            - A-delta
                - Pain (fast and localised)
            - C fiber
                - Pain (delayed and poorly localised)
            - A-delta + beta
                - Tactile, vibration
        - Co-released with glutamate, from peripheral and central nerve terminals
            - Release invovles SNARE complex → can be inhibited by Botulinum Toxins
        - CGPR modualtes glutamatergic transmission, no effect on spontaneous neuronal firing
        - CGPR facilitate nociceptive activation (driven by glutamate release)
            - Glutamate is the excitatory neurotransmitter in the ascending trigeminal pathway
        - Can be blocked by activation of 5-HT1 receptors (triptans)
        - CGRP levels are increased during migraine attacks
- Postdrome phase

Sound

Sound is a mechanical disturbance from a state of equilibrium that propagates through an elastic material medium.

Wave not equal to particle, particle movement creates wave (back and forth movement)
Sensitivity of hearing organs very high
Medium required for sound to propagate → no sound in vacuum

Coupling ‘sound receivers’ into mechanical disturbances!

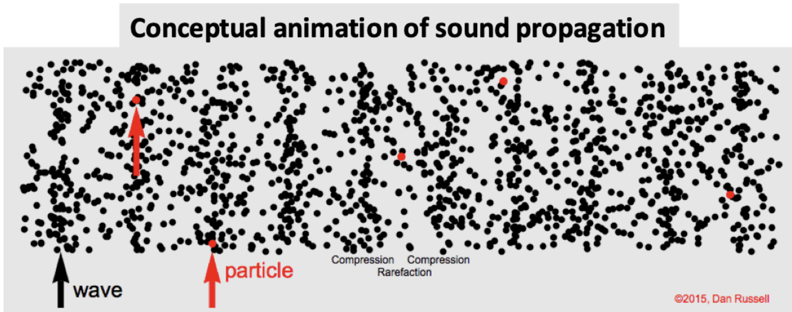
Media: Gas (air), fluid (water), solid (bones)

Displacement (x)
Velocity ($\dot{x}$)
Acceleration ($\ddot{x}$)
Frequency (1/s)

Force ($m\vec{a}$)
Pressure (F/m^2)

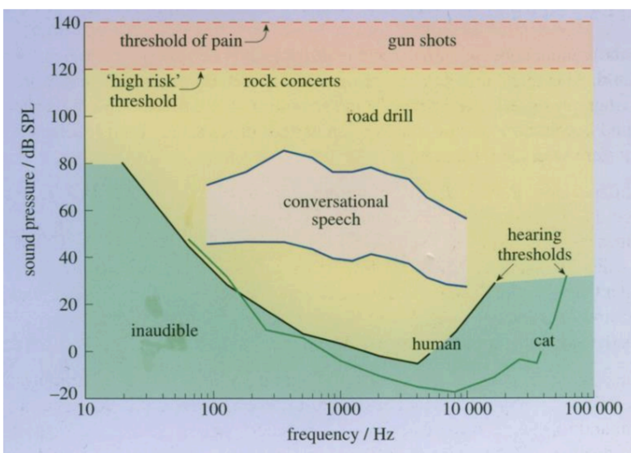
Direction of Sound

Speed of Sound



Lower sound pressure hearing threshold = better hearing as lower intensity can be heard as well
Lower hearing threshold = more sensitive (lower amplitudes can activate)

The dynamic range: … to panic room!



SPL (sound pressure level, in decibels)

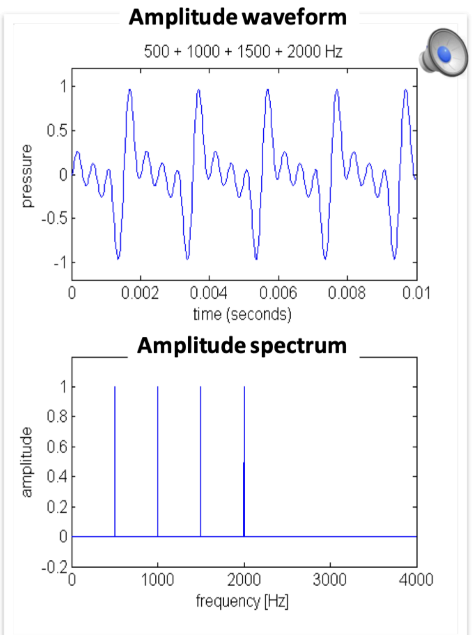
- Reference level is 20 microPa, atmospheric pressure = 100kPa
- $SPL = 20 \times log_{10}(\frac{p}{p\,reference})$

For pure tones:

Amplitude = loudness
Frenquecny = pitch

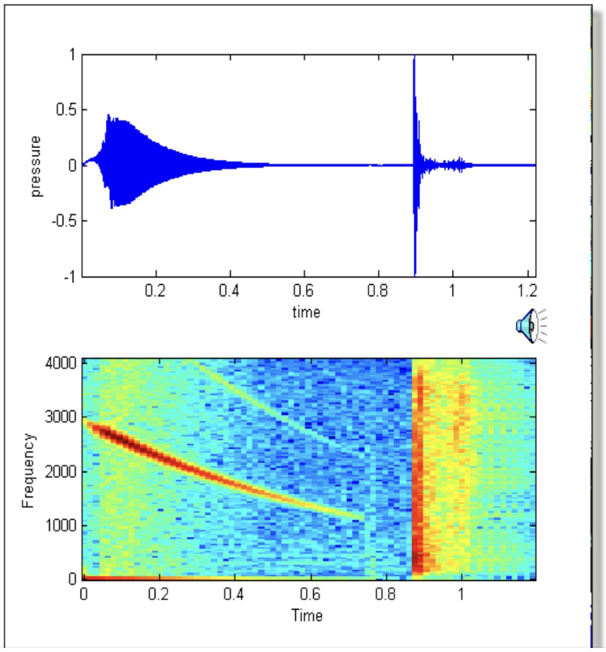
- Sounds are usually a mixture of different pure tones with different frequencies

- This representation of sound is known as the spectrum and is the fundamental organising principle of the auditory system

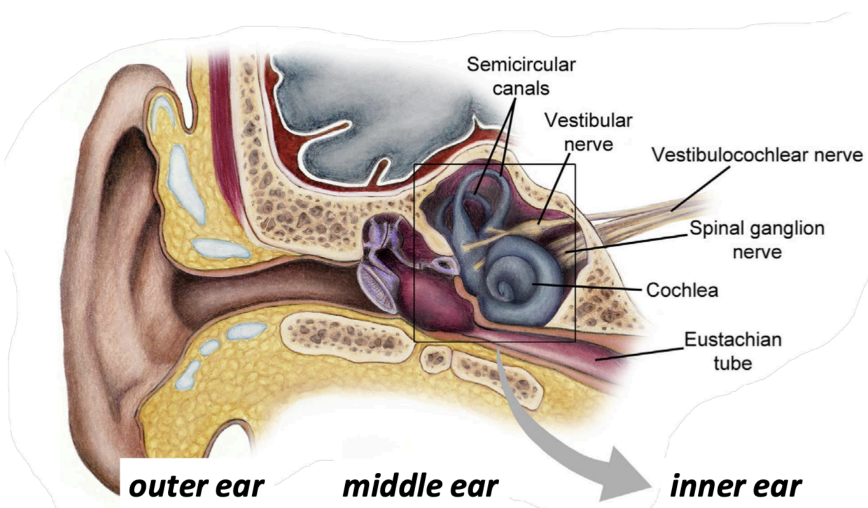


Spectrum is a complete description of a sound only if the frequency of the sound is constant over time. However, natural sounds usually do vary with time.

Spectrogram → divide sounds into short time segments, and calculate spectra for each time segment in turn, decoding the sound into small components (at time 0, the loudest/highest amplitude tone indicated by the red colour, has a frequency of around 3000)



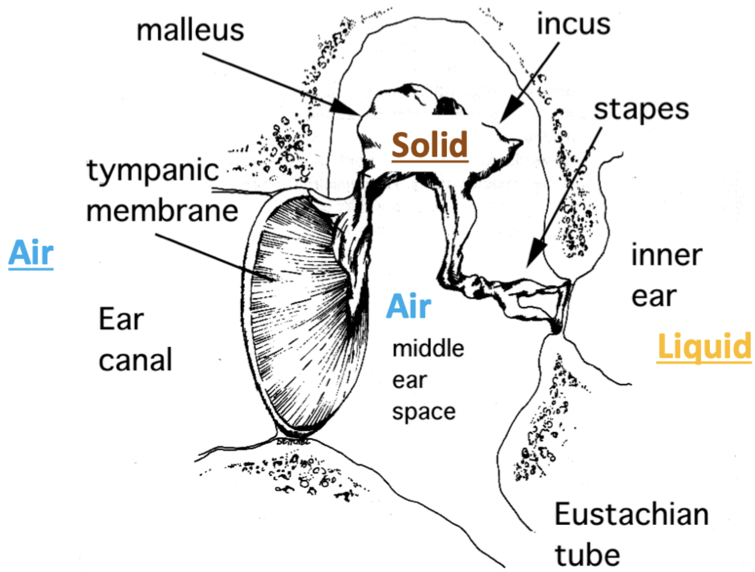
Human Ear



Human ears are pressure detectors

Outer + Middle Ear

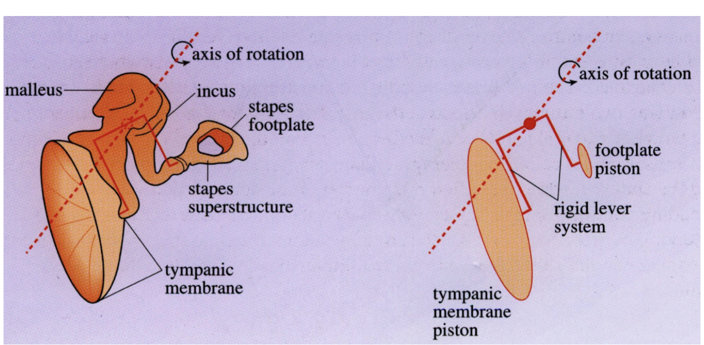
The middle ear :

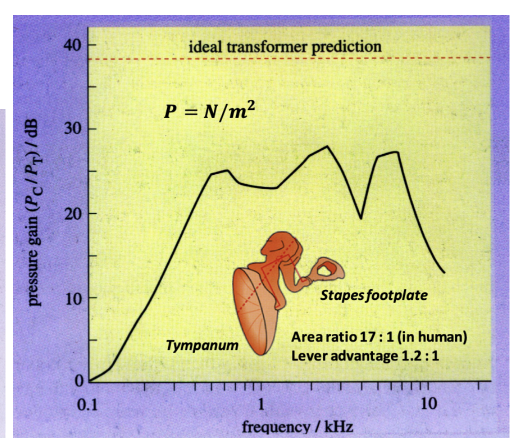


Impedance loss without middle ear:

99.9%
(-30dB)

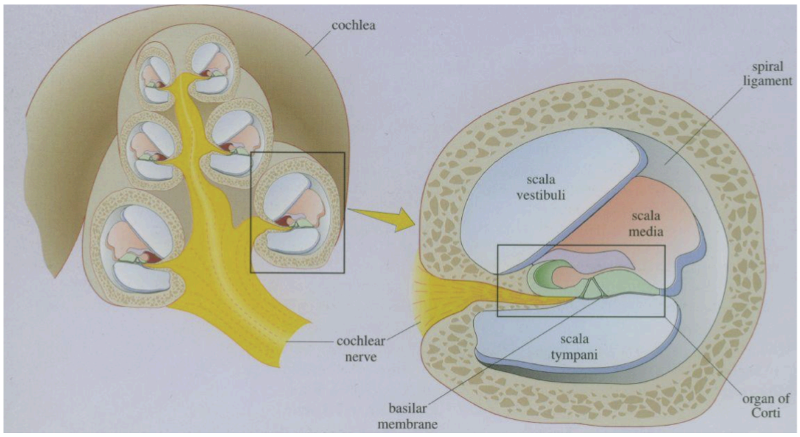
- Outer ear receives sound, amplifies sound (by pinna) before reaching tympanic membrane
  - Increase pressure wave by 30 to 800 times
- Middle air allows for impedance matching between air in outer ear and liquid in inner ear → sound effectively travels into inner ear
  - Tympanic membrane → malleus → incus → stapes → inner ear
  - Large surface area for tympanic membrane, but oval window has small surface area
    - Important for impedance matching
      - Middle ear has air → low impedance
      - Inner air has liquid → high impedance
        - Sound waves may be lost as it travels from low impedance to high impedance
      - Increase pressure of sound wave
      - Sound efficiently travels to inner ear
  - Shape of middle ear is like lever
    - Amplify mechanical activation
    - Impedance matching

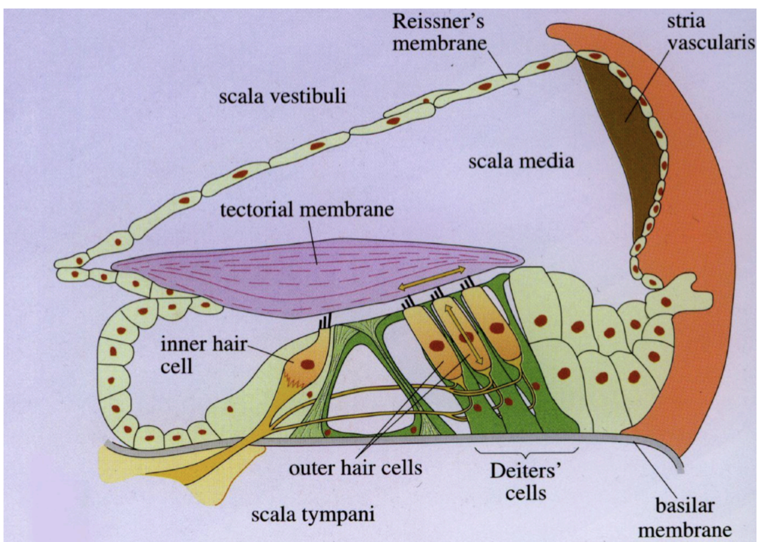




Inner Ear

Organ of corti → Sound signal decomposed by organ of corti into amplitude, frequency and phase
Inner ear transform sound pressure into electrical signals





Hair cells are not neurons, only sensory receptors → only generate receptor potentials, no axons and no AP, can release neurotransmitters

Sound wave reaches oval window, this moves the endolymph (which is inside the organ of corti), basilar membrane will move due to movement of endolymph, stereocilia will be deflected as the tectorial membrane doesn't move but the cell that sterocilia is connected to moves

1 Inner hair cell + 3 outer hair cells

Basilar membrane thickness different → different part detect different frequencies

Thicker and narrower on basal side; thinner and wider on apical side

- Lower frequencies detected by apical side

Basilar memrbane decode frequency of sound coming in → tonotopy

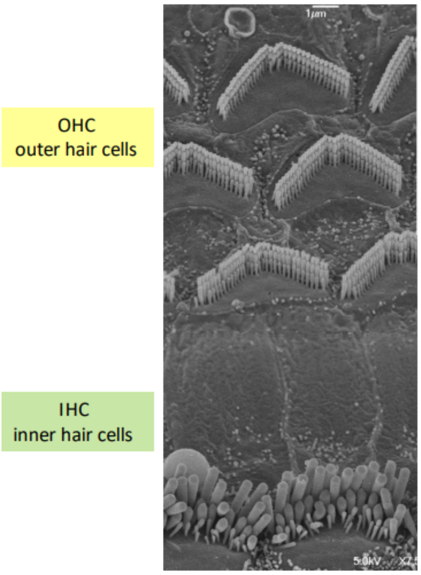
Outer hair cells only amplify signal, inner hair cells send electrical signals

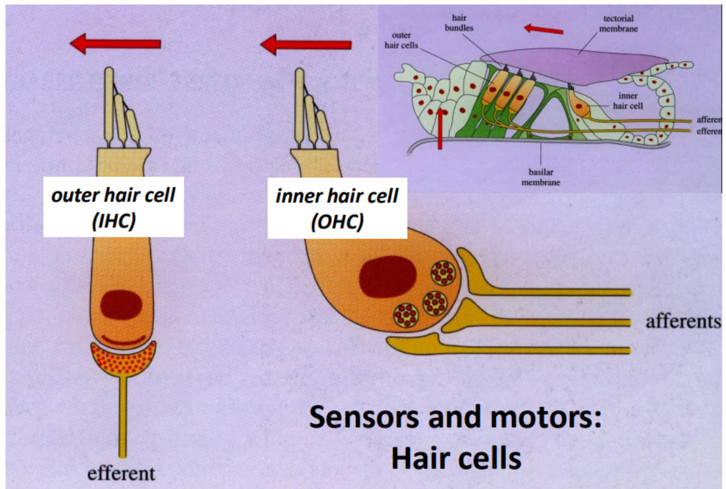
Outer hair bundles:

- V or W shaped
- Organised ina stair-case like arrangement
- Enable amplifications of mechanical vibrations
    - Electro-motile prestin
        - Prestin coupled to cytoskeleton change shapes as driven by receptor potential
        - Compressed when depolarised→ changes length of stereocilia of outer hair cell
            - Amplifies signals
    - Send very little information to brain but receive info form brain
        - Brain able to control amplification of sound
    - Have dense **efferent** inhibitory innervation, but some afferent innervation
- Reqruied for sensitive hearing
    - Loss of OHC leads to loss of hearing sensitivity, IHC still functions, however hearing threshold is raised
- Positioned over most flexible part of basilar membrane
- Longest stereocilia of OHC embedded in the underside of the tectorial membrane

Inner hair bundles:

- Fence like
- Organised in stair-case like arrangement
- Are primary sensory receptors
    - Release NT
    - Have dense **afferent** innervation **only** → send signals to brain
        - Around 20 afferent fibers
        - 3 sub-populations of afferent fibers
            - Provides mechanism for coding for loudness
        - Efferent fibers synapse with afferent endings below hair cell
- Completely surrounded by supporting cells
- Positioned on inner side of basilar membrane, less flexible part

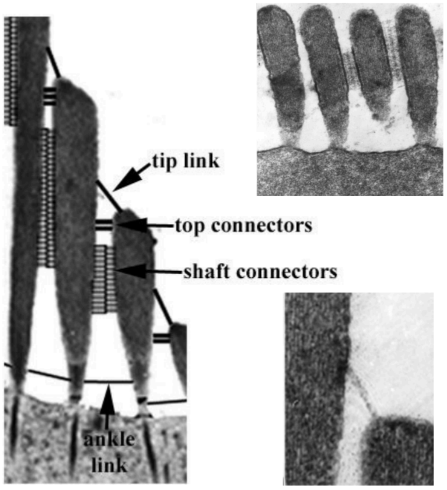




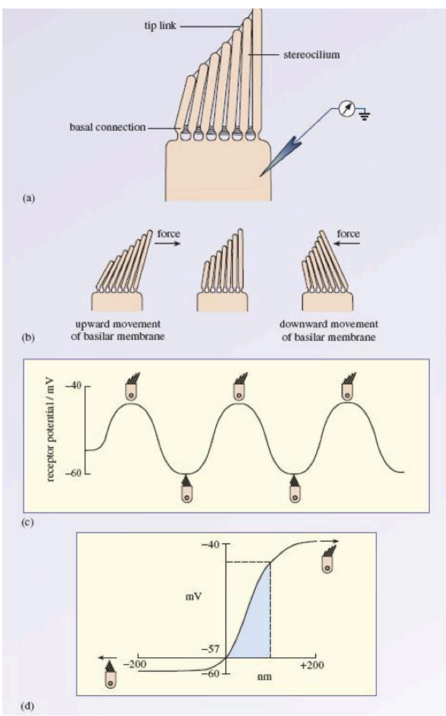
Links between stereocilia

- **Lateral cross-links** between shafts of stereocilia
- Act to convey displacements between stereocilia
- Allows the bundle to move as a single unit

- **Tip links** are extracellular fibrillar structures
- Connect tip of shorter stereocilium to longer stereocilium
- Tip links gate the mechano-electrical transduction (MET) channels
  - Stereocilia is deflected
  - Tip link is stretched and MET channels are opened
  - Open channels allow K^+influx which causes depolarisation and increase in Ca^{2+} levels (from extracellular fluid or intracellular stores)
    - No second messengers involved, hence transduction of sound is very quick
  - Calcium levels will cause neurotransmitter release



Hair bundle deflection (by how many micrometers) modulates receptor potential, certain degree of deflection causes the greatest voltage change

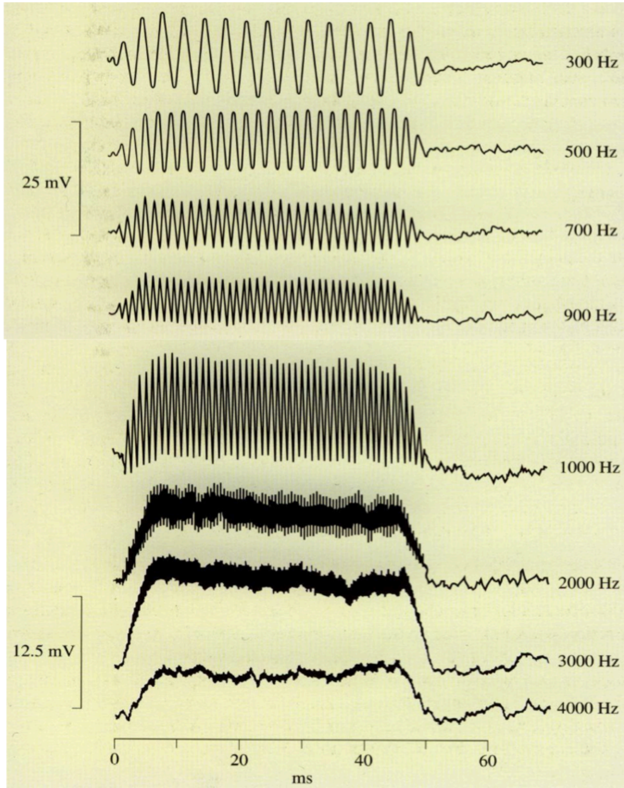


- Monitor membrane potential with an electrode
- Deflect hair bundle
- Deflection toward tall stereocilia opens MET channels
- Opposite deflection closes MET channels
- Membrane potential changes dynamically with MET
- Known as the *receptor potential*
- Small positive deflection causes large change of RP
- Negative deflection inhibits hair cell action

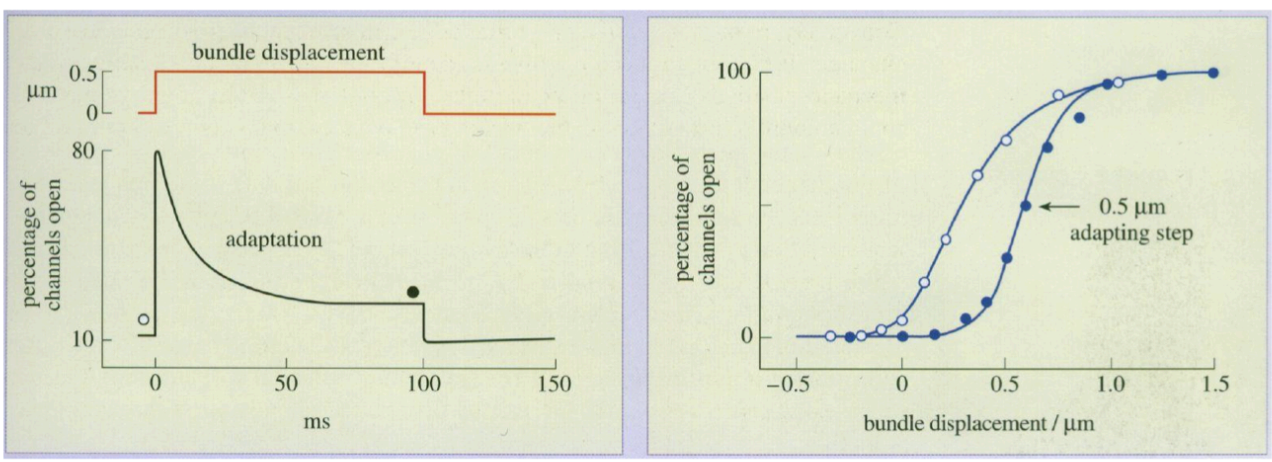
Hair cell response phase locked to frequency of sound signals
Low frequency signals → hair cell response is "slower", lower frequency response

Hair cell response behaviours:

Phase-locked and DC responses



Hair cells can adapt → may reduce the amount of signal sent to brain for a particular sound



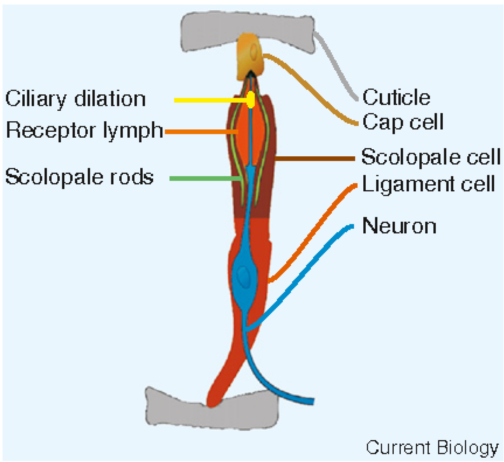
Insect Ears

Sound emissions have two fields: Near and Far

In far field, particle velocity movement is in phase with sound pressure wave movements
Single microphone can be used for far field

In near field, particles are not in phase, thus to understand sound, we need to record sound waves at different points

Chordotonal organs are structurally complex Type I mechanoreceptors that are distributed throughout the insect body and functionto detect a wide range of mechanical stimuli → has a role in hearing

- 

    - Scolopidia
    - All chordotonal organs and all insect ears have scolopidia as their elementary unit
- Chordotonal organs consists of multiple units of scolopidia
- Chordotonal organs contain neurons that can signal directly to the brain
    - The neuron is coupled to a vibration sensor

Drosophila **atonal** gene determines chordotonal (stretch receptor organs) organs
Mouse MATH1 gene determines hair cells

Mutant atonal genes → no chordotonal organs
Able to develop mechanosensitive organse by implemnetaing the mouse homologue gene MATH1

Mutant MATH1 gene → nohair cells
Can be rescued by drosophila atonal gene insertion

Mosquito Hearing

Insects have two types of ears:
- Velocity sensors (of particles)
- Pressure sensors

Mosquito ear are particle velocity detectors
Flagellum = sound receiver

Johnston's organ = hearing organ for mosquito

- Largest chordotonal organs found in insects
- Contains auditory neurons

Auditory sensitivity for mosquitos are in nanometer range

- Around 15,500 auditory neurons

Direct transducer gating

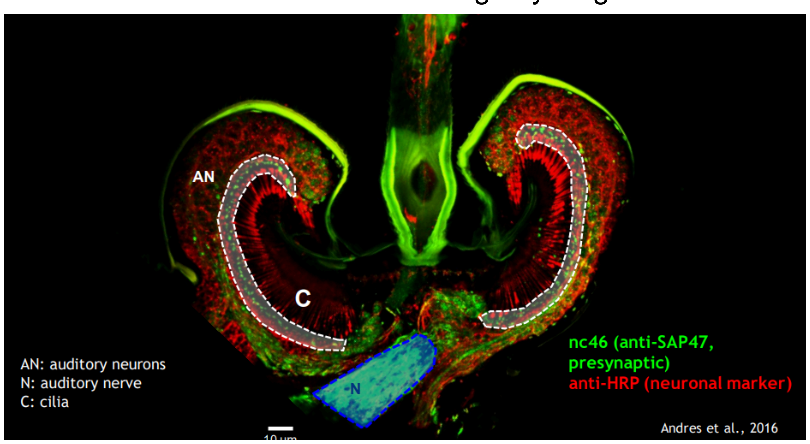
- No second messenger cascades
- Vibration of flagellum directly open mechanosensory channels located in auditory neuron membrane

Active mechanical amplification of sound

- There is a amplification of sound which is frequency dependent
- Active process, no more amplification after animal is dead

1. Opening of mechanoelectrical channels in the JO
2. Influx of K^+ and Ca^{2+}
3. Stretching of dynein and microtubule filament displaced

Efferent system modulating auditory function

- Controls mechanical amplification
    - Brain sends info back to ear to control it
- If unilateral flow of info from JO to brain, then there would be no presynaptic markers in JO because neuron in JO would not be receiving anything from neurons
    - 

- Pattern innervation across different species of mosquitoes are very similar
- There are different types of terminals (sites of release) in the JO
- Different neurotransmitters are released in the JO:
    - Octopamine
    - Serotonin
    - GABA
    - They are released in different regions, implying that they have different functions

Insect ears are sexually dipmorphic (sex difference)

- Receiver anatomy
- JO anatomy