The Neuroscience of Pain: Towards Objective Pain Assessment

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Purposes of This Presentation

- To provide a broad overview of the field of pain research
  - Acute and chronic pain.
  - The complexity of the pain experience.
- To review emerging knowledge
  - How we hurt
  - Types of pain: Somatic, neuropathic, functional disorders
  - The influence of life stress on pain
- To review approaches to pain measurement, emphasizing potential objective tools.
  - Brain imaging
  - Facial expression
  - Psychophysiology
Pain: An Aspect of Consciousness

- Pain, by current definitional standards, does not exist apart from consciousness.
  - “An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage”
    - International Association for the Study of Pain, 1979

- Nociception is non-conscious neural activity or “traffic.”

- The purpose of anesthesia is to render the surgical patient unconscious and thereby prevent pain.
Acute and Chronic Pain

- Acute pain is pain associated with tissue injury. It resolves with healing.
  - A beneficial biological function.
  - Self-limiting.

- Chronic pain is any painful condition persisting for three or more months (persists beyond tissue healing).
  - Serves no biological function; provides no benefit.
  - May stems from chronic disease or injury to nervous structures.
  - Commonly exists in the absence of a detectable or adequate cause.
  - Has a deleterious impact on quality of life.
What Could Be an Objective Measure?

- Functional brain imaging of pain-related processes that immediately precede consciousness.
- Other psychophysiological measures of brain or peripheral nervous system activity.
- Behaviors, including facial expression.
  - How can we distinguish malingering from true pain?
Pain and Nociception: A Critical Distinction

- **Pain**: Subjective awareness of tissue injury.
  - Occurs in the brain and requires consciousness.
  - An issue of psychological well-being.

- **Nociception**: Unconscious detection of tissue injury and transmission of injury signals to the brain.
  - Occurs in the body, is not conscious.
  - An issue of physiological well-being.

- The physiological impact of persisting nociception has major psychological and physical health consequences.
Pain: What Makes Us Hurt?

- **Nociceptor**: A nerve ending that detects tissue damage and initiates a message.
- A nociceptor does not habituate over time.
- It sensitizes with chemical irritation.
- It changes its own tissue environment by releasing peptides.
Impact of Nociception: Peripheral Nervous System

- Peripheral and central sensitization occurs, making minor, harmless stimuli exquisitely painful.
  - Molecular mechanisms determine how nerves function.
  - Nerve endings fire more readily and relay pathways amplify the injury signals.
  - *Allodynia*: Pain from stimuli that are not normally painful. “Touch-evoked pain.”
Inflammation

- Injury produces inflammation

Features of Inflammation
- Redness
- Heat
- Swelling (edema)
- Pain
- Loss of function

Inflammation
- Protects against infection
- Fosters tissue repair
- Sensitizes nerves and increases pain
- Chronic inflammation is destructive
Nociception and Central Transmission: Evidence from Neurophysiology

- Nociception activates:
  - Spinothalamic pathways that generate perception
  - Spinohypothalamic pathways that produce hormonal responses
  - Spinoreticular pathways that cause autonomic responses

- Injury signals drive both emotional structures and sensory structures
Nociception and Brain: Evidence from Functional Brain Imaging

- Brain structures responding include:
  - Somatosensory cortex, thalamus
  - Anterior cingulate, prefrontal cortices
  - Insula
  - Lenticular nucleus, cerebellum
  - Multiple limbic structures (the emotional brain)
Prefrontal Cortex & Amygdala: Balancing Emotion and Responsibility

- Amygdala is an integrating, coordinating center for defensive reactions.
- Medial orbitofrontal circuit has the strongest connection to amygdala.
- fMRI subjects viewing frightening faces showed bilateral amygdala activation, but putting a label on the faces increased right prefrontal activity and decreased amygdalar activity.
Nociception and Brain: Descending Influences

- The human descending tract contains almost a million fibers, but the ascending tract contains only a few thousand.

- Brain processing of injury information activates reflexes, hormone responses, and immune responses.

What goes up must come down.
What Is Emotion?

- James, Lange (19th century): feelings are a reflection of a change in the state of the body.

- Damasio (2003): An emotion is a brain process that we perceive as a feeling:
  - 1) an external stimulus activates certain regions of the brain
  - 2) those regions cause a emotional processing
    - this induces a change in the state of the body
  - 3) the "mind" perceives that change of state as a feeling.
Emotion and Cognition

- Cognition: memory, attention, reasoning, problem solving, coping, planning, meaning making.
- In humans, emotion and cognition are inseparable.
- We interpret physical arousal.
- Our thought processes including memories elicit physical arousal and emotion.
The Self: Cartesian Heritage

- Descartes’ “ghost in the machine.”
- Separation of mind and body.
- Clockwork mechanics.
- Descartes: “In order to improve the mind, we ought less to learn than to contemplate.”

René Descartes (1596-1650)

Tombstone: Bene qui latuit, bene vixit

He who hid well lived well.
“The doctrine I hold is: first, that states of consciousness ...are utterly different from nervous states; second, that the two things occur together – that for every mental state there is a correlative nervous state; third, that, although things occur in parallelism, there is no interference of one with the other. “

- J. Hughlings Jackson, 1884, p.706
Dennett’s Cartesian Theater
Stress

- The body’s response to a threat or strong demand from the environment.
- Necessary for adaptation and survival.
- Involves arousal, readiness for fight or flight.
- Can generate emotional states.
The Stress Response: HPA Axis

Miller et al., 2002
Other Stress Processes

- The autonomic nervous system causes the heart to beat faster and harder, raises blood pressure.
- Blood moves from internal organs to muscles.
- One experiences this as a racing or pounding heart, sweaty palms, rapid breathing, and a subjective state of threat and hypervigilance, with a readiness to flee or fight.
- Creates a system-wide predisposition for inflammation.
Chronic Stress

- Stress response should be self-limiting
- It may persist if the stressor persists or if a cascade of multiple stressors besets the person
- Stressor constellations exist and can include combinations of accident, illness, personal loss, and social problems such as vocational or family crisis
- Persisting stress can *dysregulate* normal biological rhythms, and promote pro-inflammatory conditions, thus contributing to chronic inflammatory
Impact of Nociception: Immune System

- **Immunity**: the ability to resist damage from microorganisms, toxins, tumors.
- Immune system is a sentient organ:
  - Detects what the nervous system cannot. Blalock, 2005
- Acute stress enhances the immune system while chronic stress suppresses it. McEwen, 2000
Life Stressors
Nociception as a Stressor

- Persisting injury signals are a stressor that triggers physiological responses.
- When this persists beyond injury or when there are chronic degenerative changes, the signaling serves no beneficial purpose.
- Fosters dysregulation of biological rhythms, systems.
- Disables normal functions, behaviors.
- Causes depression.
  - Pro-inflammatory cytokines
Pain: A Complex Phenomenon

- Injury signaling, negative emotion/cognition, and stress are interdependent.
- These three feed one another and it is difficult for the patient, a care provider, or a researcher to disentangle them.
The “Functional Pain Disorders”

- Examples: Fibromyalgia, irritable bowel syndrome, temporomandibular disorder, chronic fatigue syndrome, interstitial cystitis
- These are multi-symptom disorders that include pain.
  - Sleep problems, cognitive problems, disability
  - Highly co-morbid
- No identifiable causes.
- These patients suffer more than other sick people with pain.
Neuropathic Pain: A Family of Chronic Pain Conditions

- Chronic pains caused by damage to the peripheral or central nervous system.
- The pain is relentless, serves no useful purpose, and can seem to indicate bodily injury where there is none.
- Examples: post-herpetic neuralgia (shingles), peripheral neuropathy in diabetics, central (post-stroke) pain, spinal cord injury, CRPS, phantom limb pain.
- These pains are hard or impossible to control.
Phantom limb pain occurs in 50 – 80% of amputees. Its most common descriptions are variants of cramping, burning/tingling, shocking, shooting, and stabbing.

- One can have pain without having nociception.
- The brain generates pain all by itself.
A Classic Case

British Admiral Lord Nelson experienced a phantom arm with finger nails digging into the palm and exquisite pain. He took this as proof of the soul.
Measuring Pain: Subjective Methods

- Simple pain reports
  - 11 point or 101 point rating scales

- Complex pain instruments
  - Pain intensity
  - Interference with everyday life
  - Emotional and mood changes

- Word describing pain
  - Sensory, emotional and evaluative dimensions
  - Pain qualities
Measuring Pain: Objective Methods 1

- Functional brain imagery
- Documents activity in selected areas of the brain under certain conditions.
- Areas related to pain are well-known.
  - They vary across people and circumstances.
  - They overlap with attention, threat, etc.
Empathy

- An overlap exists between brain areas activated when a person undergoes painful stimulation and when he/she observes another undergoing such painful stimulation.
- fMRI studies indicate bilateral activation in the anterior cingulate cortex and the anterior insula during both self-experienced pain and observation of pain in others.
Saarela et al. (2006) Detecting Pain Intensity from Another’s Face

- When subjects observed pain from the faces of chronic pain patients, activations in bilateral anterior insula (AI), left anterior cingulate cortex, and left inferior parietal lobe in the observers’ brains correlated with their estimates of the intensity of observed pain.

- These and other studies in this area show that the “intersubjective representation of pain” is an aspect of human empathy and, as such, a natural basis for pain measurement.
Measuring Pain: Objective Methods 2

- Facial expression
- Is there a facial expression in humans that is unique to pain?
- A primal expression of pain invariant across cultures?

*A Man in Pain*
by Sir Charles Bell
*circa 1810*
Basic Definitions:

- **Facial expressions** are coordinated, stereotyped behavioral phenotypes that integrate with vocalization, gestures and postures to make higher order social interaction possible.

- **Prosopagnosia** is an inability to recognize people by their faces.
The Fundamental Issues

- Does a “primal face of pain” exist?
  - Across genders, cultures
  - In the infant and the demented elderly patient

- How can we gauge facial expression?
  - Complex
  - Dynamic (constantly changing)

- Can this ever become a practical tool?

- Is pain what the patient says it is, or what the patient winces it to be?
Background

- Ekman and Friesen, 1978
  - Facial Action Coding System: A Technique for the Measurement of Facial Movement
  - Designed primarily for the emotions:
- Revised 2002, Joseph Hager
- Facial action coding involves identifying muscles that produce facial appearances.
# Initial Purpose: Code Emotions

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<th>Disgust</th>
<th>Fear</th>
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The Basis of Coding
People in Pain
Action Units: Patterns of Muscle Contraction and Relaxation

- Observe and videotape a facial action sequence.
- Decompose to Action Units (AUs) and their temporal segments
- The Facial Action Coding System (FACS)
  - Comprises 32 AUs
  - Multiple action descriptors (ADs)
AUs

- # 1 Inner Brow Raiser -- Frontalis (pars medialis)
- # 2 Outer Brow Raiser -- Frontalis (pars lateralis)
- # 4 Brow Lowerer -- Corrugator supercilii, Depressor supercilii
- # 5 Upper Lid Raiser -- Levator palpebrae superioris
- # 6 Cheek Raiser -- Orbicularis oculi (pars orbitalis)
- # 7 Lid Tightener -- Orbicularis oculi (pars palpebralis)
- # 9 Nose Wrinkler -- Levator labii superioris alaquae nasi
- # 10 Upper Lip Raiser -- Levator labii superioris
AUs

- # 11 Nasolabial Deepener -- Zygomaticus minor
- # 12 Lip Corner Puller -- Zygomaticus major
- # 13 Cheek Puffer -- Levator anguli oris (also known as Caninus)
- # 14 Dimpler -- Buccinator
- # 15 Lip Corner Depressor -- Depressor anguli oris (also known as Triangularis)
- # 16 Lower Lip Depressor -- Depressor labii inferioris
- # 17 Chin Raiser -- Mentalis
- # 18 Lip Puckerer -- Incisivii labii superioris and Incisivii labii inferioris
- # 20 Lip stretcher -- Risorius w/ platysma
AUs

- # Neck Tightener
- # 22 Lip Funneler -- Orbicularis oris
- # 23 Lip Tightener -- Orbicularis oris
- # 24 Lip Pressor -- Orbicularis oris
- # 25 Lips part -- Depressor labii inferioris or relaxation of Mentalis, or Orbicularis oris
- # 26 Jaw Drop -- Masseter, relaxed Temporalis and internal pterygoid
- # 27 Mouth Stretch -- Pterygoids, Digastric
- # 28 Lip Suck -- Orbicularis oris
- # 31 Jaw Clencher
Some Additional AUs

- # 38 Nostril Dilator
- # 39 Nostril Compressor
- # 43 Eyes Closed -- Relaxation of Levator palpebrae superioris; Orbicularis oculi (pars palpebralis)
- # 45 Blink -- Relaxation of Levator palpebrae superioris; Orbicularis oculi (pars palpebralis)
- # 46 Wink -- Relaxation of Levator palpebrae superioris; Orbicularis oculi (pars palpebralis)
Some Action Descriptors

- * 19 Tongue Out
- * 29 Jaw Thrust
- * 30 Jaw Sideways
- * 32 Lip Bite
- * 33 Cheek Blow
- * 34 Cheek Puff
- * 35 Cheek Suck
- * 36 Tongue Bulge
- * 37 Lip Wipe
- * 51 Head turn left
Basic Mechanisms: The Brain

- Recognition of particular faces depends heavily on the fusiform face area (FFA) of the **fusiform gyrus** located on the ventral surface of the temporal lobe.
  - we now know that this area is not specific to faces
- The bilateral **superior temporal sulcus** processes facial expression in others, and such expression is rich in information, particularly emotion.
  - Also integrates visual and auditory information.
Fusiform Gyrus

Diagrammatic mid-sagittal view of the brain showing the right hemisphere

- paracentral sulcus
- central sulcus
- precuneus
- parieto-occipital sulcus
- calcarine sulcus
- frontal lobe
- corpus callosum
- fusiform gyrus (medial temporo-occipital gyrus)
- lingual gyrus
Two Other Key Structures: ACC and Insula
Basic Mechanisms: Mirror Neurons

- Neurons that fire both when an animal acts and when the animal observes the same action performed by another (especially conspecific) animal.

- The emotion of disgust is a mirror emotion involving insular cortex.

Fig. 1. Examples of transitive and intransitive actions performed by the experimenter in front of the recorded monkey (right column); same gestures made by the monkey (left column). Intransitive monkey actions, although rarely evoked during recording sessions, are shown here to outline their similarity with the same actions performed by the experimenter. From top to bottom: grasping of a piece of food; sucking juice from a syringe; lips protruded face.
Basic Mechanisms: Genetics

- Work by Peleg and others (2006) with blind subjects shows that people blind from birth emit facial expressions that belong to their parents, even though they have never seen these expressions.
- “Hereditary family signature of facial expression”
Recognizing the human face

- The other side of prosopagnosia: recognizing a human face where there is none.
Pain Expression in Demented Patients

- Kunz and colleagues studied the facial expression of pain in dementia patients experiencing mechanically induced pain, contrasting their observations with similar expressions in normals of similar age experiencing the same painful stimulation.

- Subjects underwent repeated trials with a pressure algometer applied to right and left forearms at two intensities.

- To score event-related facial expressions, they videotaped faces under varying experimental conditions and analyzed the recordings using the FACS.
Three Hypotheses

1) Demented patients experiencing noxious stimulation exhibit more intense and frequent facial expressions than normals;

2) This is due to nonspecific increases in facial responses in the demented vs normal patient; and

3) Demented patients encode the intensity of noxious stimuli less well than normals.
Kunz et al., Findings

1) The demented patients displayed higher frequencies and higher intensities of facial responses;
   - More AUs for the demented patients and also greater effect sizes for AUs common to the two groups.
   - Suggests that facial expression is less socially inhibited in demented patients than normals.
Kunz et al., Findings

- The second hypothesis failed to gain support because the pain-relevant AUs were more frequent and intense in the demented patients than in the normals.
  - Specific rather than nonspecific facial expression distinguished the demented patients from the normals.

- The third hypothesis failed because demented patients did as well or better than normals in the stimulus-response relationship,
  - nociception and pain reflect just as validly in the facial expressions of dementia patients as in the facial expressions of normals.
AUs, ADs Across Groups

The University of Utah
Applications

- Demented patients; other cognitively compromised patients.
- Infants.
- Partial sedation.
- Non-English speaking patients.
- A means of validating other pain assessment tools?
- BUT: What does chronic pain look like in facial expression?
- Can a skilled actor learn to produce pain expression?
Conclusions

- Human pain is extraordinarily complex, involving emotion and cognition as well as signals of tissue injury.
- Chronic and acute pain are very different and come from damage to the nervous system.
- Pain measurement has traditionally used only subjective reports.
- Recent advances in functional brain imaging and coding of facial expression open new possibilities for objective measurement of pain states.
Challenges

- FACS requires trained coders and is impractical.
  - Or automated detection and coding.
- Facial expression is not always available.
- Visual observation of muscle activity is a low sensitivity methodology.
END OF PRESENTATION