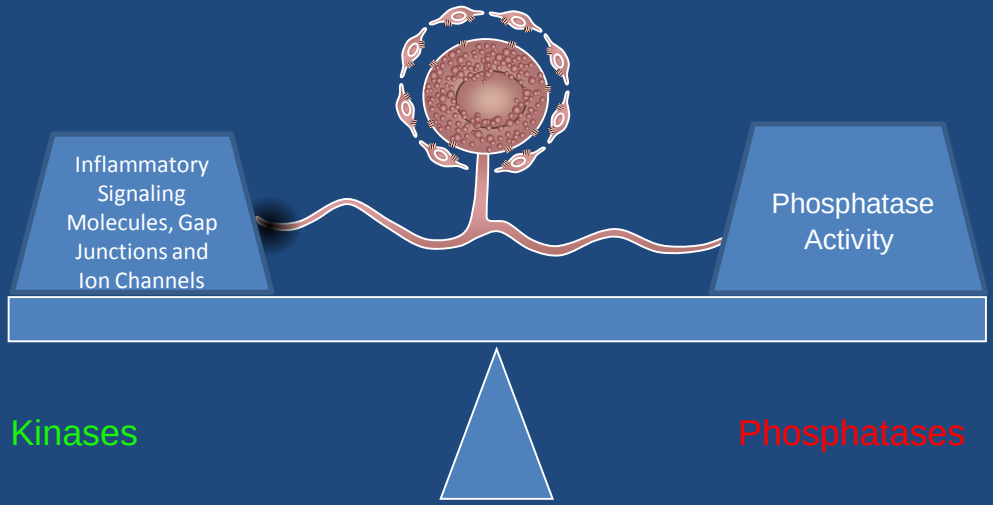
Promotion of Peripheral and Central Sensitization

TMD Pathology - Increased Expression of Pro-Inflammatory/Nociceptive Signaling Molecules and Increased Neuron-Satellite Glial Cell Communication



- Sleep deprivation – increased levels of proinflammatory cytokines (IL-1β, IL-6, TNF-α)

Normal Neuronal or Glial Cell at Homeostasis



Kinases

Present in Neurons and Glial Cells

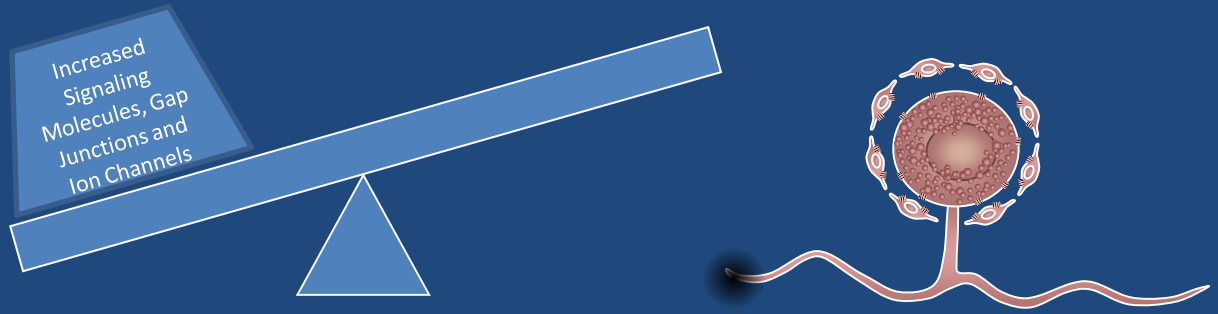
Increase Expression of Proteins and Molecules Involved in Inflammation and Nociception

Phosphatases

Present in Neurons and Glial Cells

Decrease Expression of Proteins and Molecules Involved in Inflammation and Nociception

Neuronal or Glial Cell During Painful Phase



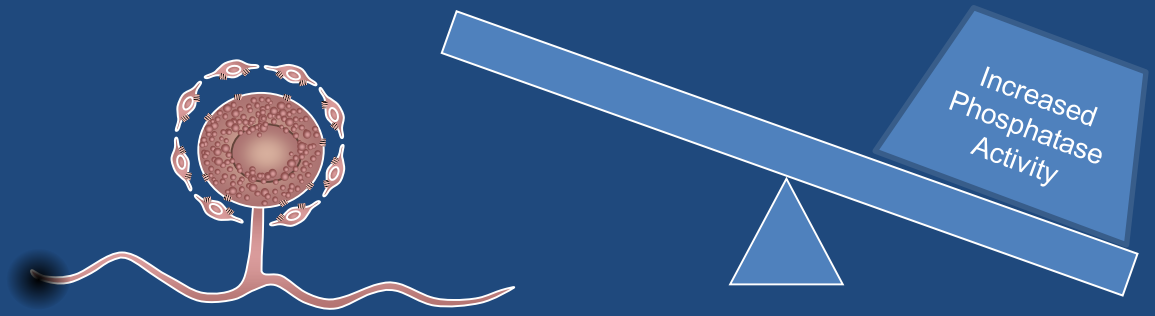
Kinases

Increase Expression of Proteins and Molecules Involved in Inflammation and Nociception

Phosphatases

Decrease Expression of Proteins and Molecules Involved in Inflammation and Nociception

Normal Neuronal or Glial Cell Restorative Phase



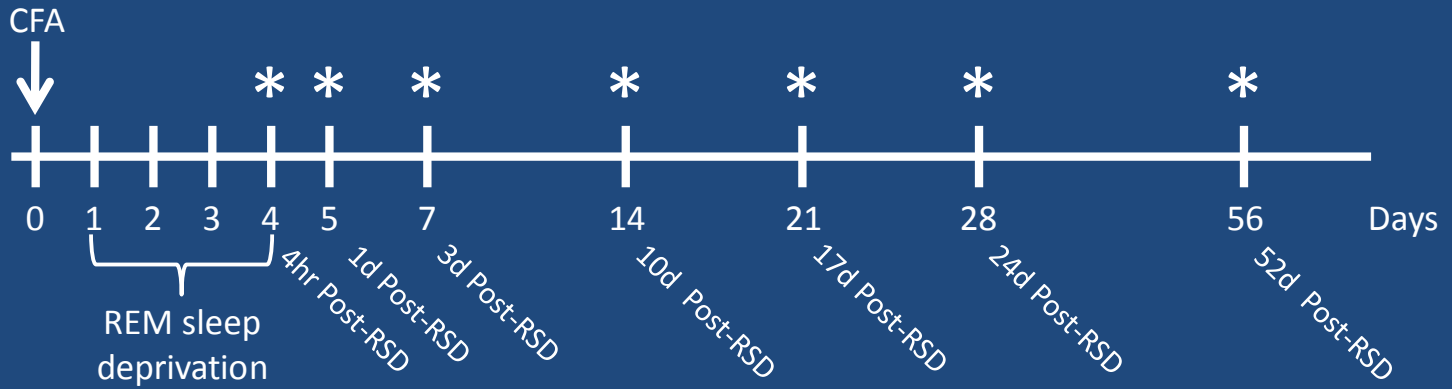
Kinases

Increase Expression
of Proteins and
Molecules Involved
in Inflammation
and Nociception

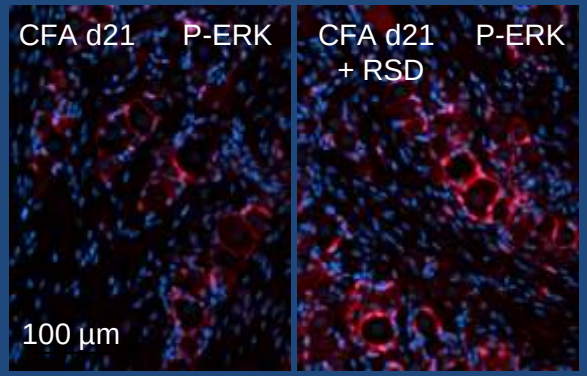
Phosphatases

Decrease Expression
of Proteins and
Molecules Involved
in Inflammation
and Nociception

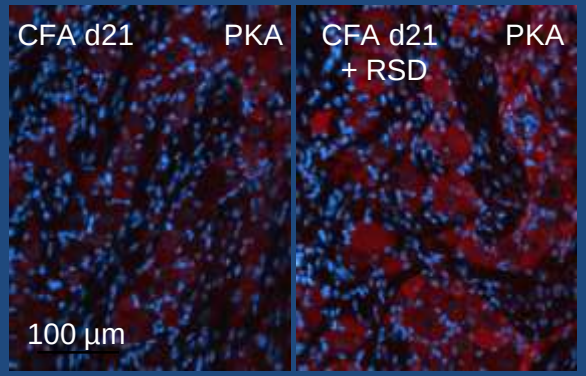
REM Sleep Deprivation After TMJ Inflammation Leads to Chronic Increased Levels of Nociceptive Proteins in Trigeminal Neurons and Glia



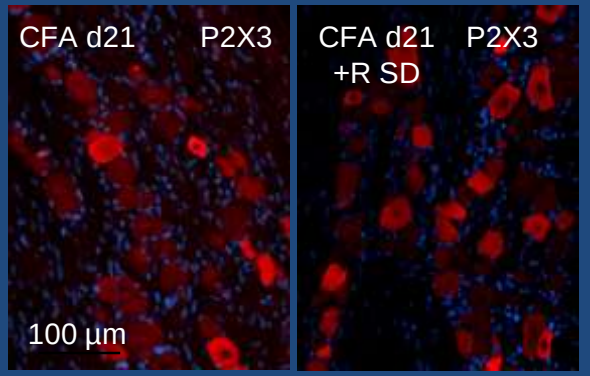
ERK = MAP Kinase



PKA = Protein Kinase A



P2X3 = ATP Ion Channel

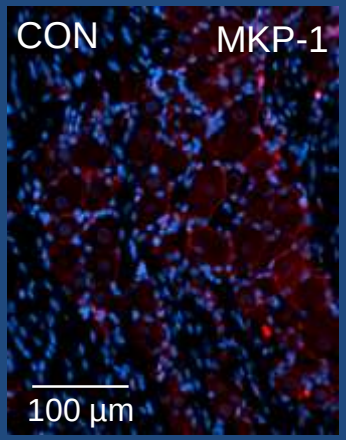


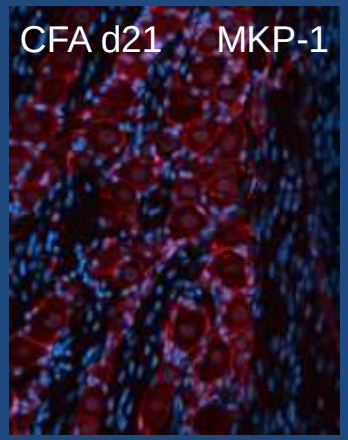
RSD = REM Sleep Deprivation; CFA = complete Freund's adjuvant; heat killed bacteria - inflammatory

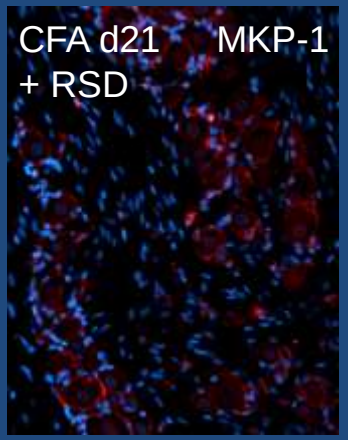
REM Sleep Deprivation After TMJ Inflammation Leads to Prolonged Decreased Levels of Phosphatases in Trigeminal Neurons and Glia

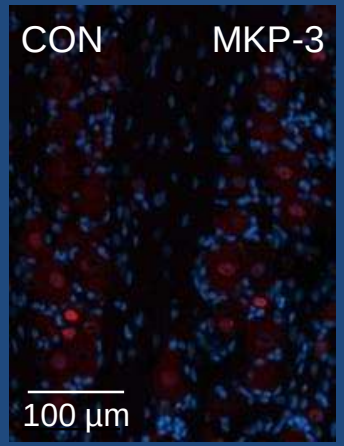
RSD =
REM Sleep Deprivation

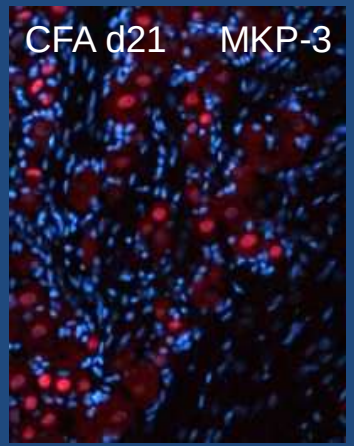
MKP-1 and MKP-3
Anti-inflammatory
proteins

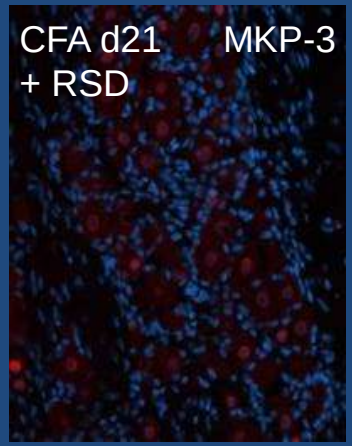




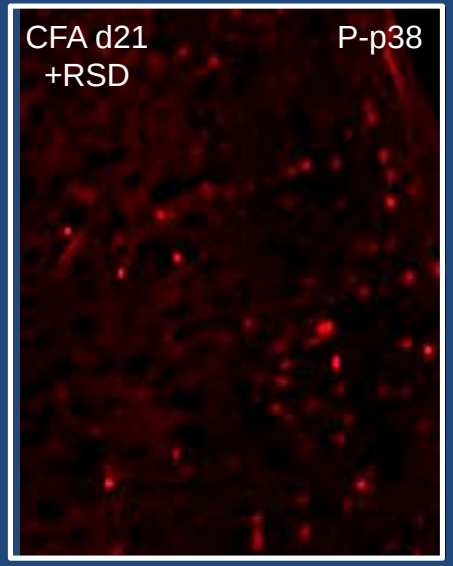


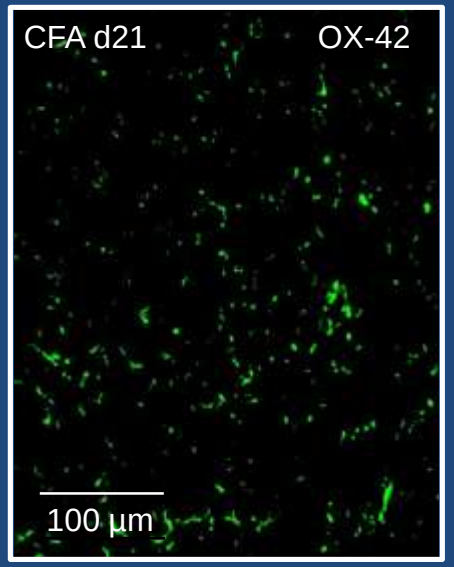


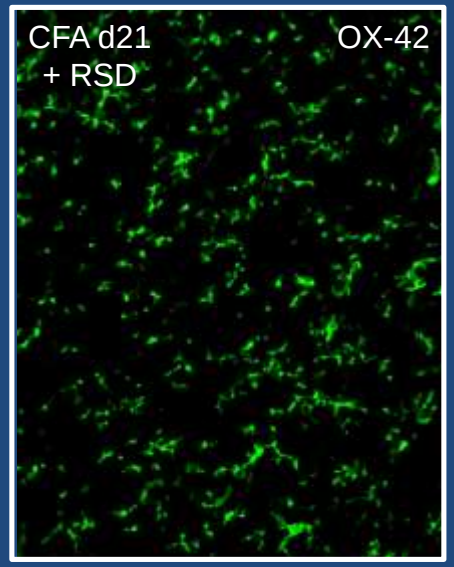




REM Sleep Deprivation After TMJ Inflammation Leads to Chronic Increased Levels of Inflammatory Proteins In STN

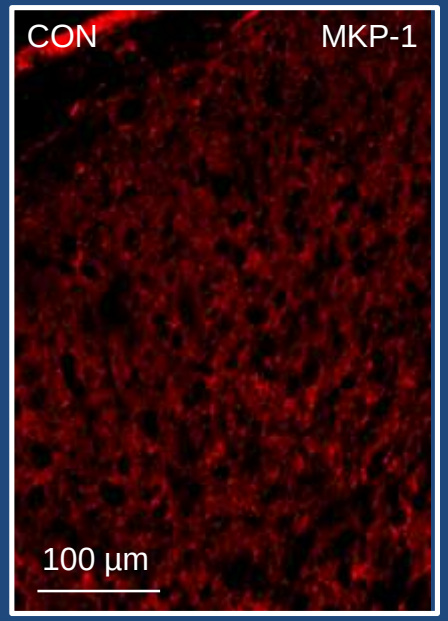


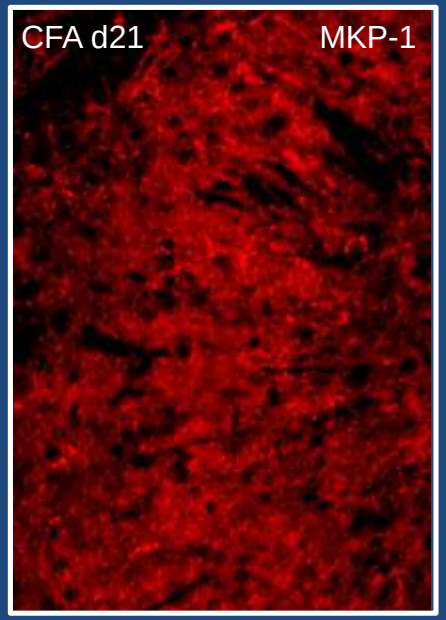




p38 - inflammatory protein; OX-42 – biomarker of activated microglia

REM Sleep Deprivation After TMJ Inflammation Leads to Chronic Decreased Levels of MKP-1 In STN





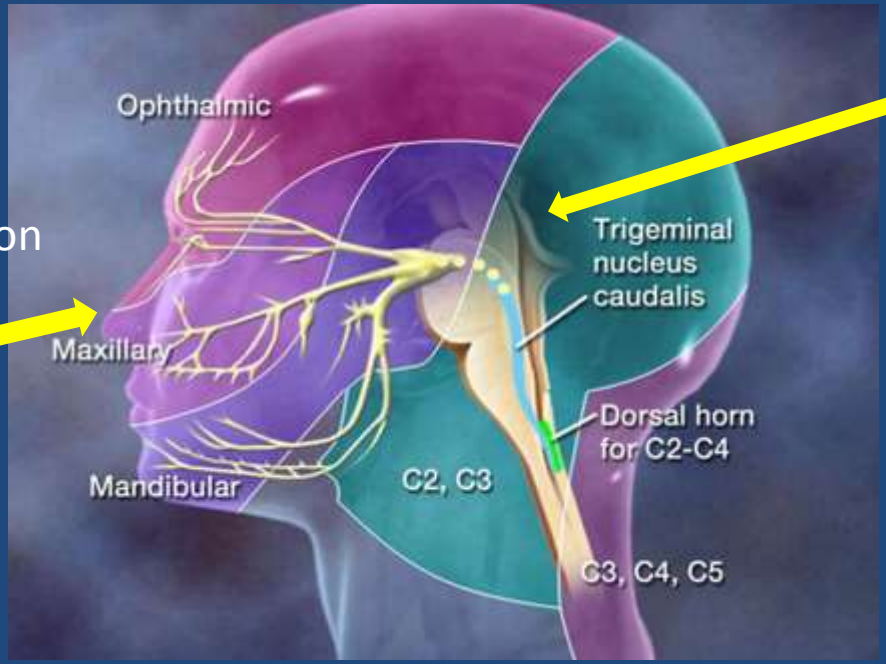
MKP-1 – role in decreasing inflammation

REM Sleep Deprivation Can Promote Prolonged Peripheral and Central Sensitization

Risk Factors and Trigeminal Sensitization

Peripheral Sensitization

Headache Tree Extract

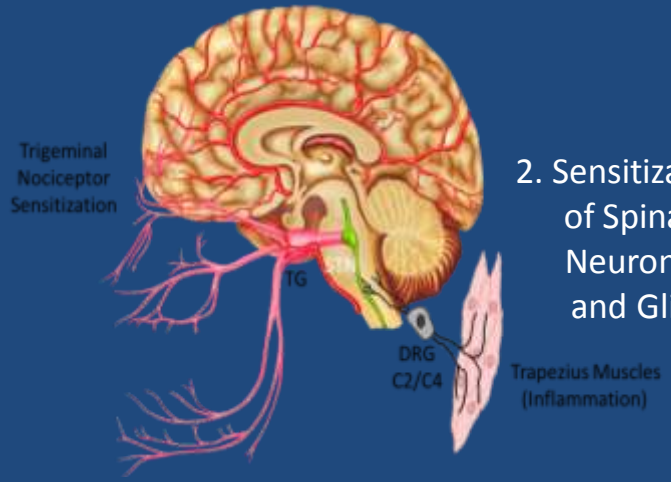


REM Sleep Deprivation

Central Sensitization

- Test the hypothesis that sensitization of the trigeminal system prior to activation of TRPA1 receptors by a pungent odor is sufficient to cause sustained hyperalgesia and allodynia.

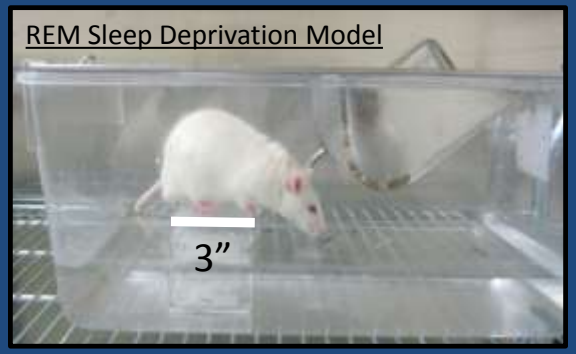
REM Sleep Deprivation Promotes Peripheral Sensitization of Trigeminal Nociceptors

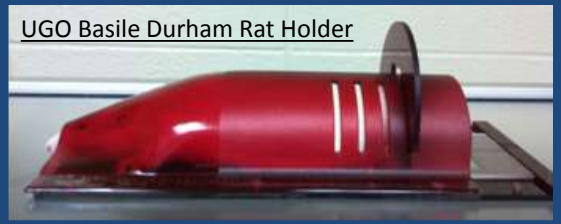


2. Sensitization of Spinal Neurons and Glia

3. Sensitization of TG Peripheral Nociceptors

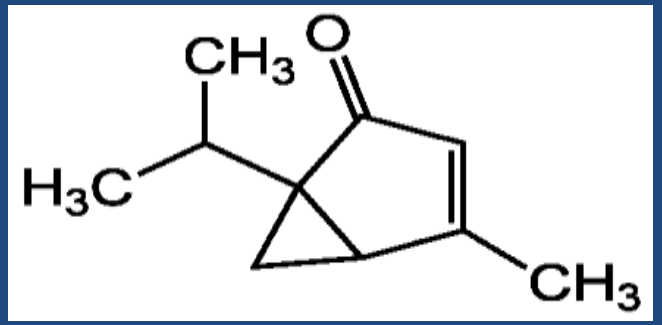
1. Sensitization of DRG Peripheral Nociceptors





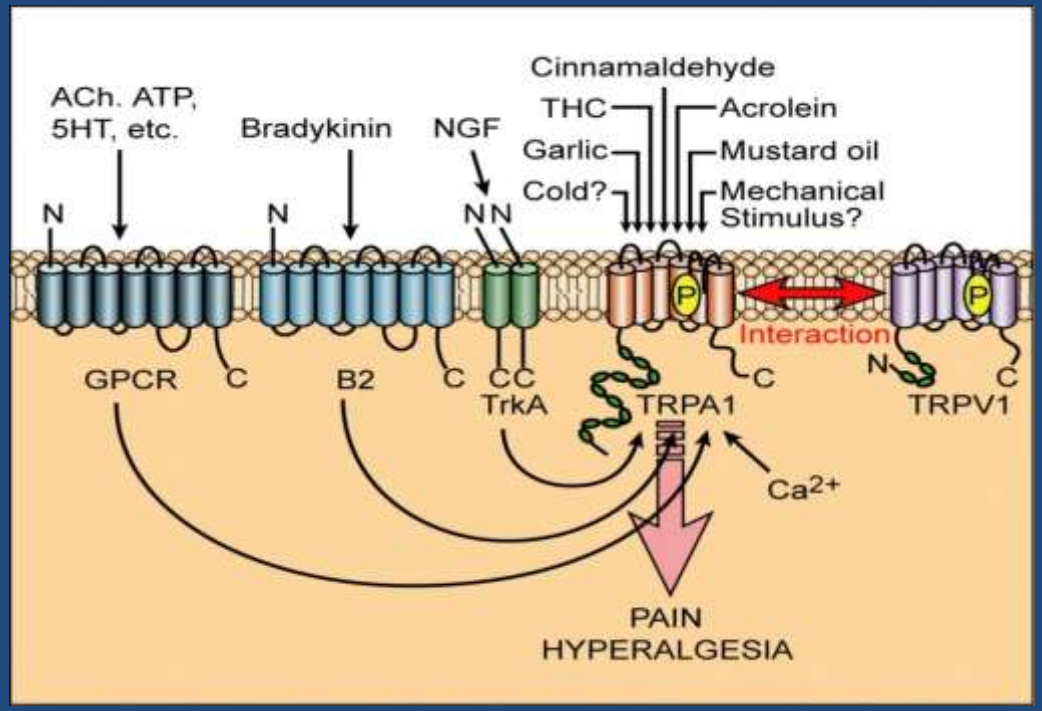
Activation of Trigeminal Nerves Via TRPA1: Headache Tree Extract

Umbellularia californica



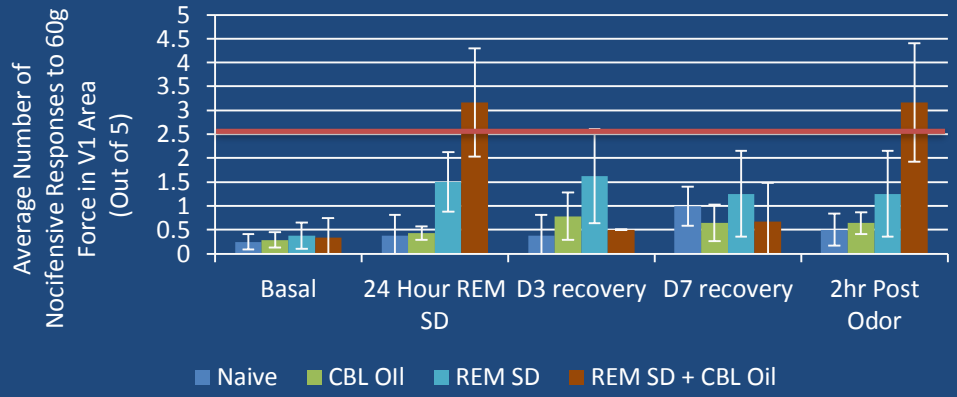
Umbellulone

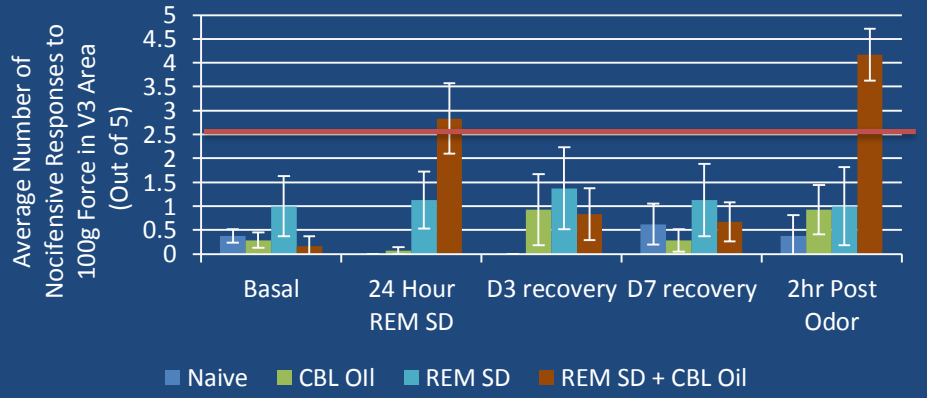
Nassini (Geppetti), Brain 2012



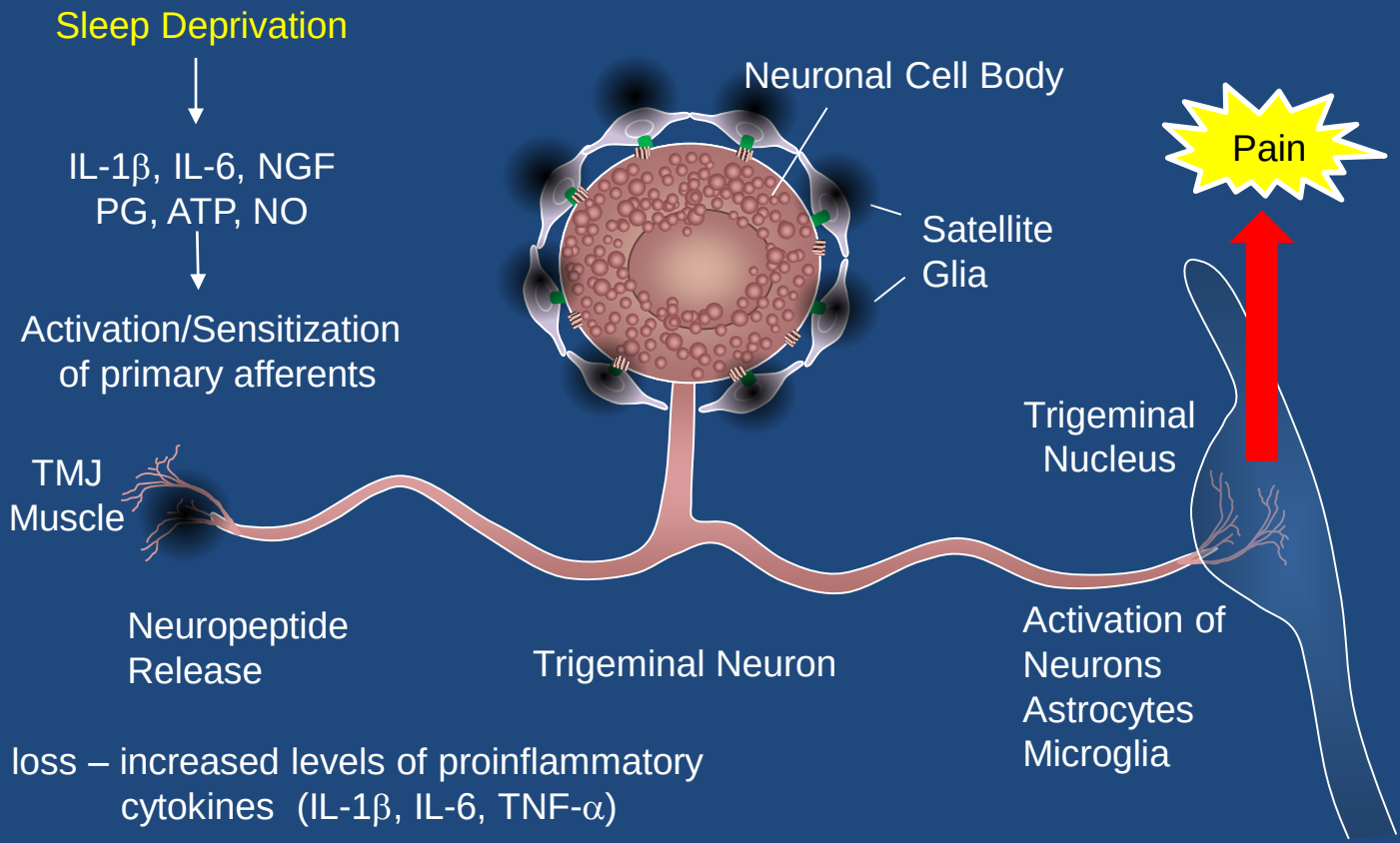
Pungent Odors: Trigger for migraine

REM Sleep Deprivation and Pungent Odor Increase Nocifensive Behaviors in V1 and V3



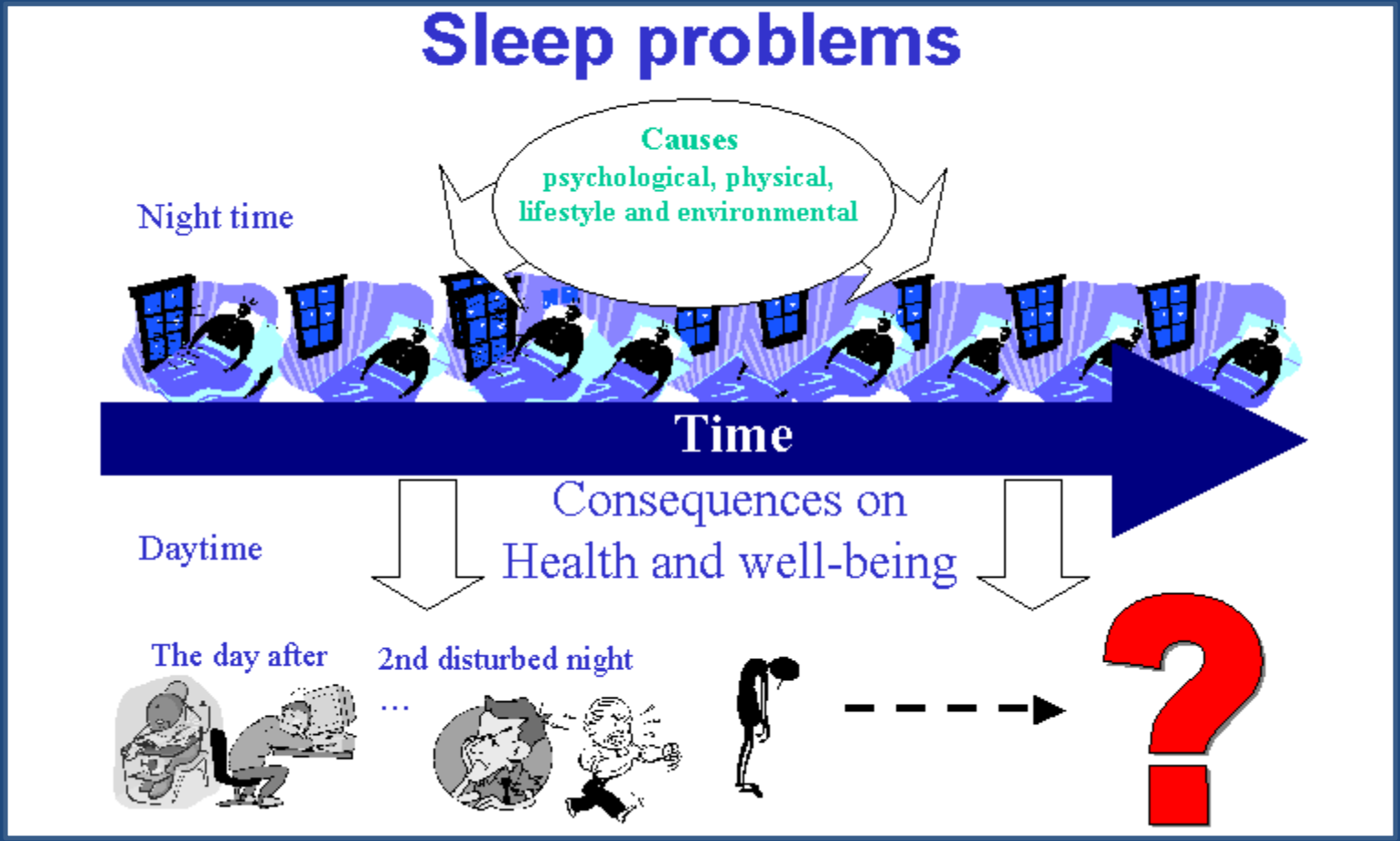


REM Sleep Deprivation Can Promote Chronic Peripheral and Central Sensitization

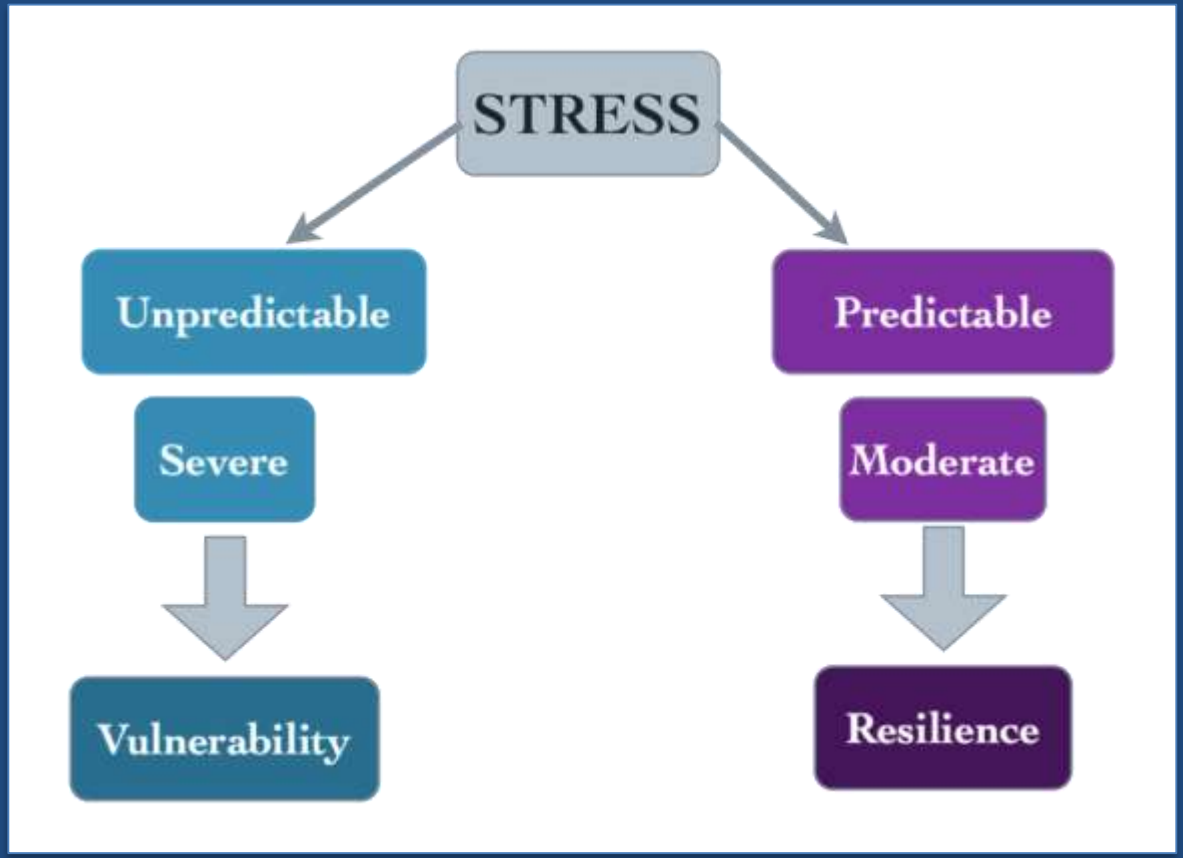


- Sleep loss – increased levels of proinflammatory cytokines (IL-1β, IL-6, TNF-α)

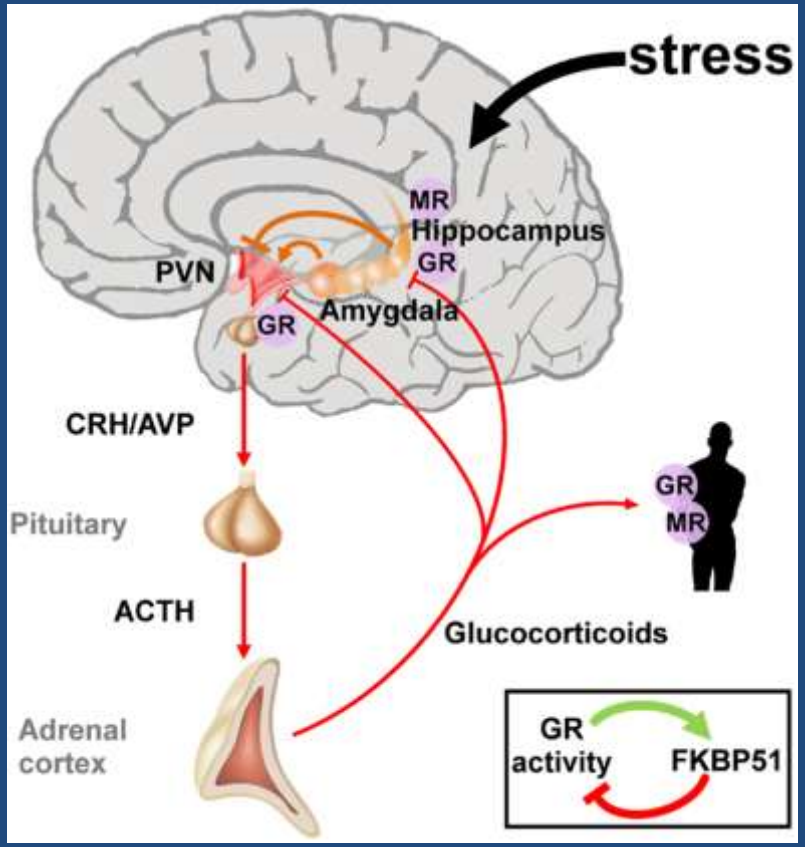
Sleep Deprivation: Consequences

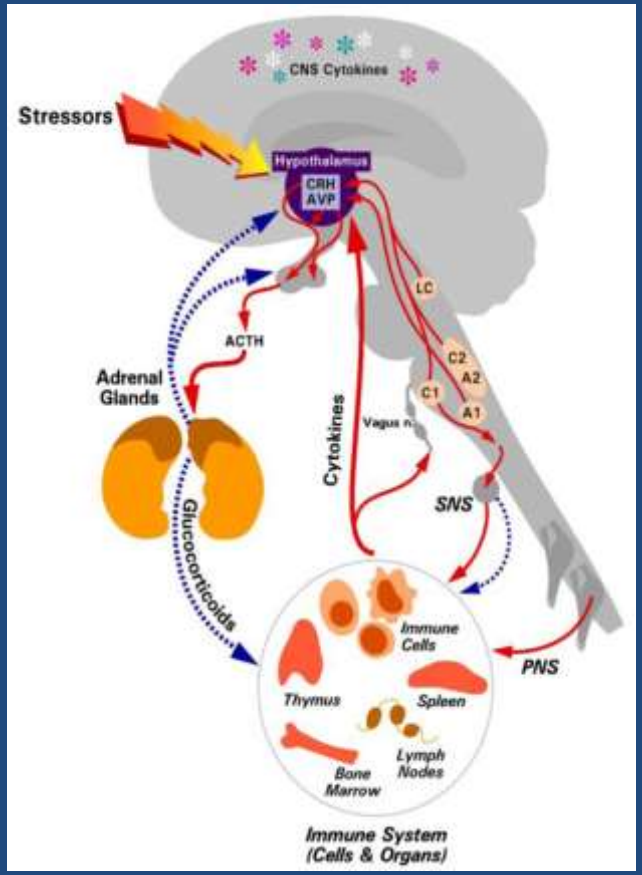


Unpredictable and Chronic Stress Promote Hypervigilant State



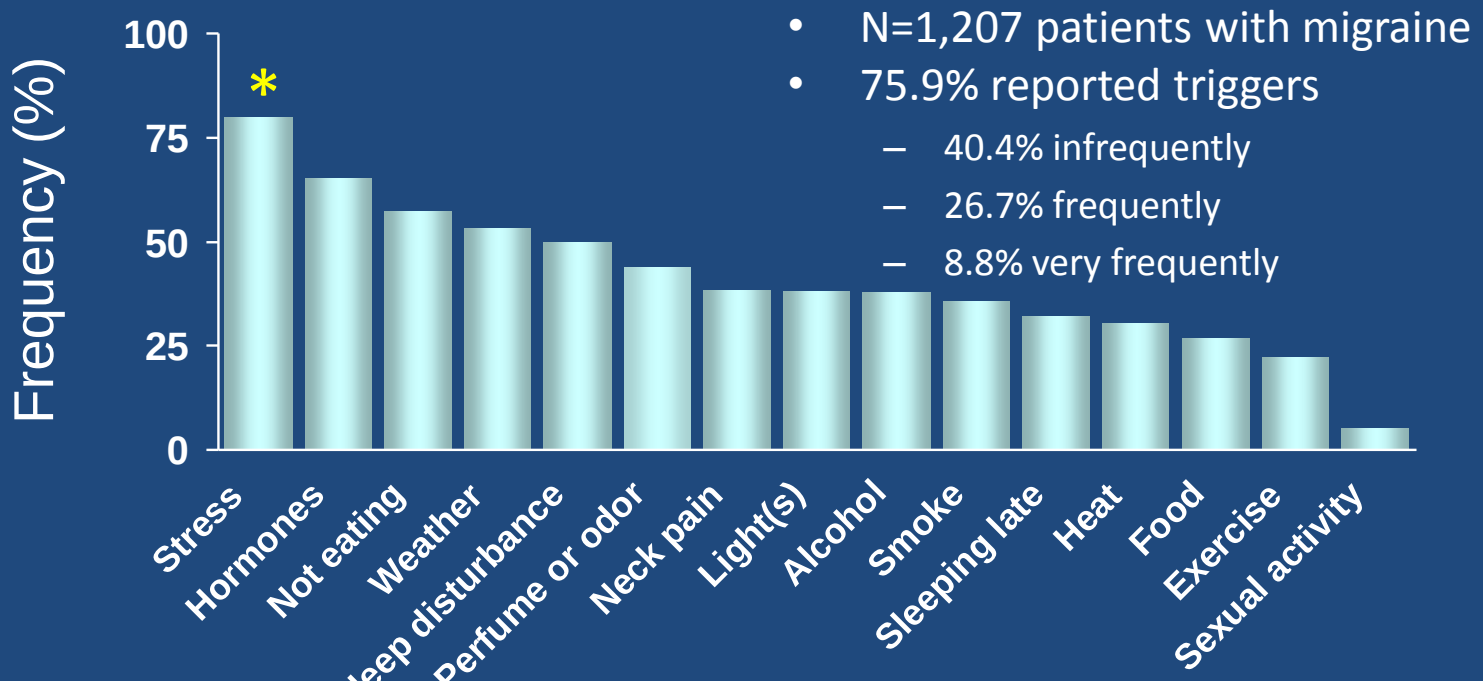
Perception of Real or Presumed Physical and Social Threats Leads to Activation of HPA Axis





Front. Psychiatry, 07 August 2013

Migraine Risk Factors and Triggers



- N=1,207 patients with migraine
- 75.9% reported triggers
  - 40.4% infrequently
  - 26.7% frequently
  - 8.8% very frequently

Adapted with permission from Kelman L. *Cephalalgia*. 2007; 27:394–402.

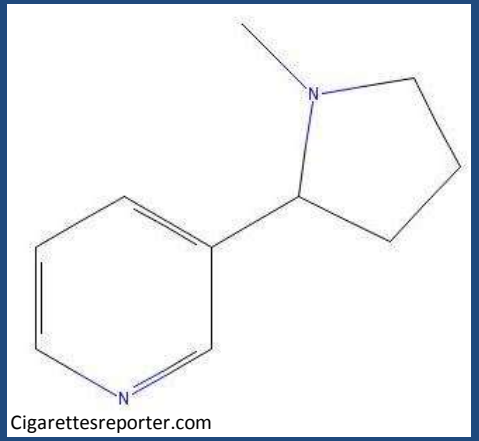
Chronic Nicotine Promotes Expression of Proteins Implicated in Development of Peripheral and Central Sensitization of Trigeminal Neurons

Nicotine

- Alkaloid found in the tobacco plant (*Nicotiana tabacum)*
- Most common forms of tobacco use include chewing tobacco and cigarette smoking
- Acts on nicotinic acetylcholine receptors (nACH) localized in peripherial and central nervous system
- Strong correlation with chronic nicotine use and higher levels of pain and sensitivity


Cigarettesreporter.com


Citycigarcomapy.org



Cigarettesreporter.com

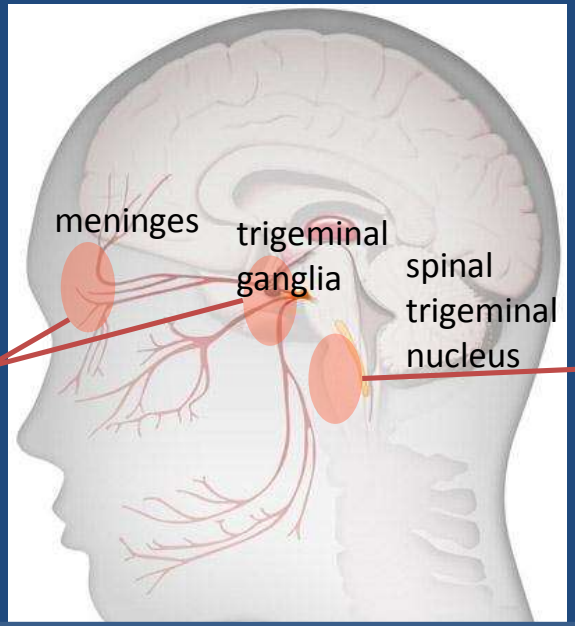

Unacoh.org

TMD/Migraine and Trigeminal Sensitization

Trigeminal Ganglion Nociceptors

Peripheral Sensitization

- Early: within ~ 20 min of the onset of pain
- Can last for up to 2 hours
- Drives central sensitization



Nicotine

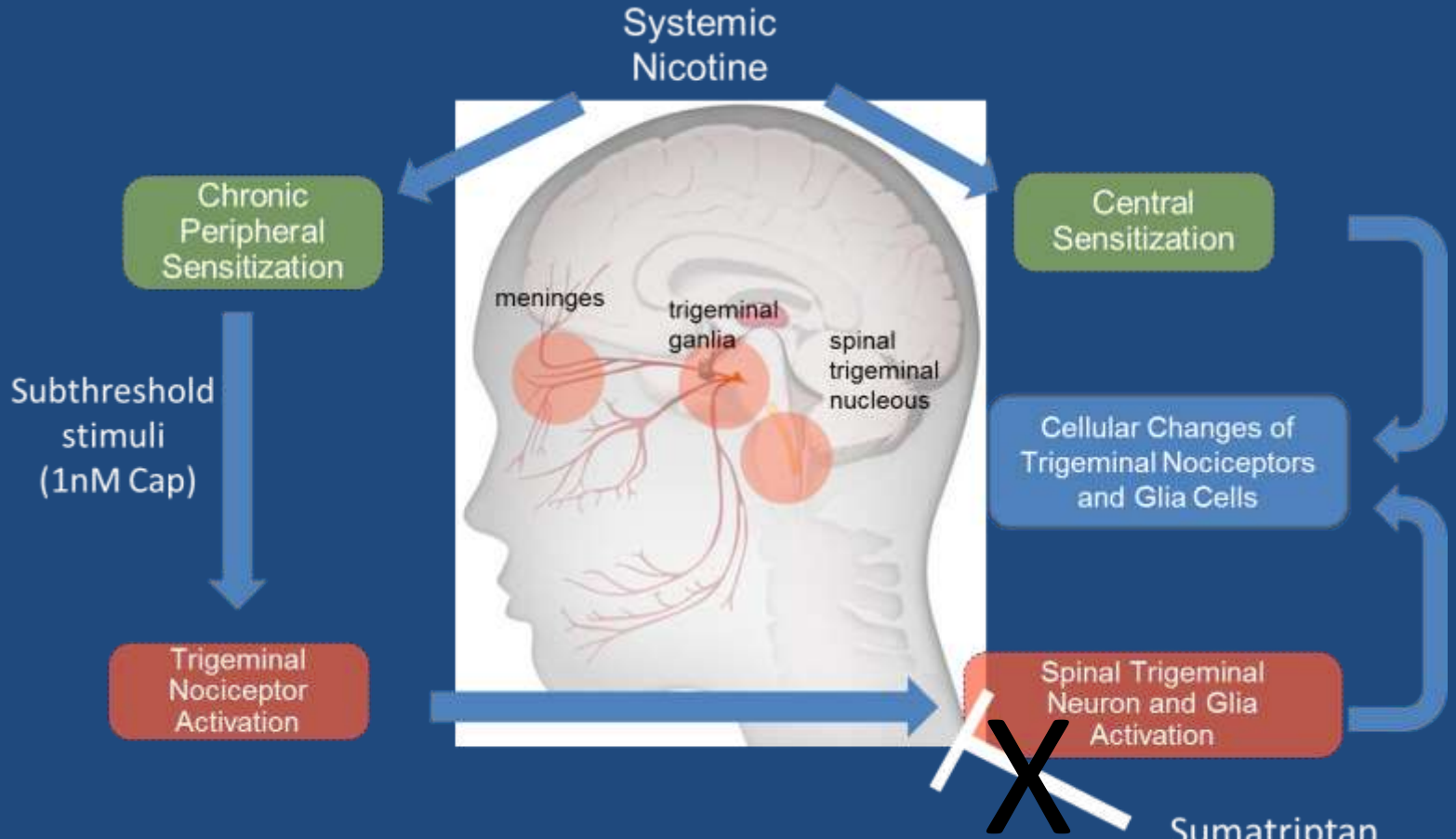
Central Sensitization

- Later: within ~60 min of the onset of pain
- Can last up to 10 hours
- Drive the maintinance of prime-state

Primed State of Trigeminal Nociceptor

Increased sensitivity to inflammatory stimuli
Involves increased expression or activity of ion channels and receptors
Sensitivity is markedly prolonged (weeks - months)

Chronic Nicotine Promotes Expression of Proteins Implicated in Development of Peripheral and Central Sensitization of Trigeminal Neurons



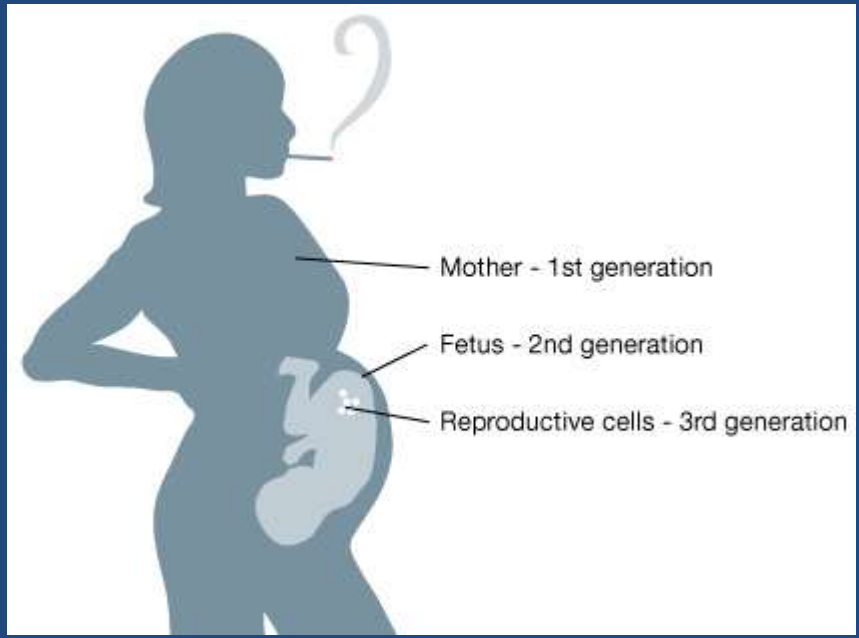
Epigenetic Inheritance - Influences Multiple Generations

Changes in gene expression – not caused by mutations (changes in DNA sequence)

As if three generations - exposed to the same environmental conditions (diet, toxins, hormones, etc.)

Epigenetic changes - transient by nature

Epigenetic change triggered by environmental conditions may be reversed when environmental conditions change again



Smoking
Stress

Malnutrition
Hypertension

Under nutrition
Diabetes

Over nutrition
Obesity

Andrew P. Feinberg
Nature **447**, 433-440 (24 May 2007)

Mechanism of Multigenerational Exposure and Transgenerational Inheritance

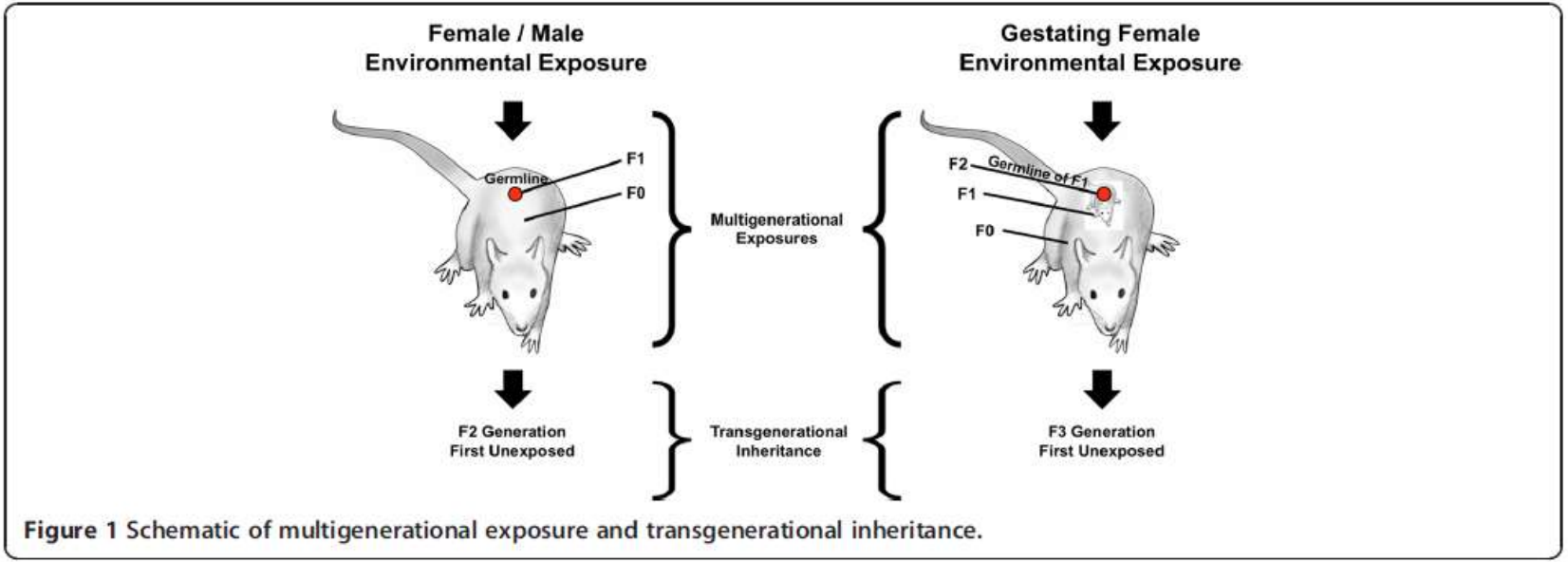
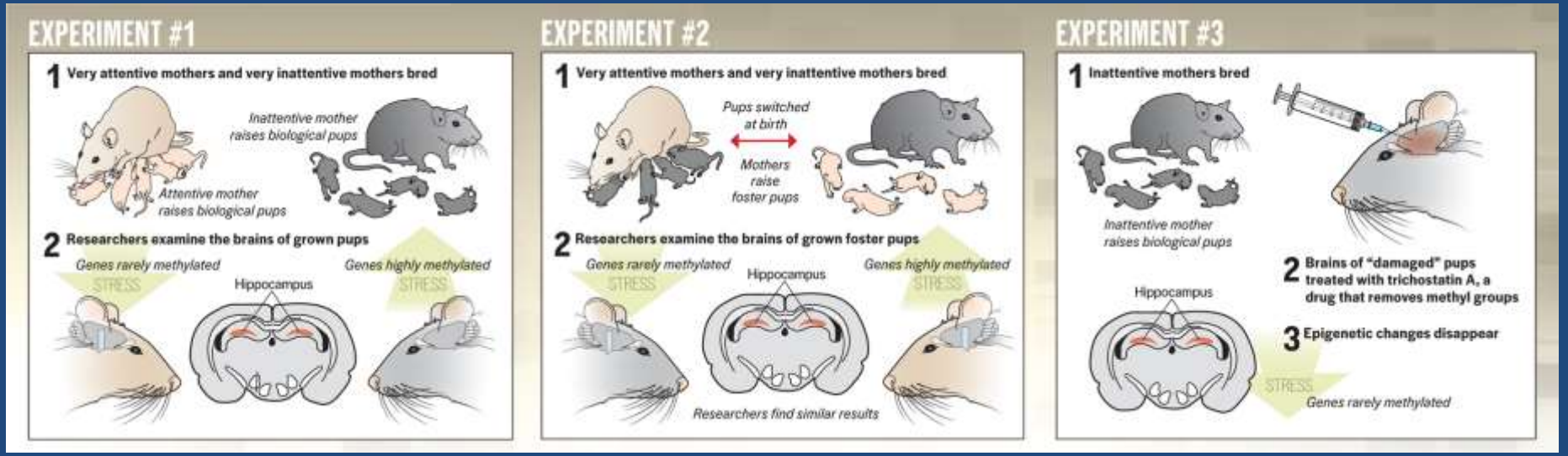


Figure 1 Schematic of multigenerational exposure and transgenerational inheritance.

Social Environment Affects Epigenetic Program



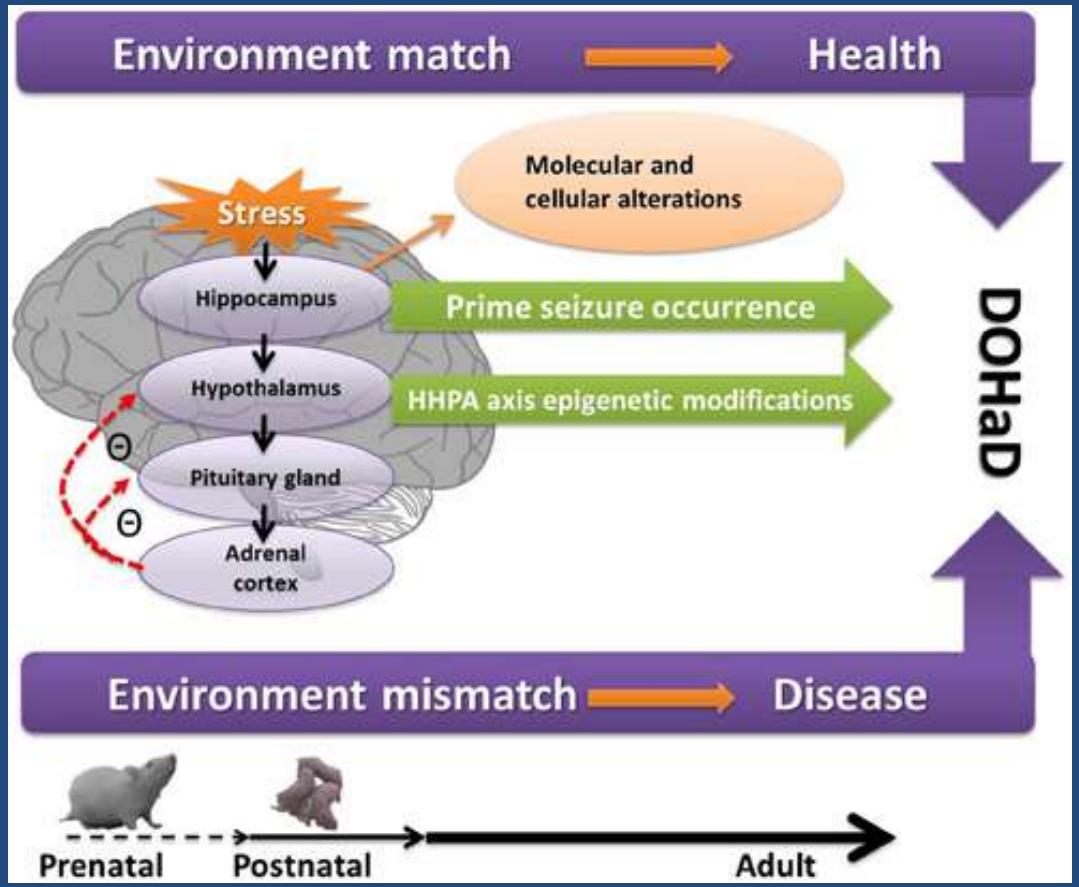
Early Life Stress – Major Risk Factor for Developing Depressive Disorders

Early life stress, such as childhood abuse, neglect and loss, is a well established major risk factor for developing depressive disorders later in life

Table 2 Stress-induced transgenerational inheritance of pathologies

Stress exposure	Pathology	Reference
Maternal separation and stress	Social anxiety and recognition and stress resilience	Franklin *et al.* 2011 [43]
Traumatic paternal stress (odorant)	Behavioral and neural metabolic responses	Dias *et al.* 2014 [44]
Gestational restraint and forced swimming	Preterm birth and prenatal growth and behavior	Yao *et al.* 2014 [1]

Early-life Stress Impacts Developing Hippocampus and Primes Seizure Occurrence



DOHaD:

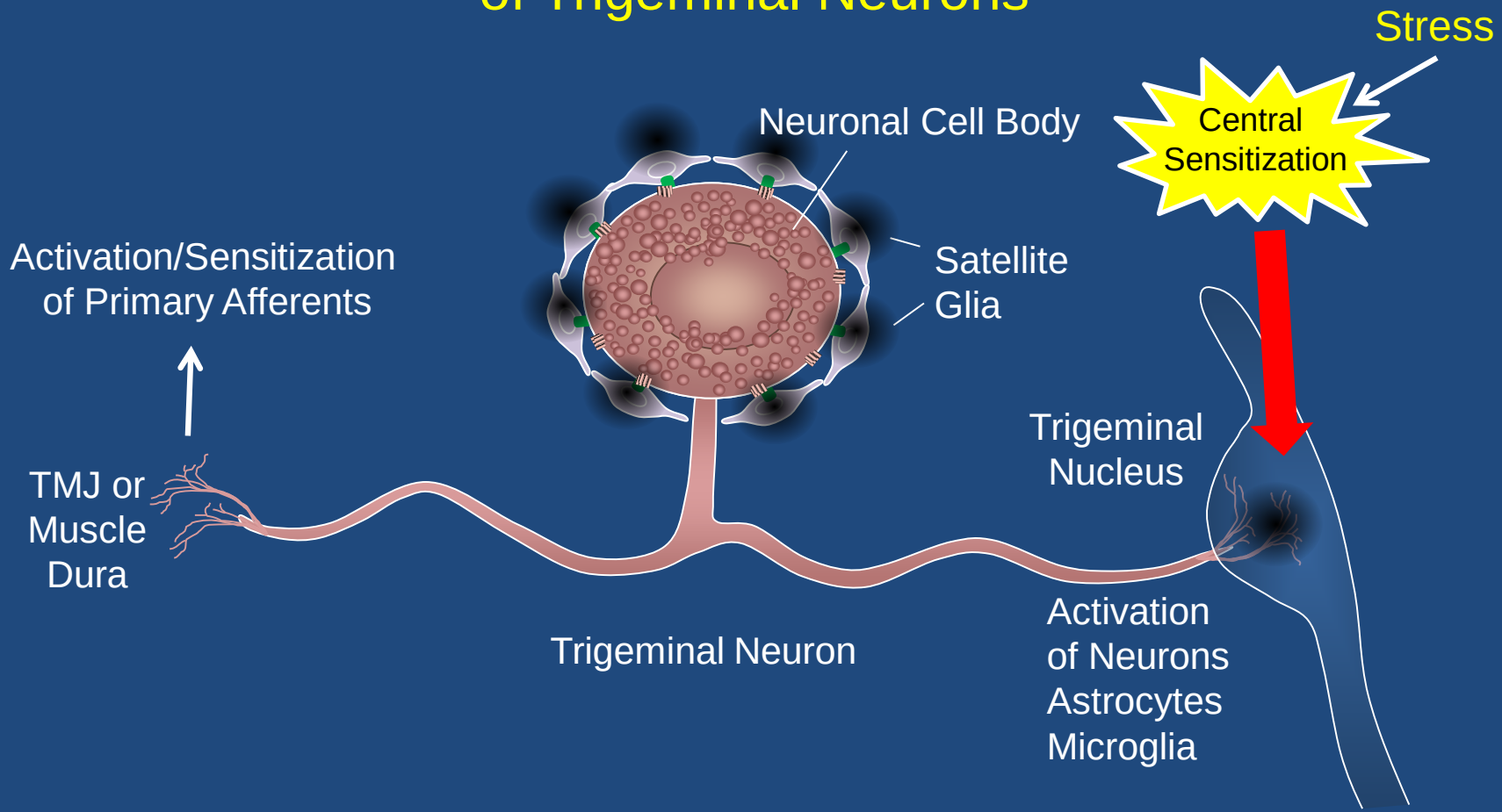
Developmental Origins of Health and Disease

Front. Mol. Neurosci., 10 February 2014

Minimizing Early Stress – Long-term Benefits

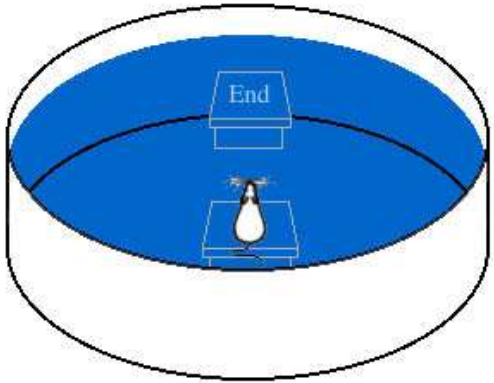
- Reducing prenatal and postnatal stress may help reduce the cost of treating adult diseases
- Ideally, intervention and prevention should be achieved before pregnancy begins
- Psychosocial interventions in early life can affect brain development and thereby benefit children at risk
- Other perinatal adversities such as perinatal infection, nutritional disorders, and toxin exposures must be cautiously avoided and treated

Secondary Traumatic Stress Promotes Sensitization of Trigeminal Neurons

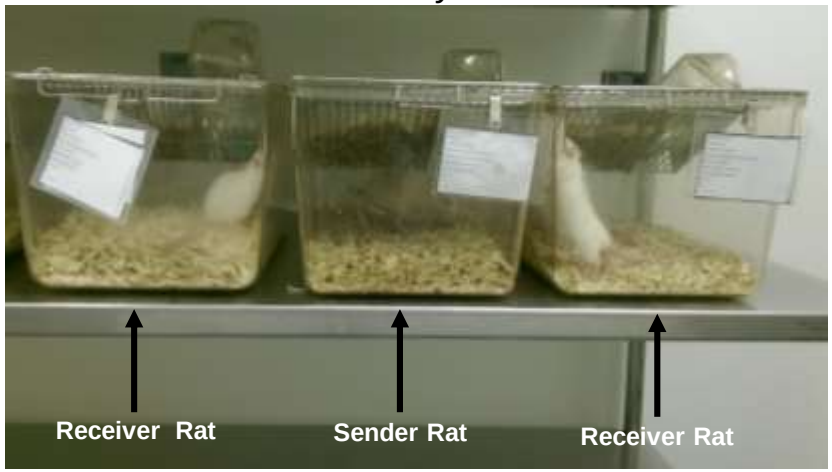


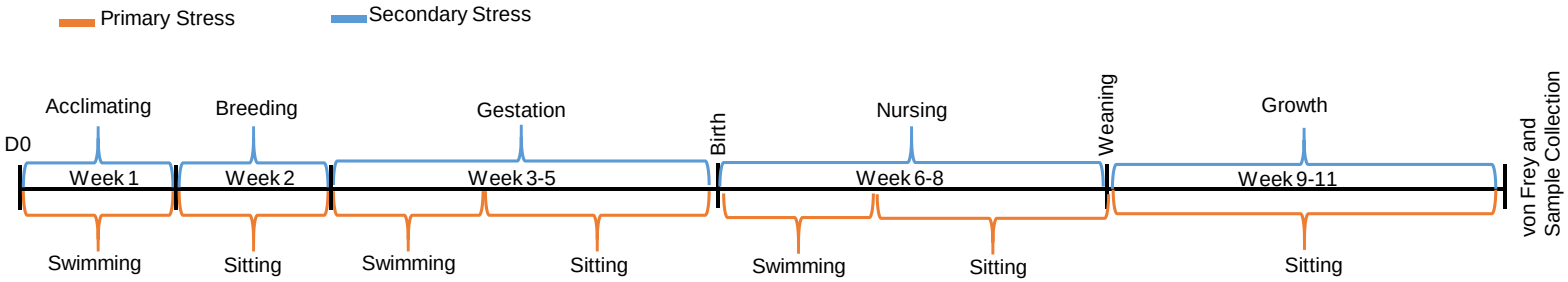
Model for Studying Secondary Traumatic Stress

Primary Stress



Secondary Stress

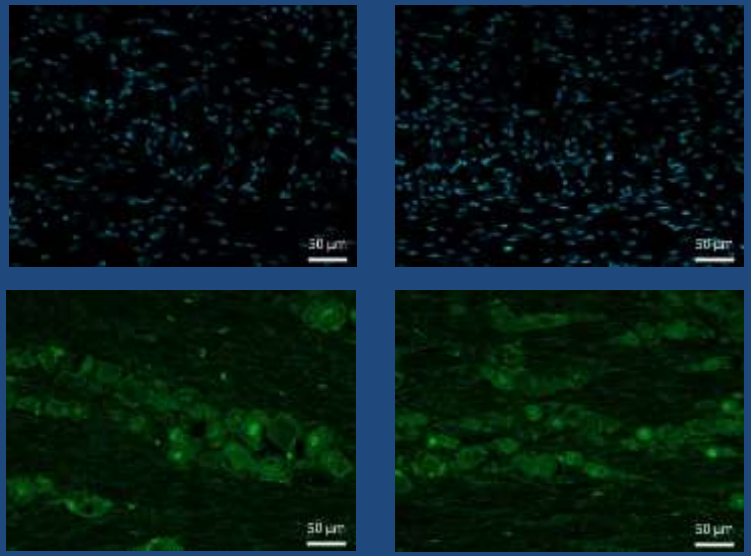




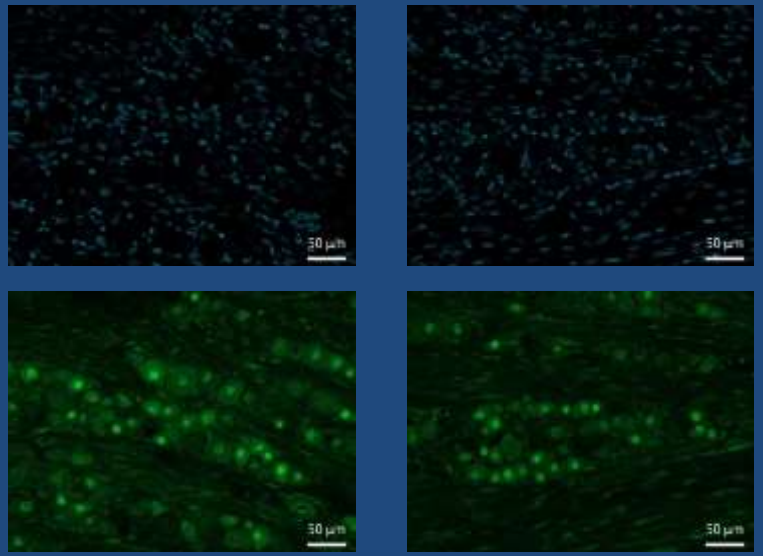
Hawkins, Moore, Miley, Durham. Brain Research 2018 May 15;1687:162-172

Prenatal or Postnatal Secondary Stress Causes Prolonged Peripheral Sensitization in TG – P-ERK

Control Naïve Animals

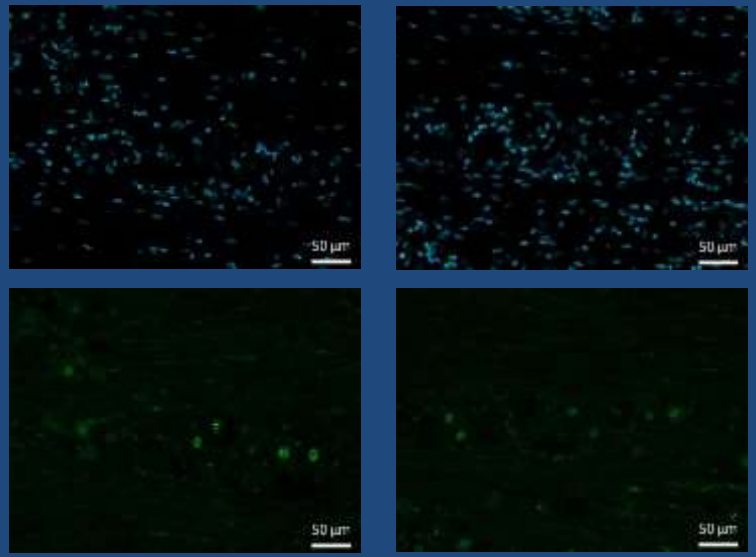


Secondary Stressed Animals

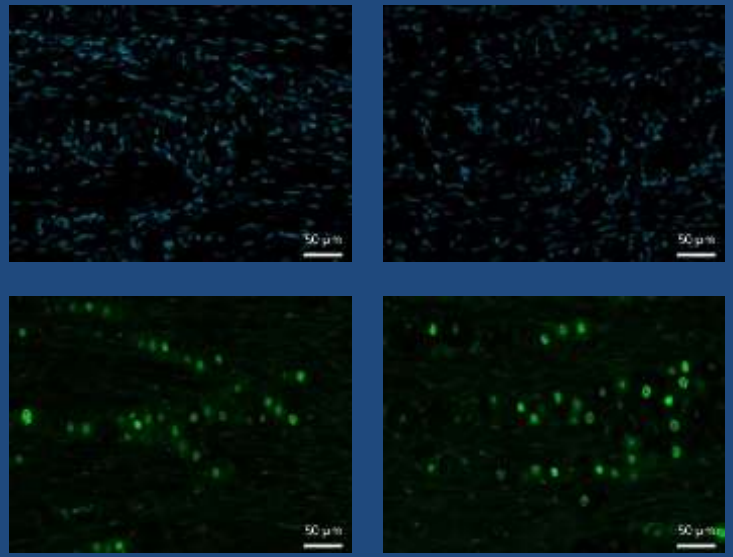


Prenatal or Postnatal Secondary Stress Causes Prolonged Peripheral Sensitization in TG – P-p38

Control Naïve Animals

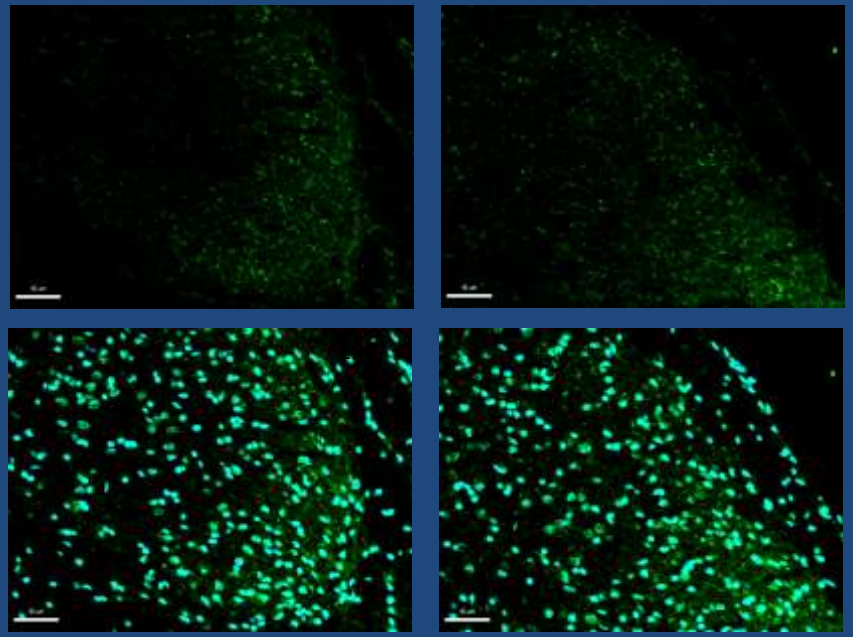


Secondary Stressed Animals

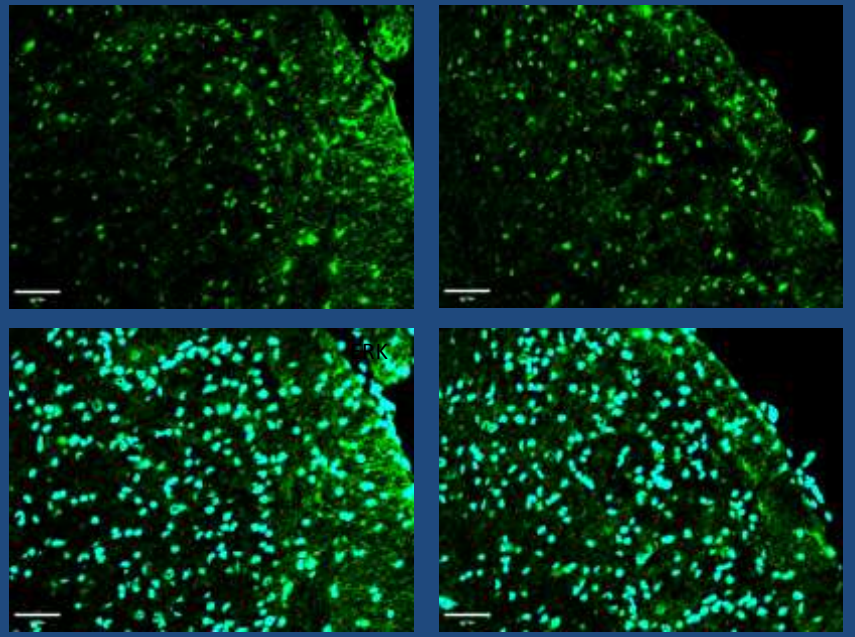


Prenatal or Postnatal Secondary Stress Causes Prolonged Central Sensitization in STN – P-ERK

Control Naïve Animals

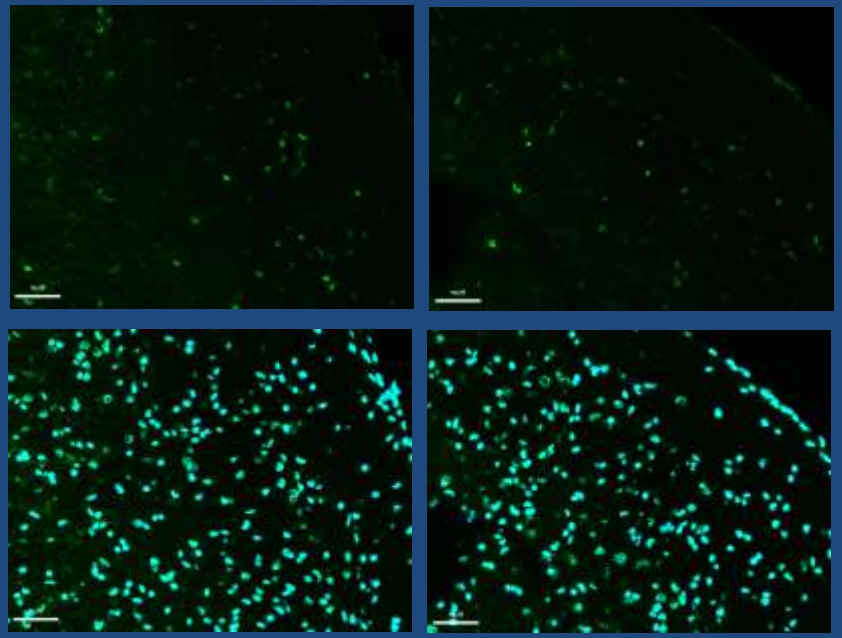


Secondary Stressed Animals

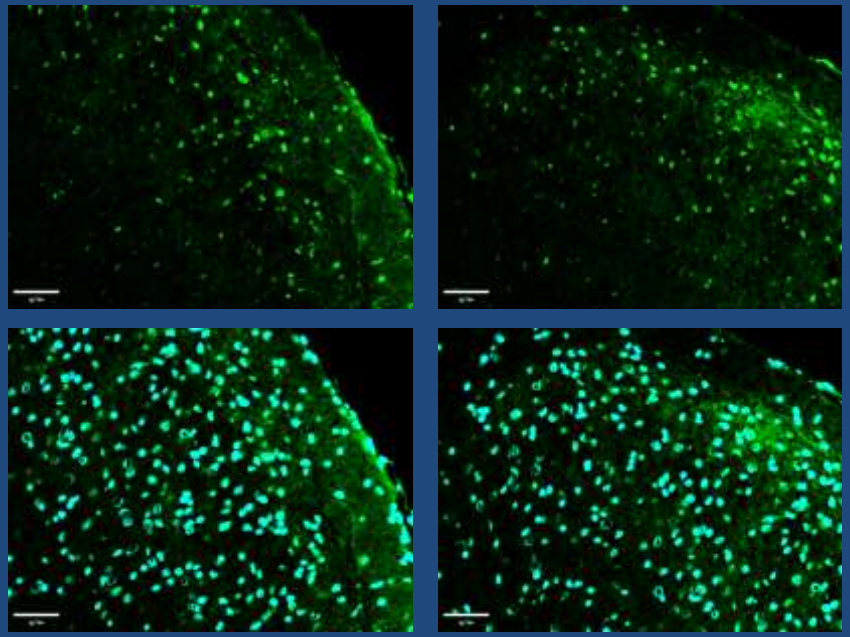


Prenatal or Postnatal Secondary Stress Causes Prolonged Central Sensitization in STN – P-p38

Control Naïve Animals

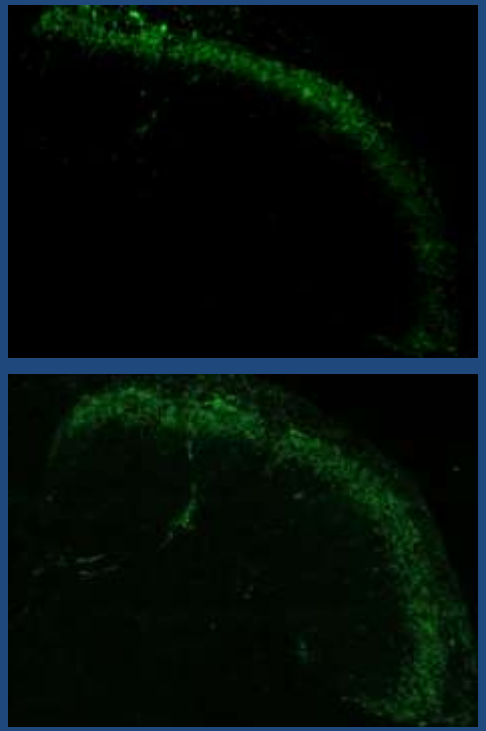


Secondary Stressed Animals

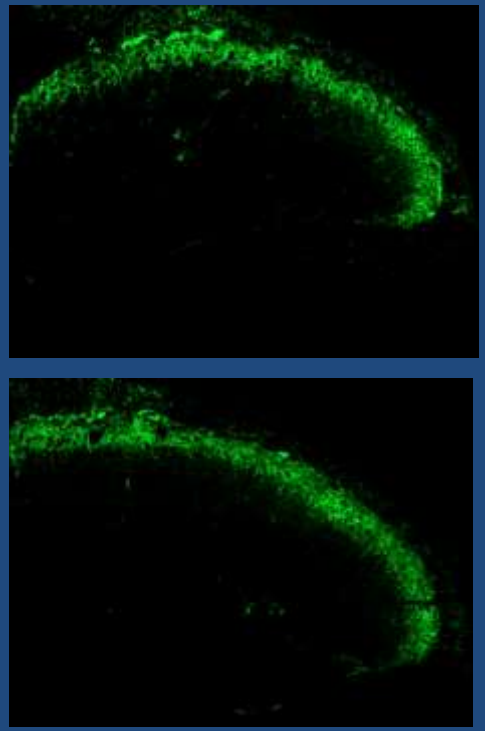


Prenatal or Postnatal Secondary Stress Causes Prolonged Central Sensitization in STN – CGRP

Control Naïve Animals

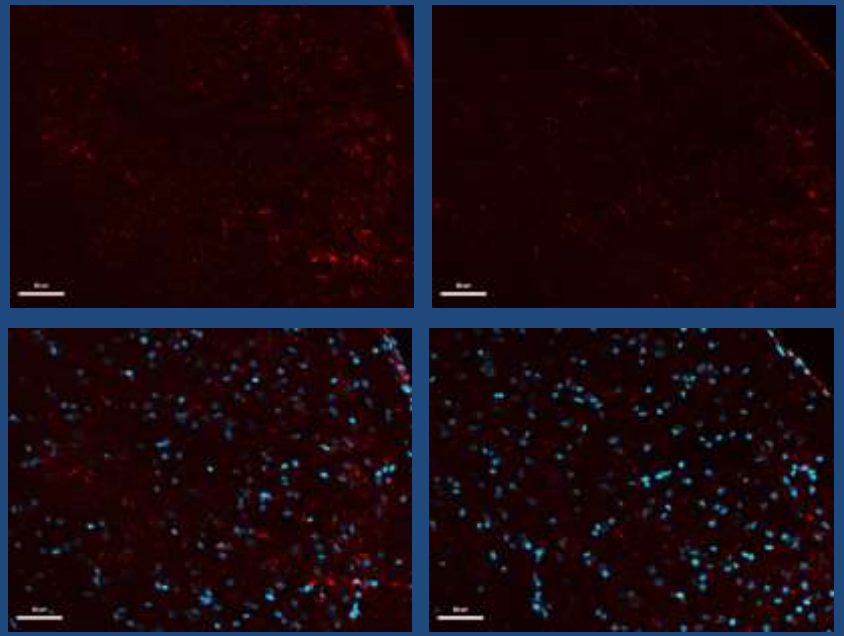


Secondary Stressed Animals

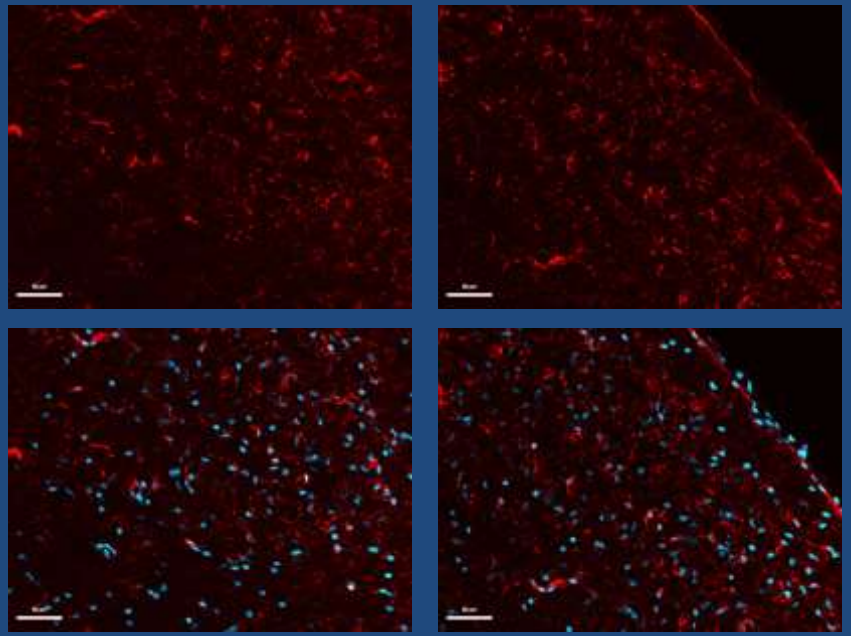


Prenatal or Postnatal Secondary Stress Causes Prolonged Central Sensitization in STN – GFAP (Astrocytes)

Control Naïve Animals



Secondary Stressed Animals



Model for Studying Secondary Traumatic Stress

Peripheral Sensitization

Pungent Odor - CBL

Primary Nociceptors

Neuronal Cell Body

Satellite Glia

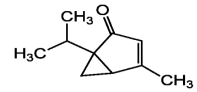
Trigeminal Ganglion

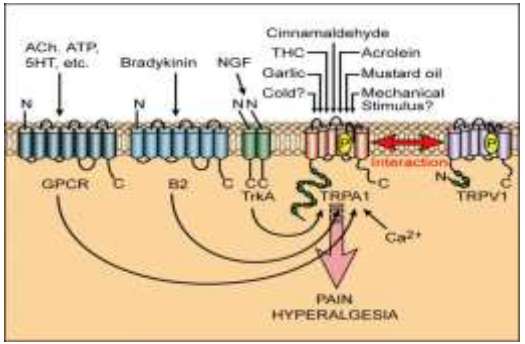
Early Life Stress

Central Sensitization

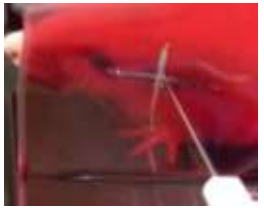
Sensitization of Second Order Neurons and Glia

STN



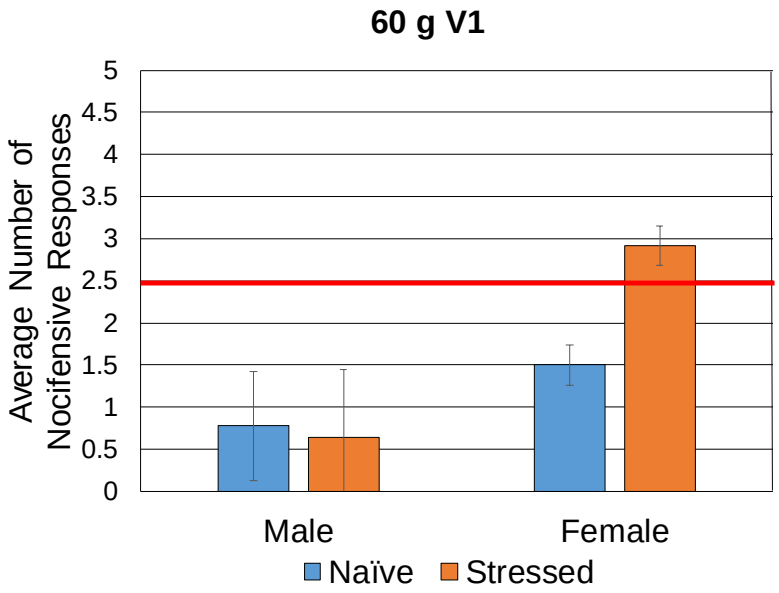


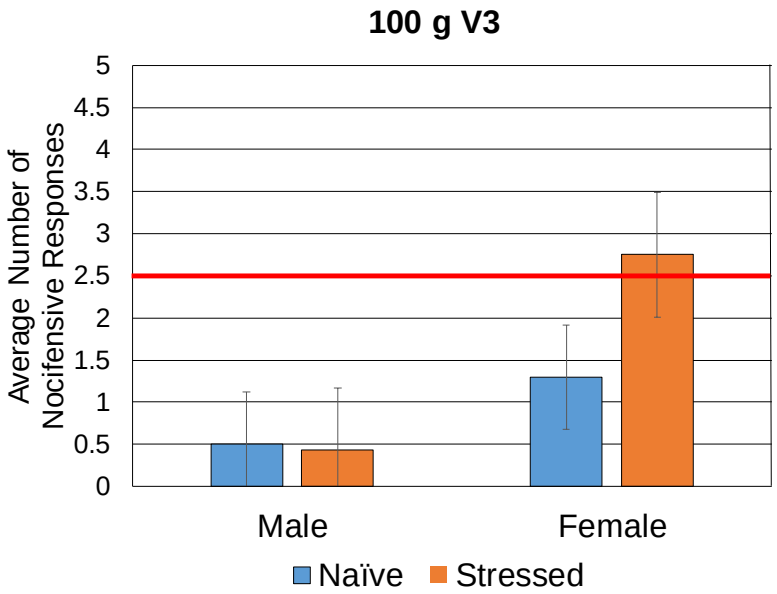
Testing mechanical sensitivity - von Frey filament



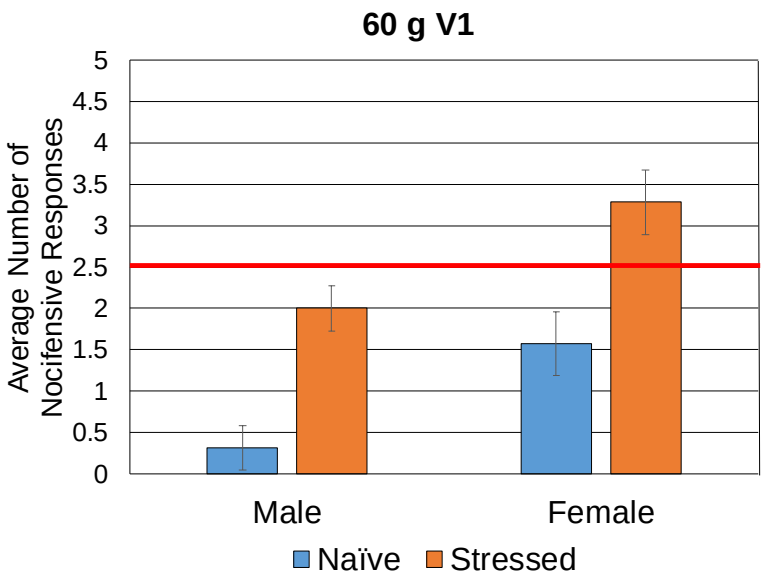
Hawkins, Moore, Miley, Durham. Brain Research 2018 May 15;1687:162-172

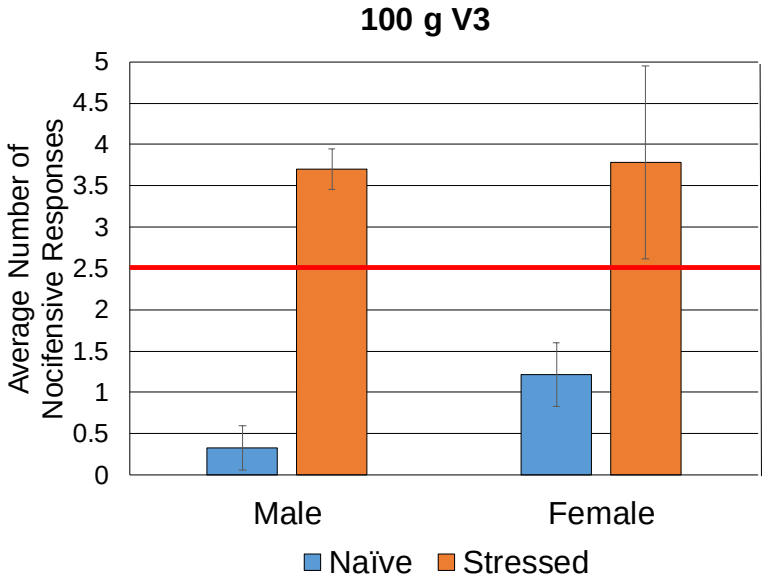
Early Life Stress Increased Basal Mechanical Sensitivity in Female Offspring



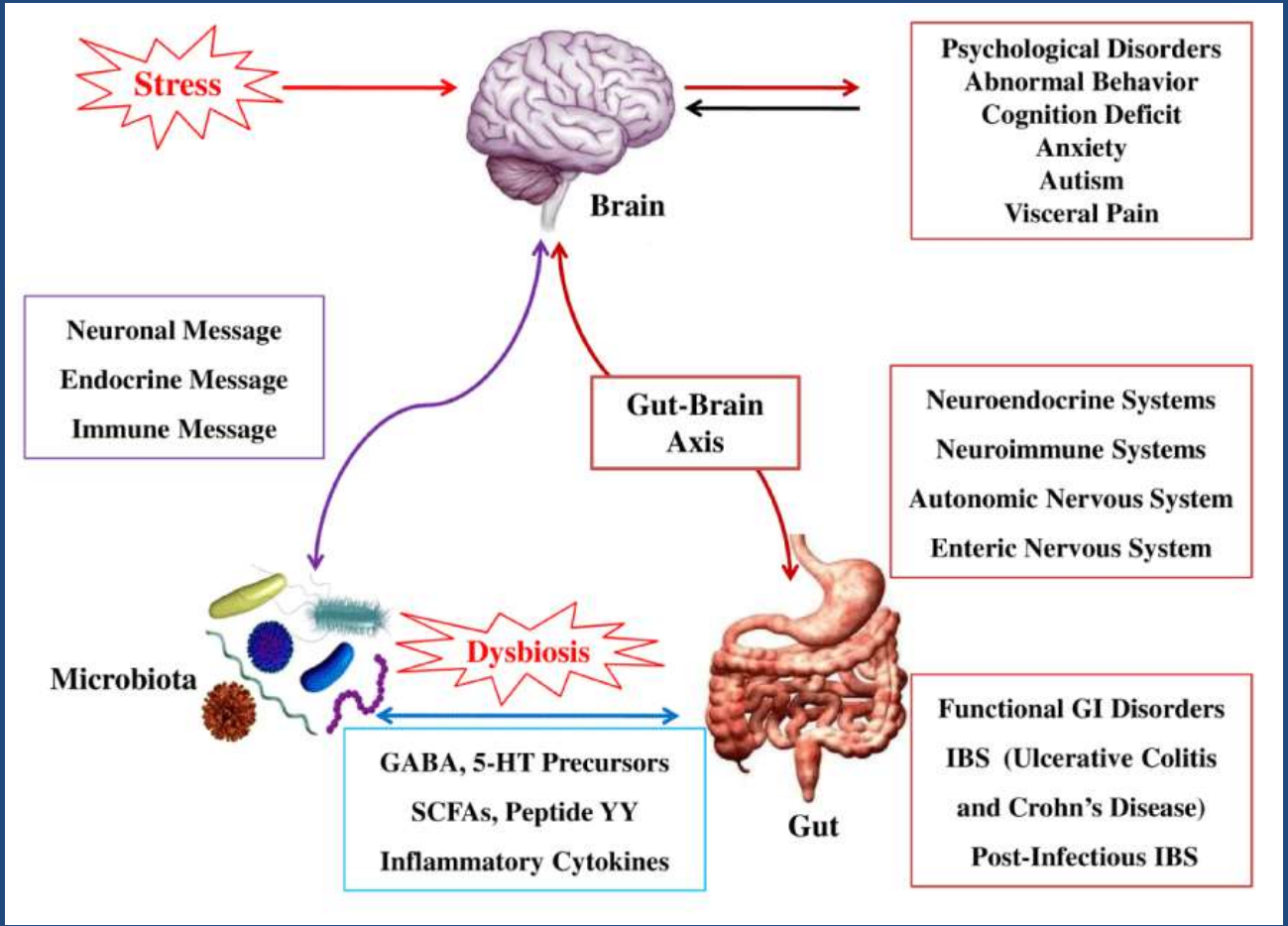


Increased Nocifensive Response to Pungent Odor in Male and Female Sensitized Animals

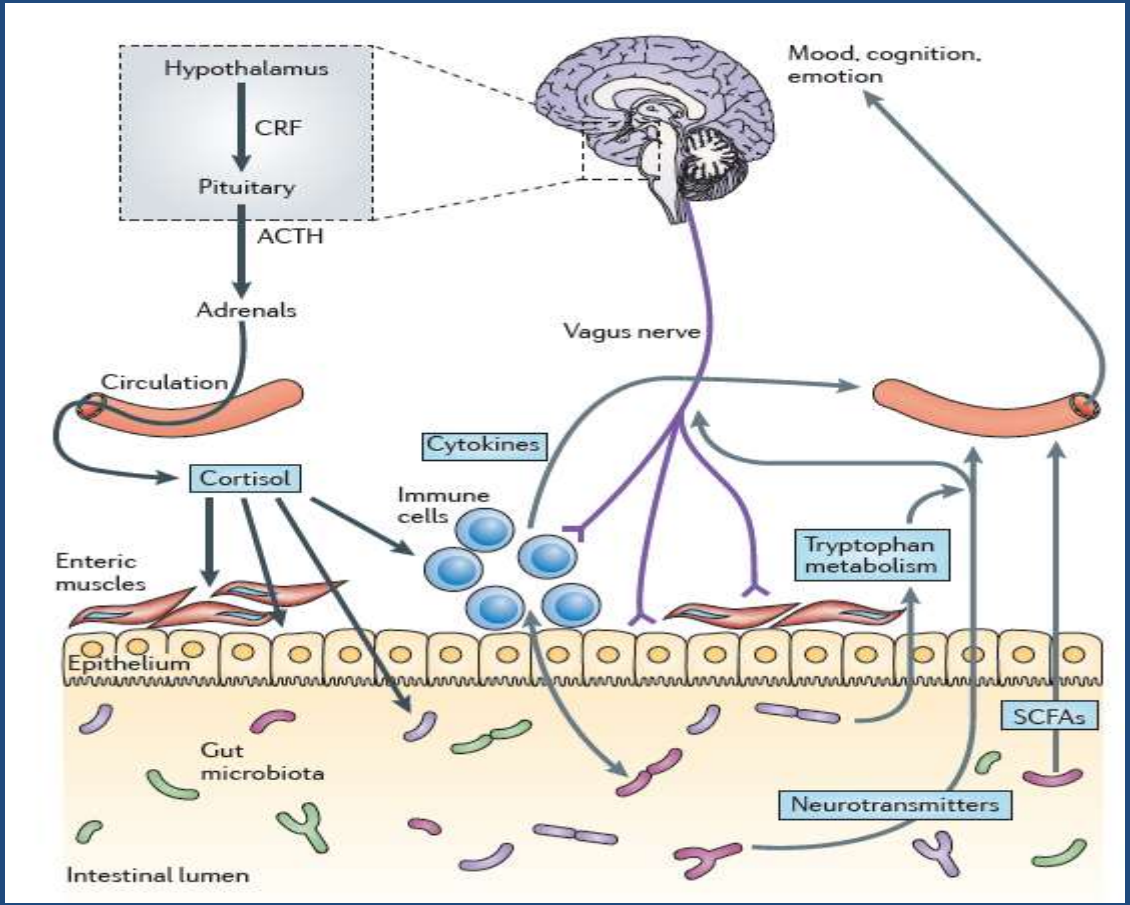




Gut-Brain Axis – Integration of Multiple Systems



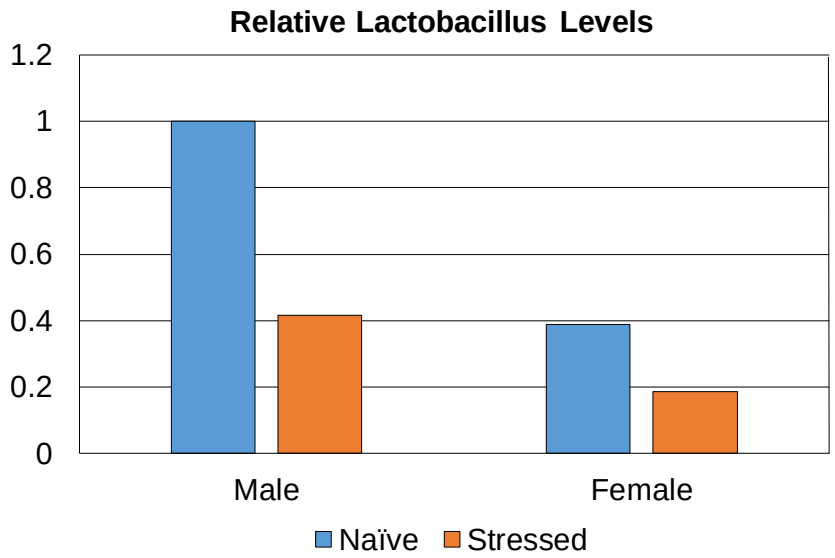
Healthy Gut = Healthy Brain

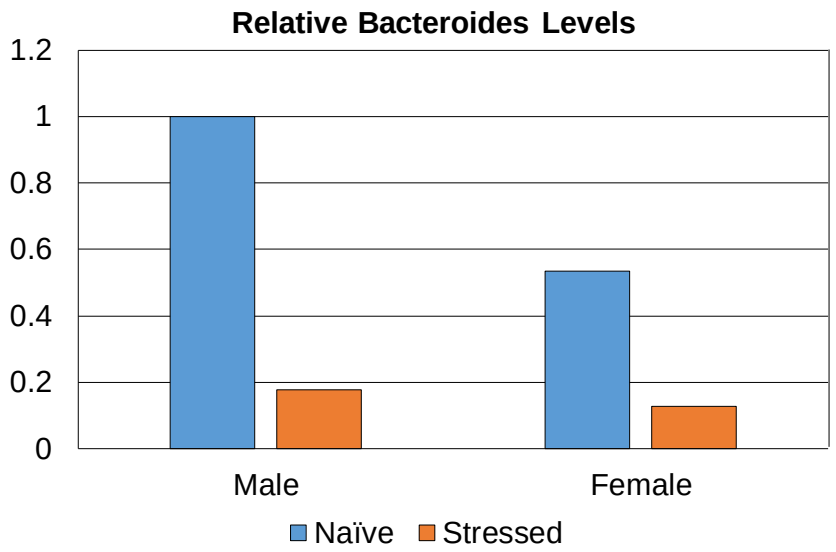


Trigeminal Neurons Express SCFA Receptors

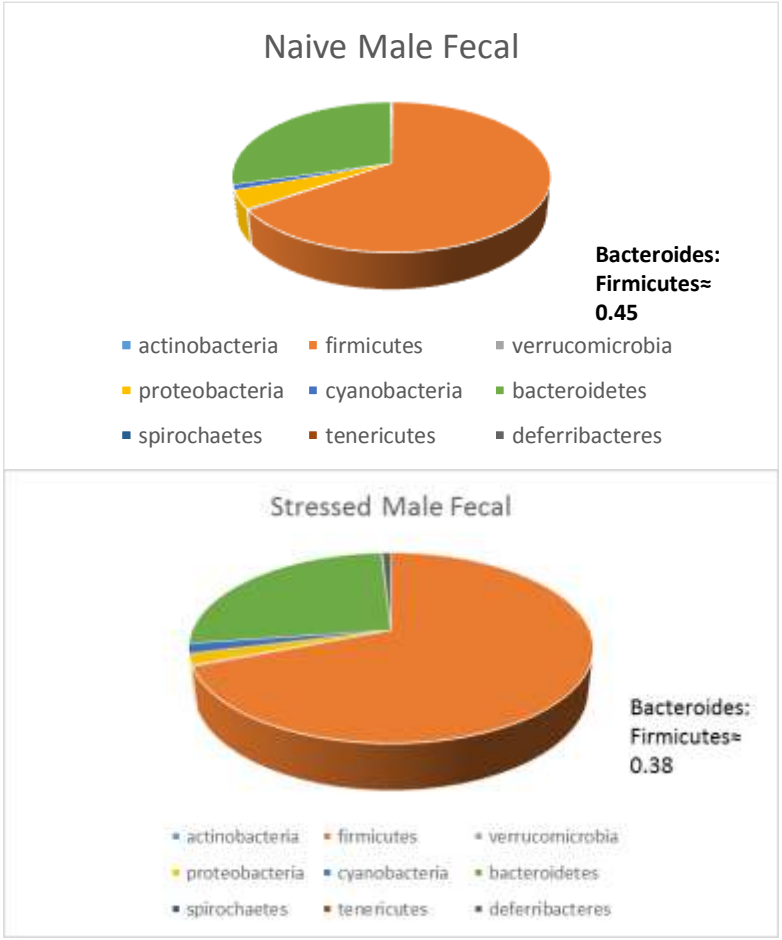
Inhibit -- Sensitization Activation

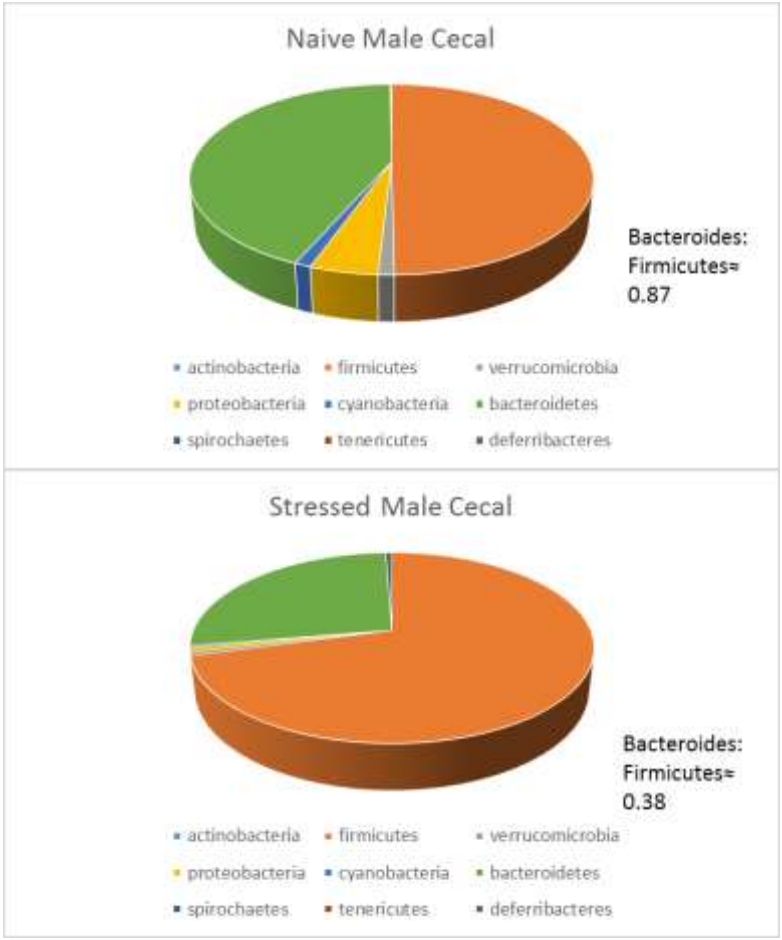
Stress Differentially Affects Microbial Populations in Cecum in Males and Females





Early Life Stress Causes Major Shift in Male Microbiota





Early Life Stress Causes Major Shift in Female Microbiota