**4/8: Pain**

People who don’t feel pain suffer from deformities through failure to adjust posture and acute injuries through failure to avoid harm

10 year old boy in family performed “street theater” – put knives through arms, walked on burning coals

Linked to genetic disorder of voltage-dependent Na+ channels

What is pain?

1.5 billion people suffer from chronic pain

~80% of physician visits are about pain relief

Affects more Americans than diabetes, heart disease, cancer combined

What neural system conveys pain information?

Information from somatosensory system

Tells us what body is up to, what’s going on in environment

Allows us to distinguish between what world does to us and what we do to it

Parietal lobe – analysis of touch, pain, spatial information, head and body positions

Defined as “unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage”

Pain is constructive in that it

Forcefully directs attention, guides behavior to minimize risk

Encourages inactivity, recuperative behaviors

Aids in social communication: grimacing, groaning, shrieking – warns others, elicits caregiving

Inflammation – induced by injury – increases sensitivity

This minimized movement of injured region and contact with other objects, reducing chances of further injury

Pain has different dimensions – McGill Pain Questionnaire

Sensory-discriminative – throbbing, gnawing, shooting

Motivational-affective – tiring, sickening, terrifying

Cognitive-evaluative – mild, excruciating

Pain can be fast or slow, easy or difficult to localize

Prickling

Aching

Prickling – needles, pin pricks, cuts

Sharp quality, rapid stinging sensation

Precisely localized, short duration

Fast pain

Burning (aching) – inflamed, hot, swollen, sore

More diffuse, longer in duration

Annoying, intolerable, not distinctly localized

Slow pain

Does not occur in a vacuum

Learning, experience, emotion, culture, context all shape pain experiences dramatically

Wounded soldiers, athletes, & “over-reactors”

“The intensity of suffering is largely determined by what the pain means to the patient”

Someone who intentionally injures you causes more severe pain than accidental injury

How do we sense pain?

Sensitivity to different somatosensory stimuli depends on receptors that process different streams of information

We have receptors for:

Nociception

Perception of tissue damage, temperature, itch

Bare (or free) nerve endings

Hapsis

Perception of fine touch and pressure, helps to identify objects that we touch, grasp

Activated by mechanical stimulation of hair, tissue, capsules

Proprioception

Perception of location, movement of body

Sensitive to stretch of muscles, tendons, and movement of joints

How do we sense pain?

Pain sensation begins with nociceptors

Least specialized of all receptors (free nerve endings)

Nociceptive (nocer – to injure, hurt) means sensitive to noxious stimuli that cause tissue damage, activate nociceptors

Because cells and stimuli don’t feel, we make a mistake when we say pain cells, pain receptors, and pain stimuli

We try to say nociceptors and nociceptive stimuli

Pain refers to subjective experience; nociception refers to detecting tissue damage

Nociceptors

Sensory receptors that detect signals from damaged tissue

Found in skin, muscles, joints, bone, viscera (internal organs)

No nociceptors in CNS

Activation of nociceptors initiates process by which we feel pain

They relay afferent information to CNS about type, intensity, location of noxious stimulus

Not uniformly sensitive to all noxious stimuli

Fall into categories, depending on responses to these kinds of stimuli

Mechanical

Thermal

Chemical

Mechanical nociceptors

High-threshold mechanoreceptors – free nerve endings that respond to intense pressure, which might be caused by something striking, stretching, or pinching us

Thermal nociceptors

Respond to extremes of heat, cold, acids, presence of capsaicin – active ingredient in chili peppers

Thermal nociceptors that respond to capsaicin contain TRPV1 receptors

Transient receptor potential vanilloid type 1

Vanilloid – group of chemicals to which capsaicin belongs

Mice lacking TRPV1 respond to mechano-sensory pain, but not heat pain or capsaicin

TRPV1’s job is to report rises in temperature to warn us

Chili peppers evolved capsaicin to ward off predators – falsely signal burning heat

Eating spicy food is uncommon in nature

Chemical nociceptors

Contain TRPA1 receptors

Sensitive to pungent irritants in mustard oil, wintergreen oil, horseradish, garlic, wasabi

Also to environmental irritants

Nociceptors

2 basic kinds of axons (fibers) that transmit nociceptive (afferent) information to brain

A delta fibers

C fibers

A delta fibers

“Large” (2-5mm) diameter, myelinated

Action potentials reach spinal cord fast (5-30 m/s)

Carry info mainly from mechanical, thermal nociceptors

Receptive fields are small, provide more precise localization of tissue damage (pain)

C fibers

“Thin” (0.4-1.2mm), un-myelinated

Action potentials reach spinal cord more slowly (0.5-2 m/s)

Carry information from many nociceptors

Compromise ~70% of all nociceptive fibers

Large receptive fields, less precise for pain localization

A delta and C fibers

When you burn your hand on a stove

Initial sharp pain (A delta)

Long lasting, dull pain (C)

Phenomenon known as “double pain sensation”

**4/12: Pain (continued)**

What are the pain paths?

Nociceptive fibers enter dorsal horns of spinal cord

Synapse onto neurons that project to other side of cord, then up to thalamus

This forms the spinothalamic tract

Spinal cord arrangement

Dorsal and ventral horns

31 pairs of spinal nerves – one on left, one on right

Spinal nerves divide close to cord

One branch called dorsal root goes to dorsal horn, the other, called ventral root, goes to ventral horn

Spinal cord message trafficking

Nerves entering from dorsal root carry sensory (afferent) information and nerves exiting ventral roots carry motor (efferent) information

Cell bodies of sensory cells are located in ‘clusters’ outside spinal cord, called the dorsal root ganglia

Unipolar neurons: PNS 🡪 CNS, traffic in afferent information

What are the pain paths?

Nociceptive fibers release glutamate

As stimulation increases, they also release substance P (neuropeptide that increases pain sensitivity)

Spinothalamic tract

Carries nociceptive information

Axons from dorsal-root ganglia neurons enter cord, cross over, synapse onto neurons in contralateral side

Axons from contralateral spinal cord ascend until synapsing with neurons in thalamus

Neurons from thalamus project to somatosensory cortex (parietal lobe), anterior cingulate, and other regions

What are the paths for different parts of pain?

Pain thought to have 3 different perceptual, behavioral components:

1. Sensory – pure perception of intensity

2. Emotional – degree of immediate distress

3. Long-term appraisal – threat of (chronic) pain to one’s future comfort, well-being

Purely sensory component – mediated by path from spinal cord to thalamus (ventral posterior nucleus) to primary, secondary somatosensory cortex

Immediate emotional component – appears to be mediated by paths from thalamus to anterior cingulate cortex (ACC), insular cortex

Long-term component appears to be mediated by paths that reach prefrontal cortex via ACC

PFC damage impairs ability to plan for future, recognize personal significance of situations

People w/ PFC damage tend to not be concerned with long-term implications

How do people study pain paths?

Rainville et al. produced pain in humans by putting their arms in ice water while using PET

In one condition, used hypnosis to diminish feelings of unpleasantness

Hypnosis worked

Ice water increased activity in somatosensory cortex, ACC

Under hypnosis, decreased ACC activity but similar activity in somatosensory cortex

Somatosensory cortex appears more important for sensory perception of pain

ACC more involved in immediate emotional effects – its unpleasantness

Can we control pain?

Neuropathic pain – pain that persists long after injury, healing (chronic pain)

Thought that nociceptors, nociceptive pathways continued to signal to brain

These signals can be amplified, expanded even in absence of actual damage, injury

Hyperalgesia – increased painful sensation in response to additional noxious stimuli

Lower threshold for feeling pain, especially in area near injured site

Inflammation often plays important role – activates nociceptors, prolongs, amplifies stimulation

Allodynia – pain from stimulus that does not usually cause pain

Example: light touch to sunburned skin

Nociceptors likely sensitized

Damaged PNS neurons can reroute (i.e., touch (hapsis) fibers reroute, make synaptic connection in areas of spinal cord that normally get input from nociceptors)

If we can control pain, what circuits are we affecting?

Work beginning in 70s revealed brain circuits for analgesia – relief from pain

Activity in these circuits associated with endogenous opioids (endorphins)

Crucial role for periaqueductal gray (PAG)

Electrical stimulation causes analgesia, profound enough to serve as anesthetic for surgery in rats

PAG sends axons to raphe nuclei in medulla

Raphe contains neurons that project to dorsal horn of the spinal cord, which inhibit their afferent signals

Destruction of raphe axons eliminates analgesia induced by morphine

Raphe axons inhibit release of substance P in spinal cord

Mice lacking substance P cannot feel intense pain

PAG gets input from amygdala, hypothalamus, thalamus, and cerebral cortex

Provides basis for thoughts, emotions, learning, experience to shape pain

Neuromodulation

Main model and modes of pain relief

Dominant model of pain and pain relief (analgesia) is called gate control theory

Hypothesizes existence of “gates”

These facilitate or block nociceptive information to brain

Non-pain stimuli around damaged area can modify intensity of pain

Placebo

Drug or other procedure with no pharmacological effect

Works as analgesic sometimes

Likely decreases pain perception by decreasing emotional component of pain but not sensory component

Transcutaneous electrical nerve stimulation (TENS)

Mechanism not clear

Might close the spinal “gate” for pain

Might be more efficient at stimulating haptic-proprioceptive nerves compared with “rubbing area”

Acupuncture

Only minority achieve lasting relief for chronic pain

Release of endorphins appears important

Effects resemble placebo in brain imaging studies

Placement of needle has little effect, expectation of benefit appears to matter more

Social pain

Resemble physical pain in many regards

Increased activity in ACC when getting left out, rejected by others

People taking acetaminophen reported fewer incidences of hurt feelings and social pain

**4/15: Pain (continued) and Mental Health**

Phantom limb pain

Phantom limb refers to continuation of sensation of amputated body part

Cortex reorganizes after amputation by becoming responsive to other parts of the body

Some axons degenerate, leaving vacant synapses into which other axons sprout

Leads to sensations in amputated part of body when other parts of body are stimulated

Touch on face can result in sensation of touch or pain in arm

Ramachandran’s hypothesis – phantom limb pain caused by reorganization of somatosensory cortex following amputation

Mental health context

~25% of adults in US suffer from diagnosable mental illness

Schizophrenia

“Splitting of psychic functions” – poor links between emotion, thought, action

Affects 1.2% of population

Men show first symptoms during teens/twenties; women about a decade later

Chronic symptoms – develop gradually, can persist for a long time, poor prognosis

Acute symptoms – develop suddenly, more responsive to treatment, reasonably good prognosis

“Positive symptoms” – something present which should not be there

“Negative symptoms” – something missing which should be there

Positive symptoms

Hallucinations – false perceptions of events

Delusions – abnormal beliefs, contrary to reality

Thought disorder – loose links between thoughts, incoherence, illogical train of thought

Negative symptoms

Flattened or abnormal emotional response

Social withdrawal – isolating from others

Anhedonia – inability to feel pleasure

Etiology and causal factors in schizophrenia

Some evidence for genetic risk

Associated with various early stresses – birth complications, nutritional deficiencies, toxins, prenatal infection

Environmental factors also suspected

Genetic liability

Familial disorder – incidence is higher among closer relatives (heritability between .6 and .9)

Vulnerability model – some threshold of forces must be exceeded for illness to occur

Environmental challenges combine with a person’s genetic liability to exceed that threshold

Brain structure and function in schizophrenia

Enlarged ventricles

Hippocampus disorganization

Smaller frontal, temporal lobes

Smaller thalamus

More loss of gray matter in adolescence

Neurochemistry of schizophrenia

Alterations seen in multiple transmitters, especially dopamine, acetylcholine, glutamate (main treatment targets)

What is depression?

All of us have depressed moods – normal reactions to negative life events

Some experience these more than others – often for no reason, at levels that stop them from functioning – this is clinical depression (MDD)

Depression – course

Episodic

Symptoms develop over days to weeks, often starting with mild symptoms and anxiety

If untreated, lasts 6 months or more

Support for focus on monoamines

Depression can be treated by drugs that increase monoamines in brain

Led to hypothesis that depression is caused by insufficient activity of monoaminergic neurons – specifically serotonin & norepinephrine pathways

A big problem for emphasis on neurochemistry

Do not explain why monoamine antidepressants take 3+ weeks to work, but increase monoamines in 2-3 hours

Maybe changes in receptor sensitivity or networks over longer time are important

How do drugs that do not influence monoamine levels reduce depression?

Cognitive behavioral therapy can be as effective as pharmacological approaches, especially when combined

Treatment of depression with brain stimulation

2008 study found that electrical stimulation in part of ACC relieved depression in treatment-resistant patients

Bipolar disorder

Person alternates between periods of depression and mania

Excess energy, decreased need for sleep and increased sex drive and (often) drug use

In some cases, a period of agitation replaces mania

Brain changes in affective disorders

Volume deficits, decreased activity in prefrontal areas especially dorsolateral cortex

Also tissue loss in hippocampus

Increased activity in ventral prefrontal cortex

Increased volume and activity of amygdala

Anxiety disorders

Anxiety – fear in absence of threat

Anxiety disorder – when anxiety interferes with normal functioning

Many physiological symptoms – tachycardia, hypertension, sleep disturbances, nausea, etc.

Often seen with other psychiatric illness

Suspected biology

Amygdala, GABA, 5-HT systems consistently implicated

Chronic stress may damage stress response system early in life – increasing vulnerability

Treatment of anxiety disorders

CBT and SSRIs common: but drugs may not be fast acting

Behavioral approaches: exposure therapy for phobias

**4/19: Review**

Pain

People who can feel pain can still feel temperature and touch normally

Nociception is a different channel than hapsis and proprioception

Can’t feel pain – linked to a disorder of voltage-dependent Na+ channels

Post-central gyrus is consistently implicated in pain

Prickling pain is analogous to “fast” pain

Hapsis is what enables us to identify objects we touch and grasp

Nociceptors have free nerve endings

Nociception and pain are not interchangeable – nociception is perception of tissue damage while pain is a psychological experience that arises from sensation of tissue damage

Nociceptors are not widely found in brain and spinal cord (can have brain surgery without any sensations of pain)

TRPV1 receptors are what allow us to feel the burn of capsaicin in chili peppers

TRPA1 receptors are what allow us to feel the burn of wasabi

A delta fibers are what allow you to feel initial “fast” pain

C fibers are for slow pain

A delta fiber cell body is located in dorsal root ganglion

Damage to the prefrontal cortex (not insula) is concerned with the long term implications of pain

Allodynia – something that does normally not cause pain cause pain (putting on a t-shirt the day after a sunburn)

Hyperalgesia – double whammy (normally causes pain causes a greater amount)

Substance P is a neuropeptide inhibited by raphe nuclei

Mental Health

Positive symptoms of schizophrenia – intellectual impairments are less common (more often seen in negative symptoms)

Bipolar disorder is more heritable than depression

Reducing amount of a person’s REM sleep can also reduce depression (427-428)

SSRI is most commonly prescribed drug for anxiety disorder

Anxiety disorders have a very high co-occurrence with mood disorders

In some affective disorders, there appears to be tissue loss in the medial temporal lobe