

L19: PAIN

Pain

- actual/potential tissue damage → unpleasant sensory & emo experience (fear/anxiety/stress)
- sensory-discriminative: pain location, intensity, duration
- motivational-affective: unpleasant feeling, symp drive (↑HR, sweat)
- protection
- subjective & learned (resolved → still feel pain)
- nociceptive pain / acute pain
 - actual/threatened damage (heat/cold/acid/mechanical) to non-neural tissue
 - nociceptor activation → reflex
 - warning/protective pain
 - withdrawal in SC, pain/avoidance/emo in brain
 - diff noxious stimuli activate specific R &/or ion channels on peripheral nociceptors (several R on 1 nociceptor)
- inflam pain
 - inflam
 - inflam mediators → activate peripheral nociceptor → pain
 - others → change peripheral nociceptor sensitivity to noxious stimuli
 - resolved but ✓ changes to R sensitivity → remain sensitivity → still has pain sensation → chronic pain
- neuropathic pain
 - affect NS structure/nerves that transmit signal up
 - somatosensory NS lesion/disease
 - injury to PNS/CNS → permanent changes in circuit sensitivity & CNS connection
 - chronic, hard to resolve
 - carpal tunnel syndrome, SC injury, stroke

Nociception

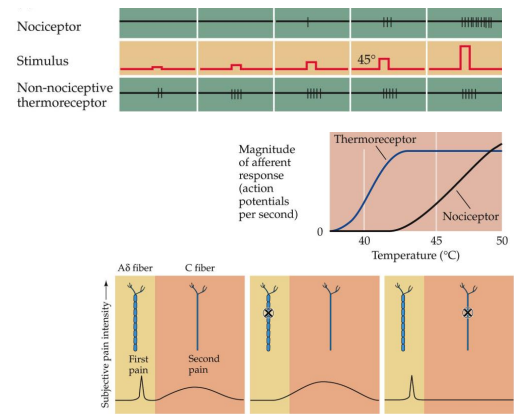
- neural process of encoding noxious stimuli by activation of entire NS cells
- nociceptors: cells activated by noxious stimuli
- pain sensation/exp is not necessarily implied
- everything before cerebrum (real pain experience) = easier to target

Pain Signalling

- noxious stimuli → peripheral tissue
- nociceptors (peripheral neurons) transduce noxious stimuli → AP
- ascending pathway: SC → brainstem (modulation)
- cerebrum = pain perception
- descending modulation of pain signalling → suppress pain

Peripheral Nociceptors

- 1° afferent neurons
- transduce noxious stimuli → AP
- code for noxious stimuli intensity
 - >42°C → more AP
 - thermoR activated earlier than nociceptor → X code intensity well
- respond to ↑ threshold stimulation
- unspecialised free nerve endings
 - slow conduction
 - ↓ threshold sensory neurons (myelinated) = fast
- classified based on **axon conduction**
 - Aδ-fibre axon
 - thin myelination, conduction velocity 5-30m/s, fast (sharp) pain
 - C-fibre axon
 - unmyelinated, conduction velocity <2m/s, slow (burning) pain
- classified based on **modality** (sensory stimuli that activate them)
 - modality specific nociceptors & mol heterogeneity
 - mechanical nociceptor
 - noxious mechanical stimuli (cut, crush, pinch)
 - thermal nociceptor
 - noxious temp
 - polymodal nociceptor
 - mechanic, heat, chem, inflam mediator
 - TRPV1: heat/acid/capsaicin → Na⁺/Ca²⁺ influx
 - cornea
 - immunostain for TRPV1
 - put capsaicin → activate nerve terminal (diff morphology to other nociceptors)
 - specific combination of ion channel/R for transduction



Sensory Neuron Classification based on Full RNA Transcriptome Analyses

- 11 subpop of nociceptors
- low threshold mechanoreceptive, proprioceptive, nociceptive cells

Dorsal Horn of Spinal Cord

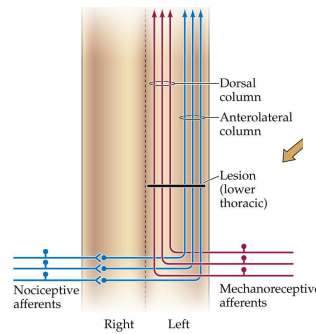
- nociceptor input (cell body in DRG) → synapse in **superficial dorsal horn**
- 2nd order neurons: originate in diff lamina → ascend towards brain
- interneurons: processing, communicate btw lamina
- 2nd order neurons & interneurons crossover at midline (decussation)
- synapse with thalamic cortical neurons → cortex (pain/motivational)

Ascending Pathway

- pain/temp for body: spinothalamic tract
- pain/temp for face: trigemino-thalamic tract

Pathway Anatomy

- predict loss of pain
- anterolateral column
 - cross midline at low level (whr input comes in)
 - body pain in left side → right side in cortex
 - lesion in bottom left → affect right side temp/pain
- dorsal column medial lemniscus
 - normal sensory (vibration, proprioception)
 - cross midline at brainstem
 - lesion in bottom left → affect left side sensory



Supraspinal Centre

- anterolateral system → info to brainstem/forebrain
- sensory-discriminative
 - anterolateral → ventral posterior nucleus (thalamus) → somatosensory cortex (S1/S2)
- affective-motivational
 - anterolateral → reticular formation, superior colliculus, periaquiductal grey, hypothalamus, amygdala, midline thalamic nuclei
- if cut SC → inhibit pain transmission

Postsynaptic Dorsal Column Pathway (Alternative Pathway)

- visceral pain, GIT

Pain Modulation

(1) Neurogenic Inflammation

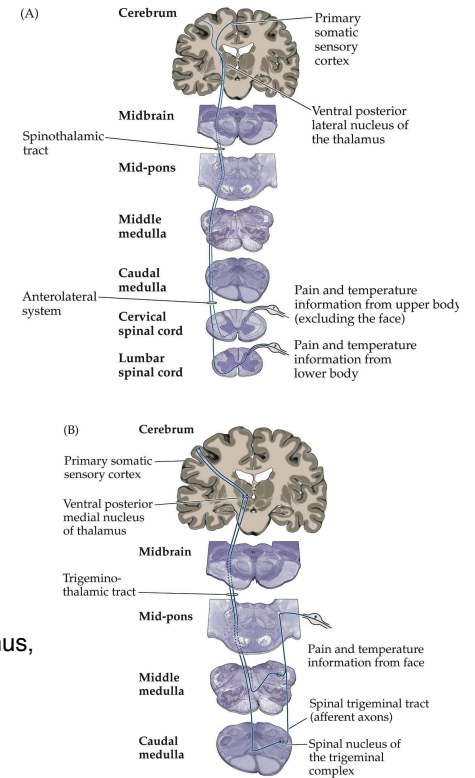
- flare
- reflex
 - mediators activate peripheral nociceptors
 - nociceptors → mediators (subs P) to BV/MC/neutrophils → produce/↑ local tissue inflam → ↑ sensitivity

(2) Sensitisation

- nociceptors: ↑ responsiveness to normal noxious input, ✓ response to subthreshold (innocuous) input
- cause: ↓ activation threshold, ↑ nociceptor response (AP) = more excitable
- based on nociceptor phys, not pain characteristic
- sometimes persist after resolved → hard to treat/manage
- hyperalgesia
 - ↑ pain from stimulus that normally provoke pain
- allodynia
 - pain from stimulus that normally ✗ provoke pain (sunburn → pain to normal touch)
- peripheral sensitisation
 - ↑ responsiveness & ↓ threshold of peripheral nociceptors to their receptive field stimulation
 - inflam mediators ✓ sensitise peripheral nociceptors (inject algescic subs → ↑ neurons sensitivity → sensitisation)
- central sensitisation
 - ↑ responsiveness of CNS nociceptive neurons to their normal/subthreshold afferent input

(3) Descending Inhibition

- cortex → activate inhibitory interneuron in dorsal horn → modulate (inhibit) ascending pain signal transmission
- also ✓ shut down pain in higher centre
- Henry K Beecher
 - psych aspect of pain perception in injured soldiers (60% said ✗/slight pain due to survival instinct, 24% rated bad pain)
 - all men were sensitive to pain (inept iv insertion → acute pain)



(4) Analgesics

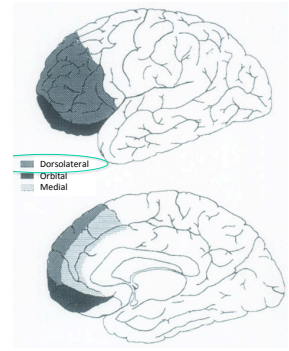
- site of injury
 - NSAIDS (ibuprofen): ↓PG production that activate/sensitise peripheral nociceptor
 - local anaesthetic (bupivacaine & lidocaine): inhibit AP propagation in peripheral sensory neuron
- spinal cord dorsal horn
 - opioids: inhibit excitatory NT release
- brainstem
 - opioids: supraspinal opioid R (in PAG), ↑ descending inhibition
- cerebrum
 - paracetamol: inhibit brain COX (X understand action)
- surgery, neurostimulation, acupuncture

L30: PFC & REASON

- ratiocinate: to reason
- much of our conscious mental activity relates to abstraction
 - model & analysis (how things work), calc & estimation, planning & strategising
- brain areas are known by lesion/functional study ∴ X vast histology diff
- motor — central sulcus — perception

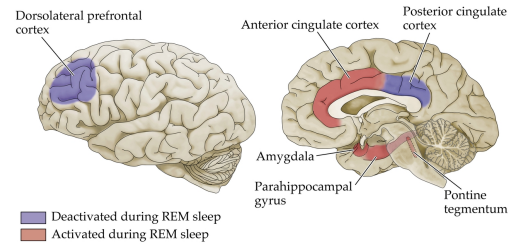
Dorsolateral Prefrontal Cortex

- thinking
- working memory: rmb phone no, rmb & apply rules (count backwards from 100 in steps of 7)
- memory of the future: plan, goals, temporal structuring of behaviour (delayed gratification)
- how things work: analysis, estimation, hypothesis, calc, decision
- dorsolateral PFC damage → distractibility, impulsive, perseverative error (X re-strategise)



Dreams / REM Sleep

- dorsolateral PFC deactivated
 - unreal, relax reality, X conform to rules
- posterior cingulate cortex deactivated
 - action ↔ emo (escape/defence)
 - deactivated → relax motor → X move in dreams
- amygdala activated
 - fear
- anterior cingulate cortex activated
 - feeling



Retina

- covered by blood vessels
- macula (cones, ↑ resolution, colour) vs periphery (rods)
- info in → brain learn how to construct & model reality
 - if X model world → colour in middle, periphery B&W, see BV

Painting

- attention: focused, directed, sustained strategy
- show a painting → see eye movement by Q&A
 - examine at will (look everywhere), estimate wealth (look at outfit/house), estimate age (look at ppl), guess previous activity (look everywhere), rmb clothing, rmb position, time since last visit (look at those 4 ppl)
- everyone use diff strategy to answer ques ⇔ use strategy via PFC

PFC Higher Order Inference

- categorisation, multiple regression, principle component
- proverbs meaning
- word similarity, word definition
- estimation

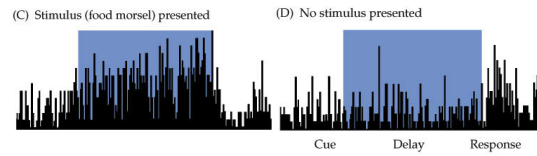
Measure PFC Function

- list words beginning with a letter (female better)
- mental rotation task (male better): same shape?
- wisconsin cardsort test
 - measure ability to change categorisation strategy
 - prob solving, rule following, flexibility, perseveration
 - apply a rule then change rule (sort by colour/shape/number) → see if patient ✓ re-strategise
 - if X re-strategise → damaged dorsolateral PFC
- standard stroop task
 - name ink colour ASAP
 - incongruent condition: blue - red - green
 - congruent condition: blue - red - green
 - incongruent is slower: word meaning interferes with colour naming
 - if PFC damage → X apply rule that's contradicting with a condition
- emotional stroop task
 - name ink colour ASAP
 - emotional condition: cancer, danger, attack, tumour
 - neutral condition: house, laugh, animal, modern
 - anxious participant: emo condition slower
 - non-anxious participant: X diff btw emo & neutral condition

- tower of london / hanoi task
 - become possible btw 3&6
 - brodmann area 10
 - temporal domain
 - enlarged in humans → plan the future
 - strongly activated for this task (temporal calc, delayed gratification, planning)
 - sometimes need to take indirect route to reach a goal (rule → intermediate solution → end solution)

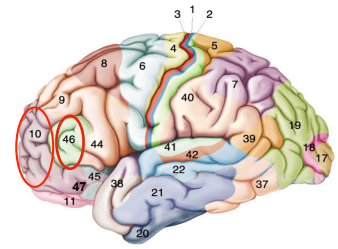
Measure Dorsolateral PFC Neurons

- use a simple task to measure single neurons
- neuron activation near principle sulcus of frontal lobe
- cue: randomly place food in a well visible to monkey
- delay: close the screen & cover food for some time
- response: raise screen & monkey uncovers the well with food
- memory task (form stable representation) + delayed response task (some neurons maintain info for a time duration)
- we can temporally organise behaviour



Abstraction

- brodmann area 46
 - last area to mature (full myelination)
 - top of the hierarchy in behavioural control
 - info from sensory association area (when/where of event/obj) → dorsal stream → BA46
 - ideate space, time, abstraction (atomic structure & god)
 - abstract concept, possibility, general principle of action, hypothesis
- categorise & name stuff based on key features
- include reification
 - look at abstract stuff → form concrete idea, make it a material thing
- basic/elemental insight-relayed prob solving
 - compound remote associate prob (CRAP)
 - what 1 word can be joined to make a compound word with:
 - crab, sauce, pine → crabapple, applesauce, pineapple
 - bongard sets
 - what's the diff btw left & right



Theory of Mind

- make models of other ppl with the same capacity as us, infer other's motivation, know that ppl have diff PoV/ideas
- advanced social competency give rise to unique human brain function
- ability to conceptualise entities & possibilities beyond perceptual experience → limitless imagination
- NO "theory of mind" in animals
 - A put food in container, B looks at A, C covered in a pail
 - monkey has no preference in asking anyone to know where's the food → haven't model their brain
- children <3yo will also fail this monkey test
- 3yo: self-evaluative emo → model the world & ppl, conceptualise other's mental state
- 12yo: ✓ logical operation, conceptualise abstract, personal sets of construct (belief)