The evolution of the science of chronic pain: from the gate control theory to central sensitization

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Dr Ballantyne has no conflicts of interest or disclosures

Before Descartes

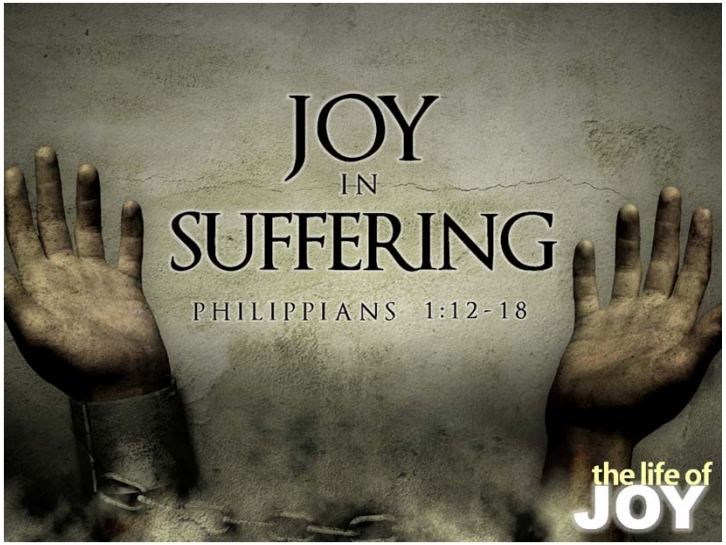
Pain produced by external events

“Make me fully understand that the ills of the body are nothing else than the punishment and the encompassing symbol for the ills of the soul. O Lord, let them be the remedy, by making me aware, through the pain that I feel, of the pain that I did not feel in my soul, deeply sick though it was and covered with sores. ….

Blaise Pascal “Priere pour demander a dieu le bon usage des maladies” prayer circa 1659

….Because, Lord, the greatest sickness is insensibility … Let me feel this pain sharply so that I can make whatever is left of my life a continual penance to wash away the offenses I have committed.”

Blaise Pascal “Priere pour demander a dieu le bon usage des maladies” prayer circa 1659

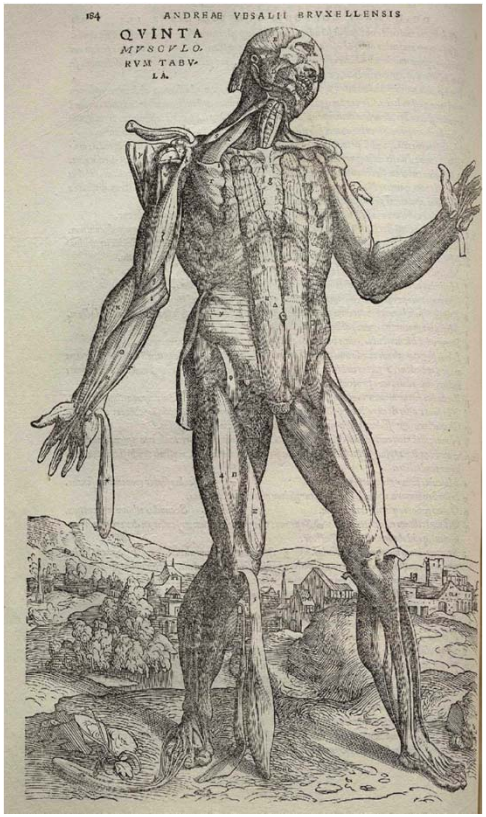


L'*homme de Rene Descartes*. Paris: 1664

Pain carried in a line labelled system

- Early reductionist view
- First to describe pain as a perception, existing in the brain
- Distinguished from sensory transduction

Roman times Galen demonstrating nerves



1543 Vesalius
De humani corporis fabrica
Detailed images of brain and peripheral nervous system

Towards a reductionist view of pain

Until Descartes, external events caused pain

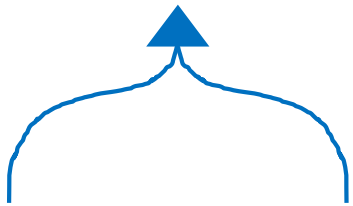
Digging deeper and deeper into micro events

Relationship

Impersonal, mechanistic terms

Focus on nociception

Encompassing yet transcending micro events



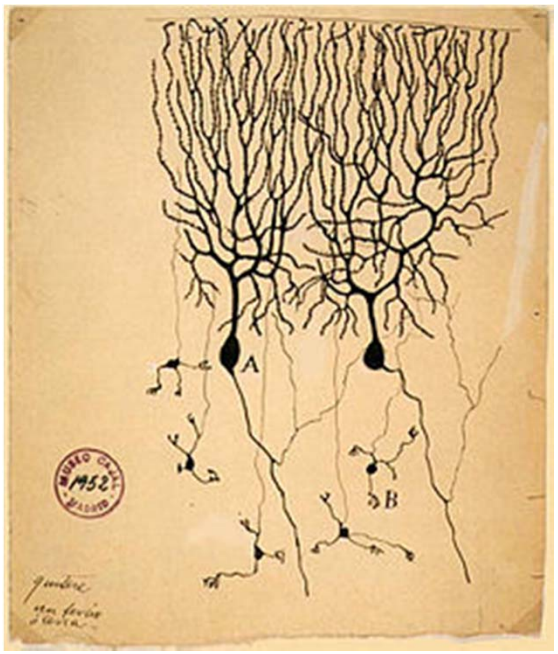
dimension

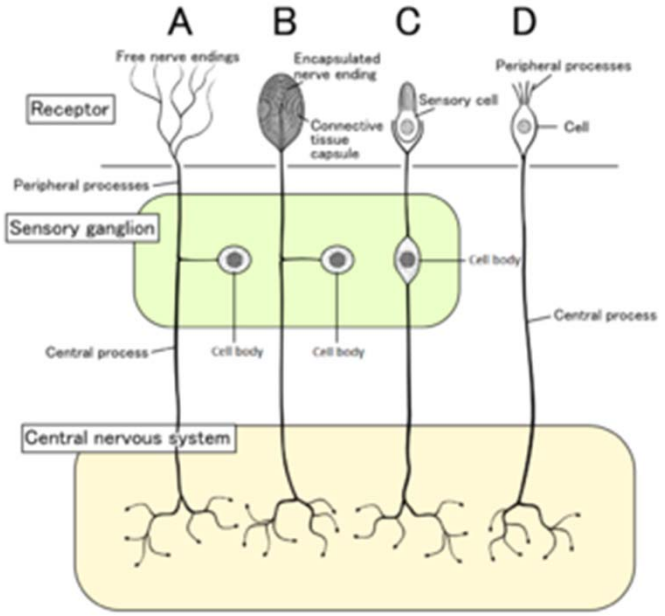
Group processes

Family, job, culture

Public health, community base, teams, system

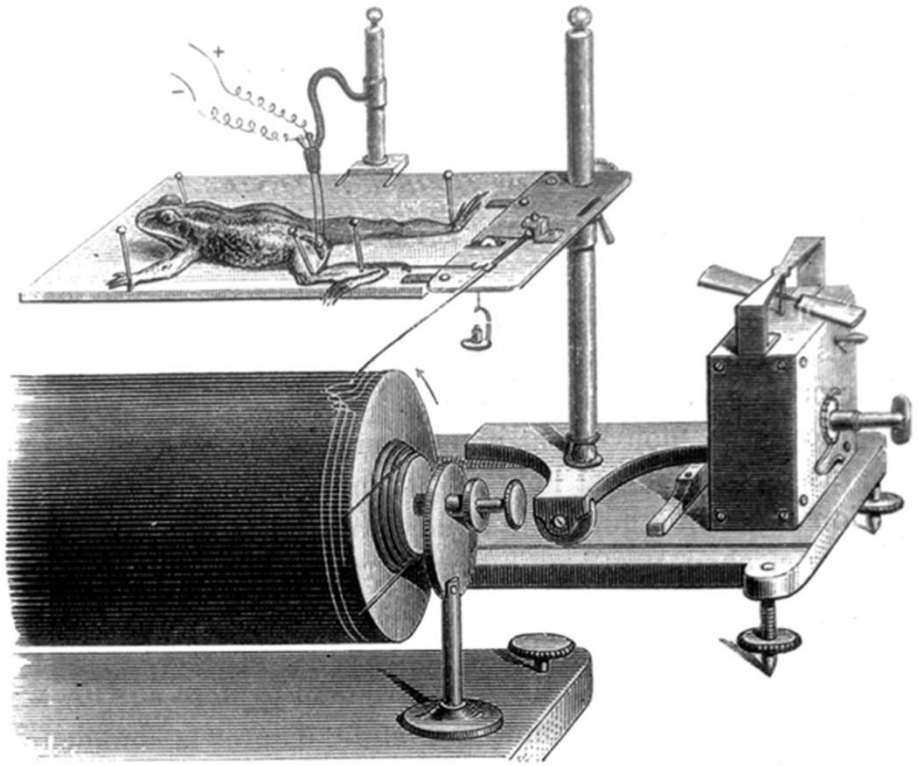
1837 Purkinje Microscopy opened up a whole new understanding progressing beyond a crude understanding of neural anatomy



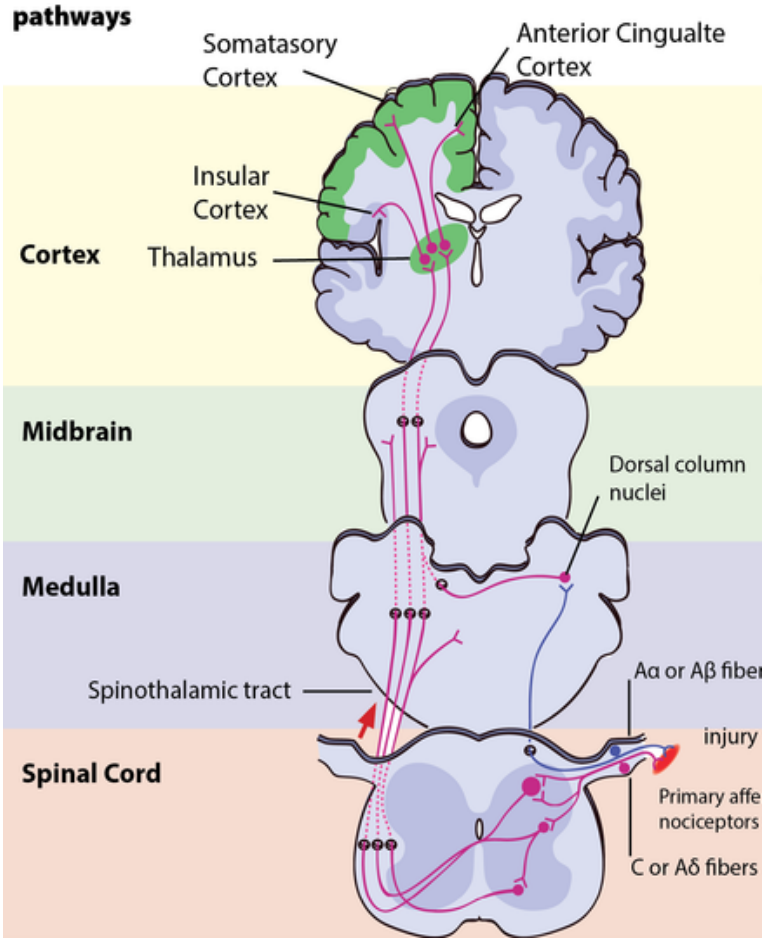


1906 Sherrington The Integrative Action of the Nervous System

Discussed neuron theory, the ’synapse’, the communication between neurons and a mechanism for ‘reflex arc’ function



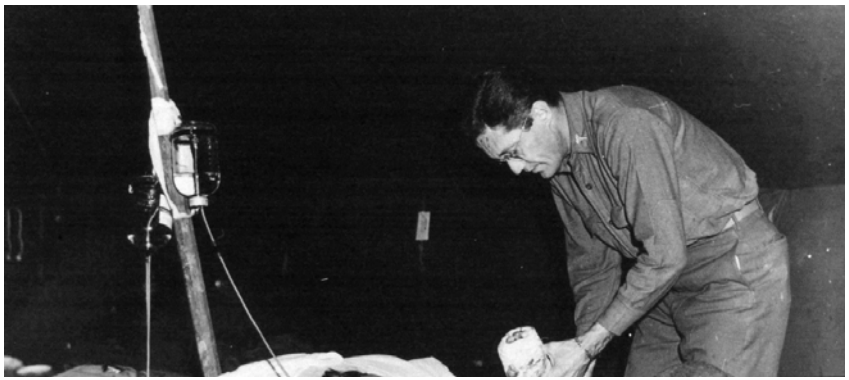
Pain Processing Pathways



Henry Beecher and John Bonica

1940s-1960s

- Reminded us that context plays a major role in the experience of pain
- Identified the important role of placebo
- Identified stress induced analgesia

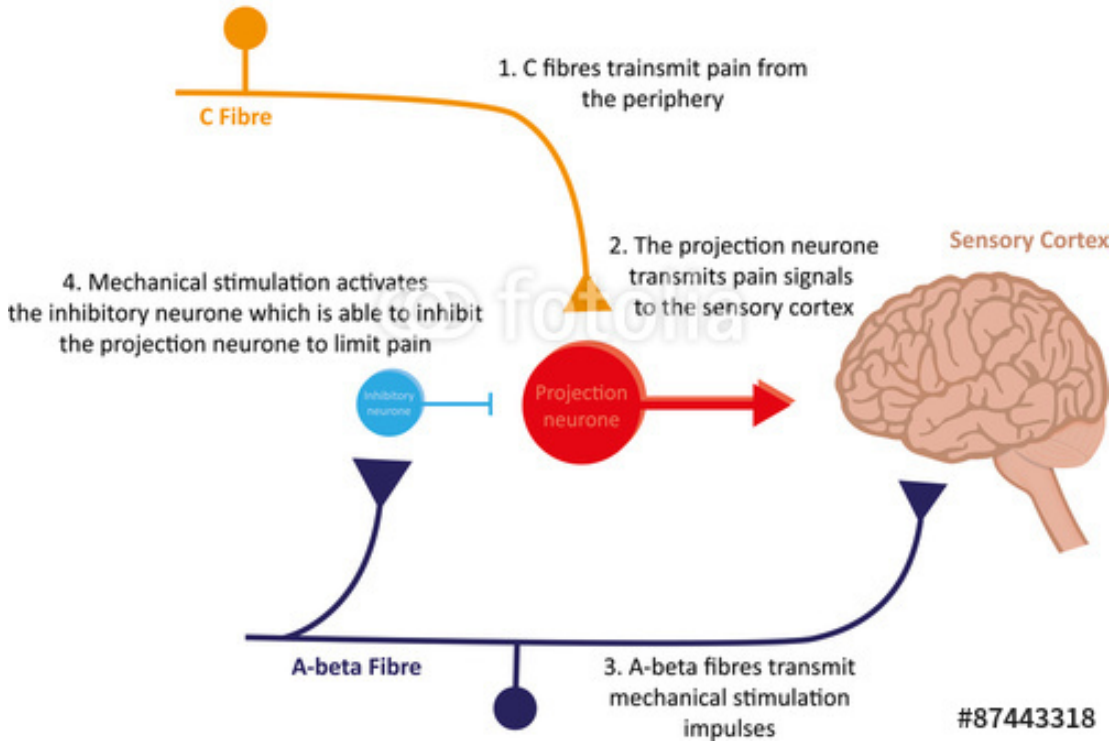


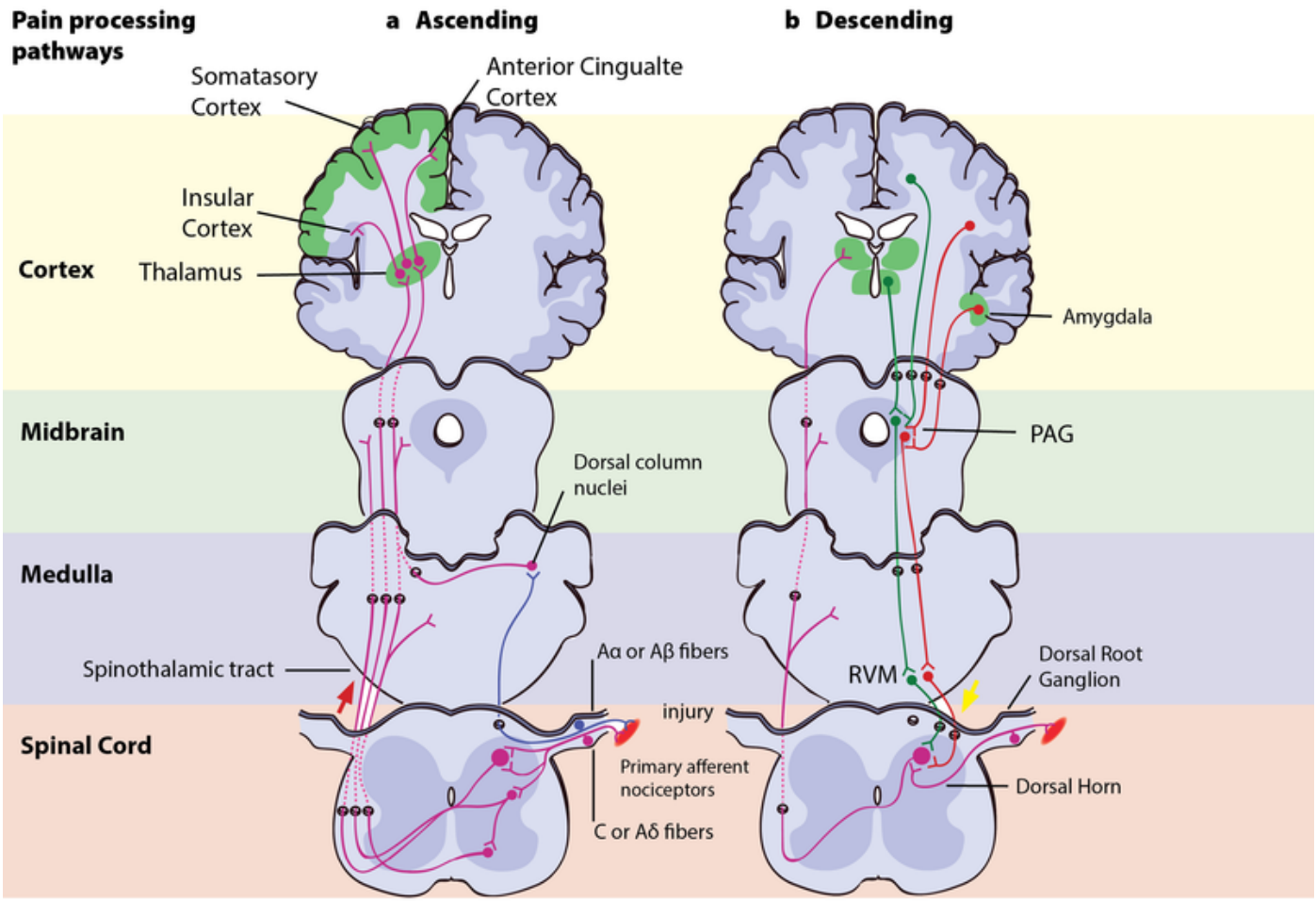
Ronald Melzack and Patrick Wall

1965

- Gate control theory of pain
- Pain not transmitted along a line-labelled system
- Pain neuroplastic
- Pain altered by stress – stress induced analgesia

Gate Control Theory of Pain




Pain processing pathways
a Ascending
b Descending
Somatasory Cortex
Anterior Cingualte Cortex
Insular Cortex
Cortex
Thalamus
Amygdala
Midbrain
PAG
Dorsal column nuclei
Medulla
Spinothalamic tract
Aα or Aβ fibers
RVM
Dorsal Root Ganglion
injury
Spinal Cord
Primary afferent nociceptors
Dorsal Horn
C or Aδ fibers

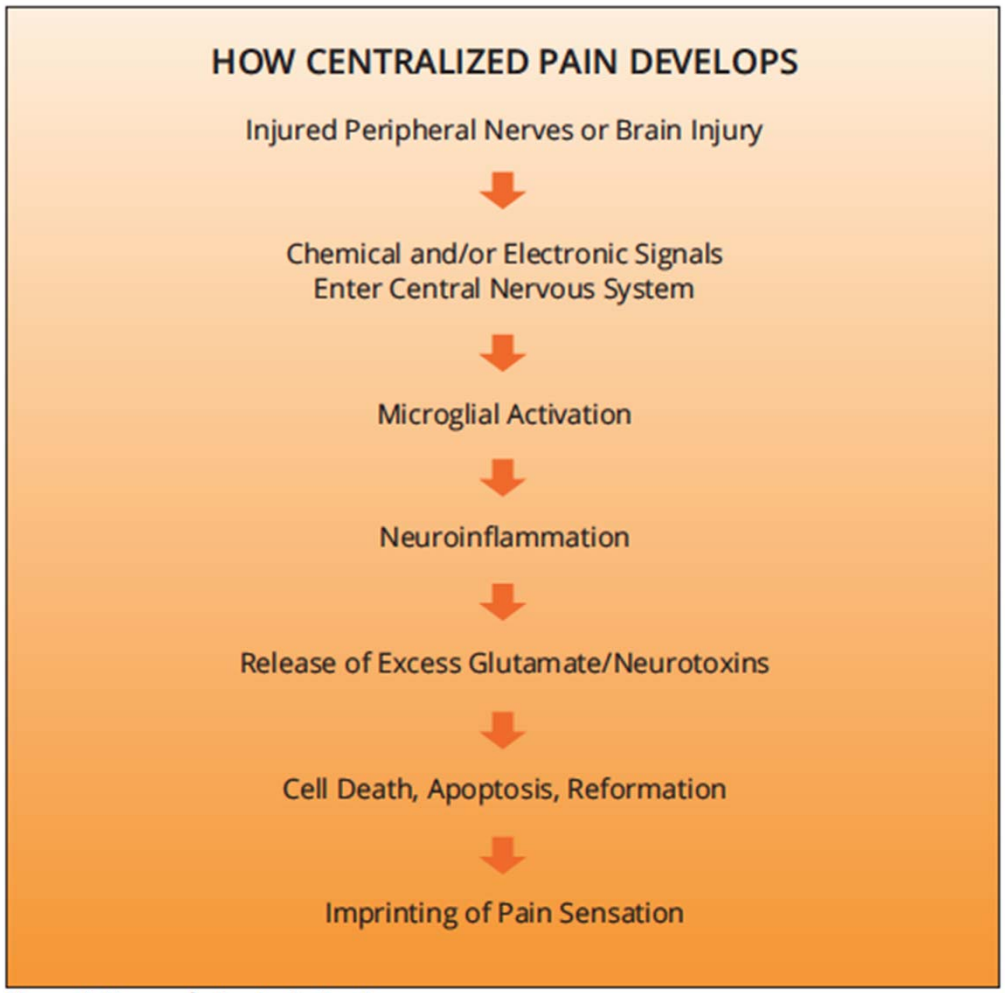
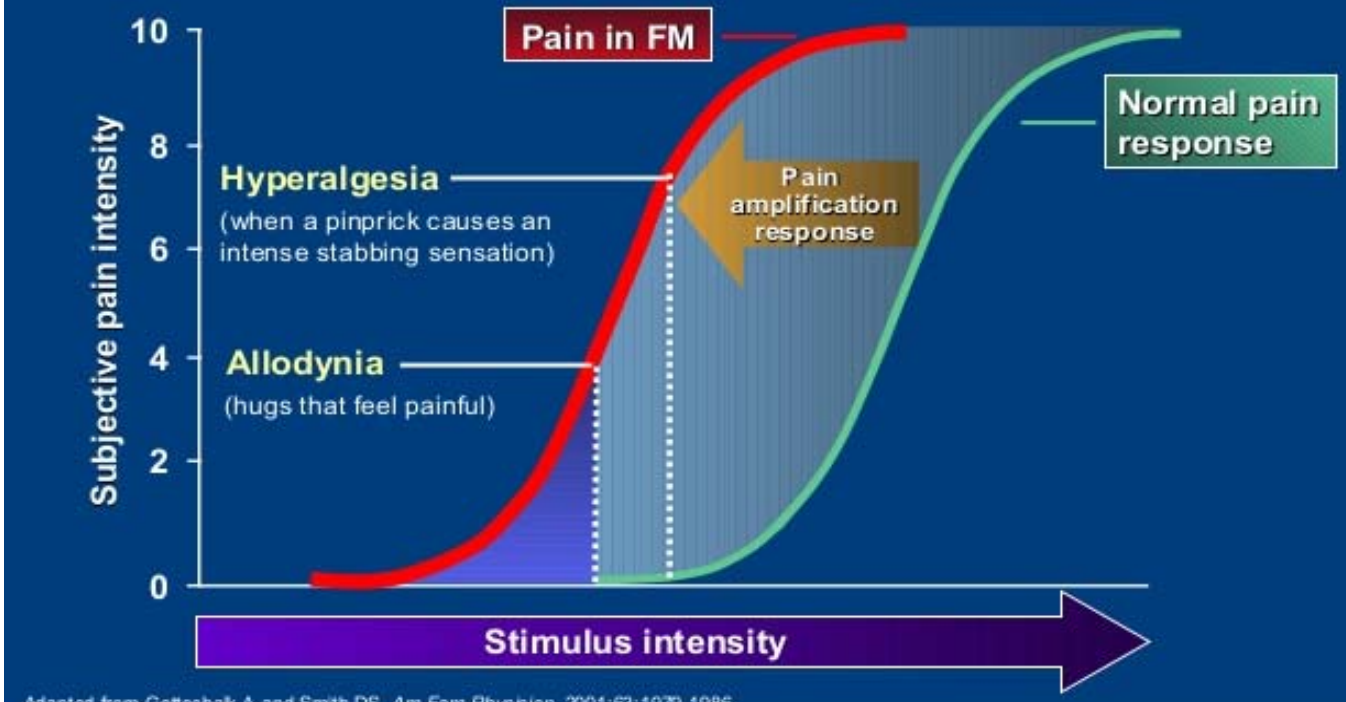


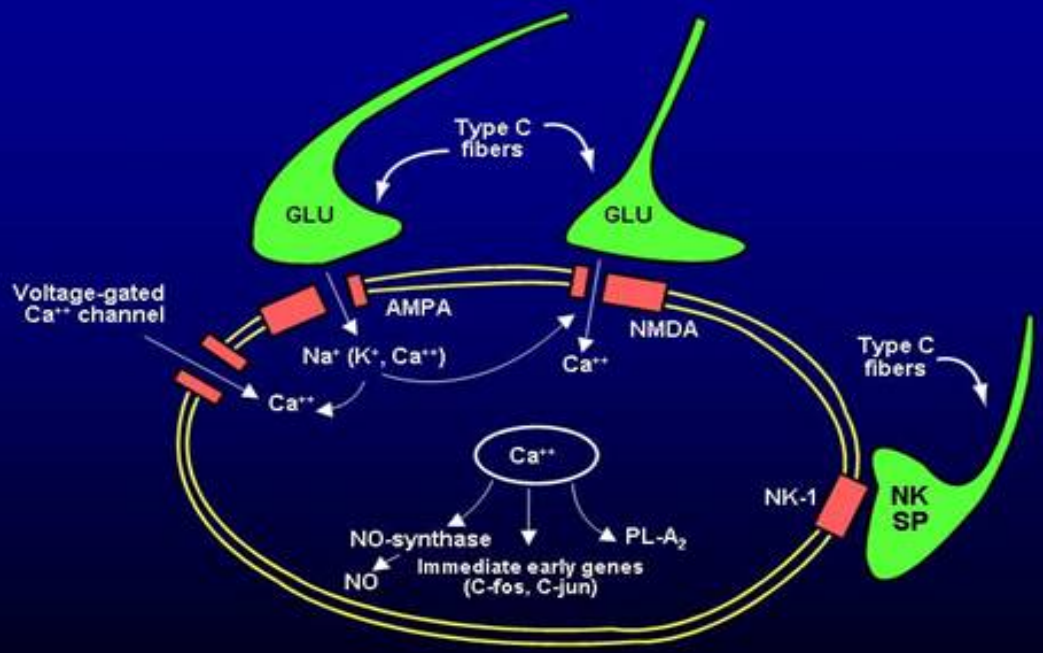
Figure 1. How centralized pain develops.

FM: An Amplified Pain Response



Adapted from Gottschalk A and Smith DS. *Am Fam Physician*. 2001;63:1979-1986.

Central Sensitization



Ollat H, Cesaro P (1995), Clin Neuropharmacol 18(5):391-404

Expanding our view of pain

Digging deeper and deeper into micro events

Encompassing yet transcending micro events

Until Descartes, external events caused pain

Anatomy of pain not understood

Mi

Relationship to er tood

Reductionist starting point

Impersonal, mechanistic terms

Focus on nociception

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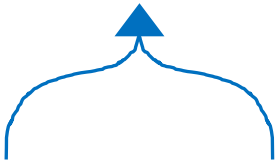


Imp ial dimension

Isolation, withdrawal, distress

Group processes

Family, job, culture

Public health, community base, teams, system

Reductionist viewpoint

- Subcellular and cellular scale
- Aberrant ion channel expression
- Cellular processes
- Neurotransmitters, ion channels, ligand-receptor interactions

Microscale events culminating in the action potential

Drives mechanism based treatment with a focus in nociception

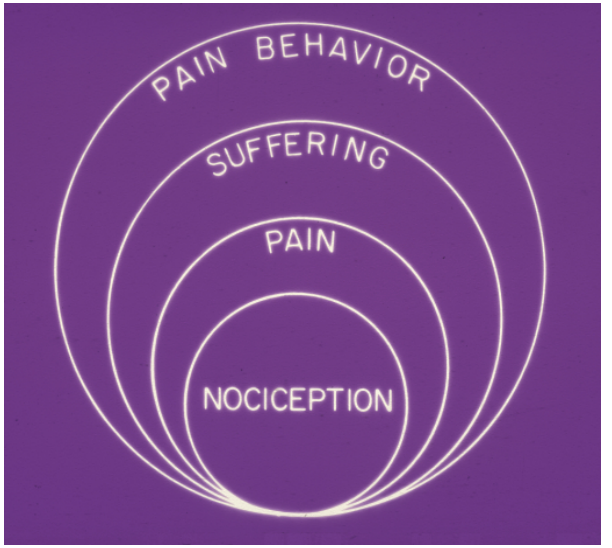
Top down viewpoint

- Dysphoric social dimension
- Contributes as much as nociception
- Accepts that mechanisms at the cellular level have evolved through evolutionary processes over millions of years

Encompasses yet transcends microscale events

Drives community based approaches, public health, healthcare systems

- Pain SOCIOpsychobiological not BIOpsychosocial?



Taken from "Flipping the Pain Curriculum: biosychosocial to sociopsychobiological" D B Carr

… my love had gone away and left me standing here in a puddle of grief.

My world yesterday had the lightness and glossy tension of a freshly inflated party balloon; now, today, with her gone, everything was suddenly slack, and tacky to the touch. Anguish, this constant, unremitting anguish, made me tired, terribly tired, yet I did not know how I might rest. I felt dry all over, dry and hot, as if I had been scorched, and my eyes ached and even my fingernails pained me.

Ancient Light, John Banville Alfred A Knoff, NY 2012

fMRI and biochemical measurement

- Dysphoric social dimension
- Isolation, withdrawal, distress
- Contributing as much as nociception

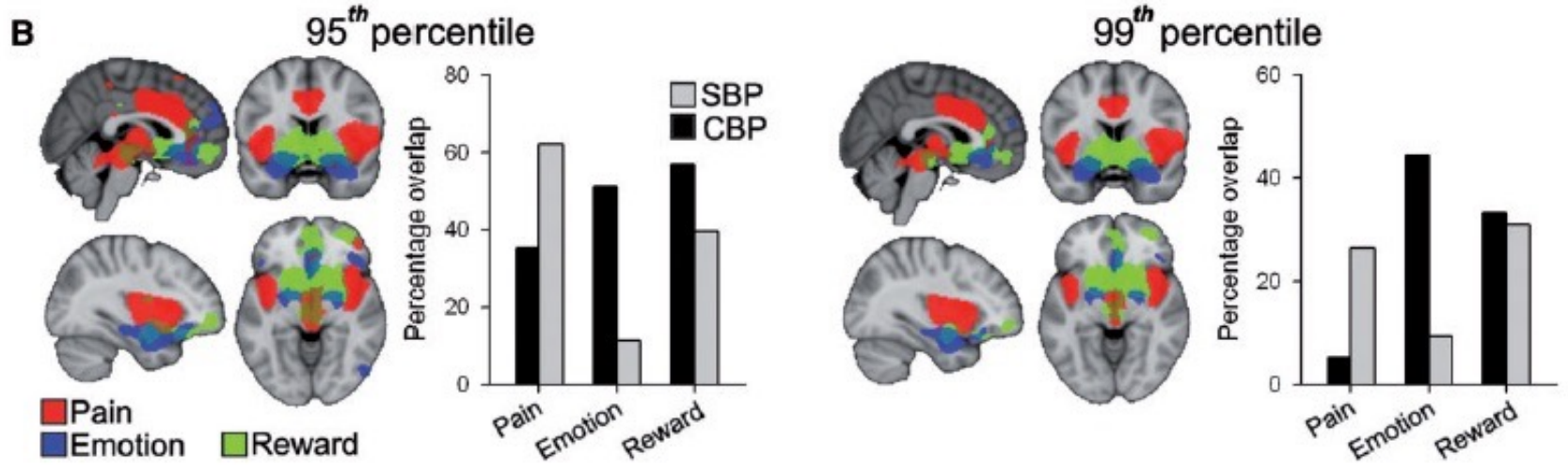
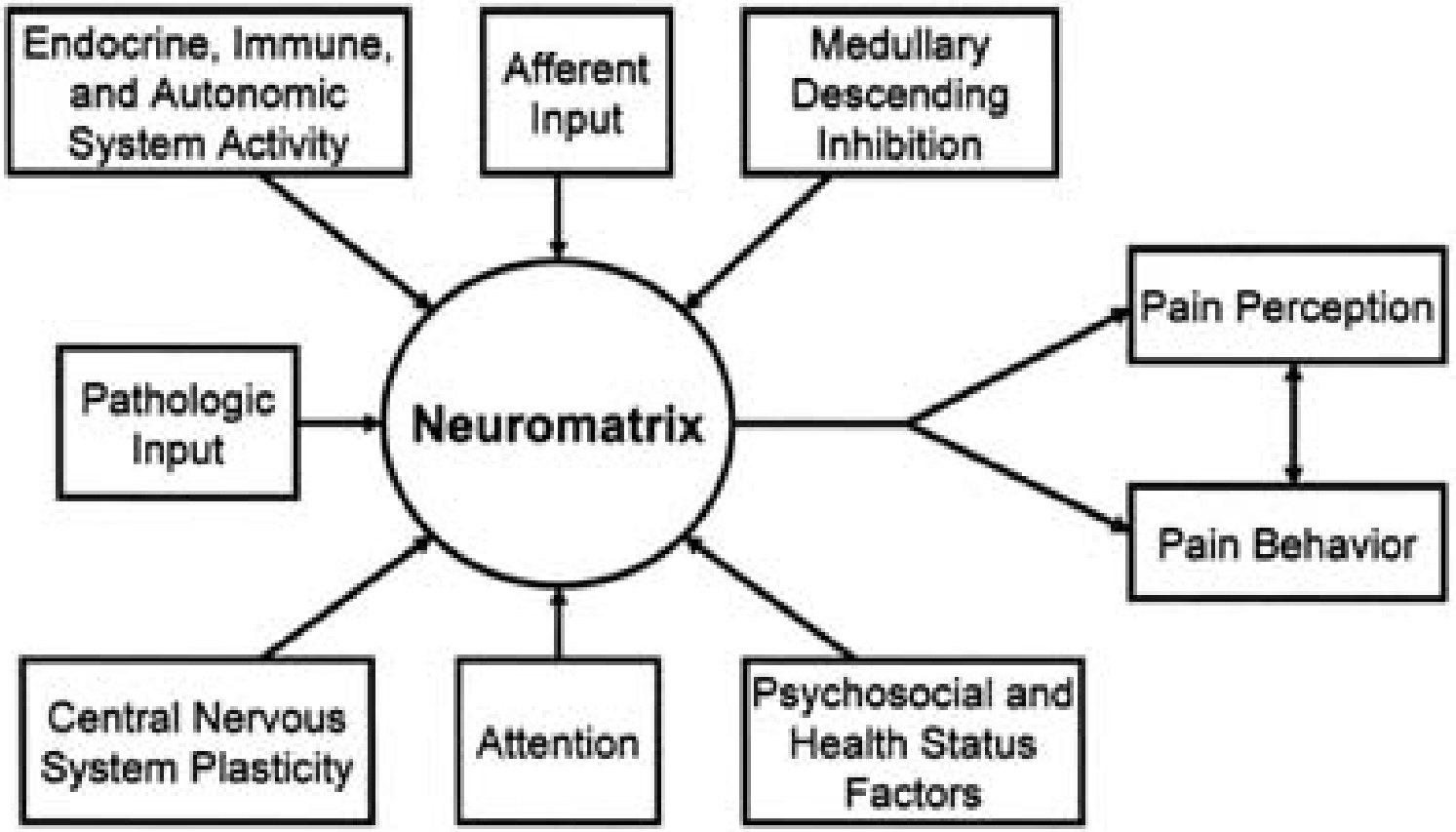
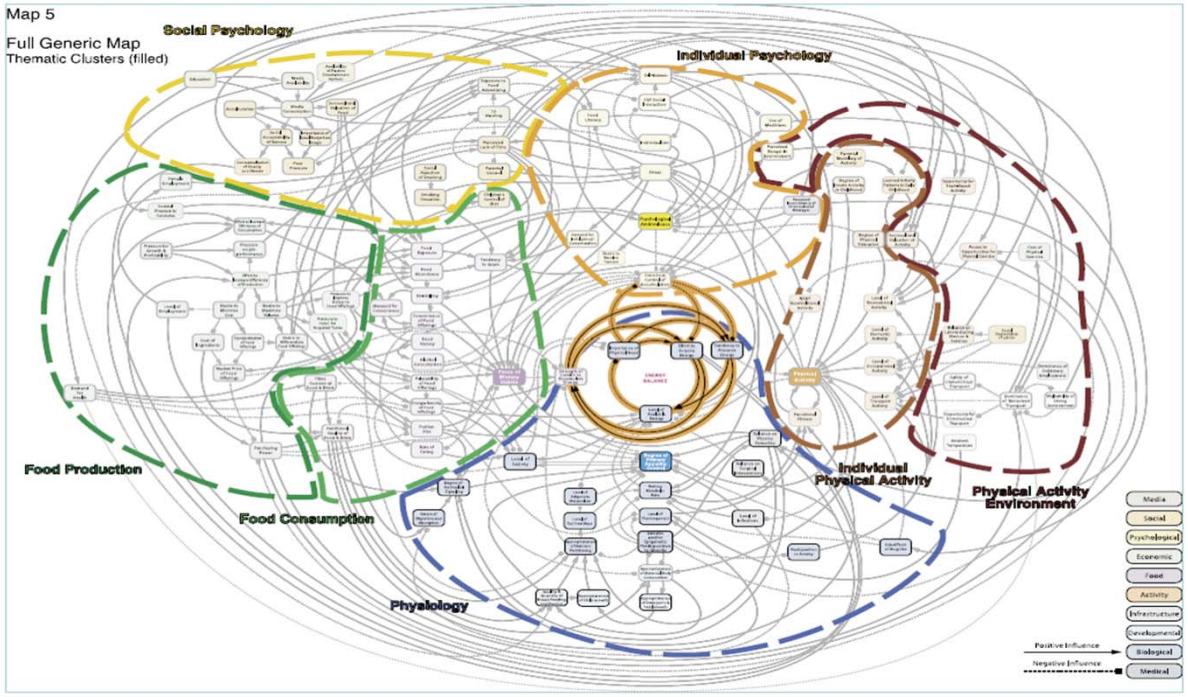


Figure 2 Early SBP (SBPe) and CBP activation maps correspond to distinct meta-analytic circuits. (**A**) Brain meta-analytic maps for the terms: pain, emotion and reward, from Neurosynth (Yarkoni *et al.*, 2011). (**B**) Brain images represent masks derived from maps above at different thresholds (top five and one percentile voxels) for pain (red), reward (green) and emotion (blue) meta-analytic maps. Bar graphs represent the % overlap for CBP (black) and early SBP (grey) with the three meta-analytic maps at the 95th and 99th percentile thresholds. Overall SBP activity is more similar to the pain term related mask, whereas CBP activity is similar to emotion term related mask. Activity in both groups engage parts of the reward mask. (**C**) Brain images show the overlapping (yellow) and non-overlapping (blue) voxels for early SBP (*top* row) and CBP (*bottom* row) with the 95th percentile thresholded meta-analytical masks. Early SBP overlaps with pain mainly in bilateral insula, thalamus and anterior cingulate cortex (ACC), whereas CBP overlaps with emotion in bilateral amygdala and medial prefrontal cortex (mPFC).


Endocrine, Immune, and Autonomic System Activity
Afferent Input
Medullary Descending Inhibition
Pathologic Input
Neuromatrix
Pain Perception
Pain Behavior
Central Nervous System Plasticity
Attention
Psychosocial and Health Status Factors

Systems Map (Obesity)

Figure 5.2: The full obesity system map with thematic clusters (see main text 5.1.2 for discussion)[17,18] Variables are represented by boxes, positive causal relationships are represented by solid arrows and negative relationships by dotted lines. The central engine is highlighted in orange at the centre of the map.



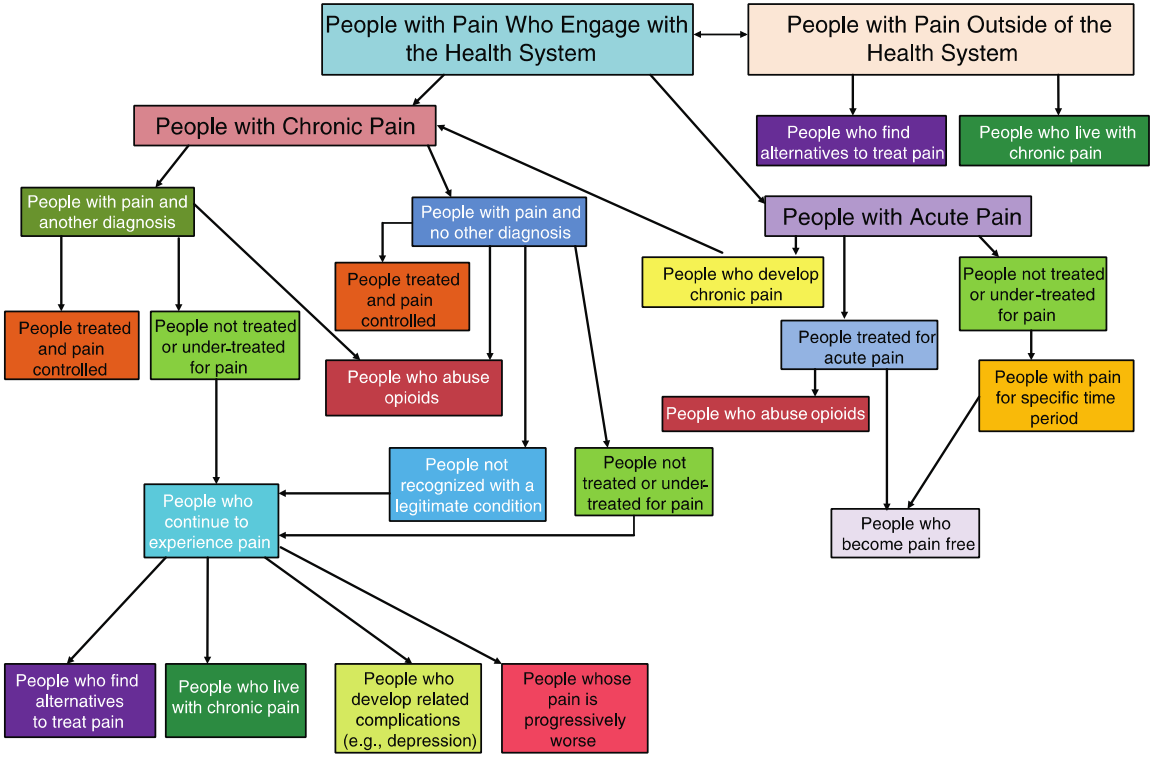


FIGURE 1-1 The picture of pain.
NOTE: People can move between and among these groupings and can be in more than one group simultaneously. Similar colors represent similar endpoints (e.g., for those within or outside the health system, or for those with chronic or acute pain).

So what about opioids?

A human activity since Sumerian times

5000 BC

1803-1805
Morphine first isolated
Friedrich Serturner

1827 marketed by Merck

OPIUM

narcotic actions

morphine papaverine codeine narcotine thebaine

50%

strychnine-like actions

1960s-70s

Ronald Melzack and Patrick Wall 1965

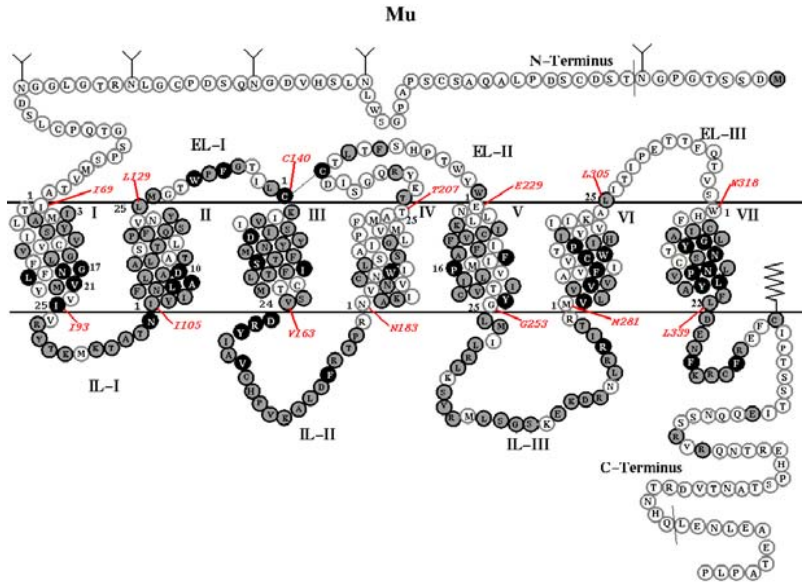
- Gate control theory of pain
- Pain not transmitted along a line-labelled system
- Pain neuroplastic
- Pain altered by stress – stress induced analgesia

- researchers in the Addiction Research Center in Lexington, Kentucky proposed opioid receptors purely on the basis of pharmacological studies

Martin WR Pharmacol Rev 1967;19:463-521
Martin WR et al J Pharmacol Exp Ther 1976;197:517-32
Lord JAH et al Nature 1977;267:495-9

1970s

- researchers identify specific opioid receptors in brain and peripheral tissue



Pert CB and Snyder SH Science 1973;179:1011-14
Pert CB and Snyder SH Mol Pharmacol 1974;10:868-79
Simone EH et al Proc Natl Acad Sci 1973;70:194709

- fact that receptors were highly sensitive to morphine but morphine was not endogenously expressed led to search for endogenous morphine-like substances

- mid 1970s, several groups of researchers identified enkephalins, dynorphins and beta-endorphin

Hughes I et al Nature 1975;258:577-79
Goldstein A et al Proc Natl Acad Sci 1979;76:666-70
Bradbury A et al In: Proc Fourth Am Peptide Symposium 1975

Current theories about the purposes of the endogenous opioid system suggest two important categories:

- to provide stress-related pain relief and pain enhancement (injury-related “physical pain”)
- to facilitate maternal-infant and other attachments

Top down viewpoint

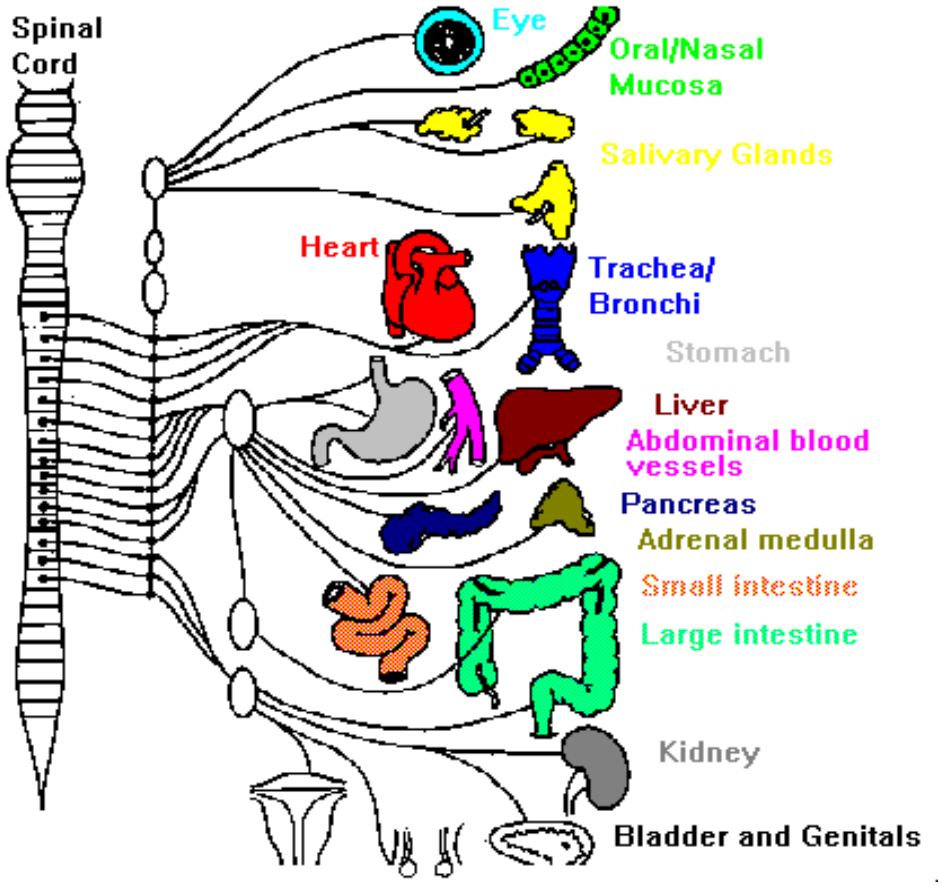
Disruption of social attachments, particularly maternal-infant attachments is one of the primary causes of “social and emotional pain”

- Dysphoric social dimension
- Contributes as much as nociception
- Accepts that mechanisms at the cellular level have evolved through evolutionary processes over millions of years

The suffering of chronic pain patients encompasses both physical and emotional pain that has often been refractory to treatment other than opioids

Fight and flight

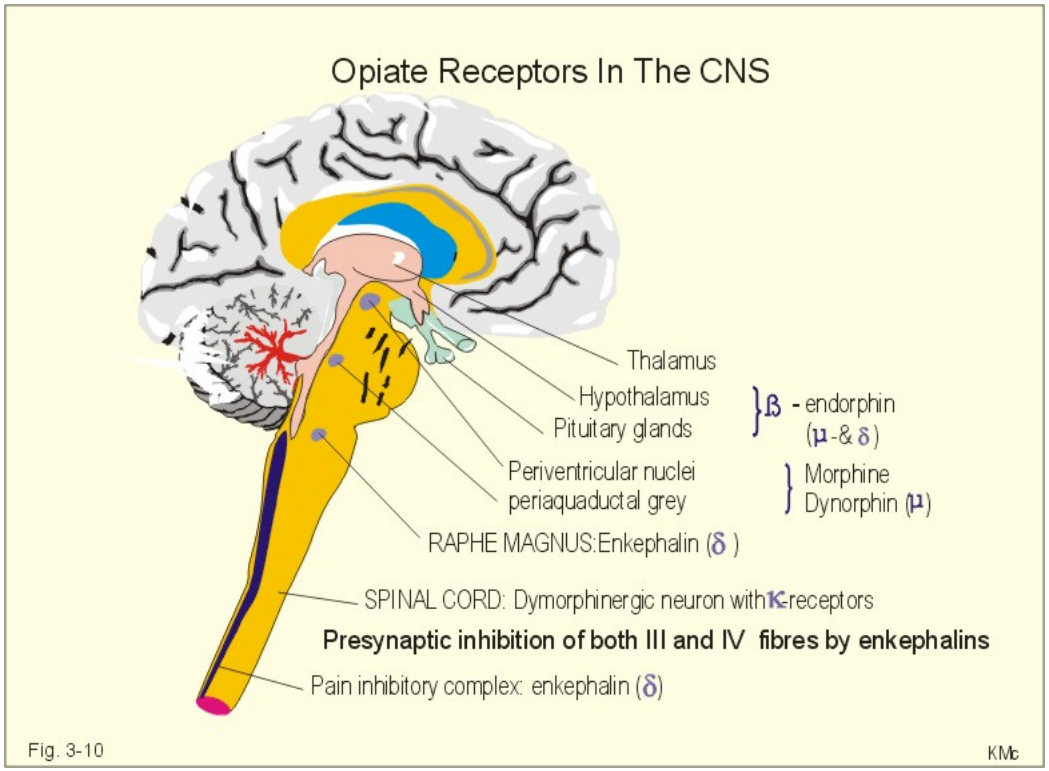
- Acceleration of heart and lung actions
- Inhibition of stomach and intestinal actions
- Liberation of nutrients for muscular action
- Relaxation of bladder
- Constriction of sphincters
- Inhibition of lacrimal glands and salivation
- Constriction of blood vessels in many parts of the body
- Dilatation of muscle vasculature



Mediated via hypopituitary-adrenal axis

catecholamines
corticosteroids
insulin
ADH

endorphins



At rest

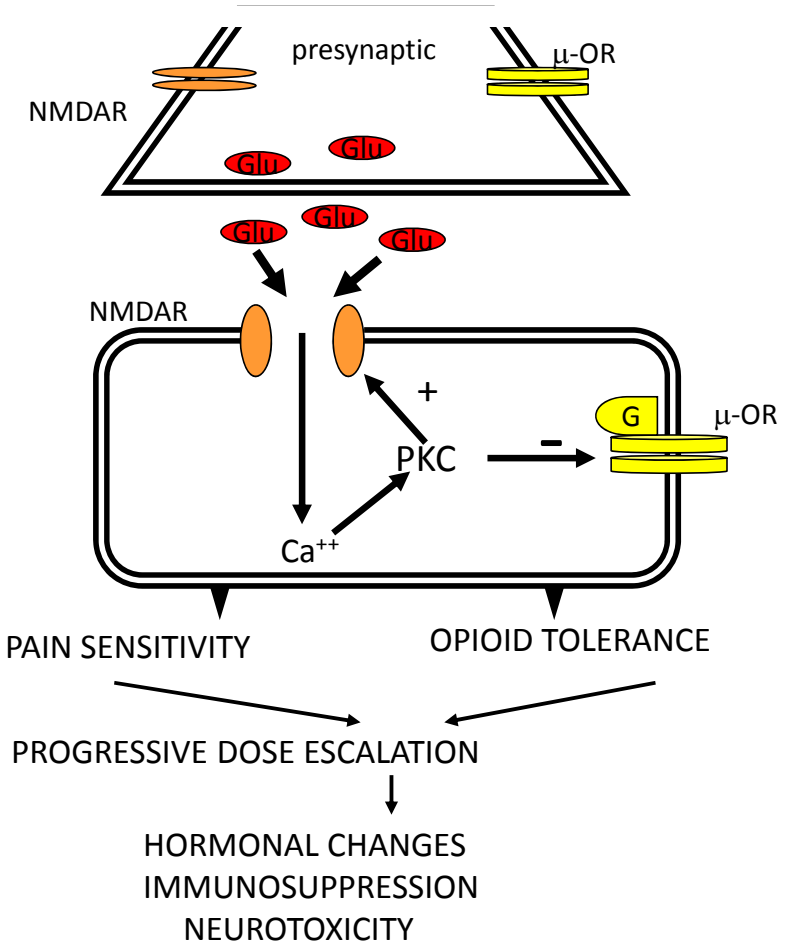
Injured

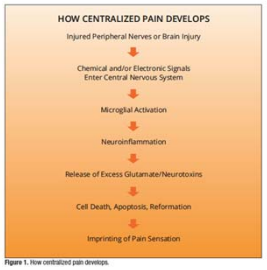
(analgesic but tender)

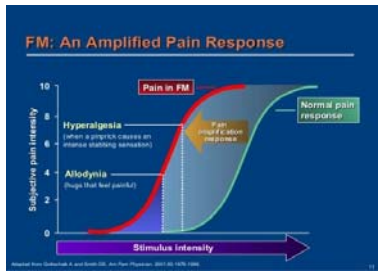
In chase

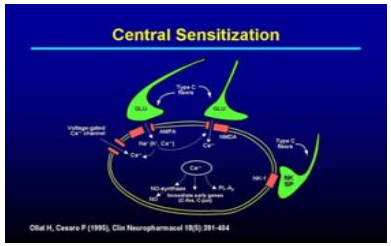
1980s – 1990s

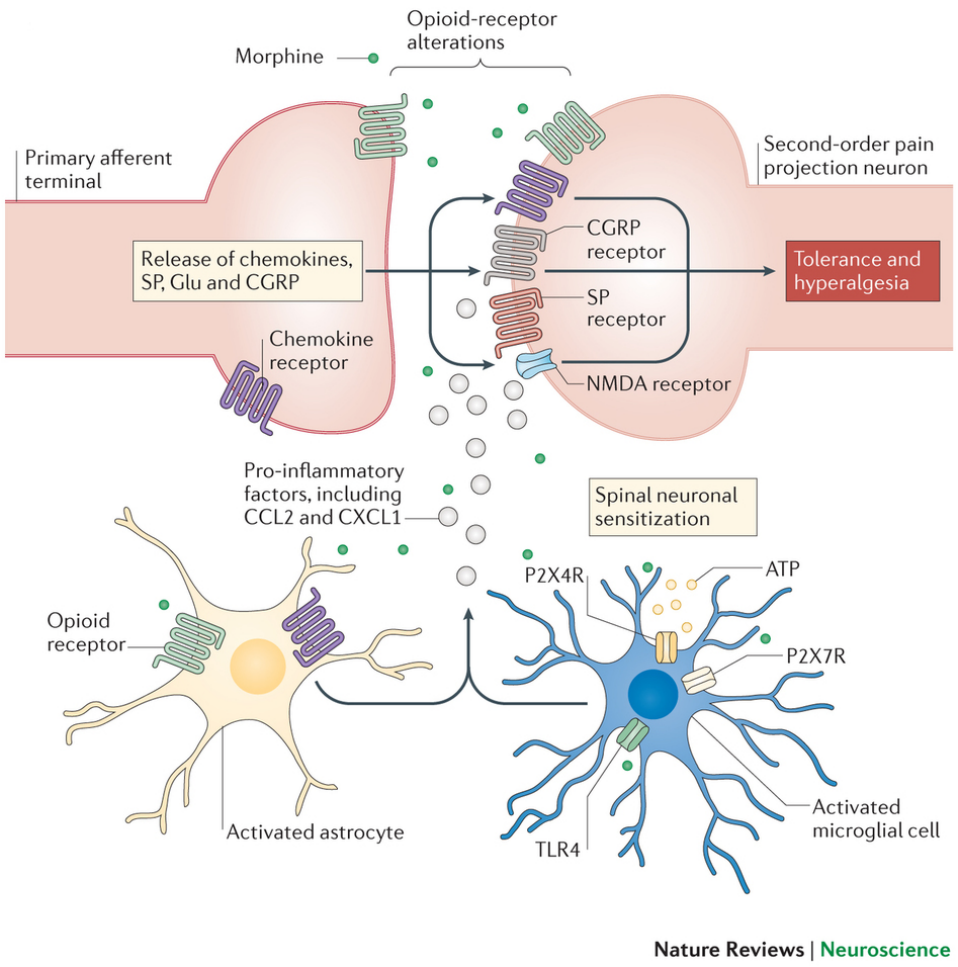
Understanding opioid induced hyperalgesia





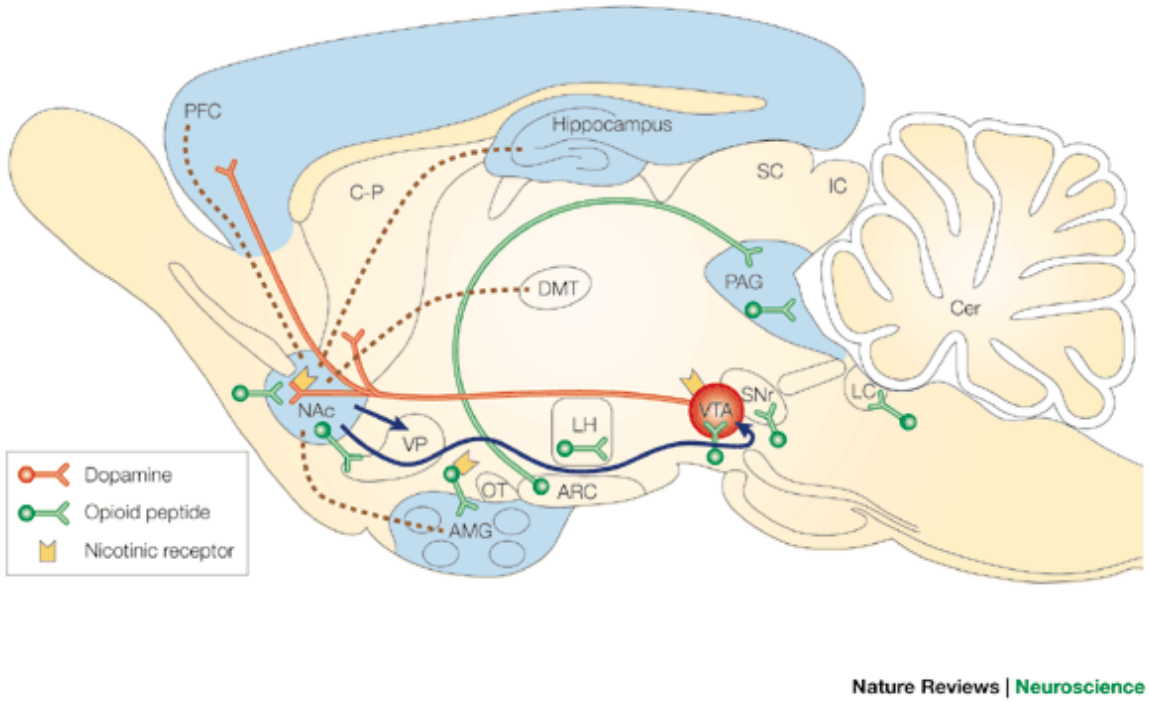






Chronic morphine treatment for chronic pain leads to opioid-receptor alterations that result in a decreased analgesic effect of morphine. Additionally, chronic morphine treatment directly activates glial cells (for example, astrocytes and microglia) in the spinal cord. Activated glia release pro-inflammatory factors (white circles) such as CC-chemokine ligand 2 (CCL2), CXC-chemokine ligand 1 (CXCL1), tumour necrosis factor-α (TNFα), interleukin-1β (IL-1β), IL-6 and IL-10. Microglia activation also results in a strong upregulation of the expression of cell-surface receptors, such as purinergic receptor P2X, ligand-gated ion channel 4 (P2X4R), P2X7R and Toll-like receptor 4 (TLR4), which participate in the neuroinflammatory process[109]. Concomitantly, at the presynaptic level, chronic morphine treatment also enhances excitatory synaptic transmission by the release of chemokines, substance P (SP), glutamate (Glu) and calcitonin gene-related peptide (CGRP). Together, these cellular mechanisms lead to spinal neuronal sensitization[91] and contribute to the development of tolerance to morphine-induced analgesia and/or morphine-induced hyperalgesia.

Nature reviews neuroscience 2015;16:69-78

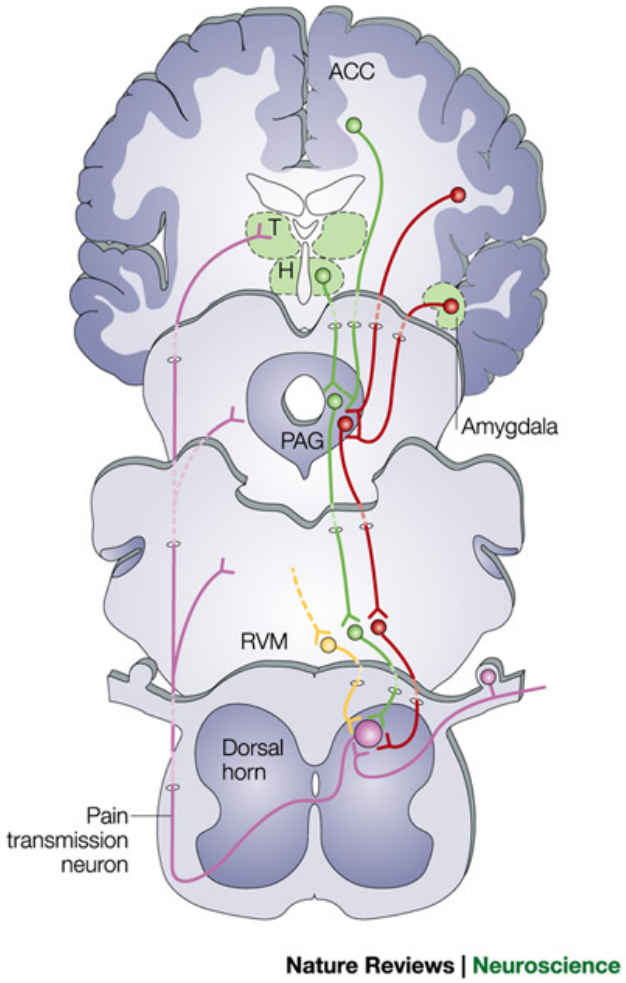


Nestler EJ Molecular basis of long-term plasticity underlying addiction Nature Rev Neurosci 2001;2:119-128

2004

State-dependent opioid control of pain
(linkage of circumstance and behavior to pain)

Fields, Nature Rev Neurosci 2004;5:565



Neurons in DH laminae are subject to powerful control by supraspinal sites including hypothalamus and limbic forebrain, via PAG

- the top–down pathway can be activated by both external painful stimuli and motivational states

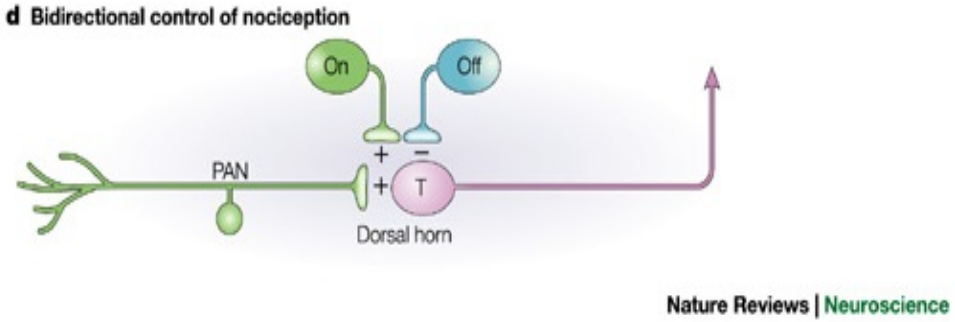
- in turn it indirectly controls pain transmission in the dorsal horn through the rostral ventromedial medulla (RVM) & can exert both inhibitory (green) and facilitatory (red) control

Reciprocal and state-dependent neuronal activity

- activation of RVM (rostral ventromedial medulla) neurons generates either facilitation or inhibition of pain transmission under different conditions

- this dual control results from the activity of two neuronal subpopulations

- these subtypes exhibit phasic reciprocal changes in firing during withdrawal reflexes, ie are both pain-inhibiting and pain facilitating



'*on* cells' → burst of activity
(faciliate nociceptive transmission)

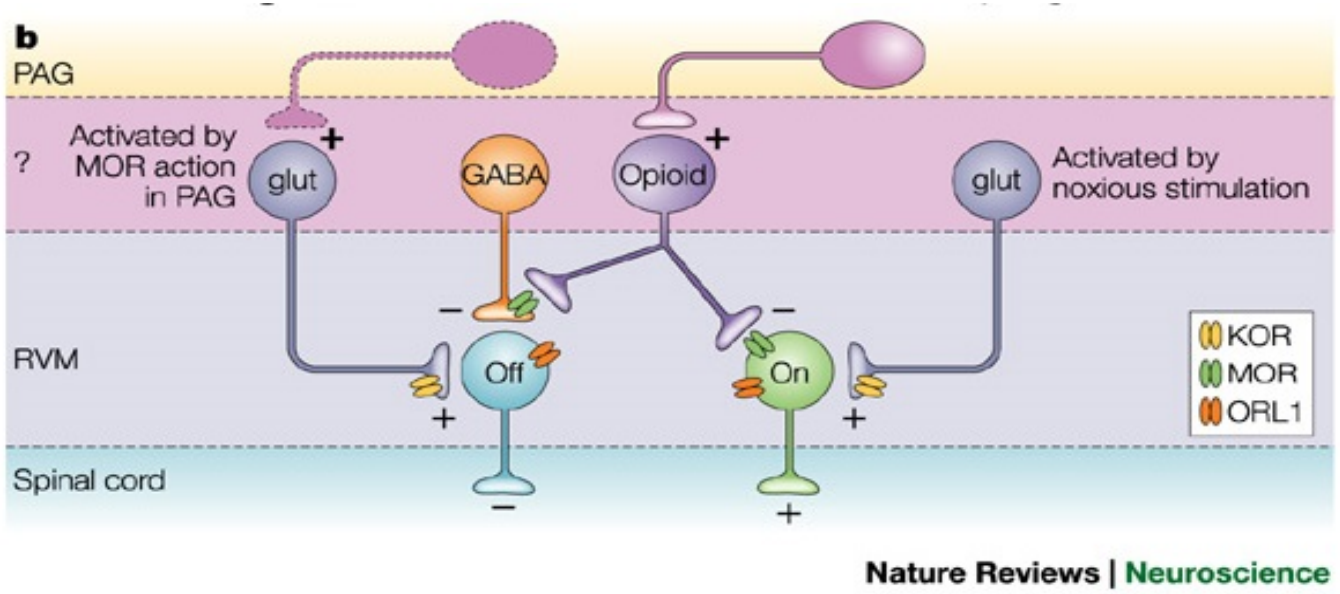
'*off* cells' → pause in firing
(inhibit nociceptive transmission)

The concept that the modulatory circuit can operate in two distinct modes is crucial for understanding how a given opioid ligand can have different behavioral effects when given at different times

- the action of opioids contributes to and is determined by the state of the circuit

- opioid drugs can either relieve or worsen pain, depending on behavioral state, even when only one receptor (or circuit) is involved

Synaptic distribution of opioid receptors within the RVM



MOR agonists produce anti-nociceptive effects by disinhibiting *off* cells and inhibiting *on* cells.

Pain is primarily a motivational state that has a powerful influence on decision making

- because the biologically relevant output of the nervous system is behavior, circuits are meaningfully defined in relation to a specific behavior

- it appears that the state of the circuit is determined by aversive and appetitive motivational states which contributes to adaptive behavioral choice

- through classical conditioning, initially neutral contextual cues can acquire the motivational power to elicit opioid-mediated analgesia

Table 1 | **Rostral ventromedial medulla (RVM) neurons and behavioural state**

	On cell	Off cell	Nociceptive response	Blocked by MOR antagonist	Blocked by ORL or KOR agonists
MOR agonist	–	+	–	Y	Y
Acute MOR abstinence	+	–	+	N/A	Y
Tonic noxious stimulus	+	–	+	N/A	N/A
Low dose neurotensin (In RVM)	+	0	+	N/A	N/A
Threat or appetitive motivational state	–	+	–	Y	Y

+, increases; –, decreases; 0, no effect. KOR, κ-opioid receptor; MOR, μ-opioid receptor; N/A, not applicable; ORL, opioid receptor-like; Y, yes.

What does all this mean when it comes to treating chronic pain?

Pain diagnosis is not always clear

- *There may be no obvious pathoanatomic diagnosis*
- There may be a diagnosis that is easy to conceptualize and one that may respond to primary treatment (eg diabetes, osteoarthritis, rheumatoid arthritis)
- There may be a diagnosis, but pain persists beyond the expected duration (eg post-trauma, post-op, low back pain)
- There may be a diagnosis but no curative treatment (eg sickle cell disease, pancreatitis)

Each scenario requires a different approach; the unifying factor is that it is chronic

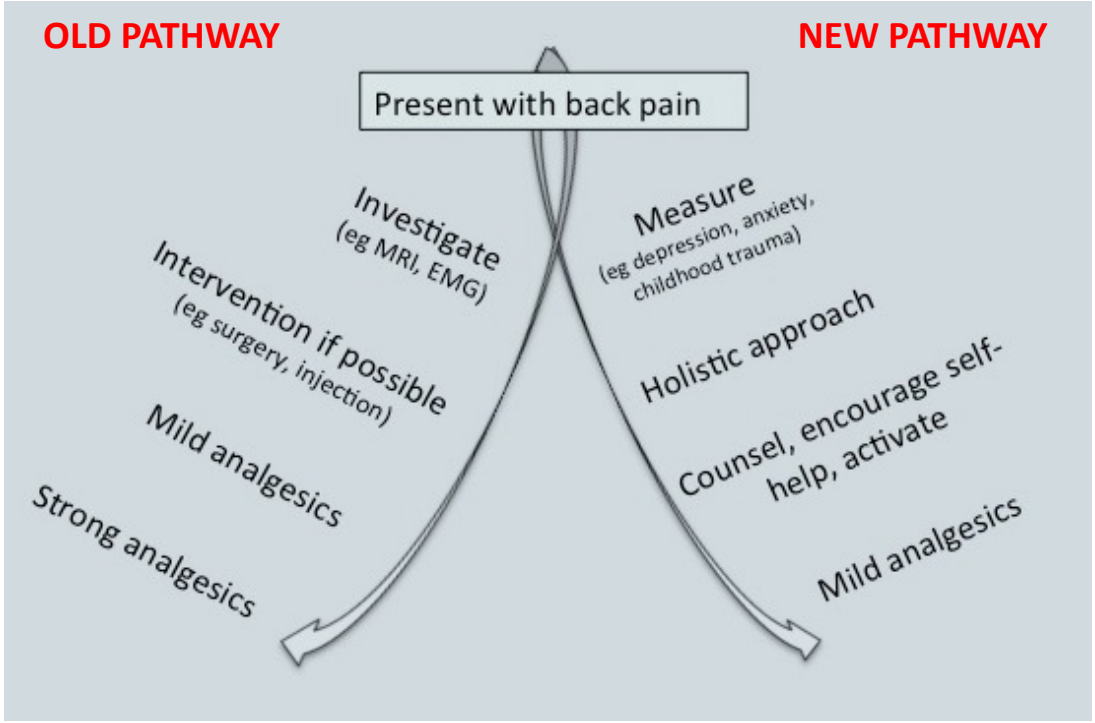
- When patients seek medical treatment for pain, they frequently report suffering
- This suffering is expressed as physical pain, but its roots lie much deeper
- These roots are created by past experiences and present fears, not found in the body or explained by pathology
- Modern imaging enables us to see most pathological causes of pain
- Thus, we understand that two individuals with the same pathology on an image may experience this condition very differently
- For one person the physical pain becomes the focus for a life of suffering, while for another, the physical pain is sublimated, or even disappears.

- Opioid systems are intimately involved in the group processes, the top down effects
- Isolation, withdrawal, distress, family, job, culture all influence the development of chronic pain and are indicators of derangement in natural (opioid) systems
- The pain and opioid systems evolved through evolutionary processes over millions of years
- Giving exogenous opioids overwhelms these natural systems and prevents the protective, defensive mechanisms from taking place
- Central control (top down) contributes as much as nociception to the experience of pain and is a powerful means of controlling pain

Top down viewpoint

- Dysphoric social dimension
- Contributes as much as nociception
- Accepts that mechanisms at the cellular level have evolved through evolutionary processes over millions of years

Cultural transformation needed is demedicalization of the most common pain conditions



Digging deeper and deeper into micro events

Encompassing yet transcending micro events

Until Descartes, external events caused pain

Anatomy of pain not understood

Mi

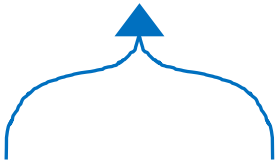
Relationship to er tood

Reductionist starting point

Impersonal, mechanistic terms

Focus on nociception

nt



Imp ial dimension

Isolation, withdrawal, distress

Group processes

Family, job, culture

Public health, community base, teams, system

National Pain Strategy

A Comprehensive Population Health-Level Strategy for Pain

- Employing self management programs to improve patient quality of life as an important component of acute and chronic pain prevention and management
- Use of integrated, multimodal and interdisciplinary treatment approaches
- Reducing incentives for treatments with little absolute benefit or a limited benefits relative to risks
- Increasing incentives and reimbursement strategies to promote high-quality coordinated pain care through an integrated biopsychosocial approach
- “Safe use campaign” for opioids

Draft National Pain Strategy A comprehensive population health-level strategy for pain 2015; http://iprcc.nih.gov/docs/DraftHHSNationalPainStrategy.pdf

Systems Map (Obesity)

Figure 5.2: The full obesity system map with thematic clusters (see main text 5.1.2 for discussion)[17,18] Variables are represented by boxes, positive causal relationships are represented by solid arrows and negative relationships by dotted lines. The central engine is highlighted in orange at the centre of the map.