Vestibular Function and Usher Syndrome

James O. Phillips, Ph.D.

Seattle Children's Hospital
Division of Ophthalmology
CIBR

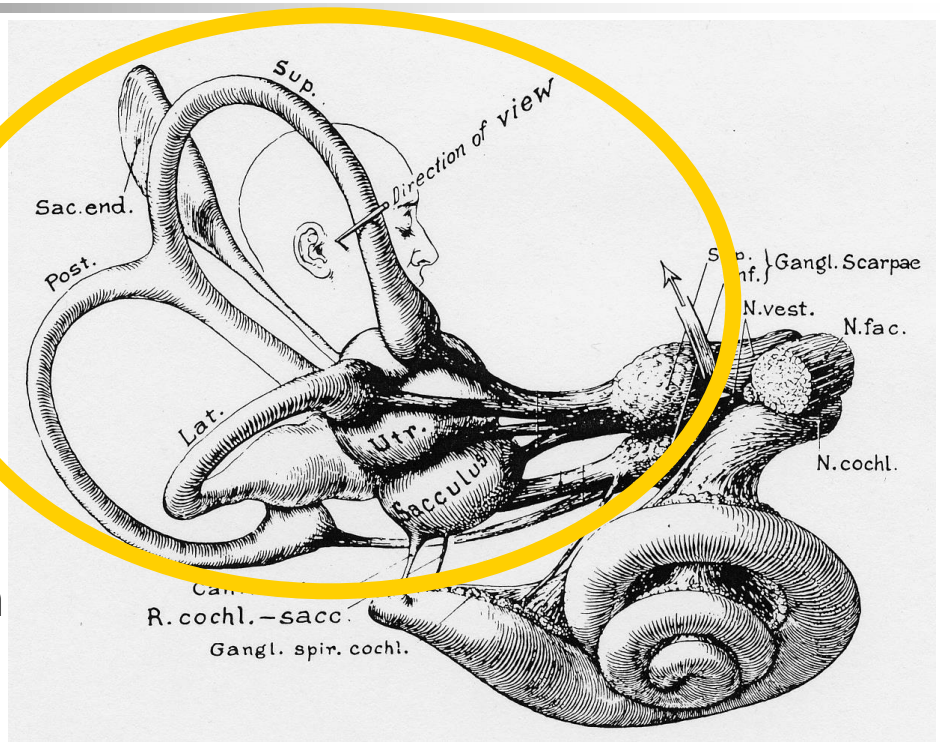
University of Washington
Dept. of Otolaryngology / HNS
CHDD, VMBHRC

What is the vestibular system?

- The vestibular system includes the structures in the inner ear that contribute to balance and orientation.
- It includes the nerves that relay balance and orientation information from the inner ear to the brain.
- It includes the neurons in the brain that make sense of that information, by combining information from a variety of sources.
  - different parts of each inner ear
  - from both ears
  - from the visual system
  - from muscles and joints

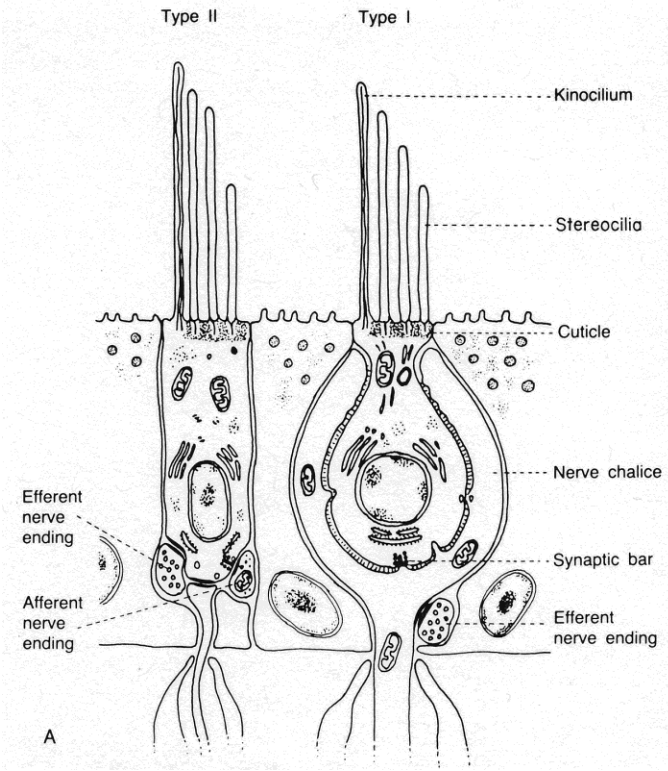
What parts of the inner ear are parts of the vestibular system?

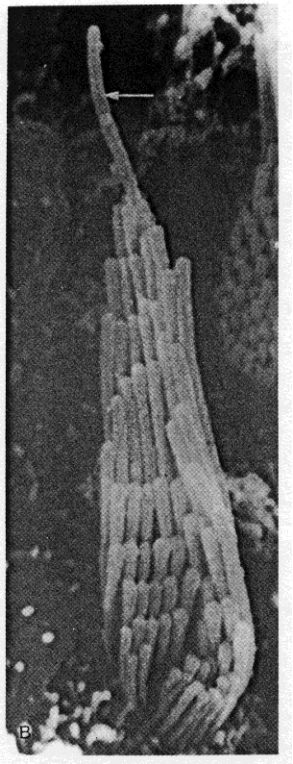
- semicircular canals
  - turning
- otolith organs
  - utricle
  - saccule
  - Front-back, right-left, up-down
  - Tilt
- vestibular ganglia



It all starts with hair cells!

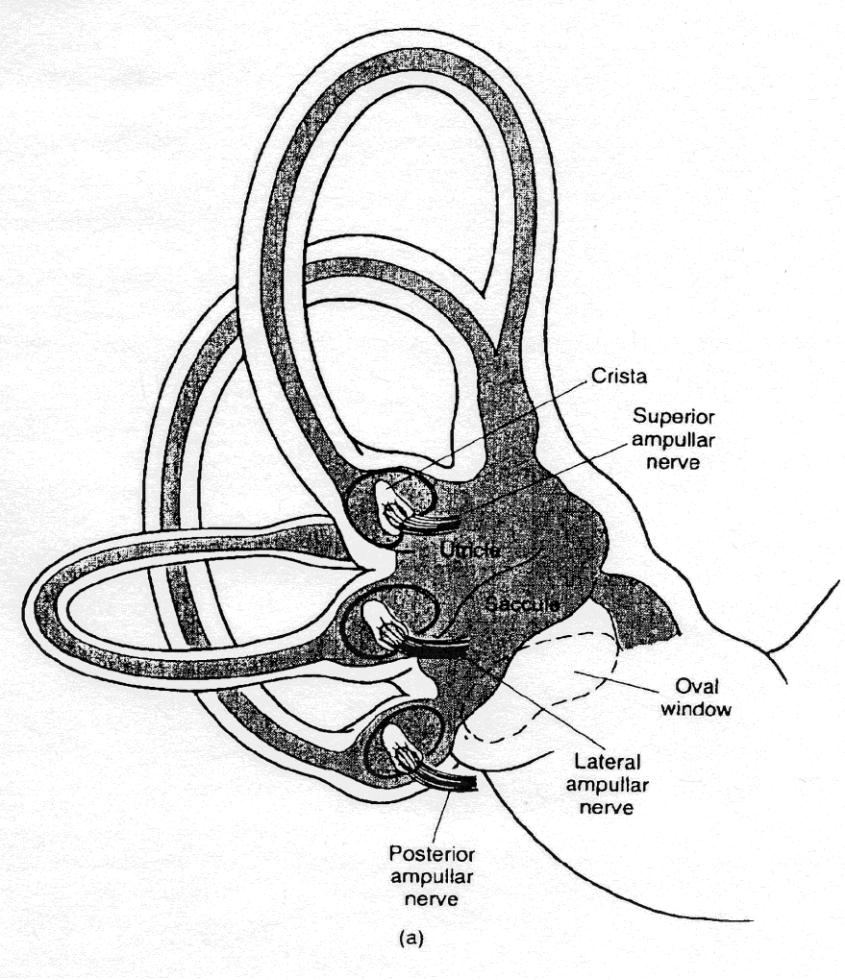
- hair cells
  - Type I and Type II
    - shape
    - innervation
  - Cilia (apical surface)
    - kinocilium
    - stereocilia
      - hairs
  - polarized
    - location of kinocilium
    - size of hairs
    - toward kinocilium
      - depolarization
      - excitatory transmitter release (glutamate)
      - excitation
    - away from kinocilium
      - hyperpolarization





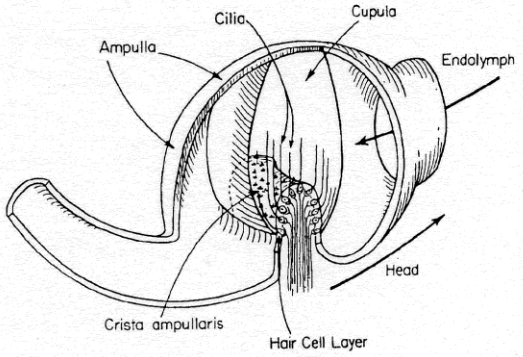
What are the semicircular canals?

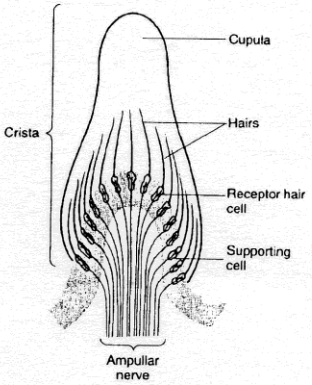
- 3 canals
- orthogonal
  - fluid filled
- ampulla
  - location of hair cells
    - like those in the cochlea
  - neural transduction
    - convert movement into neural signals



How do the semicircular canals work?

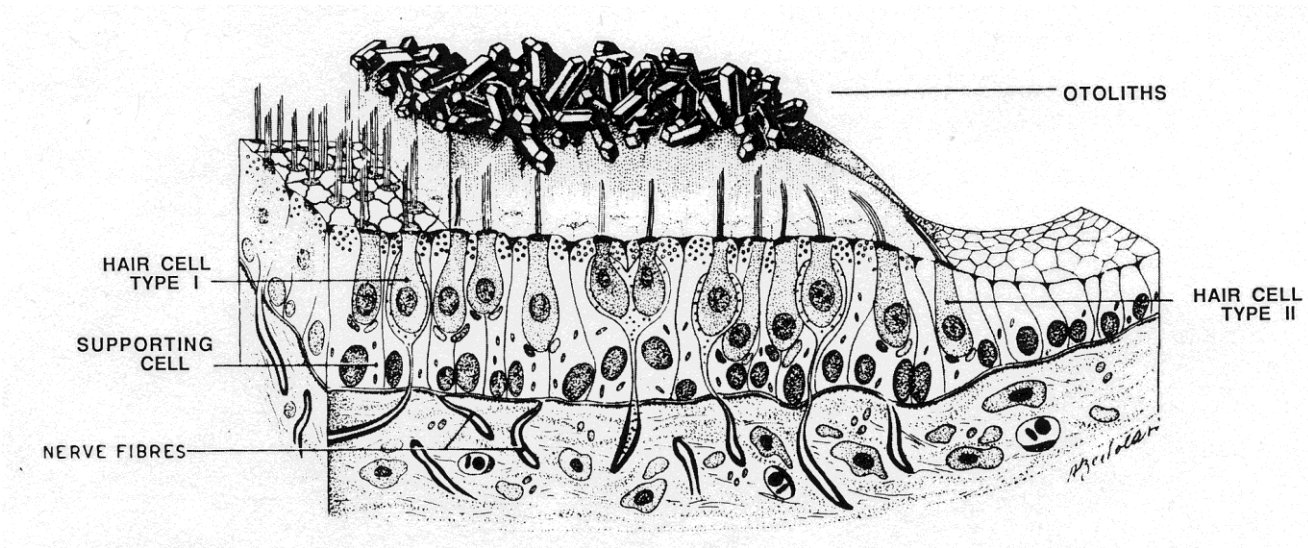
- When you turn your head fluid moves in the semicircular canals.
- Each ampulla contains a cupula, which billows when the fluid moves, which in turn bends the hairs of the hair cells.
  - gelatinous tongue
  - embedded hair cells
  - sense rotational acceleration





How do the otolith organs work?

- The otolith organs contain a gelatinous cap (otolithic membrane) and otoliths (otoconia, calcium carbonate crystals). They also contain hair cells.
- When we slide or tilt, the gelatinous cap deforms, and the hairs of the hair cells bend.
  - shear
  - sense tilt and linear acceleration



What happens when the inner ear vestibular system fails unilaterally?

- One ear stops working
  - Vertigo - sense of whirling or spinning
    - tends to be short lived
  - Nausea
    - natural response to conflicting sensory input
  - Fatigue
  - Disorientation
    - swimmy headed feeling
    - varies with context
  - Anxiety
    - not knowing when you will be disoriented
    - knowing that some situations are challenging
  - Cognitive impairment
  - Postural and gait instability

What happens when the inner ear vestibular system fails bilaterally?

- Both ears fail to work.
  - No Vertigo
  - Nausea and fatigue
    - conflicting sensory input is still present
  - Significant Disorientation
    - swimmy headed feeling
  - Anxiety
  - Cognitive impairment
  - **Oscillopsia**
    - Failure to stabilize your eyes when you turn your head
    - The visual world moves when you move
    - Reduces your vision
  - Postural and Gait Instability

Is there compensation for inner ear vestibular loss?

- YES
- Over time we can compensate well for vestibular loss
  - Especially true of children
  - Our brains are designed to adjust for loss of input.
- Compensation is dependent on learning:
  - not to misinterpret sensory cues from a non working vestibular system
  - to use contextually appropriate cues
  - to develop a general strategy that is adaptive over a range of situations
  - to substitute useful information from other sensory systems
    - SOMATOSENSORY SYSTEM
    - **VISUAL SYSTEM**

Vestibular Loss and Usher Syndrome

- Usher syndrome (USH) is characterized by varying degrees of:
  - congenital hearing loss
  - retinitis pigmentosa
  - **vestibular dysfunction**
- 12 loci, 9 causative genes, 1 modifier gene
- 3 clinical subtypes of USH
  - USH1, USH2, USH3

Vestibular Loss and Usher Syndrome

- USH1 - Usher Syndrome Type 1
  - 30-40% of all cases
  - Classic USH1 vestibular phenotype
    - Severe vestibular dysfunction
    - Bilateral areflexia within the first year of life
  - USH1B
    - Classic phenotype, 50% of USH1
  - USH1C, CDH23, PCDH15
    - Either classic phenotype
    - Or only non-syndromic hearing loss
      - CDH23 missense mutations vs. truncating mutations

Vestibular Loss and Usher Syndrome

- USH2 - Usher syndrome Type 2
  - Normal vestibular function

- USH3 - Usher syndrome Type 3
  - 2-4% of all cases
  - Varying degrees of vestibular dysfunction
    - 45% vestibular hypofunction (Sadeghi et al)
      - 36% of the cohort that walked before 16 months showed variable dysfunction later - progressive loss

Vestibular Loss and Usher Syndrome

- Summary:
- Usher syndrome can produce
  - Bilateral vestibular areflexia, bilateral sensorineural hearing loss, and prepubertal vision loss
  - Bilateral vestibular areflexia, bilateral SNHL, later progressive vision loss
  - Partial vestibular loss, hearing loss, and partial vision loss
  - Progressive vestibular loss, hearing loss, progressive vision loss.

USH1 clinical presentation

- Profound bilateral SNHL at birth
- Bilateral vestibular areflexia at birth
- Missed motor milestones
- Catch up with somatic motor function
  - Central compensation and sensory substitution
- Onset of visual loss
- Return of disequilibrium and imbalance
  - Decompensation due to loss of sensory substitution
  - Seek new strategies

Detection of vestibular loss

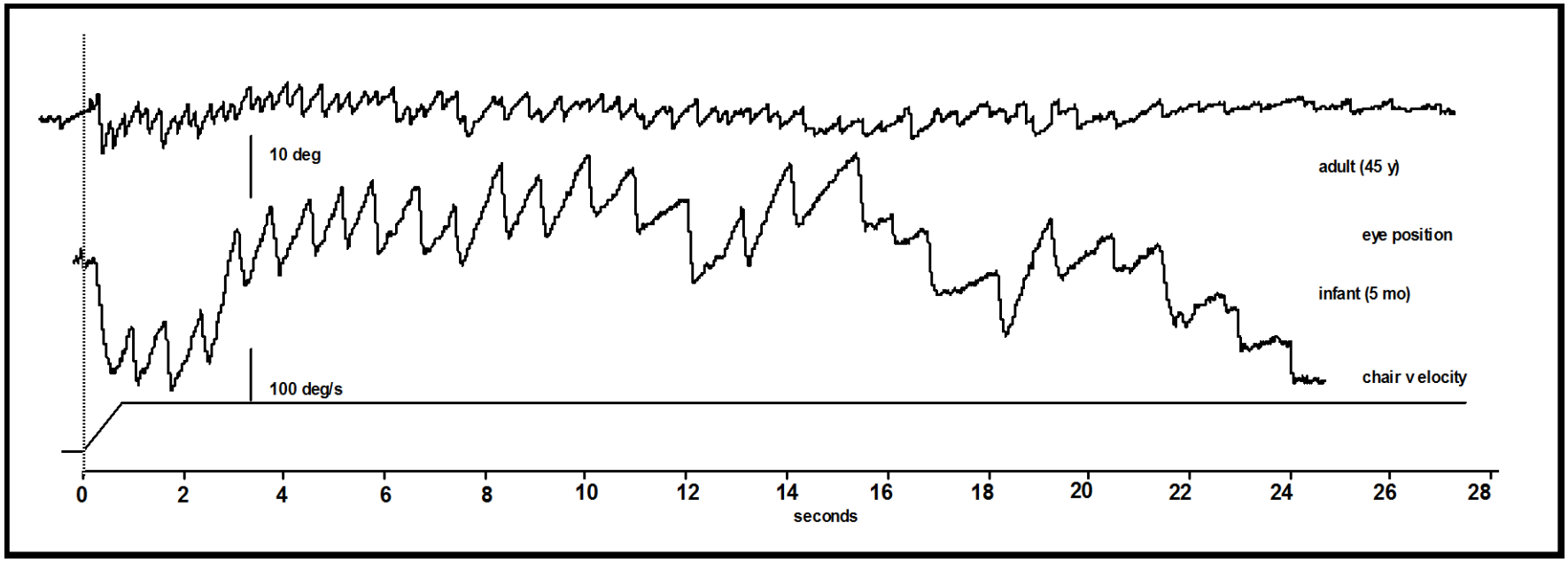
- Clinical tools to detect loss of vestibular function
- Important to define the amount of vestibular function
  - Early sign of classic USH1 phenotype
    - Visual loss occurs progressively and later
    - Vestibular loss is complete, bilateral, and early onset
  - Important to know if vestibular loss is
    - Present or absent
    - Bilateral or unilateral
    - Complete or partial
    - Progressive, static or fluctuating
  - Each type of loss has a different treatment strategy

Assessment of vestibular loss

- Good clinical exam
  - Uses simple tests
  - Can detect a problem
- Laboratory Examination
  - Uses complicated technology
  - Can fully define vestibular status

Rotary chair test

Infant rotary chair test



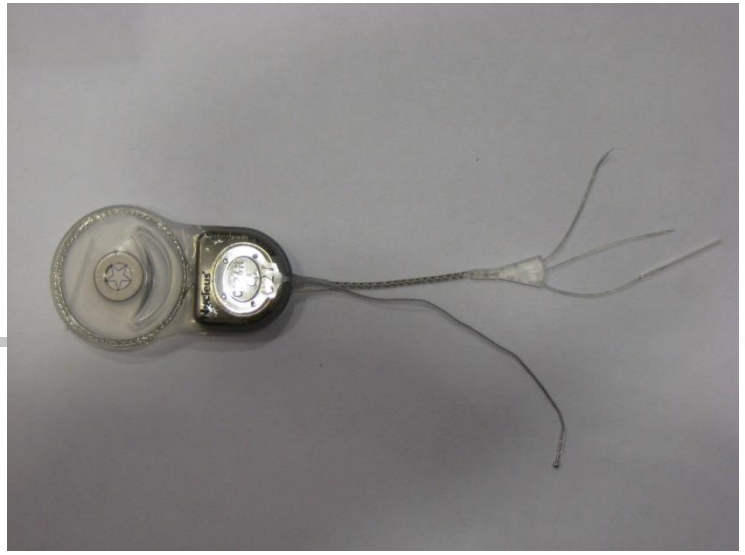
Platform Test

Computerized Dynamic Posturography

Treatment Options

- Current
  - Vestibular rehabilitation
    - Develop optimal substitution strategies
    - Compensate and adapt more quickly
- Future
  - Gene therapy
  - Hair cell regeneration
    - May be effective for hearing and vestibular loss

Treatment options



- Around the corner
  - Implantable vestibular prostheses
    - 3 groups in US (UW, Harvard, Johns Hopkins)
    - May be combined with a cochlear implant
  - First trial in adults is ongoing in Seattle, WA
    - Provides balance information for
      - Eyes
        - Drives appropriate eye reflexes
      - Body
        - Drives appropriate postural reflexes
      - Mind
        - Drives appropriate motion perception