A combined cochlear and vestibular prosthesis for the treatment of Usher syndrome

James Phillips

Otolaryngology-HNS
Virginia Merrill Bloedel Hearing Research Center
Center on Human Development and Disability
University of Washington, Seattle, WA

Seattle Children's Hospital
Division of Ophthalmology
CIBR

Our group (alphabetical order)

Steven Bierer[5], Christina DeFrancisci[6], Albert Fuchs[1,3], Justin Golub[9], Elyse Jameyson[1], Chris Kaneko[3], Leo Ling[2,3], Frank Miles[3], Shawn Newlands[8], Kaibao Nie[1,2,4], Amy Nowack[2], Trey Oxford[3], Christopher Phillips[2], James Phillips[1,2], Farrel Robinson[5], Jay Rubinstein[1,2,4], Sarah Shepherd[7], Shanece Washington[6]

[1]Virginia Merrill Bloedel Hearing Research Center, [2]Dept of Otolaryngology - HNS, [3]National Primate Research Center, [4]Dept. of Bioengineering, [5]Dept of Biostructure, [6]Dept. of Speech and Hearing Sciences,

University of Washington, Seattle, WA

[7]Vanderbilt Bill Wilkerson Center, Vanderbilt University, Nashville, TN

[8]Dept. of Otolaryngology, University of Rochester, Rochester, NY

[9]Dept. of Otolaryngology, Columbia University, New York, NY

Acknowledgements

- **Support**
  - **NIH/NIDCD**
    - **Optimization of a human vestibular prosthesis**
      1 R01 DC014002-01 (JR)
  - **NIH/NIDCD Neural Prosthesis Development Program**
    - **Neurophysiological Studies of Electrical Stimulation for the Vestibular Nerve, HHS-N-260-2006-00005-C (JOP)**
  - **NIH/NCRR-ORIP ITHS Ignition Awards**
    - **Vestibular prosthesis for bilateral and uncompensated unilateral loss (JOP)**
    - **Dissolution of perineuronal nets to aid adaptation to a vestibular prosthesis. (FR)**
  - **Wallace H. Coulter Foundation**
    - **Clinical Feasibility of a Vestibular Neurostimulator for Meniere's Disease (JOP/JR)**
  - **Kranwinkle Gift (Humans only)**
    - **Clinical Study of the UW/Nucleus Vestibular Neurostimulator (JR)**
  - **Cochlear Ltd.**
    - **Development of a vestibular prosthesis. (JR/JOP)**
  - **NSF SBIR Phase 1**
    - **ACT drug delivery system (JOP)**

Intellectual Property

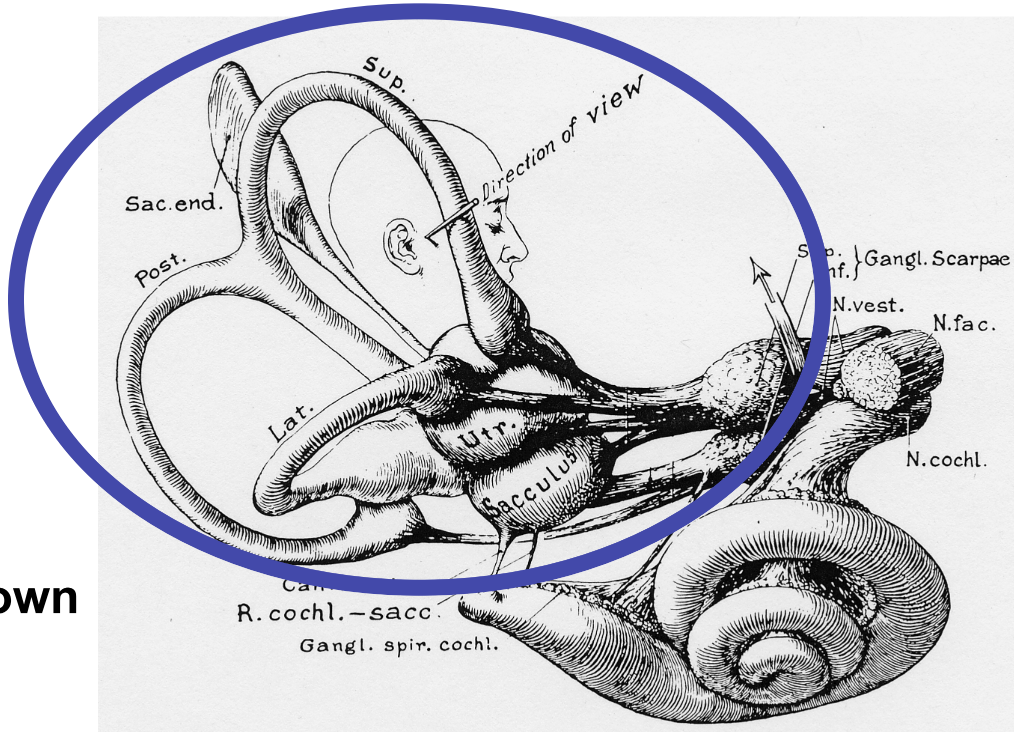
- **The members of our research team, the University of Washington, and Cochlear Ltd. all have IP associated with this technology**

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

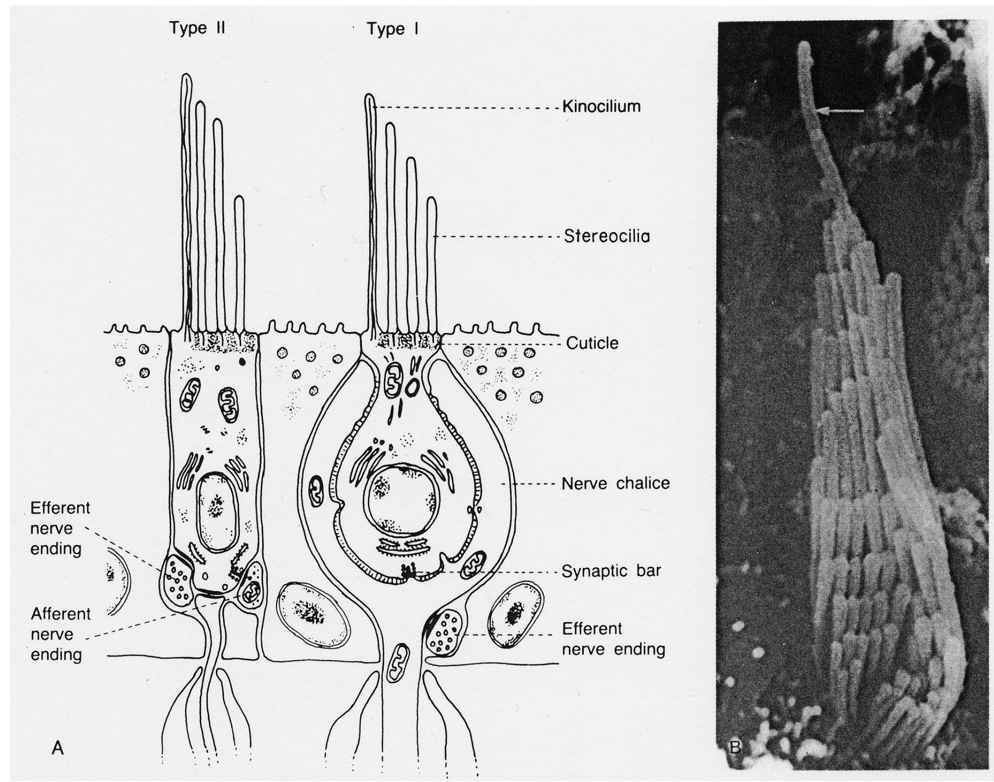
What parts of the inner ear are parts of the vestibular system?

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



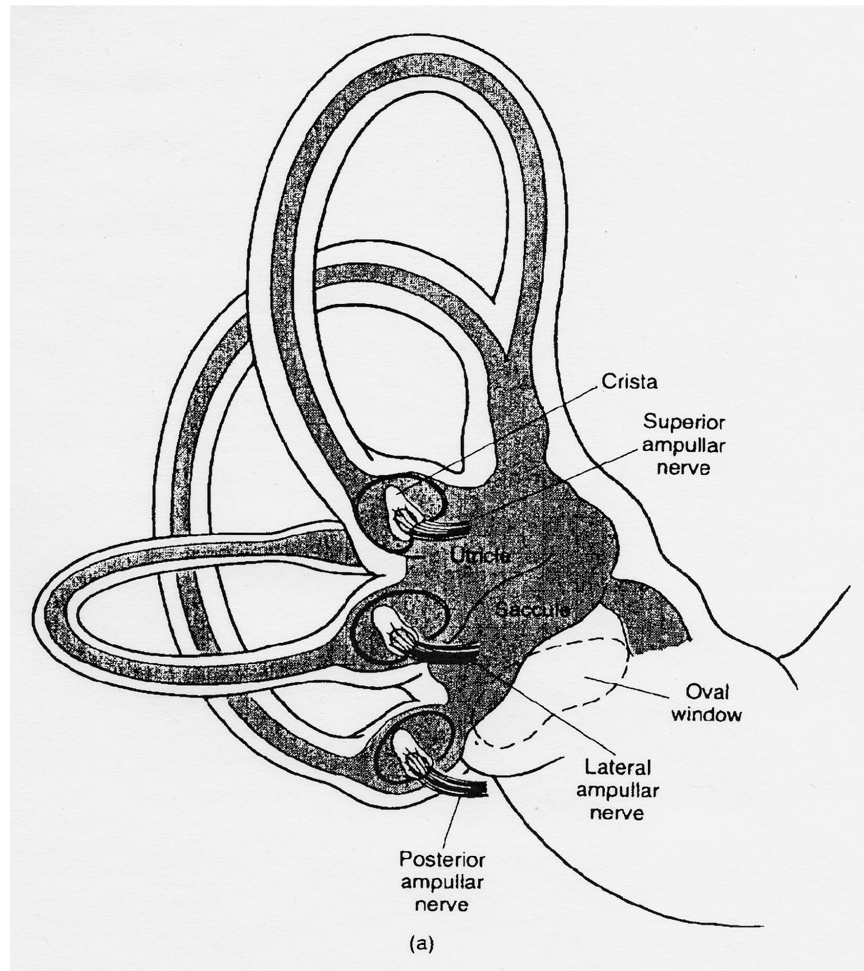
It all starts with hair cells!

- 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?

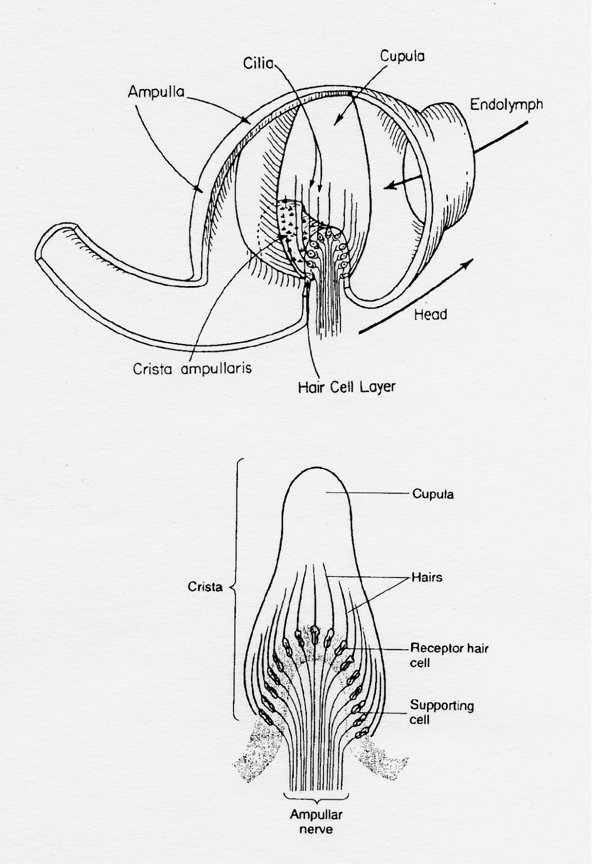
- 3 canals
- orthogonal
  - fluid filled
- ampulla
  - location of hair cells
    - like those in the cochlea
  - neural transduction
    - convert movement into neural signals



(a)

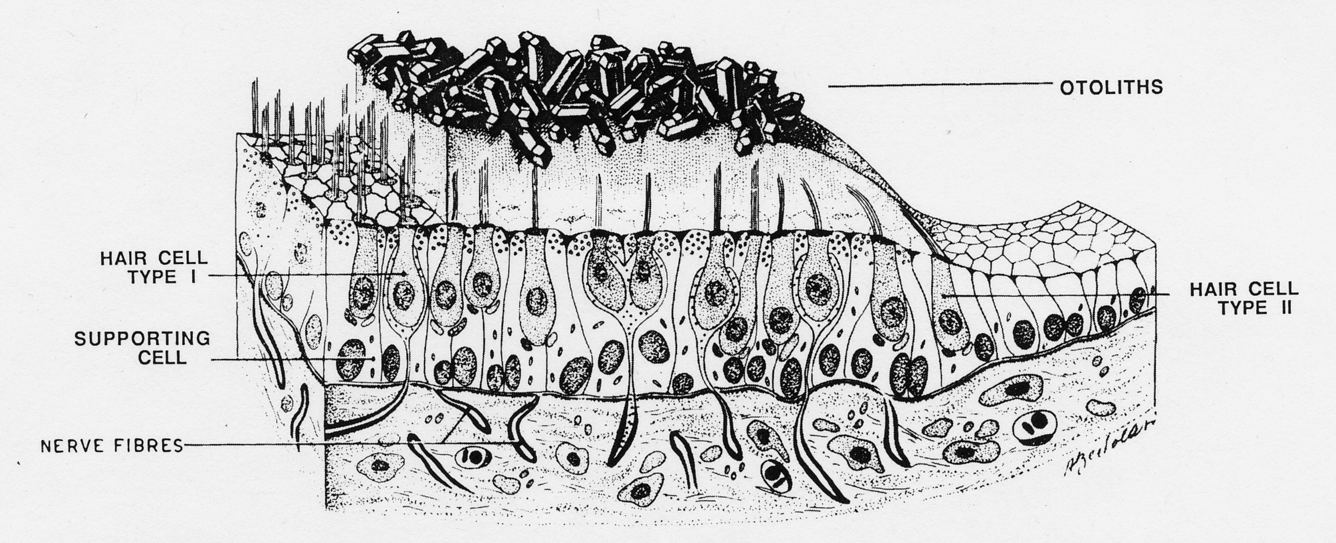
How do the semicircular canals work?

- 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 bilaterally?

- **Both ears fail to work.**
  - **No whirling vertigo**
  - **Significant Disorientation**
    - **swimmy headed feeling**
  - **Nausea and fatigue**
    - **conflicting sensory input**
  - **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
  - <u>to substitute useful information from other sensory systems</u>
    - SOMATOSENSORY SYSTEM
    - VISUAL SYSTEM
- Compensation requires sensory stability
  - defeated by change or fluctuation

Vestibular Loss and Usher Syndrome

- **Usher syndrome (USH) is characterized by varying degrees of:**
  - **congenital hearing loss**
  - **retinitis pigmentosa**
  - **vestibular dysfunction**
- **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

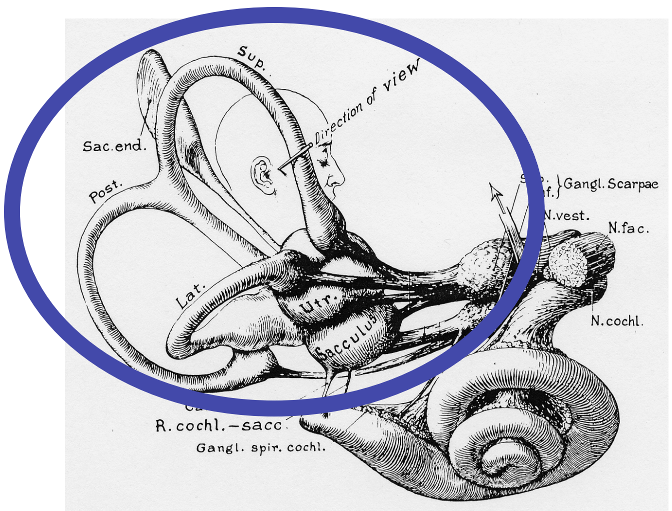
Vestibular Loss and Usher Syndrome

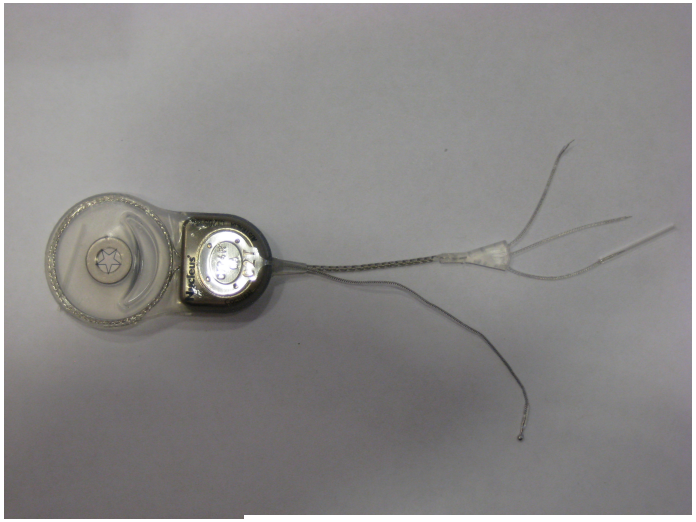
- USH2 - Usher syndrome Type 2
  - Typically normal vestibular function
- USH3 - Usher syndrome Type 3
  - 2-4% of all cases
  - Varying degrees of vestibular dysfunction
    - 45% vestibular hypofunction (Sadeghi et al)
      - 36% of the cohort that walked before 16 months showed variable dysfunction later - progressive loss

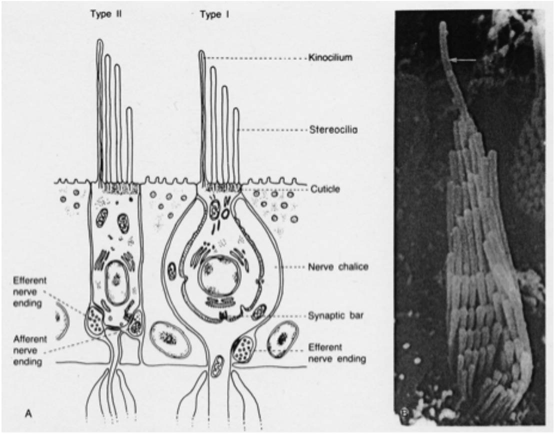
Vestibular Loss and Usher Syndrome

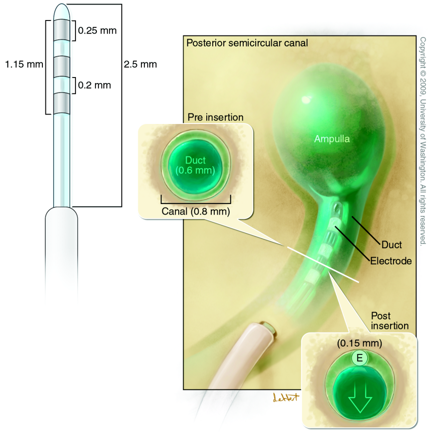
- Summary:
- Usher syndrome can produce
  - Bilateral vestibular areflexia, bilateral sensorineural hearing loss, and prepubertal vision loss
  - Bilateral vestibular areflexia, bilateral SNHL, later progressive vision loss
  - Partial vestibular loss, hearing loss, and partial vision loss
  - Progressive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

Can we replace the inner ear vestibular system?









Who would you treat with a vestibular prosthesis?

- <u>Not patients with a single acute transient loss of function</u>

- Patients with bilateral loss of balance function
  - Often iatrogenic
    - Exposure to ototoxic drugs
- Patients with uncompensated unilateral loss of balance function
  - Large numbers of patients do not adapt to a loss from one ear
- Patients with fluctuating balance function
  - Meniere's disease
    - Extreme intermittent vertigo
      - destructive therapy
        - » Injected ototoxin, surgical ablation, nerve section

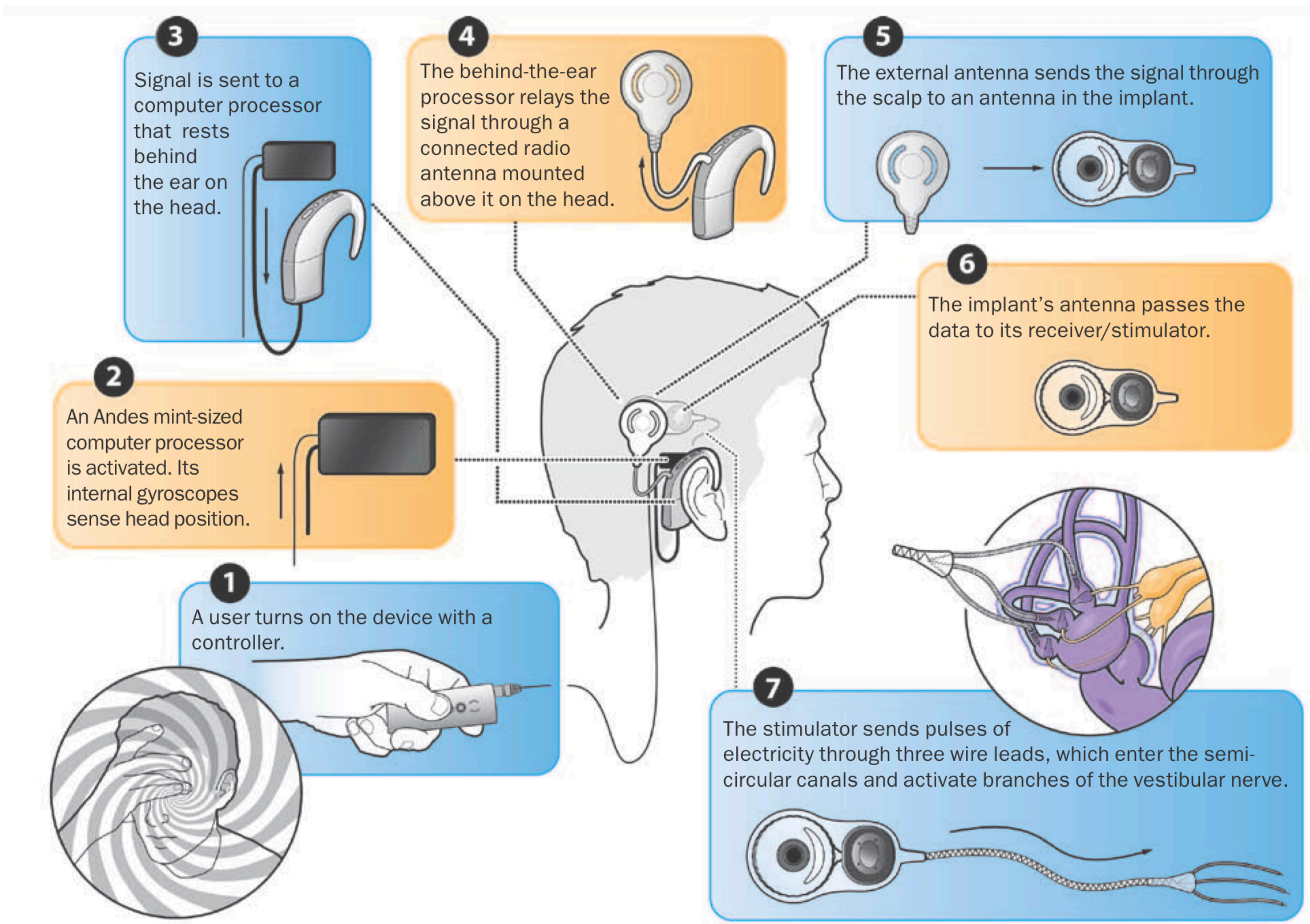
Who would you treat with a vestibular prosthesis?

- <u>**Why not treat Usher Syndrome patients with such a device?**</u>
  - **bilateral loss of balance function**
  - **combined with hearing loss**
    - **Usher Syndrome patients already have inner ear implants**
      - **Cochlear implants**

- **To effectively treat Usher Syndrome vestibular loss**
  - **Requires a combined implant**

The implanted device

The scheme



3
Signal is sent to a computer processor that rests behind the ear on the head.
4
The behind-the-ear processor relays the signal through a connected radio antenna mounted above it on the head.
5
The external antenna sends the signal through the scalp to an antenna in the implant.
6
The implant's antenna passes the data to its receiver/stimulator.
2
An Andes mint-sized computer processor is activated. Its internal gyroscopes sense head position.
1
A user turns on the device with a controller.
7
The stimulator sends pulses of electricity through three wire leads, which enter the semi-circular canals and activate branches of the vestibular nerve.

Road to human trials

- 1. design a device to stimulate vestibular afferent fibers
  - leverage a highly developed existing technology
    - cochlear implant
  - modify the software and hardware
    - create a minimally invasive electrode technology
    - create appropriate stimulation strategies
      - FM not AM
  - partner with an existing CI manufacturer
- 2. develop a simple surgical approach with the right target
  - three semicircular canals
    - coherent rotational information
- 3. construct prototype devices
  - identical to the final production device

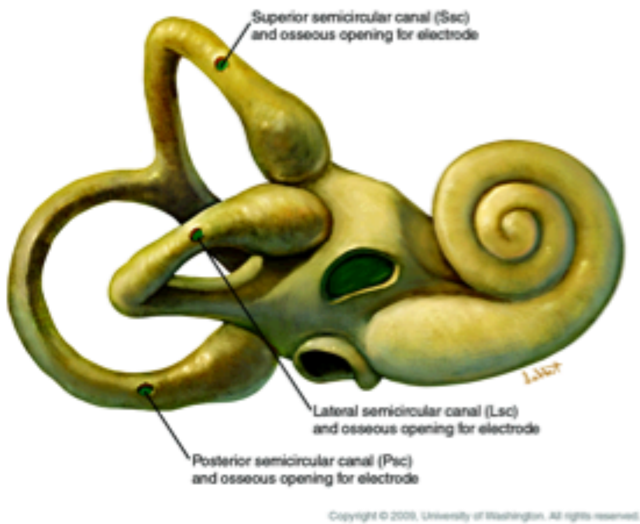
Road to clinical trials

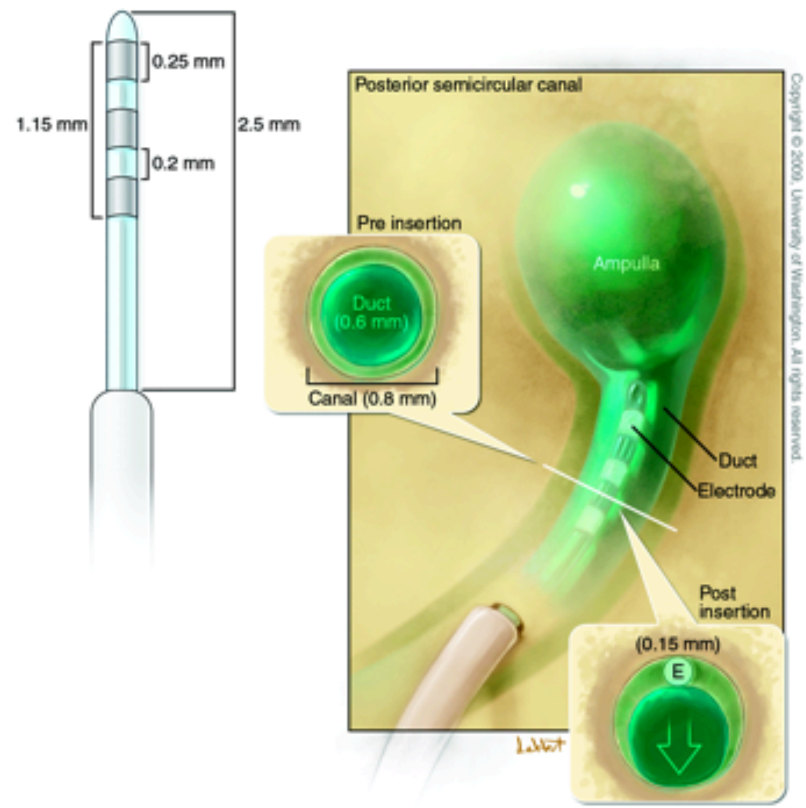
- 4. evaluate the device in animal model
  - Implanted devices in 14 rhesus monkeys
    - similar inner ear anatomy to humans
    - test in intact and lesioned animals
      - ideal model for unilateral and bilateral loss
    - evaluate risk
      - longitudinally evaluate inner ear function
        - » using identical clinical tests to those that are used diagnostically in humans
    - evaluate efficacy
      - longitudinally evaluate prosthetically elicited function
        - » using clinically relevant behavioral and physiological measures

Road to clinical trials

- **5. Test the device in human patients with vestibular loss**
  - **In human 4 Meniere's patients**
    - **Can the device restore vestibular function lost from the destructive treatment?**
- **6. Modify our devices to create a combined cochlear and vestibular prosthesis.**
- **7. Test the new device in rhesus monkeys.**
- **8. Modify our existing FDA IDE to test patients with hearing and vestibular loss with the new combined implant.**
- **9. Test the new device in human patients with combined hearing and vestibular loss**

Putting it in



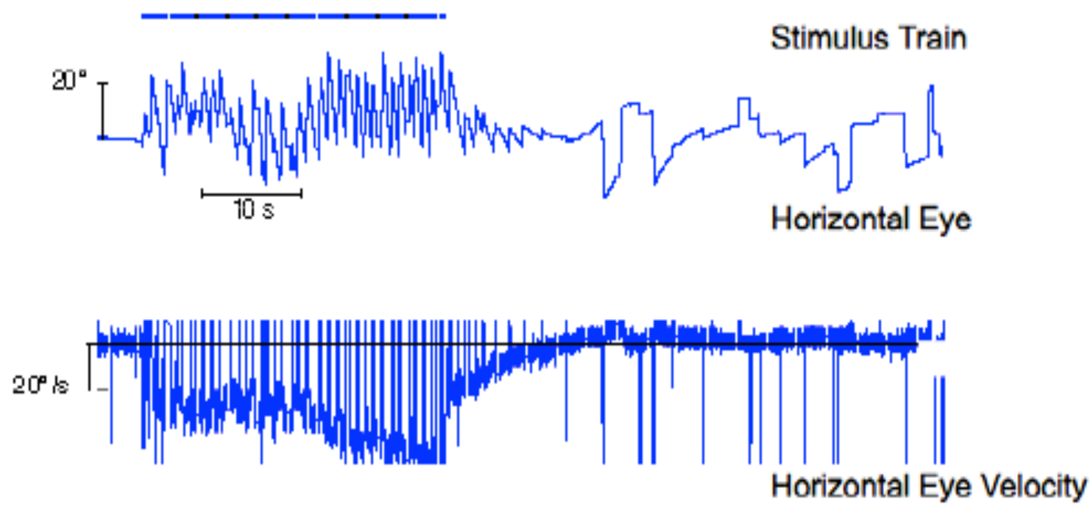


Turning it on

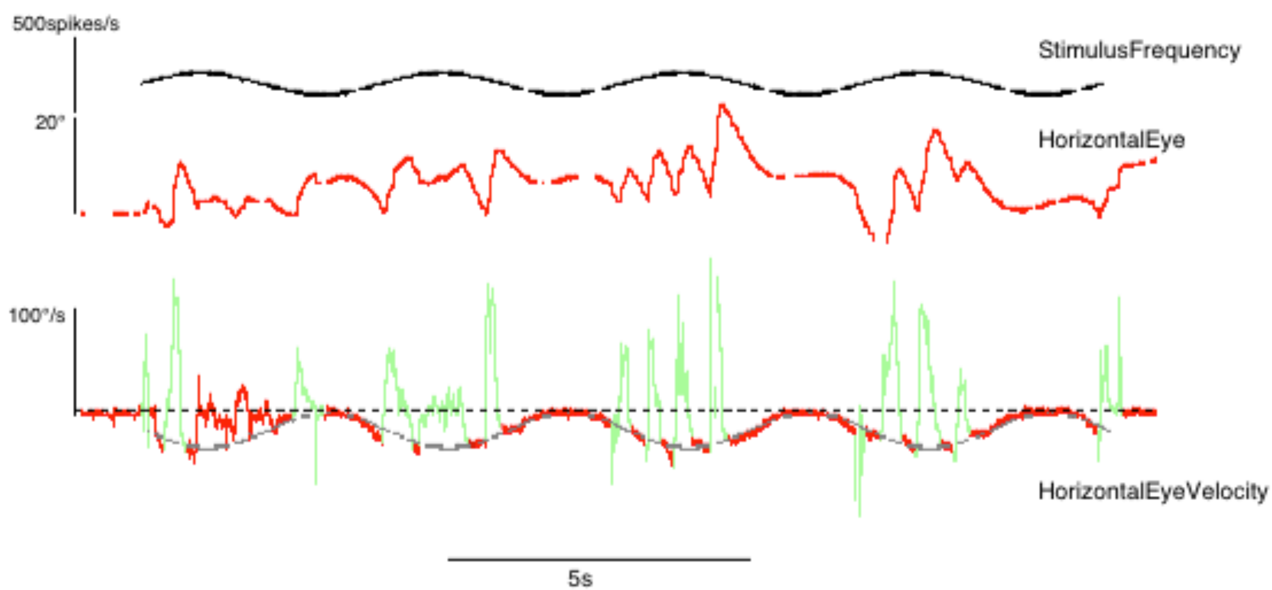
- Electrical stimulation with biphasic pulse trains
- Produces
  - Eye movements - eVOR
  - Body sway
  - Sensation of motion
- Effective vestibular stimulation does not produce
  - Nausea
  - Pain
  - Sound sensation
  - Facial nerve activation

Turning it on

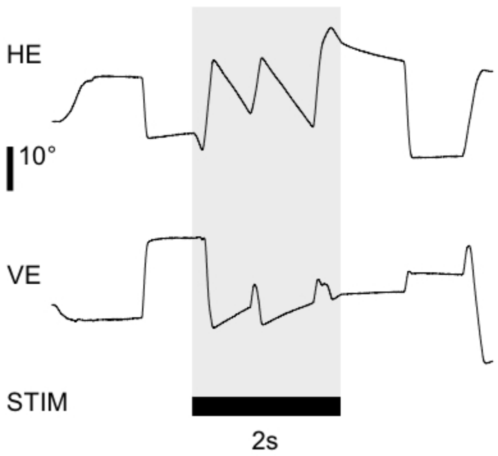
Constant Frequency and Current



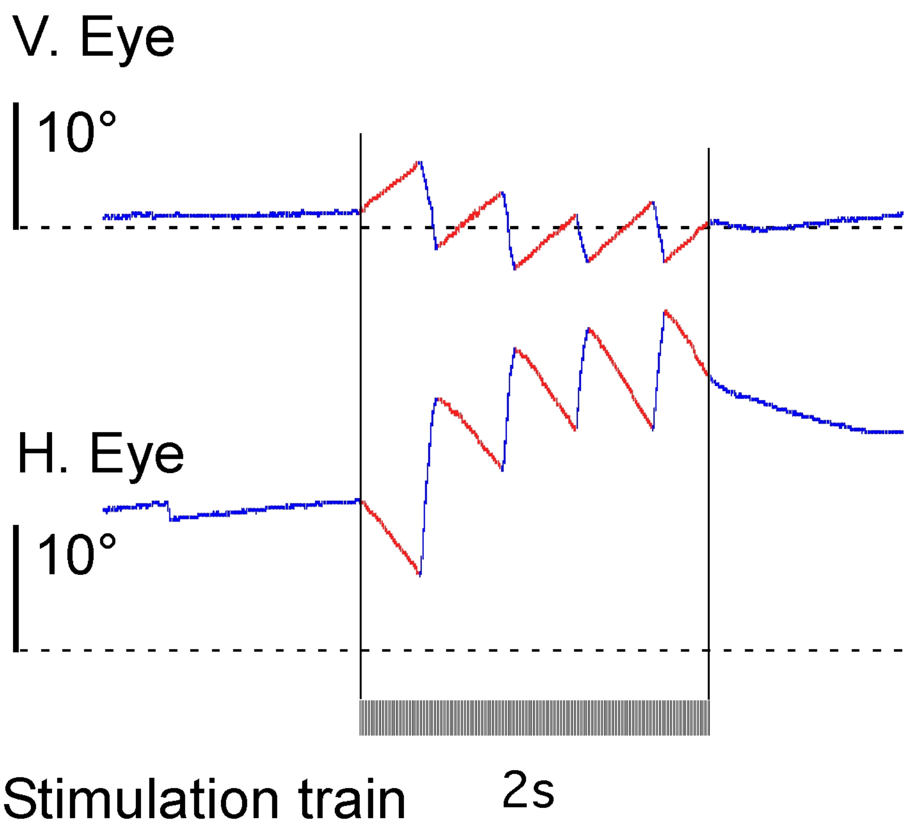
Sinusoidal modulation



Short trains of biphasic pulses produce nystagmus

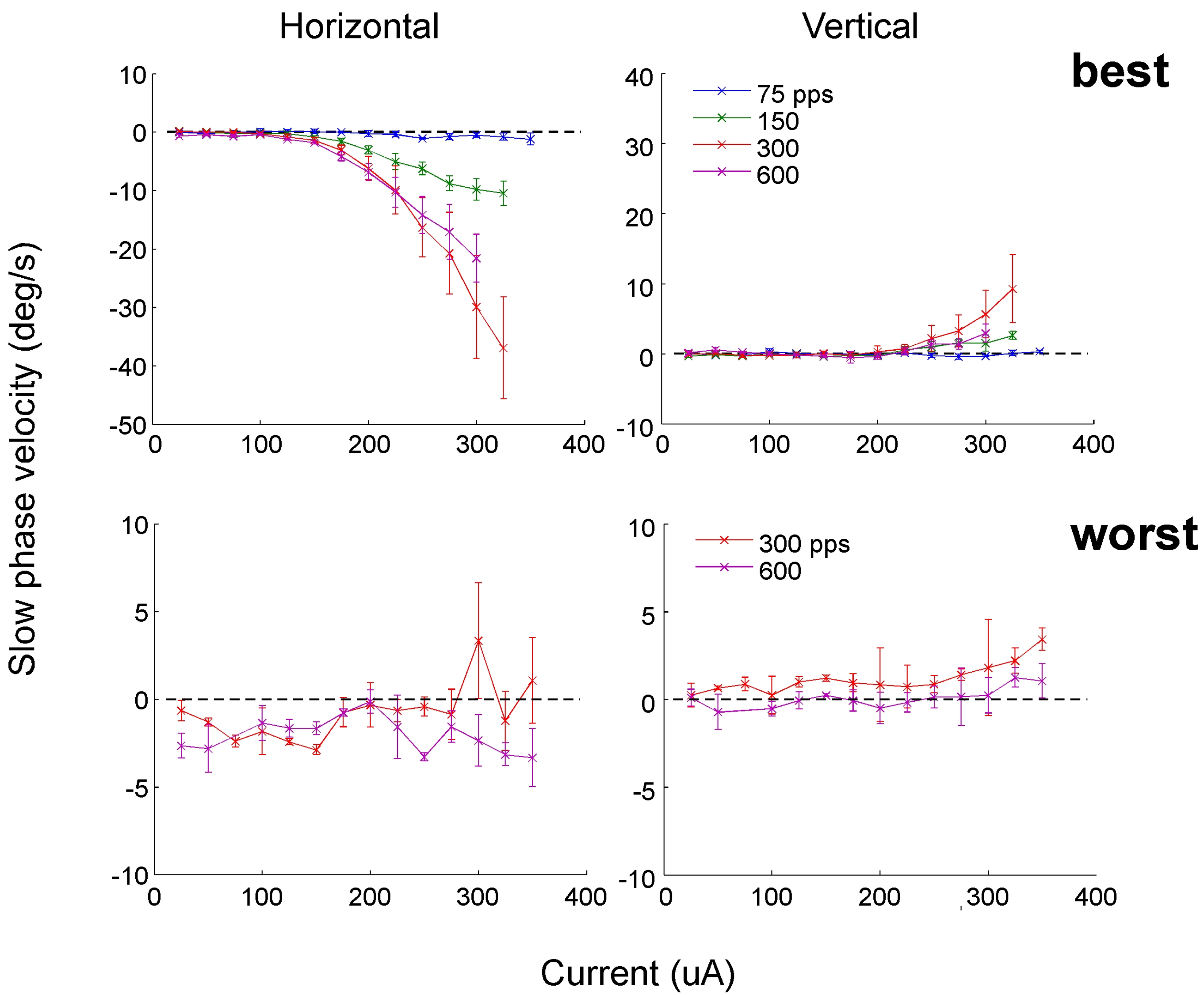


Monkey



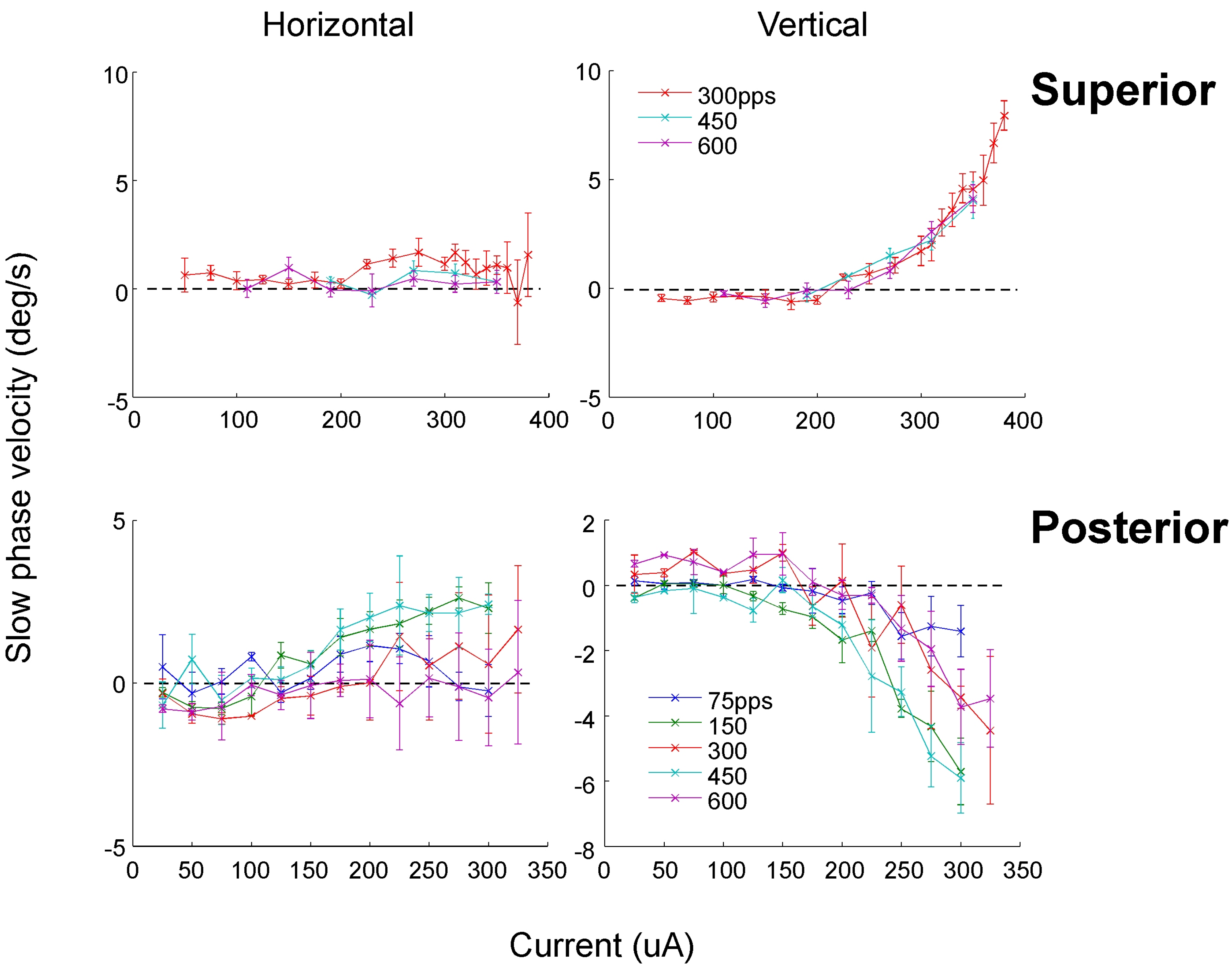
Right lateral canal stimulation

Eye movements parametrically controlled

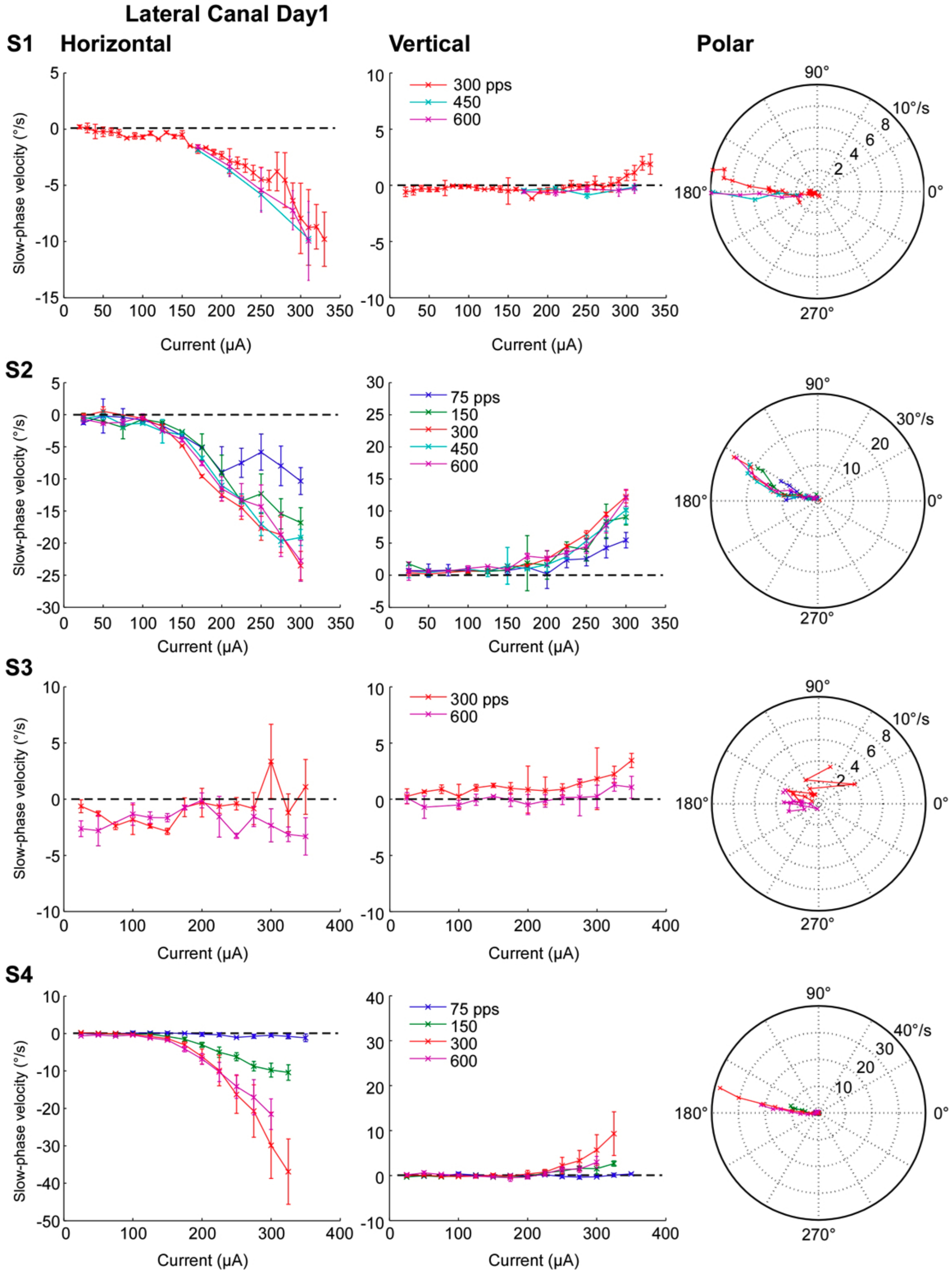


Right Lateral Canal Stimulation

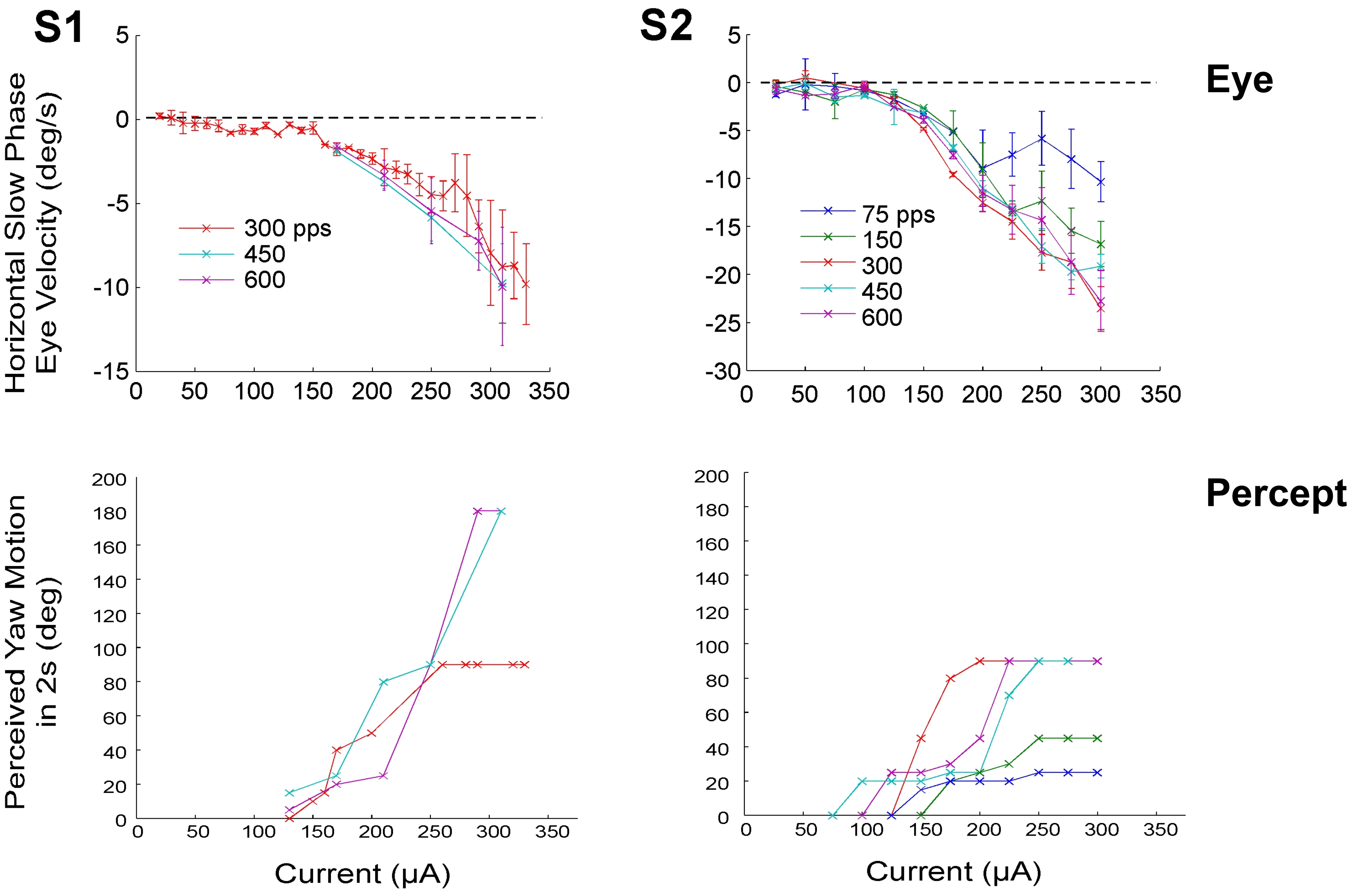
Eye movements parametrically controlled



Lateral Canal
all subjects

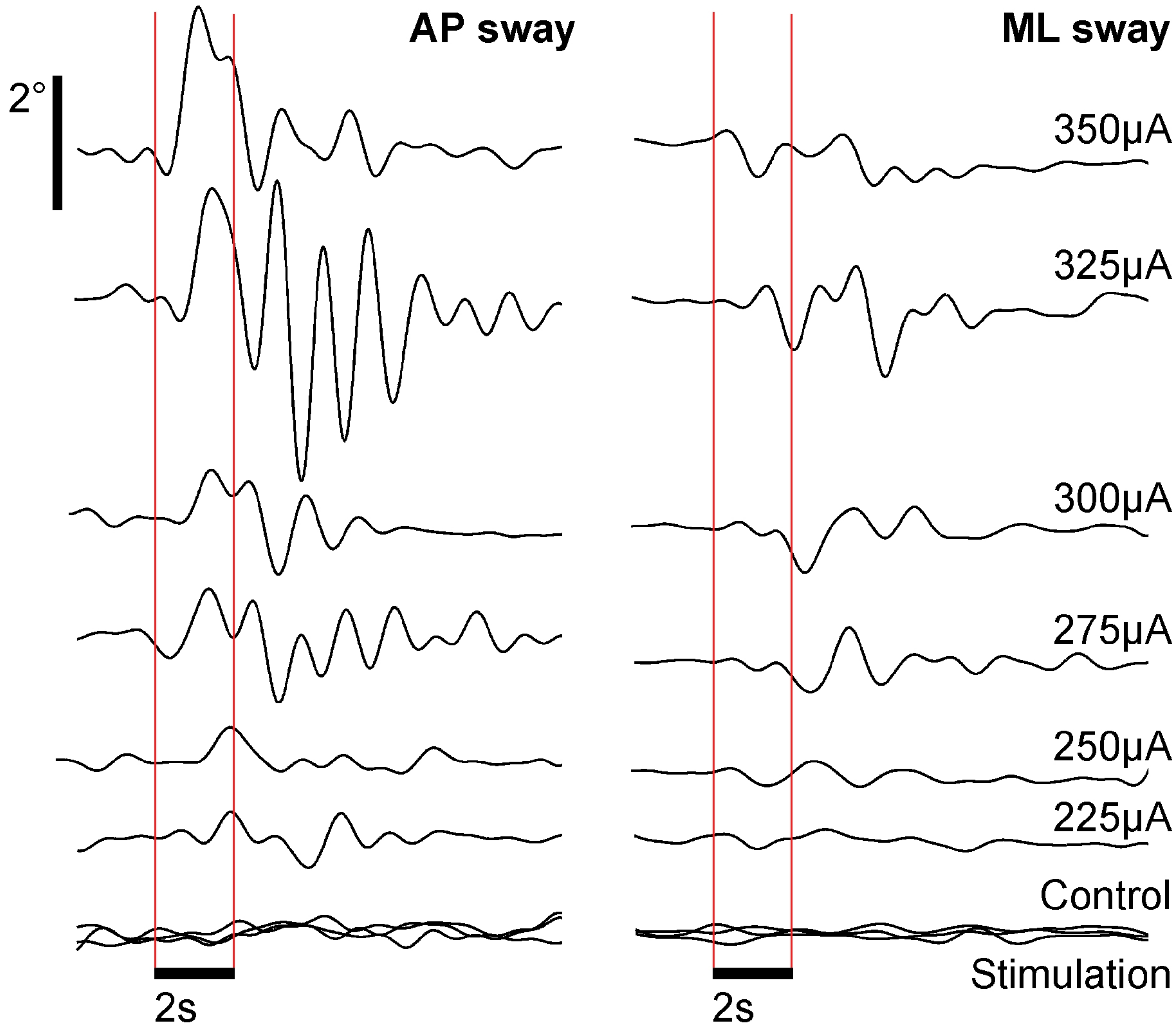


Perception of motion



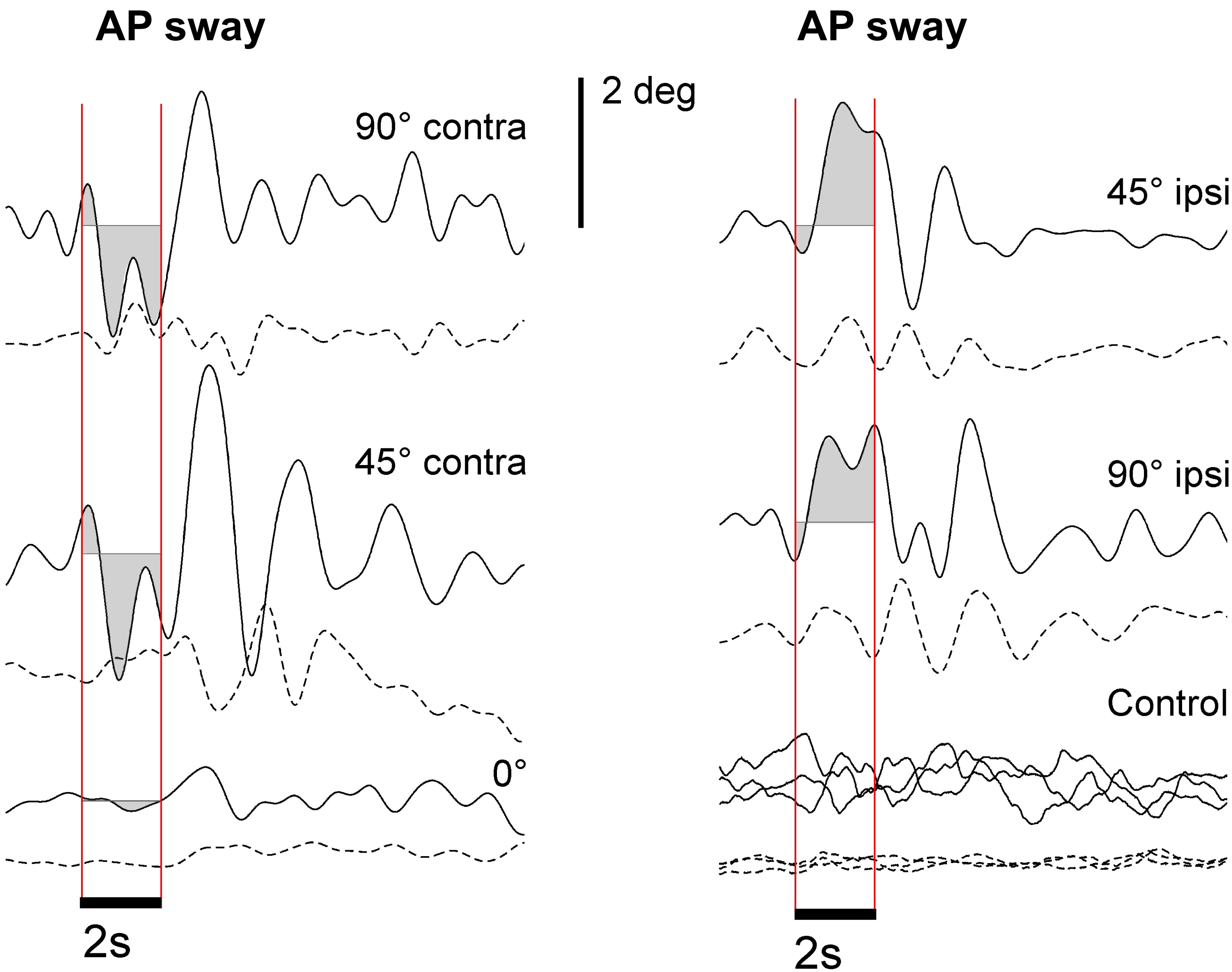
Lateral Canal 2s Stimulation

Postural sway



Right posterior canal stimulation

Postural sway at different head positions



Right lateral canal stimulation

Conclusions

- **We know that a vestibular implant works**
- **We have tested such a device in humans and animals.**
- **We have an existing approval to test these devices in patients**
- **We have built a combined cochlear and vestibular implant**
- **We are currently testing it in monkeys**
- **We are working with the FDA to modify our existing human trial to test this new device.**
- **We are not the only ones doing this!**