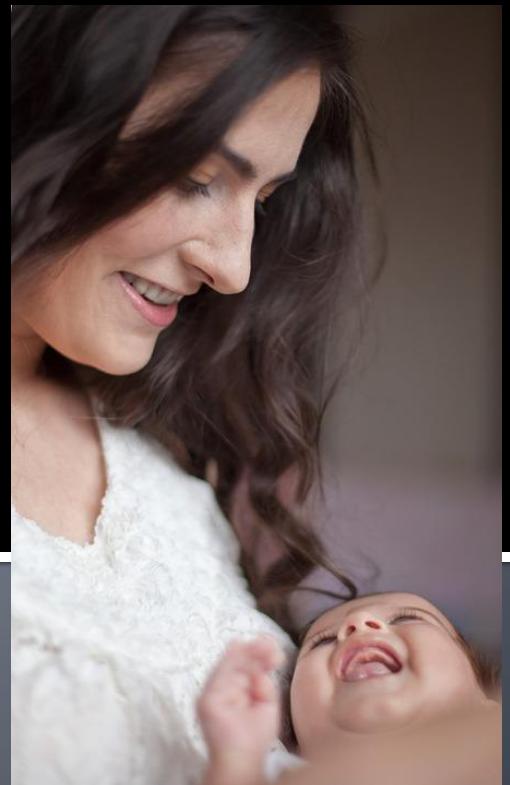
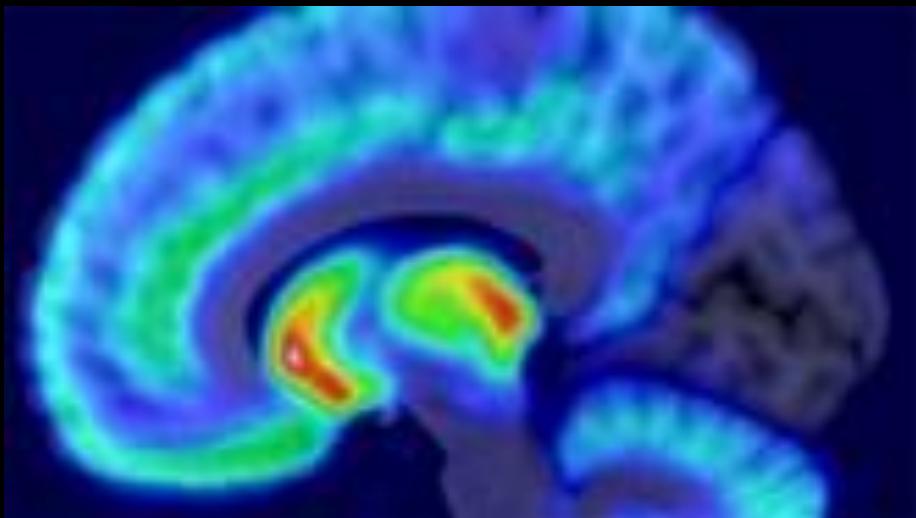


Pain and Opioids: damage and danger, mechanism and meaning



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Disclosures

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Descartes' sensory-mechanical theory of pain



- Usual errors cited:
 - Pain proportional to tissue damage
 - Only afferent neuronal activity relevant to pain
- Additional errors:
 - Why is the boy's foot in the fire?
 - What to do next?
 - Who will help?

Chronic pain is the problem

- Chronic pain prevalence
 - 15% of world population (Murray, Lopez, 2013)
 - 30% of US population, \$600B cost/yr. (IOM 2011)
- Chronic pain severity
 - 33% rate their chronic pain as severe (Breivik 2006)
 - 40% are not satisfied with their care (Johannes 2010)

My thesis:

Pain exists more to protect than to inform, so survival implications affect pain processing. The salience and valence of pain are continually adjusted to promote survival.

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 with 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: traditionally understood as a sensory problem

- IASP defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage."
- This aversive sensory experience can prompt a separate protective motor response, which can include reflexive withdrawal, splinting and resting of the painful body part, and avoidance of activities that can increase pain.
- This sensory understanding of pain implies that the pain experience must be reduced to reduce motor reactions (Sullivan and Vowles, 2017)

Pain as biopsychomotor problem

- Pain includes feelings and also behaviors:
 - Protective and communicative behaviors
 - Usually considered consequences not integral
- “without a pain behavior system there would be no adaptive value to the pain signal itself”
 - “as adaptive as a fire station without firemen”
- Biopsychomotor; “sensory component is accompanied by a behavioral system”
(MJSullivan, 2008)

Pain behavior: effect and cause

- CRPS-1: Chronic regional pain syndrome
 - exquisitely painful disorder of limb
 - loss of sensorimotor integration
 - distorted body representation
 - learned neglect and disuse
- Pharmacological, procedural, psychological treatment effective only if it promotes use of affected limb for intentional action

Opioids for injured workers failed

- Clinicians have long hoped that reducing pain of injured workers with opioids would promote rehabilitation and return to work.
- Unfortunately, multiple prospective cohort studies have shown that early opioid therapy decreases the likelihood of an injured worker with back pain returning to work. (Franklin 2008)
 - A national study of early opioid therapy that adjusted for injury severity, demographic characteristics, and job tenure found an opioid dose-related increase in the duration of job disability. (Webster 2007)
- The deactivating effect (physical, social) of opioids appears to be more potent and important in injured workers than the chronic pain relieving effect. (Deyo, 2015)

From pain to salience neuromatrix

- OLD Melzack: pain intensity encoded in distributed neuromatrix of brain centers
- NEW Legrain: these brain centers more properly considered a multisensory salience network activated not just by nociception, but also by visual, auditory etc. stimuli that provide the context determining *relevance of nociception to organismic survival*
- Borsook: “pain is not a purely sensory experience”

From sensory-specific to action-specific cortical network

- Legrain: “Under the assumption that this (salience) network acts as a defensive system signaling potentially damaging threats for the body, emphasis is no longer on the quality of the sensation elicited by noxious stimuli but on the action prompted by the occurrence of potential threats.”
- In this salience-focused approach, the purpose of the network is not to produce a sensation of some specific intensity but to produce effective threat-defusing action.

Patient action as means and end in chronic pain care

- Expanding available repertoire of patient action in the presence of pain is a viable goal for chronic pain treatment
 - Pain intensity is often the last thing to improve in successful chronic pain treatment
 - Increasing opportunities for purposive action by patients may alter pain salience
- Fordyce: “people who have something better to do don’t suffer (hurt) as much”

From psychomotor to enactive model of pain

- Perception as enactment not representation: pain serves action and is shaped by it
 - pain $\leftarrow \rightarrow$ action, not pain \rightarrow behavior
- Enactivism argues that cognition arises through a dynamic interaction between an *acting* organism and its environment. It claims that our environmental niche is one which we selectively *create* through our capacities to interact with the world.

Pain perception as action— active not passive process

- Noe: "...perceiving is a way of acting. Perception is not something that happens to us, or in us. It is something we do."
- "The world makes itself available to the perceiver through physical movement and interaction.... Only through *self-movement* can one *test* and so *learn* the relevant patterns of sensorimotor dependence."
- "...when we perceive, we perceive in an idiom of *possibilities for movement*."

What's wrong with pain in the brain?



- “Experience is not caused by and realized in the brain, although it depends causally on the brain. Experience is realized in the active life of the skillful animal.”
- “...my brain is affected not only by what happens to me; by sights, sounds, odors, etc. What I do also brings about changes in my brain.”
- Pain arises from active animal w active brain

Evidence for active brain in attention to pain

- Kucyi and Davis 2015:
- “Given that pain is intrinsically salient, it can dramatically affect behavior. Conversely, attention-demanding tasks, stimuli, and thoughts can alter the quality and salience of pain and neural processing of nociceptive input. Thus, pain and attention mutually influence one another.”
- “Regardless of noxious stimulation level, pre-existing brain states determine what level of pain will subsequently be perceived and whether near-threshold stimuli will be perceived as painful or not”

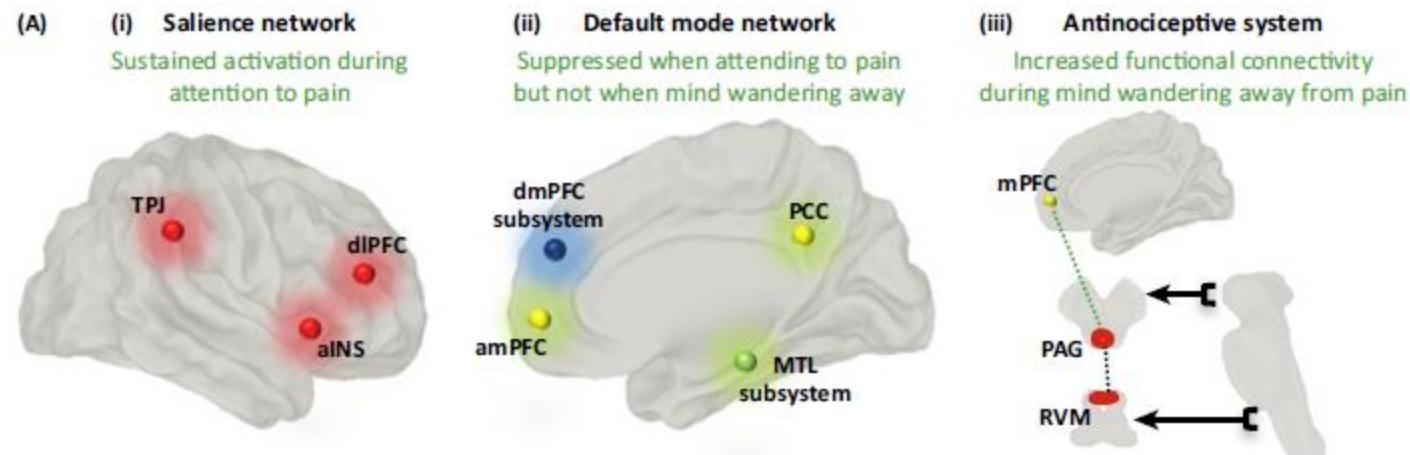
Mind wandering from pain: variable salience of pain

fMRI reveals 3 brain systems involved in pain attention:

Salience network: aINS, MCC, TPJ, dIPFC

Default mode network: PCC, precuneus, mPFC, lat and med parietal

Descending pain modulation network: PAG, RVM



Kucyi and Davis, 2015

Most nociception does not produce pain

- Baliki/Apkarian: “One commonly forgets the fact that most humans... spend most of their lives free of pain and with no obvious tissue injuries. This must be ascribed to active nociceptors, because there are no other alternative neuronal mechanisms available to continuously protect the body and subvert the potential for injury and resulting pain perception.”
- “acute pain is not a warning signal but rather is the failure of the machinery (nociceptor activity) designed to avoid pain.

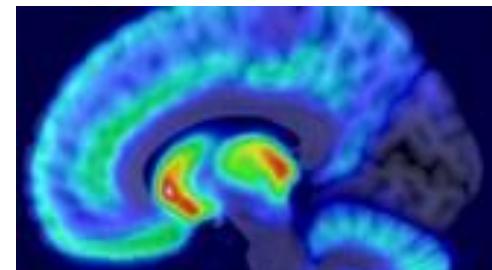
Danger/safety overrides damage: valence of pain is variable

- Danger/safety/reward can override damage
 - "...conscious acute pain perception is highly malleable and a standardized nociceptive barrage does not translate into a fixed brain activity or to a prototypical perception."
- Consider when nociception signals reward
 - "for rodents...food trumps pain-related escape behavior when both are simultaneously present"
 - "Pavlov was able to train his dogs to salivate for painful stimuli"



Pain's protective function extends to other negative emotional states

- Pain motivates injury avoidance and healing behaviors in the immediate body vicinity
 - Anxiety is as an emotional state with sympathetic arousal that promotes safety within relatively short time and space scales.
 - Depression is a more global generalization of perceived averseness to one's environment.
- B+A: "Overall, there seems to be a remarkable overlap between the brain structures that either impart vulnerability or are affected by pain chronification and pathological negative moods. It is therefore not surprising that these conditions are often comorbid..."



Nociception → pain → chronic pain: similar processes

- “Long-term shifts in the threshold mechanisms that gate the conversion from nociception to pain also underlie the transition to chronic pain. We further propose that the threshold shift is dependent on... a lowered mesolimbic threshold for the conscious perception of pain”
- “Ventral striatal circuitry links nociception, acute pain, and chronic pain. This circuitry assesses salience of impending pain as well as expected reward value for relief of pain.”

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-affect 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)

Pain: enactive and protective

- Enactive pain
 - Pain perception is an active process. It arises through and serves action promoting survival.
- Damage-danger protection
 - Nociception is received by an active brain that is processing other survival-relevant inputs
 - Nociception, acute pain, chronic pain support a continuum of protective feelings and actions that include anxiety and depression

From pain theory to clinical care

- What relevance does this discussion of pain mechanisms have for clinical care and policy?
- Does this discussion help us understand and address the opioid epidemic?
- Turn back to Ms. B and her fibromyalgia...

Centralized and generalized pain: fibromyalgia

- Altered CNS nociceptive processing similar to IBS, IC, TMD, tension HA (Clauw 2014, 2015)
- Increased activation on fMRI: salience network, secondary somatosensory cortex... (Kutch 2017)
- Increased connectivity between insula and default mode network, proportional to pain
- Elevated substance P, NGF, glutamate in CSF
- Reduced conditioned pain modulation
- Endogenous opioid tone increased
 - More tonic, less phasic opioid release

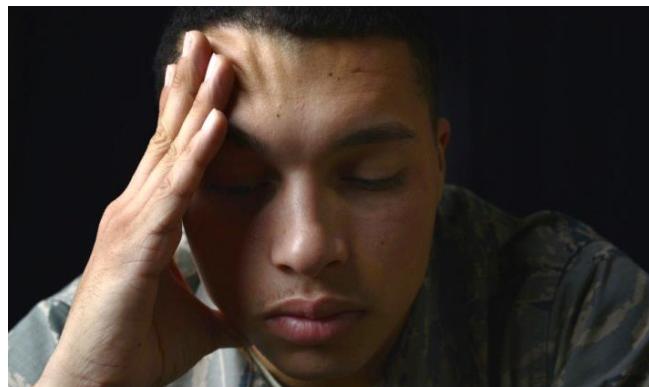
Ms. B has been psychologically traumatized by her MVA



- 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

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+: linear association with wide range of chronic 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 sxs. (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 a decade before her MVA



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 (salience network) (Eisenberger 2003)
- 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 (Eisenberger 2006)
 - 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

- 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



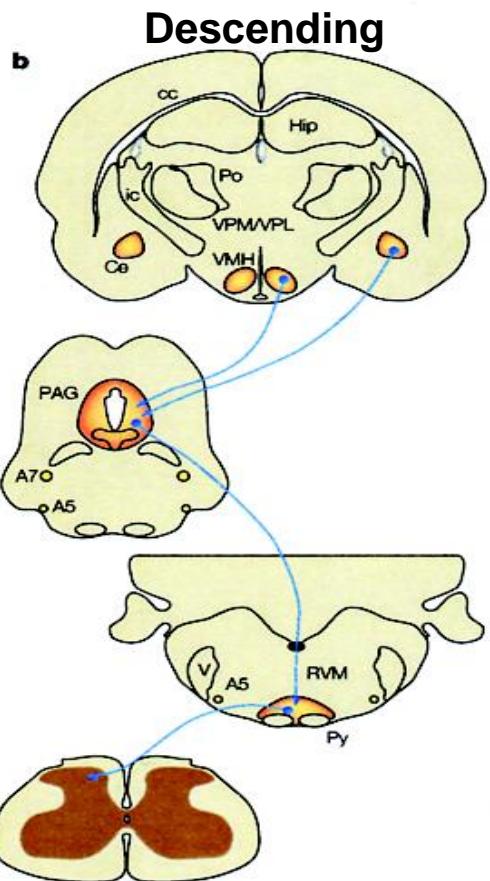
Endogenous opioid system (EOS) throughout animal kingdom

- 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 (EOS) throughout animal kingdom

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

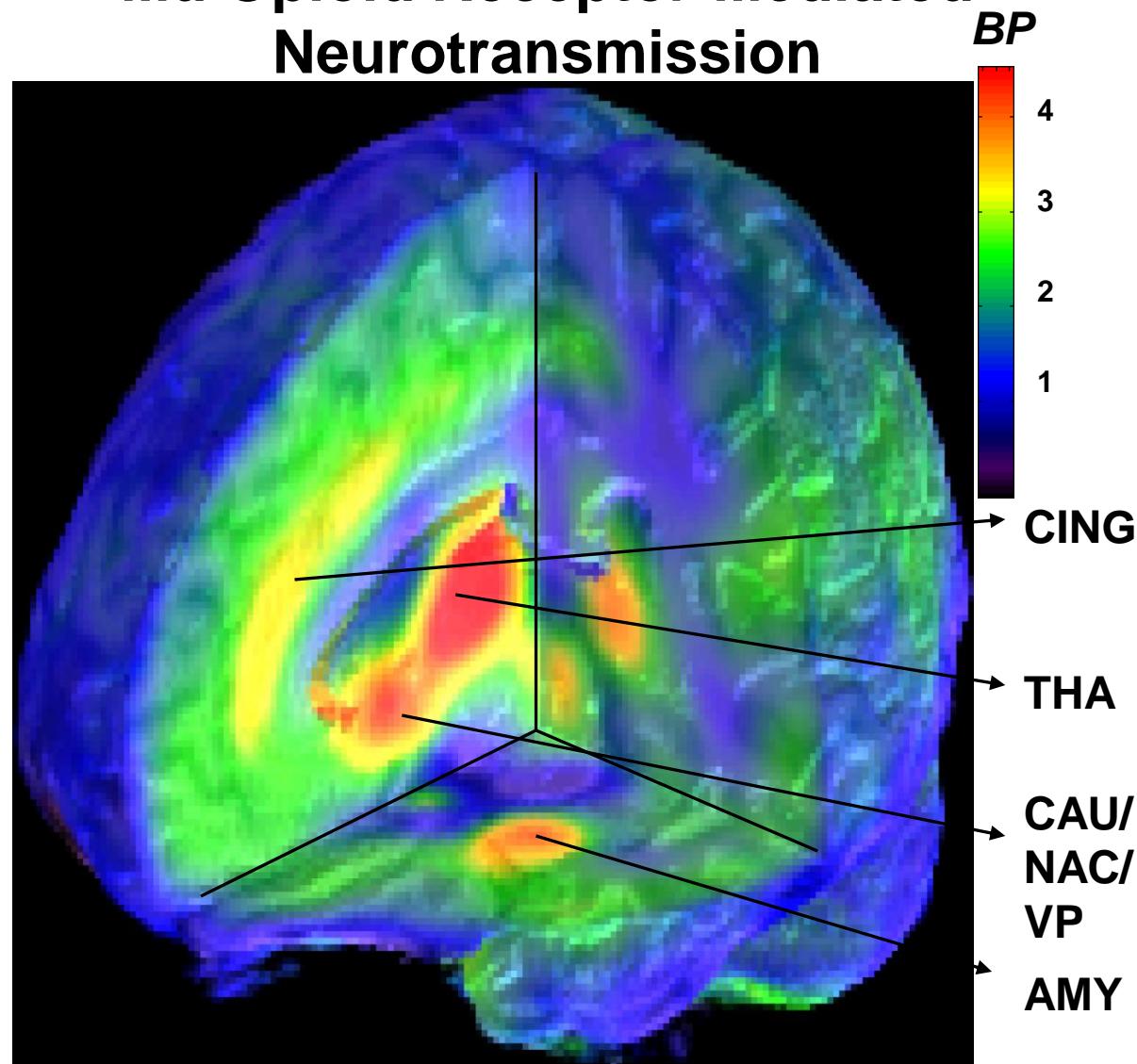




Distributed in pain regions but also “affective / motivational circuits” - neuronal nuclei involved in the assessment of stimulus salience and cognitive-emotional integration.

CNS Inhibitory Controls

Mu Opioid Receptor-Mediated Neurotransmission



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 required 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 (safety)
 - “heroin is like being hugged by God”

Psychological trauma and opioids

- Opioid use increased among FM patients with history of physical or sexual abuse (Alexander 1998)
- Adverse childhood experiences associated with increased prescription medication use and psychotropic medication use (Anda 2007, 2008)
- Childhood trauma shows dose-response relationship to adult opioid use, misuse, injection drug use (Austin 2018, Quinn 2016)
 - Emotional abuse, physical abuse → 1.5x rx opioid use
 - Neglect, emotional abuse, parental incarceration, binge drinking → 25-55% increased opioid misuse
 - Sexual abuse, witnessed violence → 3-5x incr. inj. use

Opioids as stress modulators

- Targeted rejection events (e.g., fired, broken up)
 - assoc. with 22x increase in depression (Kendler 2003)
 - MDE patients show MOR deactivation but controls show MOR activation in amygdala (Hsu 2015)
 - These social rejections are a threat to physical survival for intensely social primates (Holt-Lunstead 2015)
- SNP in OPRM1 increases sensitivity to physical pain and social rejection (Slavich 2014, Way 2009)
 - G allele carriers need more opioids after surgery, tend to fearful adult attachment (Sia 2013, Troisi 2012)

Opioids vs steroids in the CNS

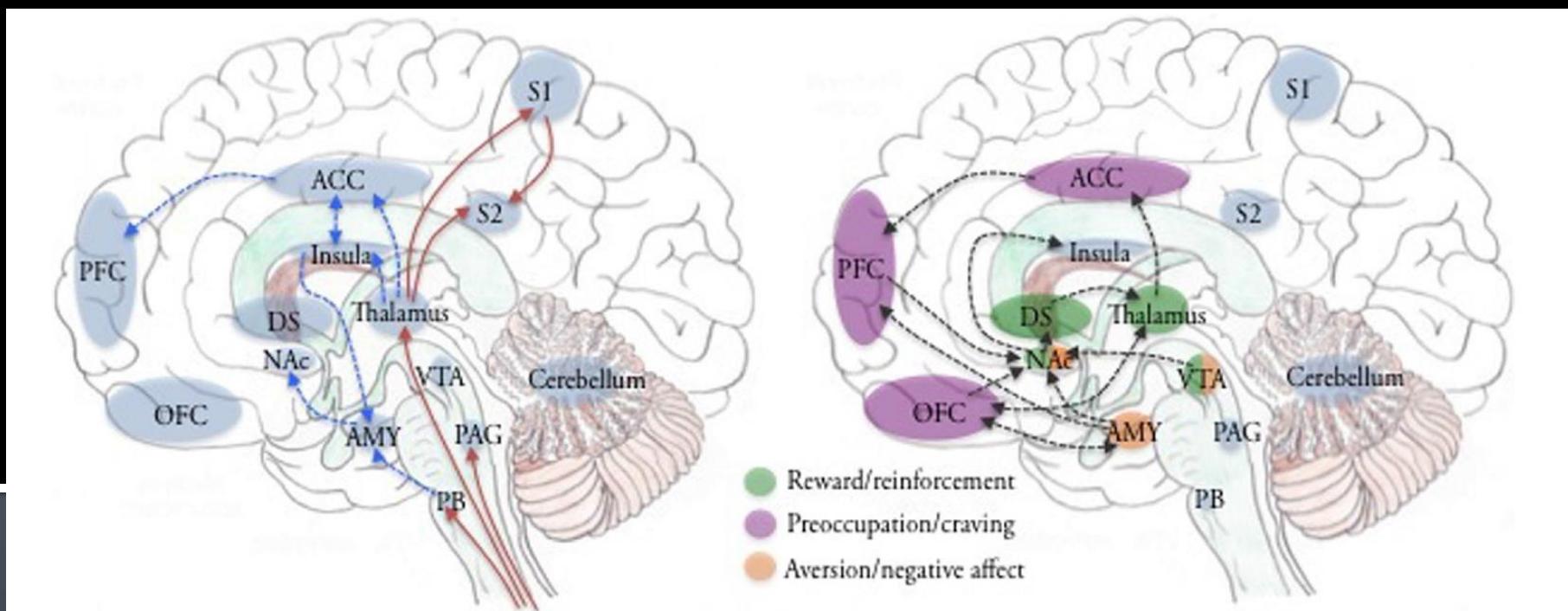
- CRF coordinates autonomic, behavioral, and cognitive response to stress w endocrine syst.
- In acute stress, CRF acts on LC to increase arousal, attention, behavioral flexibility
- EOS has opposite effect on LC, helps neurons and organism recover after stressor is gone
- With chronic stress (PTSD),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

OPPIOIDS VS. STEROIDS

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) as determined by survival-relevant context

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 perpetuation

Human physical and social pain

- Human physical and social pain systems are linked because human *physical survival* is dependent on *social survival* (Wilson 2012)
- Humans thrive in social cooperation, but must modulate disruptive stresses
- Endogenous opioids are crucial to social cooperation, but are disrupted by continuous exposure to exogenous opioid medications

Substances vs relationships

- As substances increase, relationships decrease
 - Does not require development full addiction, dependence may be enough
 - Opioids provide illusion of safety
- To reduce substances, recover relationships
 - Reach for the phone rather than pill bottle (AA)
 - But complicated restoration process in those with early, multiple or severe trauma (trust, safety)

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

- Pain is the product of an active brain in an active organism
- Human pain is a survival oriented behavioral drive that 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