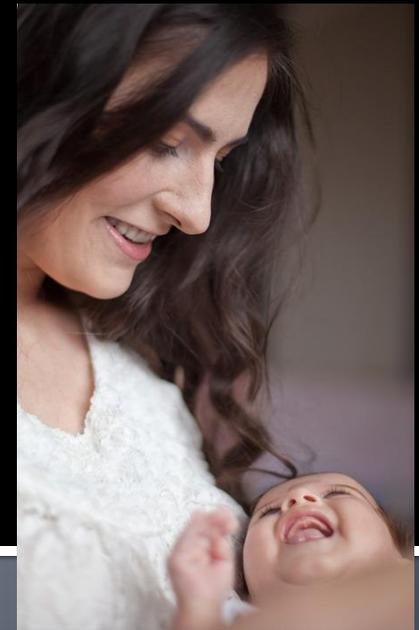


Between suffering and survival: understanding the dynamic links among physical pain, social pain and addiction



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Disclosures

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“O just, subtle, and all-conquering opium!”
-- Thomas De Quincey,
***Confessions of an English Opium Eater*, 1821**

My thesis:

For humans, physical survival depends on social survival, so our brains have evolved to make both physical and social injury painful, with our endogenous opioid system modulating both forms of pain to promote both forms of survival.



Ms. B who has fibromyalgia

- 38 yr old married RN with 2 children, 8yr, 5yr
- MVA 3 years ago when she was rear-ended
- Initially she had whiplash, chronic neck pain which gradually spread down her spine and then her limbs and whole body
- Unable to work since her accident
- Spine MRI reveals only degen. disc disease
- She reports 10/10 pain despite oxycodone SR 80mg BID (240mg MED), asks for more

Pain vs. nociception

- IASP definition of pain:
 - Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage
- IASP chronic pain types
 - nociceptive, neuropathic, visceral, central, nociplastic
 - nociplastic = centralized pain, functional pain, central sensitization, pain hypersensitivity

Functional pain: fibromyalgia

- Widespread pain but no abnormalities in painful muscles
- Hypersensitivity to pressure, heat, cold, electricity, sound
- Adverse childhood experiences common, esp. physical and sexual abuse
- Classic example of functional pain syndrome, somatization, somatoform d/o
- “We can’t find anything wrong with you”

FM like other functional pain synd.

- Similar syndromes:
 - Chronic fatigue, irritable bowel, interstitial cystitis
- Often include other dysfunction with:
 - Sleep, mood, memory, concentration
- Effective treatments
 - Antidepressants, anticonvulsants, CBT, exercise
- Ineffective treatments
 - NSAIDs, surgery, local injections, opioids

Centralized pain: fibromyalgia

- Altered CNS nociceptive processing
- Increased activation on fMRI: posterior insula, secondary somatosensory cortex...
- Increased connectivity between insula and default mode network, proportional to pain
- Elevated substance P and glutamate in CSF
- Reduced conditioned pain modulation
- Endogenous opioid tone increased

Ms. B has been traumatized

- As part of her initial work-up at pain clinic, she scored 5/5 on PC-PTSD₅ screener
 - She re-experiences her MVA in nightmares
 - She avoids driving in that part of town
 - She is easily startled, angered, w insomnia
 - She has withdrawn from colleagues, friends
 - She cannot stop blaming herself for the MVA
- She appears to have PTSD

Old psychogenic pain model

- Dualistic: psychological and biological explanations compete and exclude each other
- Psychogenic pain opposed to: real pain, somatogenic pain, purely physical pain



Purely physical pain

- Cartesian mechanical model (1664)
 - “my c-fibers are firing” (1970)
- Wager’s NEJM “neurological signature for physical pain” (2014??)
 - Ideal of a fully objectified and de-psychologized pain that is the opposite of psychogenic pain



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

An fMRI-Based Neurologic Signature of Physical Pain

Tor D. Wager, Ph.D., Lauren Y. Atlas, Ph.D., Martin A. Lindquist, Ph.D.,
Mathieu Roy, Ph.D., Choong-Wan Woo, M.A., and Ethan Kross, Ph.D.

Psychogenic pain in DSM era

- DSM-III: Psychogenic Pain Disorder
 - Severe pain *inconsistent* with anatomy or *grossly in excess of expected* based on physical exam
- DSM-III-R: Somatoform Pain Disorder
 - Drops evidence for psychological cause, adds preoccupation with pain, now a dx of exclusion
- DSM-IV: Pain Disorder
 - Medical and psychological factors, but remains diagnosis of exclusion w unclear notions causation

DSM-V Somatic Symptom Disorder

- Replaces: somatization disorder, pain disorder, undifferentiated somatoform d/o
- Not “psychologically caused” or “medically unexplained”, but “excessive concern”
- Critics: too inclusive, may label medical illness as mental disorder
- Based on idea that medical and psychological explanations exclude each other

Modern pain psychology

- Cognitive-behavioral therapy (CBT)
 - Focused on appraisal and coping with pain rather than causation of pain
 - In practice, treats pain as given by physiology, contrasted to suffering and disability which also arise from psychological and behavioral processes
 - CBT focused on helping patients live well with pain rather than reducing amount of pain experienced
 - Does not challenge somatogenic pain causation

Modern pain psychology

- Acceptance and Commitment Therapy (ACT)
 - does not challenge cognitions like CBT, but urges mindful commitment to value-based action and acceptance of pain
- ACT not focused on pain reduction, can be effective even when pain is severe
- ACT is agnostic about whether pain is psychogenic or somatogenic

Role of psychological trauma in chronic pain

- Prevalence of PTSD in US is 7.8%
- Chronic pain reported in 35-50% of PTSD pts.
- Among patients presenting for care of chronic pain, 7-50% meet PTSD criteria.
- Common chronic pain: pelvic pain, low back pain, facial pain, bladder pain, fibromyalgia



Role of PTSD in chronic pain

- PTSD: more intense pain, affective distress, disability
- PTSD: opioid therapy more likely, higher doses, multiple opioids, concurrent benzos, early refills, adverse events (Seal, 2012)
- PTSD: significant linear association with wide range of pain outcomes: pain intensity, activity interference, sleep, disability, global health, opioid risk (Langford, 2018)

Ms. B has earlier psych trauma

- As you work with Ms. B to address PTSD sx's. (prazosin), depression (duloxetine) and disability (PT, OT) she reveals that she was beaten by her first husband (age 20-23)
- She eventually left this husband, but had nightmares of beatings for years
- These had resolved about a decade before her MVA

Role of physical and psychological causes of pain may shift over time

- Prospective fMRI study of patients w LBP (Hashimi, 2013)
- LBP progresses- acute → subacute → chronic patterns of brain activation shift from sensory/nociceptive → emotion-related regions
- But as LBP shifts from somatogenic to psychogenic, *it feels the same to the patient*
- This LBP thus does not have a single cause or “neurological signature” (Wager)

Physical and social pain may share the same neurobiological structures

- Most prefer broken leg over broken heart, but medicine treats broken legs as more real
- Social rejection, exclusion, loss can be the most “painful” experiences of human life
- Physical injury and social rejection produce activation of same brain structures on fMRI: anterior cingulate, anterior insula
- Eisenberger: “social attachment system may have piggybacked onto opioid substrates of physical pain system to maintain proximity with others...”

Physical and social pain similarities

- Sensitivity to physical and social pain linked
 - Same people
 - Experiments show persons more sensitive to physical noxious stimuli also more sensitive to social rejection
 - Same treatments
 - Physical and social pain respond to same meds
 - opioids relieve separation distress (Panksepp, 1978)
 - Acetaminophen reduces social and physical pain (Dewall, 2010)

Endogenous opioid system (EOS) throughout animal kingdom

- Invertebrates have no EOS
- Amphibians, reptiles, fishes have an EOS that modulates only physical injury pain
 - Suppresses pain if injured while fleeing predator
 - Rats forced to swim in ice water
 - Injured patients who do not feel pain until at ED
- Mammalian EOS also modulates the pain of physical injury, but...

Endogenous opioid system (EOS) throughout animal kingdom

- In mammals, opioids also serve to promote social bonds essential for survival.
- In non-primate mammals, most crucial bonds are with mates and offspring
 - Known to be supported by oxytocin system
 - But EOS supports these most basic bonds too
 - Rat pups w deficient EOS do not bond to mothers
 - EOS necessary for development of social play

Endogenous opioid system (EOS) throughout animal kingdom

- In humans, social play supports social bonding and social, cognitive, emotional development
 - Adult social relationships → pain tolerance
 - fMRI: partner caress → EOS → pain tolerance



Endogenous opioid system (EOS) throughout animal kingdom

- Primate EOS allows complex social networks
 - As social networks grow from rodents to primates benefits and conflicts increase
 - Endorphin release during primate grooming helps defuse these stresses and assure relationships available, but limited to group size of about 20



Endogenous opioid system (EOS) throughout animal kingdom

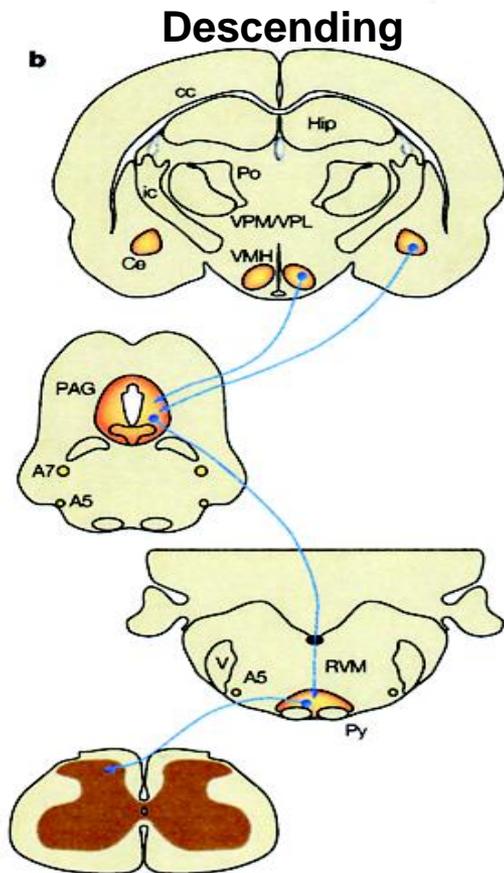
- Human social bonds more complex, extensive so need support beyond grooming (Dunbar):
 - Laughter “primitive chorusing vocalization”
 - Singing, dancing, drama, religious ceremonies
- Adult attachment style related to EOS
 - PET: avoidant attachment related to lower mu receptor availability in amygdala, ACC, insula, PFC
 - BPD, ASP show EOS dysregulation (Bandelow)

Endogenous opioid system links chronic pain and major depression

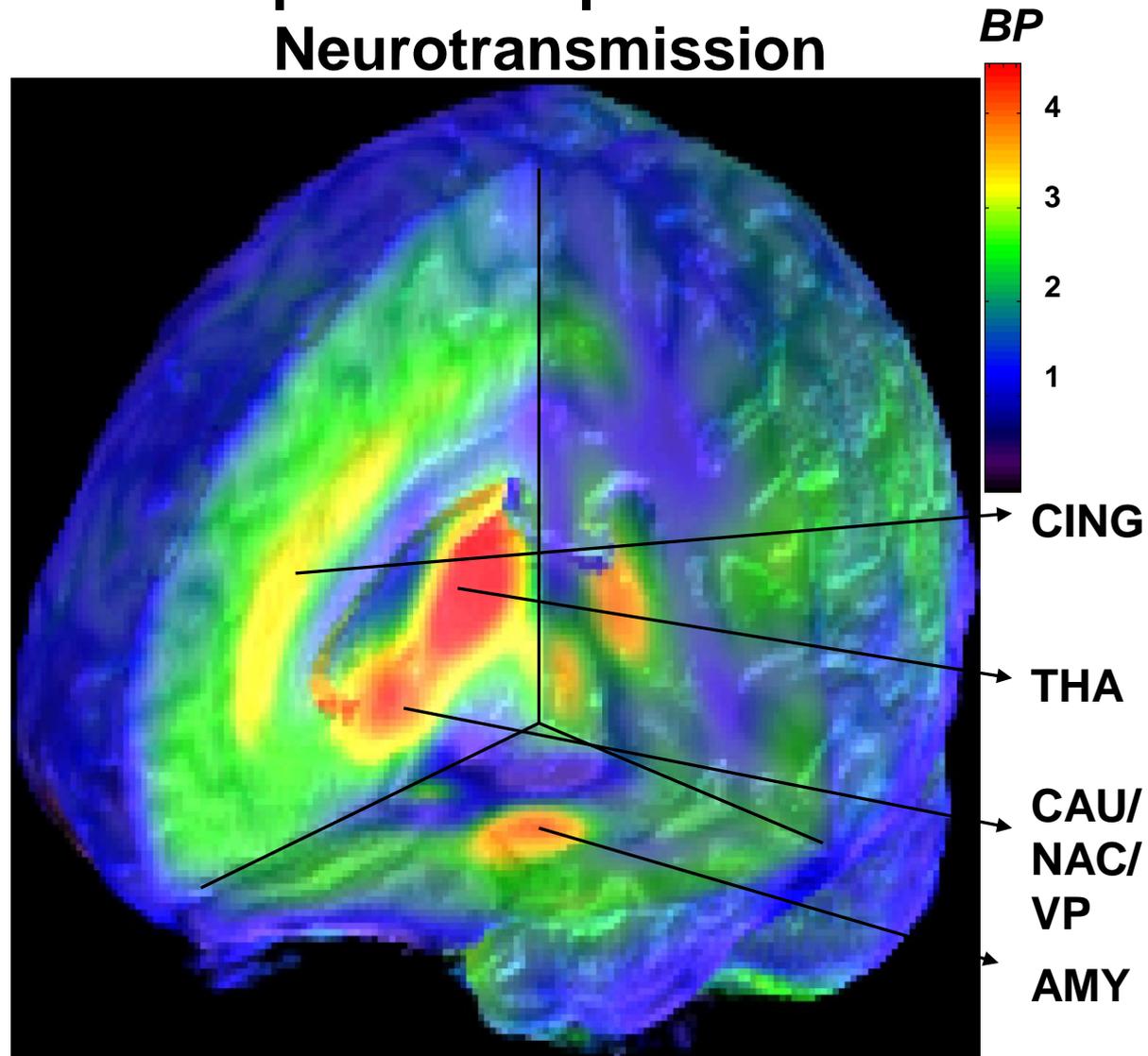
- Recent neuroimaging studies show many brain areas active during both pain and depression (ACC, insula, amygdala, and DLPFC) are laden with opioid receptors.
- Baliki and Apkarian have proposed that pain, anxiety and depression form a continuum of aversive behavioral learning, which enhances survival by protecting against threats.
- The transformation of nociception into behavior to promote survival is extended to incorporate negative moods.

CNS Inhibitory Controls

Mu Opioid Receptor-Mediated Neurotransmission



Distributed in pain regions but also “affective / motivational circuits” - neuronal nuclei involved in the assessment of stimulus salience and cognitive-emotional integration.



From Zubieta JK

Fibromyalgia as prototypical centralized pain syndrome

- FM patients have higher rates of depression, psychol trauma and PTSD than RA OA pts.
- FM- reduced mu opioid binding potential associated w increased pain affect and evoked activity in DLPFC, rACC
- EOS dysregulation leads to hyperalgesia and allodynia typical of FM, and to nonresponse to opioid therapy

Ms. B reveals sexual trauma

- During a session on pain coping with MSW, Ms. B speaks of nightmares of molestation
- She says her grandfather used to visit her room at night when stayed with them
- This occurred age 7-13 until he died
- She tried to tell her mother, but she said that “Grandpa wouldn’t do such a thing.”
- Ms. B also reports she drank heavily and took “pain pills” until she left her first husband

Ms. B reveals sexual trauma

- Ms. B's trauma history now includes the essential elements of helplessness and loneliness (Bergman)
- Survival requires dissociation from the self that has been overwhelmed and destroyed
- Repeat trauma breaks through dissociation once again making Ms. B helpless and alone
- So she turns to opioids

Opioids as stress modulators

- Targeted rejection events (e.g., fired, broken up)
 - assoc. with 22x increase in depression
 - With rejection, MDE patients show MOR deactivation but controls show MOR activation in amygdala
 - These social rejections are a threat to physical survival for intensely social primates
- SNP in OPRM1 increases sensitivity to both physical pain and social rejection
 - G allele carriers need more opioids after surgery, tend to fearful adult attachment

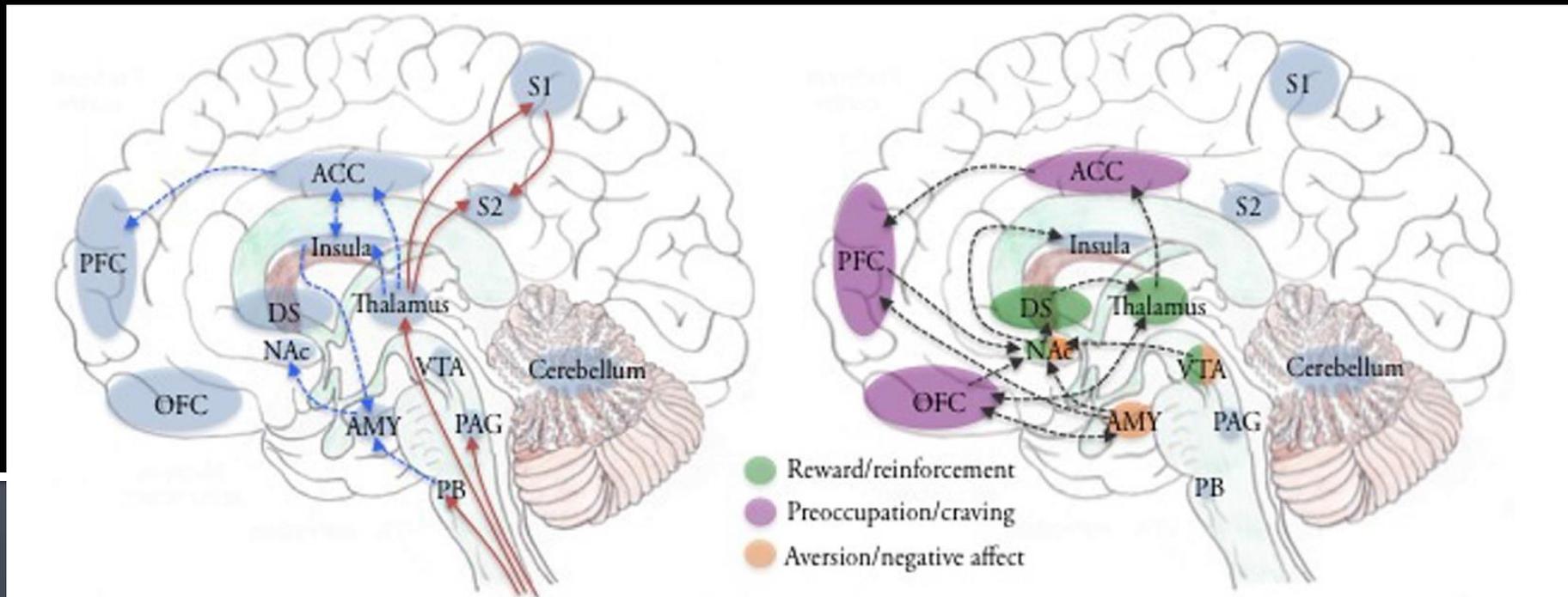
Opioids vs steroids in the CNS

- CRF coordinates autonomic, behavioral, and cognitive response to stress w endocrine syst.
- In acute stress, CRF acts on LC to increase arousal, attention, behavioral flexibility
- EOS has opposite effect on LC, helps neurons and organism recover after stressor is gone
- With chronic stress (PTSD), opioid tolerance and dependence may develop w/o meds

Rethinking the nature of pain

- Neuroscience suggests that human pain is a survival-oriented behavioral drive rather than an injury-caused aversive sensation
- EOS continuously modulates the transmission of nociception to promote survival
- Brain encodes pain salience, not pain intensity determined by survival-relevant context
- Pain system is a danger-detection system rather than a damage-detection system (Moseley)

CNS opioid and dopamine systems integrate pain with reward system



From Cahill et al, 2014

Brain's opioid and dopamine systems

- DA: in reward-driven actions-- "wanting"
Opioids: in hedonic tone-- "liking"
- These systems are integrated to modulate the valence (positive/negative) and salience (strong/weak) of pain
- DA encodes motivational salience of pain
 - whether pain should be endured for rewards
 - when pain has positive valence or low salience

Chronic pain as reward deficiency

- Chronic pain disrupts hedonic homeostasis, increasing relevance and reward of pain relief (Elman and Borsook)
- As persistent stress, chronic pain increases endogenous opioid tone, but decreases phasic changes in endogenous opioids in response to transient stressors.
- Similarly, exogenous opioid therapy initially induces pain relief, but then induces tolerance (to pain relief and mood elevation) and dependence (a need for opioids to avoid pain and distress).

Ms. B got relief from opioids

- Oxycodone provided relief of pain, insomnia, anxiety, agitation and anger
- But Ms. B kept needing more oxycodone, developing tolerance and dependence
- Opioids reduce hyperarousal, re-experiencing but deepen numbing and avoidance
- This leads to PTSD perpetuations

Human physical and social pain

- Human physical and social pain systems are linked because human physical survival is dependent on social survival
- Humans thrive in social cooperation, but must continually modulate disruptive stresses
- Endogenous opioids are crucial to this, and are disrupted by continuous exposure to exogenous opioid medications

Substances vs relationships

- As substance use deepens, relationships deteriorate
 - Does not require development full addiction, dependence may be enough
 - Opioids: “like being hugged by God”
- If substances are to be reduced, relationships must be recovered
 - Reach for the phone rather than pill bottle
 - But complicated restoration process in those with early, multiple or severe trauma

Tapering off long-term opioid therapy

- Opioid taper support trial subjects were
 - Surprised that their pain did not increase
 - Surprised they no longer felt like “zombies”
- Zombie= social/emotional dysfunction
Spouses confirmed return to old personalities
- Other research: opioid maintenance assoc w impaired emotion perception and ability to make inferences about social situations
 - Inability to discern sarcasm

Opioid therapy: pain relief or addiction?

- We can now understand that this standard framing of opioid policy is too simple and ignores what we have reviewed about EOS
- Many neuroadaptations and harms assoc. w continuous opioid therapy arise with the state of dependence, do not require addiction
 - Mass exposure only w ER/LA opioids since 1990's
 - High-dose patients may not be able to DC

Opioid dependence

- DSM-V Opioid Use Disorder is based on the idea that “opioid physiological dependence” and opioid addiction are completely distinct
- But social and emotional harms of opioids, like opioid-induced hyperalgesia, hypogonadism arise with dependence
- This dependence can arise with clinical use or non-clinical abuse, requires only sustained exposure

Ms. B: opioids to relationships

- Ms. B attempted opioid taper, but became too anxious, angry and overwhelmed
 - Opioids simulated safety too well
- She transitioned onto SL buprenorphine with improvement in her pain and anxiety
- Currently engaged in Cognitive Processing Therapy to address her PTSD and trauma
- Hopes to taper off opioids in the future

Human pain: between suffering and survival

- Human pain exists to promote both physical and psychological survival.
- Mammalian social pain system piggybacked onto physical pain system of non-mammals.
- EOS (+steroid, +dopamine) modulates the pain of both broken arms and broken hearts to promote species survival