Somatic sensory receptors. Pain.
Sensory receptors convert environmental energy into neural signals.

Sensation is a cognitive process that requires the full powers of the central nervous system (CNS).

Sensation begins with the sensory receptors that actually interface with the world, and these receptors use energy from the environment to trigger electrochemical signals that can be transmitted to the brain = sensory transduction.

Transduction also sets the basic limits of perception, determines the sensitivity, range, speed, versatility, and vigor of a sensory system.
Sensory stimuli & modalities

- **Stimulus** = a factor in the environment that produces an effective response in a *sensory receptor* (biological transducer), involving **exchanges of energy**

  *Stimulus intensity - a measure of energy content*

- **Sensory modalities:**
  - *general sensory modalities* – seeing, hearing, touching, smelling, and tasting, as well as senses of pain, balance, body position, and movement.
  - *complex sensations* (slipperiness, wetness) – combination of simpler sensations (wetness = pressure + temperature)
  - *affect* = subjective perception of the sensory modality, influenced by previous experience and learning.

Also, intricate sensory systems of which we are *not conscious*, monitor the internal milieu and report on the *body’s chemical and metabolic state.*
Sensory receptors

• Classified by
  - the nature of signals they sense: photoreceptors, chemoreceptors, mechanoreceptors, thermal receptors
  - their vantage point in the body: exteroceptors, enteroreceptors, proprioreceptors (receptors of one’s own).
    - Telereceptors are specialized sense receptors, such as those in the eyes, ears and nose, that respond to distant external stimuli
    - Nociceptors = pain receptors, detect noxious agents both internally and externally

• Are optimized (lowest threshold) for a specific stimulus

• Specificity is ensured by their structure and position, a propriety known as univariance - the sensory receptor and its subsequent neural circuits do not know what stimulated them, they give the same type of response regardless.

• Accessory structures enhance the specific sensitivity of receptors and exclude unwanted stimuli (e.g. lens of the eye)
### Classification of sensory receptors

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# What are we aware of?

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Molecular signaling mechanisms for sensory transduction

- **Integral membrane proteins: G protein–coupled receptors (GPCRs)** for vision, olfaction, some types of chemoreception (some types of taste) → the second-messenger pathways substances are the same ones used for nonsensory tasks in cells (cyclic nucleotides, inositol phosphates, kinases).

- **Modified membrane ion channels** in the primary transduction process (mechanoreceptors - hair cells of audition and the vestibular organs, some taste cells). These channels gating is sensitive to the physical distortion of the membrane that they lie in.

- To achieve a specificity for certain stimulus energies, many sensory receptors must use specialized cellular structures.
Sensory transduction changes stimuli into biological information

• Sensory transduction requires detection and amplification, usually followed by a local receptor potential (localized depolarization) = the first electrical response to a stimulus

• Stimulus/Energy \(\rightarrow\) sensory receptor
  \(\rightarrow\) graded receptor potential
  \(\rightarrow\) modulate membrane voltage/voltage-gated ion channels \(\rightarrow\) regulate Ca\(^{2+}\) into the sensory cell synaptic transmitter release
  \(\rightarrow\) triggers APs at a specific rate and pattern
  \(\rightarrow\) encode the information that the CNS receives

The quality of the stimulus is encoded in many features of the firing:

- in the firing rate and the temporal pattern, consistency of the APs transmitted down the afferent fibre
- the number of sensory receptors activated
Adaptation accounts for the decreasing effect of a stimulus

• Different sensory receptors exhibit differing degrees of **adaptation** in response to an adequate stimulus.
  • **Slowly adapting** receptors continuously signal the intensity and the duration of the stimulus (**tonic receptors**):
    muscle spindles, Golgi tendon, receptors of the macula in the vestibular apparatus, pain receptors, baroreceptors of the arteries (longest measured time for complete adaptation, about 2 days), chemoreceptors of the carotid and aortic bodies.
  • **Rapidly adapting** receptors signal changes in stimulus strength or the onset and offset of a stimulus (**phasic receptors, rate or movement receptors**):
    Pacinian corpuscle adapts extremely rapidly and hair receptors adapt within a second.

  **Tonic receptors** – slow/no adaptation → they are **intensity receptors**
  **Phasic receptors** – significant adaptation occurs → they are **velocity receptors**

• **Adaptive ability/ "accommodation" to the stimulus:** is a property of the sensory receptor and is usually associated with its structure or the morphology of the surrounding tissue.
Adaptation accounts for the decreasing effect of a stimulus

In an adapting receptor, the receptor potential & AP frequency will decline even though the stimulus is maintained

**Slow or rapid adaptation**

- As a receptor adapts, sensory input to the CNS is reduced and the sensation is perceived as less intense → *prevent sensory overload; allow less important or unchanging environmental stimuli to be partially ignored*
- Rapid adapting receptors sense the *rate of change of a stimulus*
Perception of sensory info involves encoding, transmission & decoding

• **Encoding**
  - Input intensity determines frequency/rate of APs in the initiation region
  - There is an upper limit to number of APs/sec because of the *refractory period* of the nerve membrane → restriction in the sensory process

• **Transfer to CNS**: frequency-modulated encoding, APs transmission

• **Interpretation** of the encoded and transmitted information into a **perception**:
  - depends on *neural pathway*; ex. all info arriving on the optic nerves is interpreted as light, even the signal may have arisen as a result of pressure applied on the eyeball (*univariance* – the same kind of response regardless the stimulus)
  - perception of the localization of a cutaneous sensation to a particular part of the body depends on the pathway it takes to the CNS...
  - a *sensation/pain arising in a visceral structure* (heart, gallbladder) is perceived as coming from a portion of a body surface (nerve fibers from different anatomical regions converge on the same spinal neurons) = referred pain
Transduction & Coding

- Adequate stimulus related to stimulus intensity and duration
- Sensory receptor
- Synaptic integration
- Primary afferent neurone
- 2nd order neurone
- Frequency coded action potentials conducted down primary afferent neurone
- Reduced frequency of action potentials conducted down 2nd order neurone
- Transduction and generation of graded receptor potential
- Action potentials cause transmitter release & generate graded potentials (EPSPs) in 2nd order neurone
- Generated action potentials
- Threshold
- Graded receptor potential
- EPSPs
Sensory Coding for Intensity & Duration

- Amplitude 40mv, duration 4ms
- Amplitude exceeds threshold & generates action potentials
- Action potentials conducted down sensory axon

1. Receptor potential
2. Integration at trigger zone
3. Action potentials
4. Neurotransmitter release

Recording arrangement from sensory unit

- Longer and stronger stimulus
- Amplitude 65mv, duration 7ms
- Note decay of receptor potential
- Generates higher frequency of action potentials for longer period
- More action potentials conducted down sensory axon

Small amount transmitter released

Large amount transmitter released
SOMATIC SENSORY RECEPTORS

Somatic sensation or somesthesias - is the most widespread and diverse of the body’s sensory systems (soma = body in Greek)

Somatic-sensory receptors
- are distributed throughout the body, within the skin, subcutaneous tissue, skeletal muscles, bones and joints, major internal organs, epithelia, and cardiovascular system
- vary widely in their specificity:
  - mechanoreceptors to transduce pressure, stretch, vibration, tissue damage;
  - thermoreceptors to measure temperature;
  - chemoreceptors to sense a variety of substances/chemical changes.

Somatic sensation usually considered as a combination of at least 4 sensory modalities: touch, temperature, body position (proprioception), and pain (nociception).
A variety of sensory endings in the skin transduce mechanical, thermal, and chemical stimuli

Somatic sensory receptors range from simple nerve endings to complex combinations of nerve, muscle, connective tissue, and supporting cells.

**Mechanoreceptors**
- sensitive to physical distortion (bending or stretching), account for many of the somatic sensory receptors
- monitor throughout the body
  - the physical contact with the skin
  - pressure on the teeth
  - blood pressure in the heart and vessels
  - stretching of the gut and bladder
- mechanoreceptors’ transduction site is one or more unmyelinated axon branches.
- Signal transduction in cutaneous mechanoreceptive nerve endings probably involves the gating of ion channels, some of these belonging to the TRP superfamily

**Thermoreceptors**
- respond best to changes in temperature

**Chemoreceptors**
- are sensitive to various kinds of chemical alterations
Mechanoreceptors in the skin provide sensitivity to specific stimuli (vibration, steady pressure)

Skin:
- hairy and glabrous/hairless,
- protects us from our environment by preventing evaporation of body fluids, invasion by microbes, abrasion, and damage from sunlight.
- provides our most direct contact with the world through sensory receptors, that have an exquisite sensitivity
- has an outer layer, the epidermis, and an inner layer, the dermis, over the subcutaneous tissue

The receptors in the skin are sensitive to and discriminate many types of stimuli. They respond when the skin is vibrated, pressed, pricked, or stroked, or when its hairs are bent or pulled.
Mechanoreceptors in the skin provide sensitivity to specific stimuli (vibration, steady pressure)

Hairless skin, found on the palm of the hand, fingertips, soles of the feet, pads of toes:
- Merkel disks (intensity rec, lowest layers of epidermis, slow adaptation, respond to steady pressure),
- Meissner corpuscles (velocity rec, adapt rapidly)
- Pacinian corpuscles (very rapidly adapting/acceleration rec., sensitive to fast-changing stimuli as vibration)

Hairy skin:
- hair-follicle receptors: mechanoreceptors that adapt more slowly
- Ruffini endings (in the dermis) are slowly adapting
- also present: Merkel disks grouped in tactile disks, and Pacinian corpuscles to sense vibration in the hairy skin
- non-myelinated nerve endings – limited tactile function, sense pain
Pacinian corpuscles - very rapidly adapting/acceleration receptors, sensitive to fast-changing stimuli as vibration

Meissner corpuscles - in the ridges of glabrous skin, are velocity receptors, adapt rapidly

Ruffini’s corpuscles - occur in the subcutaneous tissue of both hairy and glabrous skin; stimulated by “fluttering” vibrations; relatively slowly adapting receptors, respond best to low frequencies

Merkel disks - intensity receptors, slow adaptation, respond to steady pressure; flattened, non-neural epithelial cell that synapses on a nerve terminal; lie at the border of the dermis and epidermis of glabrous skin.
- The largest mechanoreceptor (up to 2 mm long and almost 1 mm in diameter)
- Located in the subcutaneous tissue of both glabrous and hairy skin.
- It has an ovoid capsule with 20-70 onion-like, concentric, slick layers of connective tissue (with viscous fluid between them) and a nerve terminal in the middle.
- The capsule is responsible for the rapidly adapting response; when the capsule is compressed/decompressed, energy is transferred to the nerve terminal, its membrane is deformed, and *mechanosensitive channels open*.
- Current flowing through the channels generates a *depolarizing receptor potential* that, if large enough, causes the axon to fire an AP.
- Is most sensitive to vibrations of 200 - 300 Hz, and its threshold increases dramatically below 50 Hz and above ~500 Hz.
- The sensation evoked by stimulation of Pacini’s corpuscle is a *poorly localized humming feeling*.
- If the stimulus pressure is maintained, the layers slip past one another and transfer the stimulus energy away so that the underlying axon terminal is no longer deformed and the receptor potential dissipates → Pacini’s corpuscle senses vibrations and is *almost unresponsive to steady pressure* → *adapting sensor.*
Hair is a sensitive part of our somatic sensory system.

Hairs grow from follicles embedded in the skin. Each follicle is richly innervated by free mechanoreceptive nerve endings that either wrap around it or run parallel to it.

Bending of the hair causes deformation of the follicle and surrounding tissue, which stretches, bends, or flattens the nerve endings and increases or decreases their firing frequency.

Various mechanoreceptors innervate hair follicles, and they may be either slowly or rapidly adapting.
• **Sensory unit** = a single afferent neurone with all its receptor endings distributed in a receptive field

• The size of the receptive field varies inversely with the density of receptors. High receptor density gives rise to small receptive fields, which lead to greater **acuity** or **discriminative ability** of the input.

• Pacini’s corpuscles have extremely broad receptive fields, whereas those of Meissner’s corpuscles and Merkel’s disks are very small. The last two seem to be responsible for the ability of the fingertips to make very fine **tactile discriminations**. Small receptive fields are an important factor in achieving high **spatial resolution**.

• **Overlapping receptive fields** (of identical sensory receptors) allows interactions between sensory inputs and **improves sensory discrimination**.
Two-point discrimination – measures *spatial resolution*

Arms and legs: large receptive fields – up to 40 mm
Fingertips: smaller receptive fields – 2 mm
Receptive fields and spatial discrimination of skin mechanoreceptors

A. Receptive field of Pacini’s corpuscles
B. Receptive field of Meissner’s corpuscles
C. Two-point discrimination across the skin

Different regions of the body have varying two-point discrimination thresholds.
Mechanical force is transferred from cells and their membranes to mechanosensitive channels (unclear mechanisms):

Ion channels may be physically coupled to:
- either *extracellular structures* (e.g., collagen fibers) or
- *cytoskeletal components* (e.g., actin, microtubules) that transfer energy from deformation of the cell to the gating mechanism of the channel.

- Mechanically gated ion channels of sensory neurons depend on the *actin cytoskeleton*.

- Some channels may be sensitive to stress, sheer, or curvature of the *lipid bilayer* itself and require no other types of anchoring proteins.

- Other channels may respond to *mechanically triggered second messengers such as* DAG (acting directly on the channel) or IP3 (acting indirectly via an IP3 receptor).
Skin receptors & somatosensory transduction

• Nerve endings stimulation $\rightarrow$ deflection $\rightarrow$ mechanical sensitive (stretch) cation channels

• Cation influx is directly proportional with the degree of deformation (respectively to the no. of stimulated receptors)

• AP if threshold attained

• Nerve fibres of the first order neuron $\rightarrow$ second order neuron (spinal cord) $\rightarrow$ third order neuron in the thalamus
Temperature sensation – thermoreceptors

Cold or warm… values along a temperature continuum, with differences in the amount of molecular motion

**Thermoreceptors**

= *naked nerve endings* supplied by
  - thin *myelinated fibers* (*cold receptors*, response peak at about \(30^\circ C\))
  - *nonmyelinated fibers* (*warmth rec*, response peak at about \(43^\circ C\)) with low conduction velocity
- *Phasic* (rapidly adapting, responds only to temp changes) and *tonic* (depend on local temperature) components in their response
- Different densities on the body surface, *cold* > *warmth receptors*
- **Comfort zone** – no appreciable temperature sensation, 30-36°C
- at skin temperature <17°C, *cold pain* is sensed by pain recept.
- at very high skin temperature (above 45°C) - *paradoxical cold* caused by activation of some cold receptors

Temperature perception is highly processed by higher centers
Temperature sensitivity of cutaneous thermoreceptors.
The curves represent the mean steady firing rates of neurons from warmth receptors and cold receptors.
• Dynamic changes in skin temperature
• Body temp = balance between thermogenesis/ thermolysis
Pain

- Pain is a protective experience.

1. **Somatic**: - cutaneous sensation = *superficial pain*
   - from muscles, joints, bones, connective tissue
     = *deep pain*

2. **Visceral pain**: from internal organs (strong contraction, forcible deformation…)

- Pain is sensed by **Nociceptors** (*free nerve endings*) of unmyelinated C and Aδ-fibres that transduce intense stimuli into electrical events.
  - **C-fibres** (slow, chronic pain sickening burning sensation which persists long after stimulus is removed).
  - **Aδ-fibres** (fast, acute, abrupt sensation)

- **Modalities**
  1) Heat/Cold, 2) Mechanical, 3) Polymodal (temperature, mechanical and chemical).
Types of Pain and Their Qualities: Fast Pain and Slow Pain

• **Initial, fast pain** (*sharp pain, pricking pain, acute pain, electric pain*) is felt within about 0.1 second after a pain stimulus is applied.

  Fast pain is felt when a needle is stuck into the skin, when the skin is cut with a knife, or when the skin is acutely burned. It is also felt when the skin is subjected to electric shock.

• **Delayed, slow pain** (*slow burning pain, aching pain, chronic pain*) begins only after 1 second or more and then increases slowly over many seconds and sometimes even minutes; it is usually associated with *tissue destruction* and can lead to prolonged, unbearable suffering.
Pain receptors and their stimulation

• Pain receptors are free nerve endings.

The pain receptors are widespread in the superficial layers of the skin as well as in certain internal tissues, such as the periosteum, the arterial walls and the joint surfaces.

• Pain can be elicited by multiple types of stimuli, classified as mechanical, thermal, and chemical pain stimuli.

  - In general, fast pain is elicited by the mechanical and thermal types of stimuli, whereas slow pain can be elicited by all three types.

  - Some of the chemicals that excite the chemical type of pain are bradykinin, serotonin, histamine. The chemical substances are especially important in stimulating the slow type of pain that occurs after tissue injury.

• In contrast to most other sensory receptors of the body, pain receptors adapt very little and sometimes not at all.
Types of pain

Referred Pain:

- a person feels pain in a part of the body that is fairly remote from the tissue causing the pain: pain in one of the visceral organs often is referred to an area on the body surface.

- Knowledge of the different types of referred pain is important in clinical diagnosis because in many visceral disorders the only clinical sign is referred pain.

- Mechanism of Referred Pain: branches of visceral pain fibers synapse in the spinal cord on the same second-order neurons that receive pain signals from the skin.

When the visceral pain fibers are stimulated, pain signals from the viscera are conducted through at least some of the same neurons that conduct pain signals from the skin, and the person has the feeling that the sensations originate in the skin itself.
Visceral Pain

• In clinical diagnosis, pain from the different viscera of the abdomen and chest is one of the few criteria that can be *used for diagnosing* visceral disorders.

• Often, the viscera have sensory receptors for no other modalities of sensation besides pain.

• *Visceral pain differs from surface pain* in several important aspects:
  - *highly localized types of damage to the viscera rarely cause severe pain*,
  - a stimulus that causes *diffuse stimulation of pain nerve endings* causes pain that can be severe (ischemia caused by occluding the blood supply to a large area of gut stimulates many diffuse pain fibers at the same time and can result in extreme pain).
Causes of Visceral Pain

- Any stimulus that excites pain nerve endings in diffuse areas of the viscera can cause visceral pain.
  - *ischemia* of visceral tissue
  - *chemical damage* to the surfaces of the viscera,
  - *spasm of the smooth muscle, excess distention* of a hollow viscus, and *stretching of the connective tissue* surrounding or within the viscus.

- Essentially all visceral pain that originates in the thoracic and abdominal cavities is transmitted through *small type C pain fibers* and, therefore, can transmit only the *chronic-aching-suffering type of pain*.

- **Ischemia.** Ischemia causes visceral pain in the same way that it does in other tissues: formation of acidic metabolic end products or tissue-degenerative products such as bradykinin, proteolytic enzymes, or others that stimulate pain nerve endings.

- **Chemical Stimuli.** On occasion, damaging substances leak from the gastrointestinal tract into the peritoneal cavity. For instance, proteolytic acidic gastric juice often leaks through a ruptured gastric or duodenal ulcer. This juice causes widespread digestion of the visceral peritoneum, thus stimulating broad areas of pain fibers. The pain is usually extremely severe.
Causes of Visceral Pain

• **Spasm of a Hollow Viscera:** a portion of the gut, the gallbladder, a bile duct, a ureter, can cause pain - mechanical and chemical stimulation of the pain nerve endings, as the spasm might cause diminished blood flow to the muscle. Often in the form of *cramps*, with the pain increasing to a high degree of severity and then subsiding. This process continues intermittently, once every few minutes. The *cramping type of pain* frequently occurs in appendicitis, gastroenteritis, constipation, menstruation, gallbladder disease, or ureteral obstruction.

• **Insensitive Viscera.** A few visceral areas are almost completely insensitive to pain of any type: parenchyma of the liver and the alveoli of the lungs. Yet the liver *capsule* is extremely sensitive to both direct trauma and stretch, and the *bile ducts* are also sensitive to pain. In the lungs, even though the alveoli are insensitive, both the *bronchi* and the *parietal pleura* are very sensitive to pain.
Clinical abnormalities of pain and other somatic sensations

• Hyperalgesia
  A pain nervous pathway sometimes becomes excessively excitable → hyperalgesia = hypersensitivity to pain.

  Possible causes of hyperalgesia are:

  (1) **excessive sensitivity of the pain receptors** themselves, which is called **primary hyperalgesia**: eg. extreme sensitivity of sunburned skin which results from sensitization of the skin pain endings by local tissue products from the burn (histamine, prostaglandins etc).

  (2) **facilitation of sensory transmission**, called **secondary hyperalgesia** - frequently results from lesions in the spinal cord or the thalamus.
Substance P, released from nerve endings, increases capillary permeability and contributes to inflammation.

Substance P causes mast cells to release histamine, which in turn activates nociceptor endings.

Figure 15-29  Hyperalgesia of inflammation.
The spinothalamic tracts and their sensory function.
Target sites for drugs which produce pain relief (Analgesia)

1) Block synthesis, release or receptors for proinflammatory / pronociceptive agents.

2) Block action potentials

3) Block neurotransmitter release.

4) Block pain pathways in the CNS