

## PSIG Research: Abstracts, Articles and Reviews

Every other month, the Pain Special Interest Group provides updates on new topics, new information and research related topics. Please feel free to submit a topic or research question to [dana-dailey@uiowa.edu](mailto:dana-dailey@uiowa.edu). If you would like to help in preparing information, please let me know as well.

This month, PSIG President Carolyn McManus, MPT, MA, shares articles on the topic of chronic stress, persistent pain and corticolimbic brain regions. In addition to five abstracts, she is including a link to a 5-minute powerpoint on YouTube by Yale Medical School neuroscience researcher, Amy Arnsten, PhD, that presents research on the effects of uncontrollable stress on the brain.

### March 2019 Topic: Chronic Stress, Persistent Pain and Corticolimbic Brain Regions

#### Bibliography

1. Arnsten AFT. How our brains react to uncontrollable stress. YouTube. 2017 April 17.
2. Arnsten AF. Stress weakens prefrontal networks: molecular insults to higher cognition. *Nat Neurosci*. 2015 Oct;18(10):1376-85.
3. Vachon-Preseu E, Tetreault P, Petre B, et al. Corticolimbic anatomical characteristics predetermine risk for chronic pain. *Brain*. 2016 Jul;139(Pt 7):1958-70.
4. Vachon-Preseu E. Effects of stress on the corticolimbic system: implications for chronic pain. *Neuropsychopharmacol Biol Psychiatry*. 2018 Dec 20;87(Pt B):216-223.
5. Li X, Hu L. The role of stress regulation on neural plasticity in pain chronification. *Neural Plast*. 2016;2016:6402942.
6. Thompson JM, Neugebauer V. Amygdala plasticity and pain. *Pain Res Manag*. 2017;2017:8296501.

#### YouTube Link

Arnsten AFT. How our brains react to uncontrollable stress. You Tube. 2017 (April 17). [https://www.youtube.com/watch?v=v\\_mqP7P-azU](https://www.youtube.com/watch?v=v_mqP7P-azU)

#### Abstracts

1. Arnsten AF. Stress weakens prefrontal networks: molecular insults to higher cognition. *Nat Neurosci*. 2015 Oct;18(10):1376-85.

Full text: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4816215/>

#### Abstract

A variety of cognitive disorders are worsened by stress exposure and involve dysfunction of the newly evolved prefrontal cortex (PFC). Exposure to acute, uncontrollable stress increases catecholamine release in PFC, reducing neuronal firing and impairing cognitive abilities. High levels of noradrenergic  $\alpha$ 1-adrenoceptor and dopaminergic D1 receptor stimulation activate feedforward calcium-protein kinase C and cyclic AMP-protein kinase A signaling, which open potassium channels to weaken synaptic efficacy in spines. In contrast, high levels of catecholamines strengthen the primary sensory cortices, amygdala and striatum, rapidly flipping the brain from

reflective to reflexive control of behavior. These mechanisms are exaggerated by chronic stress exposure, where architectural changes lead to persistent loss of PFC function. Understanding these mechanisms has led to the successful translation of prazosin and guanfacine for treating stress-related disorders. Dysregulation of stress signaling pathways by genetic insults likely contributes to PFC deficits in schizophrenia, while age-related insults initiate interacting vicious cycles that increase vulnerability to Alzheimer's degeneration.

2. Vachon-Preseau E, Tetreault P, Petre B, et al. Corticolimbic anatomical characteristics predetermine risk for chronic pain. *Brain*. 2016 Jul;139(Pt 7):1958-70.

Full text: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4939699/>

Abstract

Mechanisms of chronic pain remain poorly understood. We tracked brain properties in subacute back pain patients longitudinally for 3 years as they either recovered from or transitioned to chronic pain. Whole-brain comparisons indicated corticolimbic, but not pain-related circuitry, white matter connections predisposed patients to chronic pain. Intra-corticolimbic white matter connectivity analysis identified three segregated communities: dorsal medial prefrontal cortex-amygdala-accumbens, ventral medial prefrontal cortex-amygdala, and orbitofrontal cortex-amygdala-hippocampus. Higher incidence of white matter and functional connections within the dorsal medial prefrontal cortex-amygdala-accumbens circuit, as well as smaller amygdala volume, represented independent risk factors, together accounting for 60% of the variance for pain persistence. Opioid gene polymorphisms and negative mood contributed indirectly through corticolimbic anatomical factors, to risk for chronic pain. Our results imply that persistence of chronic pain is predetermined by corticolimbic neuroanatomical factors.

3. Vachon-Preseau E. Effects of stress on the corticolimbic system: implications for chronic pain. *Neuropsychopharmacol Biol Psychiatry*. 2018 Dec 20;87(Pt B):216-223.

<https://www.ncbi.nlm.nih.gov/pubmed/29079140>

Abstract

Stress has multifaceted effects on pain. On the one hand, it is a powerful inhibitor of nociception and inflammation; on the other hand, it contributes to enhanced pathological states including the establishment and continuation of chronic pain. These seemingly paradoxical effects can be better understood by investigating how stress-induced plasticity in particular brain circuitry contributes to the chronic pain state. This review presents the rationale and evidence for the interactions between stress and pain, emphasizing underlying mechanisms and putting forth the hypothesis that stress partly mediates the deleterious effects of pain on the corticolimbic system. First, a general description of the corticolimbic circuitry predisposing and amplifying chronic pain will be discussed, followed by an overview of the neurotoxic effects of stress hormones on this circuitry. Recent studies show that the resulting perturbations to these brain circuits have significant consequences both for chronic pain and for general regulation of the stress response, primarily through feedback mechanisms controlling the hypothalamic-pituitary-adrenal axis. This overlap in effected circuitry provides a key point of comparison between stress and pain, and the similarities between the plasticity

induced by chronic pain and chronic stress will be examined here. Chronic pain patients have been shown to exhibit maladaptive stress responses in general and in response to pain; the cause of this response and its consequence on pain severity will then be reviewed. Finally, factors that have been shown to lead to resilience or vulnerability for chronic pain and maladaptive stress responses will be summarized.

4. Li X, Hu L. The role of stress regulation on neural plasticity in pain chronification. *Neural Plast.* 2016;2016:6402942.

Full text: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5178373/>

Abstract

Pain, especially chronic pain, is one of the most common clinical symptoms and has been considered as a worldwide healthcare problem. The transition from acute to chronic pain is accompanied by a chain of alterations in physiology, pathology, and psychology. Increasing clinical studies and complementary animal models have elucidated effects of stress regulation on the pain chronification via investigating activations of the hypothalamic-pituitary-adrenal (HPA) axis and changes in some crucial brain regions, including the amygdala, prefrontal cortex, and hippocampus. Although individuals suffer from acute pain benefit from such physiological alterations, chronic pain is commonly associated with maladaptive responses, like the HPA dysfunction and abnormal brain plasticity. However, the causal relationship among pain chronification, stress regulation, and brain alterations is rarely discussed. To call for more attention on this issue, we review recent findings obtained from clinical populations and animal models, propose an integrated stress model of pain chronification based on the existing models in perspectives of environmental influences and genetic predispositions, and discuss the significance of investigating the role of stress regulation on brain alteration in pain chronification for various clinical applications.

5. Thompson JM, Neugebauer V. Amygdala plasticity and pain. *Pain Res Manag.* 2017;2017:8296501.

Full text: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5742506/>

Abstract

The amygdala is a limbic brain region that plays a key role in emotional processing, neuropsychiatric disorders, and the emotional-affective dimension of pain. Preclinical and clinical studies have identified amygdala hyperactivity as well as impairment of cortical control mechanisms in pain states. Hyperactivity of basolateral amygdala (BLA) neurons generates enhanced feedforward inhibition and deactivation of the medial prefrontal cortex (mPFC), resulting in pain-related cognitive deficits. The mPFC sends excitatory projections to GABAergic neurons in the intercalated cell mass (ITC) in the amygdala, which project to the laterocapsular division of the central nucleus of the amygdala (CeLC; output nucleus) and serve gating functions for amygdala output. Impairment of these cortical control mechanisms allows the development of amygdala pain plasticity. Mechanisms of abnormal amygdala activity in pain with particular focus on loss of cortical control mechanisms as well as new strategies to correct pain-related amygdala dysfunction will be discussed in the present review.