Sounds for a Young Generation, 2nd Latin American Pediatric Conference, Santiago, Chile.
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Auditory Development and Brain Plasticity

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Professor and Director of Research,
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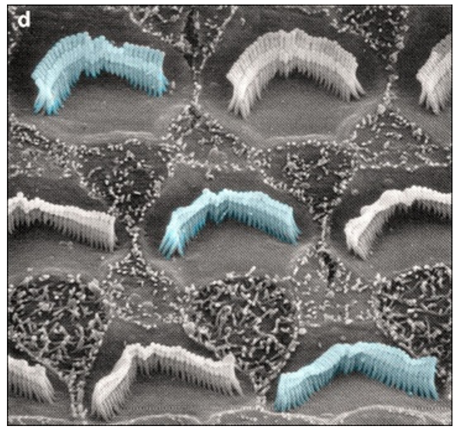
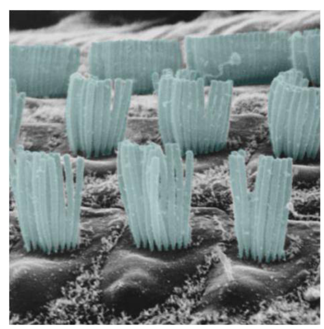
SickKids



Auditory Development and Brain Plasticity



AGENDA

Cochlear development

Connecting the cochlea to the brain

When do we first "hear"?

Early formation of the central auditory pathways.

Basic science studies of central auditory system development.

Evoked potential studies of human auditory system development.

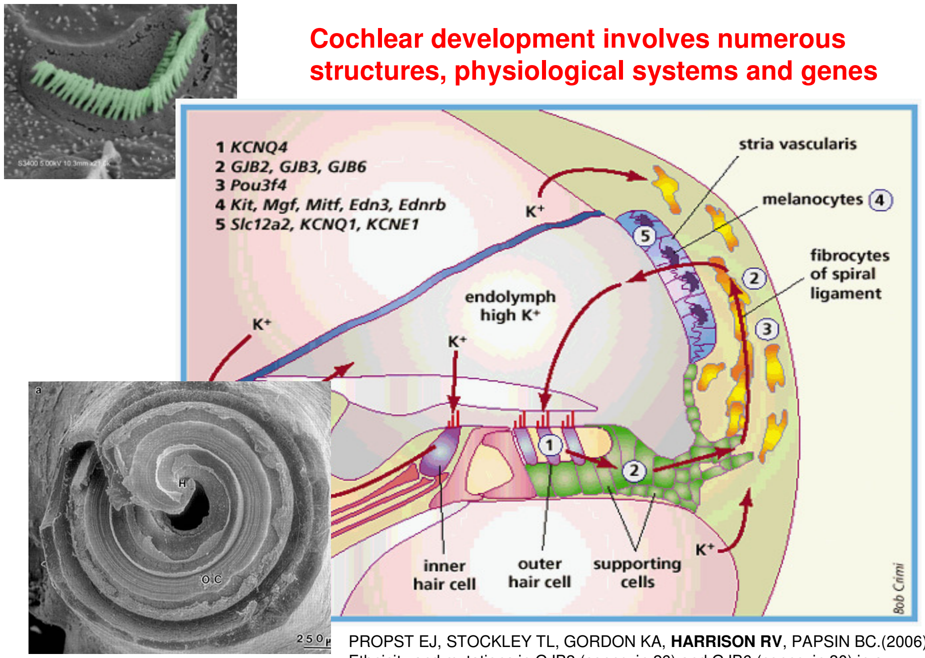
Tracking auditory brain development in children after cochlear implantation.

Age related plasticity in auditory system development.

How does basic science inform us about clinical issues?

Some "bench to bedside" discussion; take home messages.

Cochlear development involves numerous structures, physiological systems and genes



PROPST EJ, STOCKLEY TL, GORDON KA, **HARRISON RV**, PAPSIN BC.(2006) Ethnicity and mutations in GJB2 (connexin 26) and GJB6 (connexin 30) in a multi-cultural Canadian paediatric Cochlear Implant Program. Int J Pediatr Otorhinolaryngol. 2006 Mar;70(3):435-44.

Key developmental stages at the cochlear level

(time lines for human)

Onset of "hearing" ?

Hair cells connect to brainstem 20-30wks

Indications of cochlear function →

- Onset of cochlear potentials
- End of CM development
- CAP and cochlear frequency selectivity complete
- AP latency normal

HUMAN — 12 WK — 20 WK — 35 WK — **BIRTH** — 4 WK

Structural growth →

- Hair cell Differentiation. First afferent synapses
- Start of tectorial membrane growth. IHC mature
- Final maturation of basilar membrane, tectorial membrane, and OHC synapses
- Full myelination of auditory nerve

Key developmental stages at the cochlear level
(time lines for human and rat species)

Onset of "hearing" ?

Hair cells connect
to brainstem 20-30wks

Indications of cochlear function

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HUMAN: 12 WK — 20 WK — 35 WK — BIRTH — 4 WK

RAT: BIRTH — 10 DAYS — 16 DAYS — 20 DAYS — 25 DAYS

Structural growth

- Hair cell Differentiation. First afferent synapses
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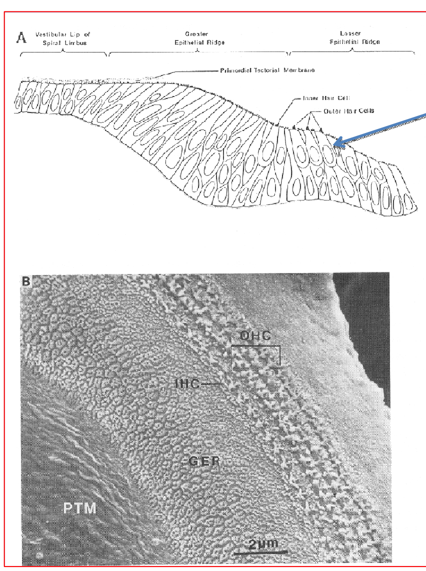
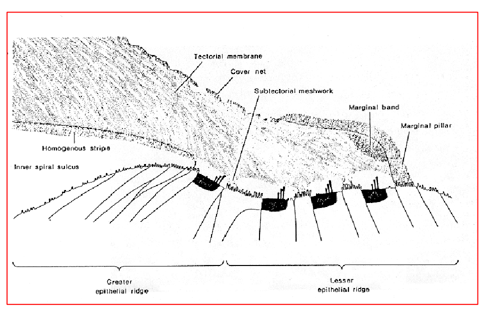
Development of the tectorial membrane



Haircells well developed before tectorial membrane growth



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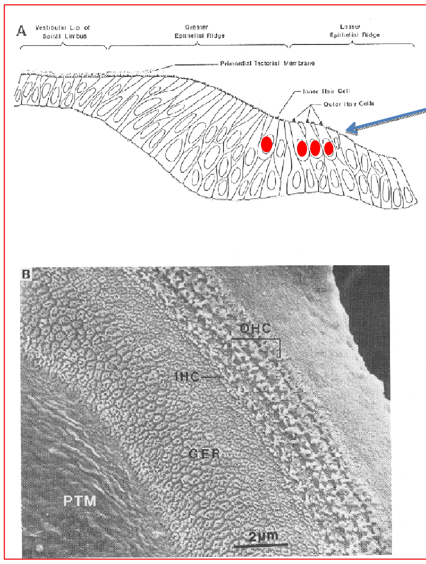

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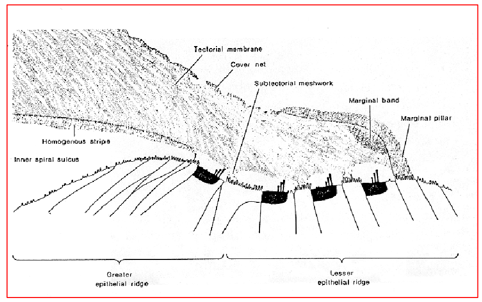
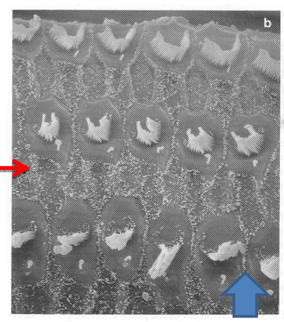
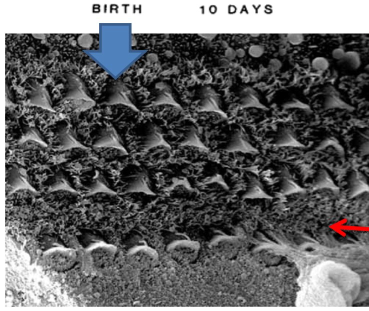


The cochlea at birth

precocious vs. altricious species

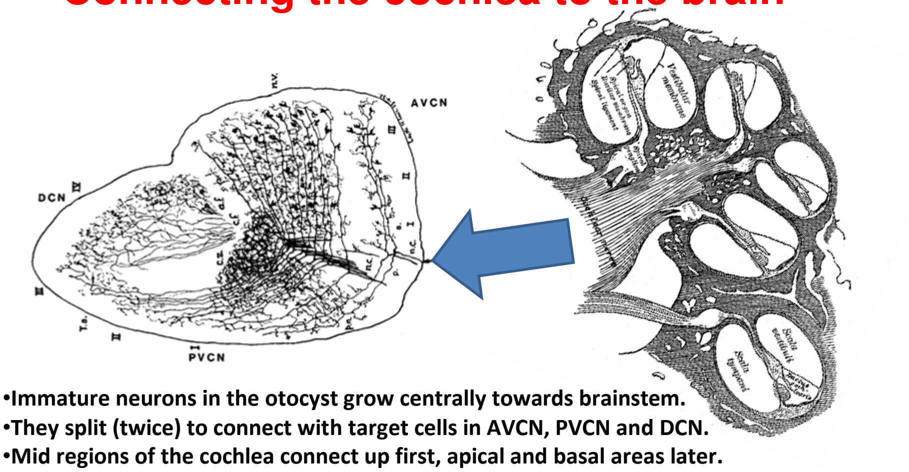
Chinchilla, Human (precocious species)





An altricious species (immature at birth).

Connecting the cochlea to the brain



•Immature neurons in the otocyst grow centrally towards brainstem.
•They split (twice) to connect with target cells in AVCN, PVCN and DCN.
•Mid regions of the cochlea connect up first, apical and basal areas later.
•Initial projections/connection are cochleotopic.
•Initial wiring occurs before any sound driven auditory input.
•May be a role for intrinsic (spontaneous) activity.

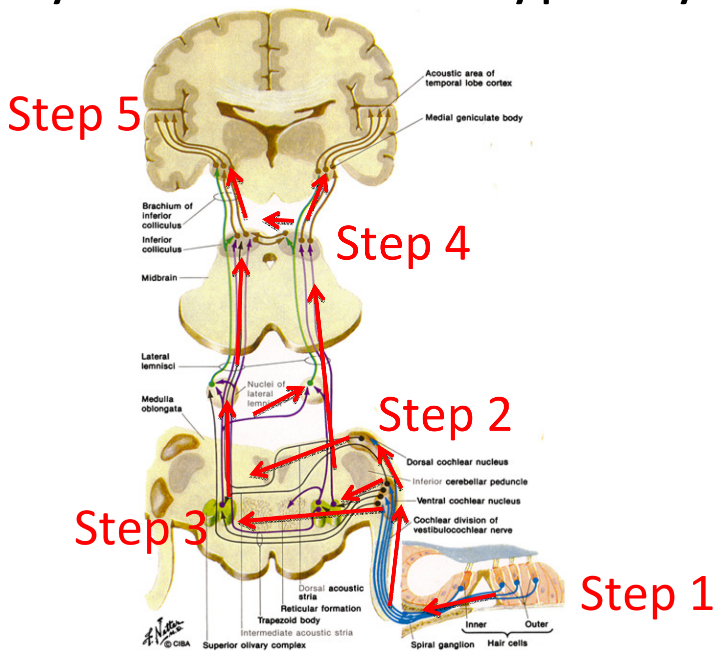
•Connections in humans complete at 20-30 weeks (i.e. 10 -20 weeks before birth)

When do we first “hear”?

- **Cochlea connects up at 10 - 20 weeks before birth**
- **First “function” is some weeks later**
- **ABR can be recorded in babies born 15 weeks premature**
- **Blink startle reflex to acoustic stimulation observed (by ultrasound) at 24-25 weeks gestational age**

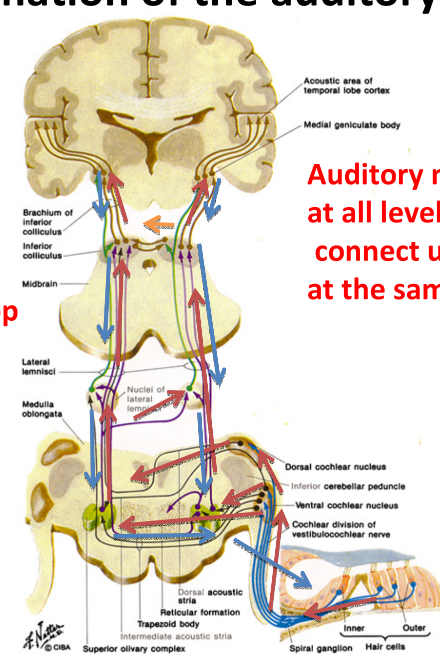
Discussion
Does this mean the baby really can “hear”?
What do we mean by “hear”?
What acoustic signals can be detected?

Early formation of the auditory pathways (?)



Early formation of the auditory pathways

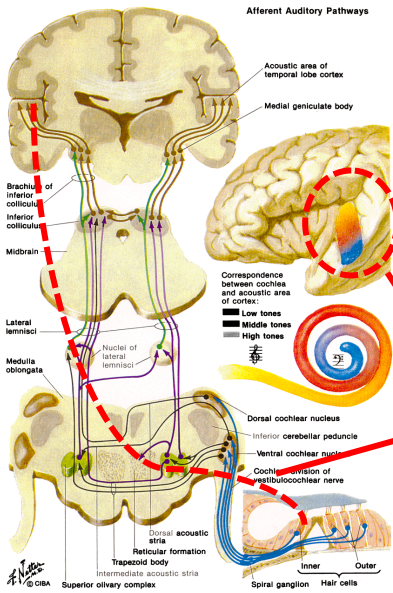
Both ascending and descending pathways develop at the same time



Auditory nuclei at all levels connect up at the same time

Initial MAINLINE connections are made BEFORE acoustically driven activity from the periphery

Developmental refinements of the auditory pathways



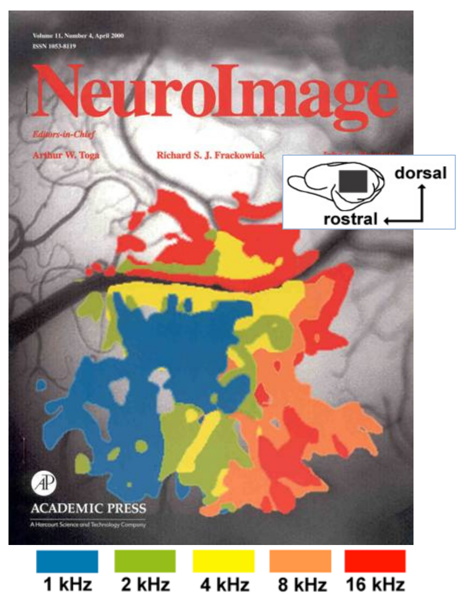
[1] Sound frequency representation (tonotopic maps) in auditory cortex

[2] Increased complexity of auditory processing in cortex

[3] Improved information transmission from cochlea to cortex

The sensory epithelium of the cochlea projects in organized way to auditory cortex.

(tonotopic /cochleotopic organization)



NeuroImage **11,** 302–312 (2000)

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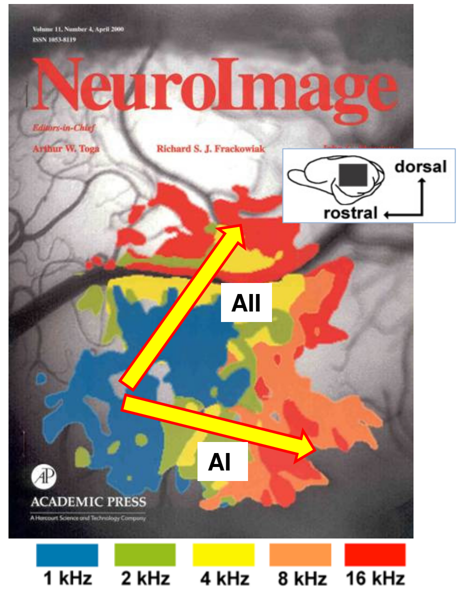
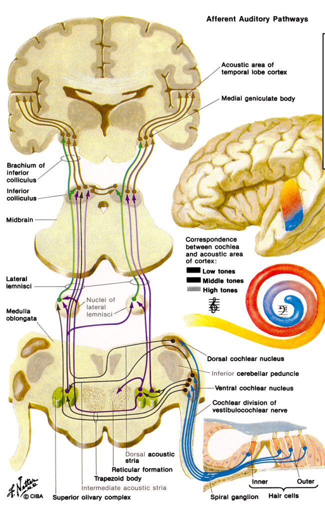
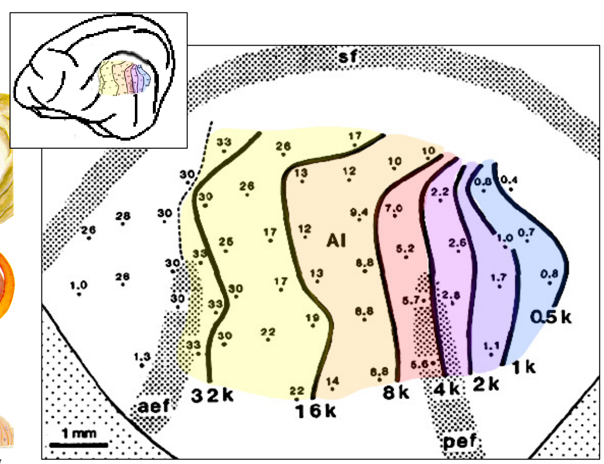


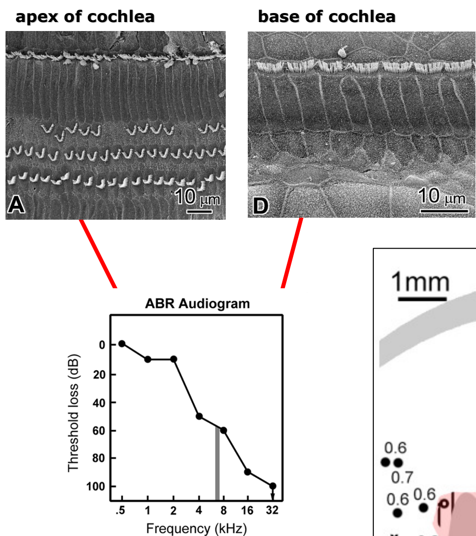
NeuroImage 11, 302–312 (2000)

Cochleotopic (tonotopic) organization of primary auditory cortex

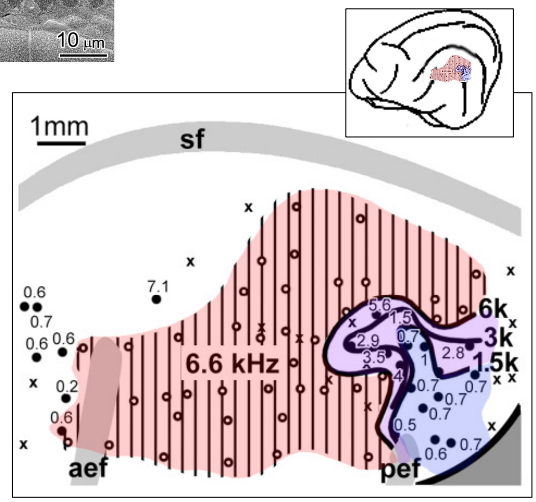
(in Human and Cat)





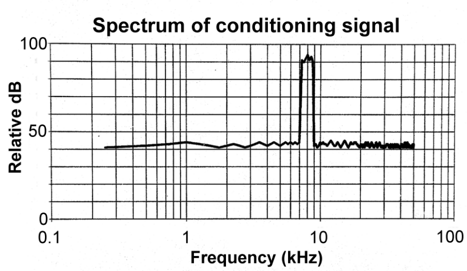


Cortical frequency map development after a neonatal cochlear lesion

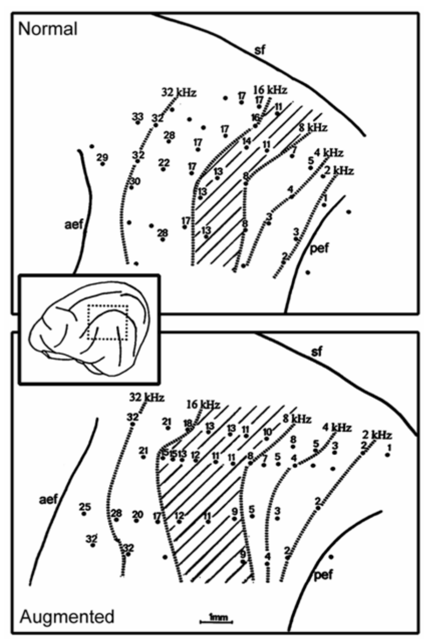


HARRISON, R.V., NAGASAWA A., SMITH D.W, STANTON S. and MOUNT R.J. (1991): Reorganization of auditory cortex after neonatal high frequency cochlear hearing loss. Hearing Research, 54, 11 -19.

Reorganization of auditory cortex by neonatal environmental sound stimulation



Subject reared with constant 8kHz signal developed cortical over-representation of 8-16kHz

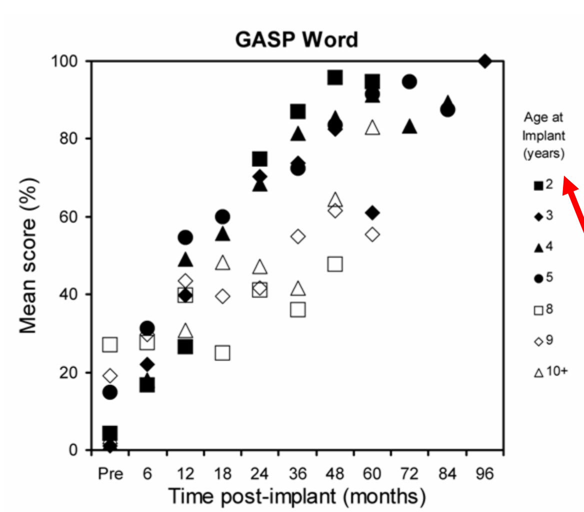


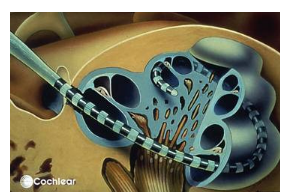
STANTON, S.G. and **HARRISON, R.V.** (1996): Abnormal cochleotopic organization in the auditory cortex of cats reared in a frequency augmented environment. Auditory Neuroscience 2, 97-107

Organization and programming of central auditory system shows age related plasticity

- All sensory systems have an early period of plasticity; visual, somatosensory, auditory.
- Early changes to cochlear activity patterns (e.g. caused by hearing loss) results in a reorganization and reprogramming of auditory cortex.
- Early changes to cochlear activity patterns also causes sub cortical reorganization (e.g. thalamus, midbrain).
- In more mature subjects the degree of plasticity is significantly reduced. Cortex can only be remodelled if sounds are “behaviourally significant”.
- Age related plasticity has very important impact on how we approach hearing loss in children. Early detection, early intervention.

Age related plasticity revealed in speech understanding in children with cochlear implants





SickKids®

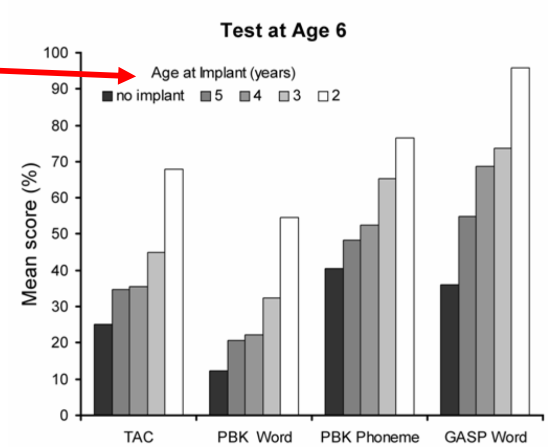
In other words, duration of auditory deprivation

Mean scores in the GASP word test, pre and post-implantation for each age at implant group as indicated by the symbols key (right).

GORDON KA, DAYA H, **HARRISON, R.V.**, PAPSIN BC (2000) Factors contributing to limited open-set speech perception in children who use a cochlear implant. Int J Pediatr Otorhinolaryngol. 56: 101-111.

Speech understanding in children at age 6 (entering school system) implanted at different times after birth

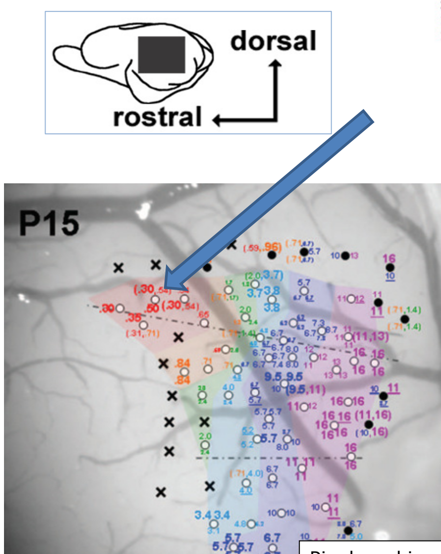
In other words, duration of auditory deprivation

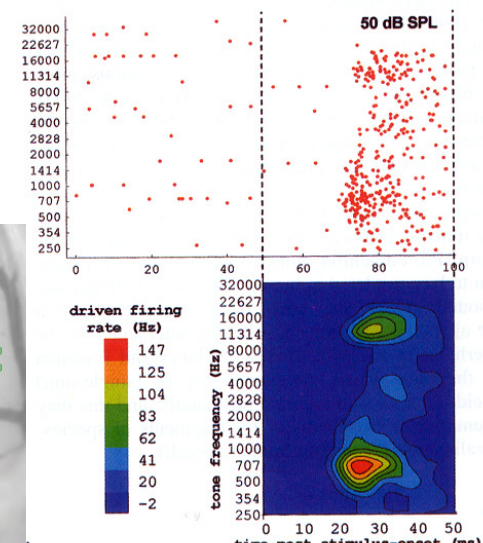


Speech perception outcome results at age 6 years. Results from four tests: TAC, PBK word; PBK phoneme; GASP word. The mean score (%) for congenitally deaf children, at six years of age, who have not yet received an implant is shown (black bar), and who had a cochlear implant device implantation at ages 2, 3, 4 or 5 years of age (see key).

GORDON KA, DAYA H, **HARRISON, R.V.**, PAPSIN BC (2000) Factors contributing to limited open-set speech perception in children who use a cochlear implant. Int J Pediatr Otorhinolaryngol. 56: 101-111.

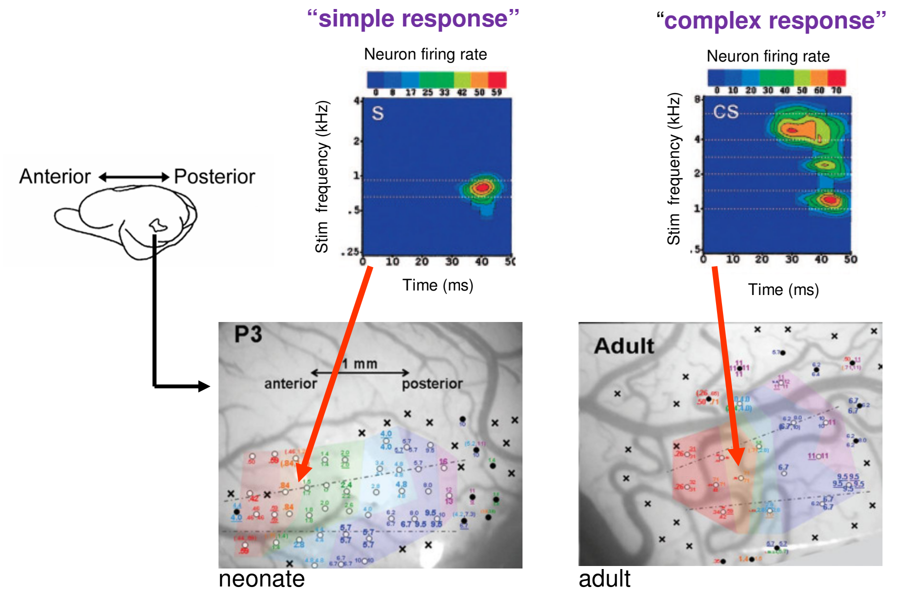
Recording the response properties of cortical neurons to tone stimuli





Pienkowski and Harrison (2005) J. Neurophysiol. 93: 454-466

Increase in complexity of neuron responses in auditory cortex with age



Pienkowski and Harrison (2005)
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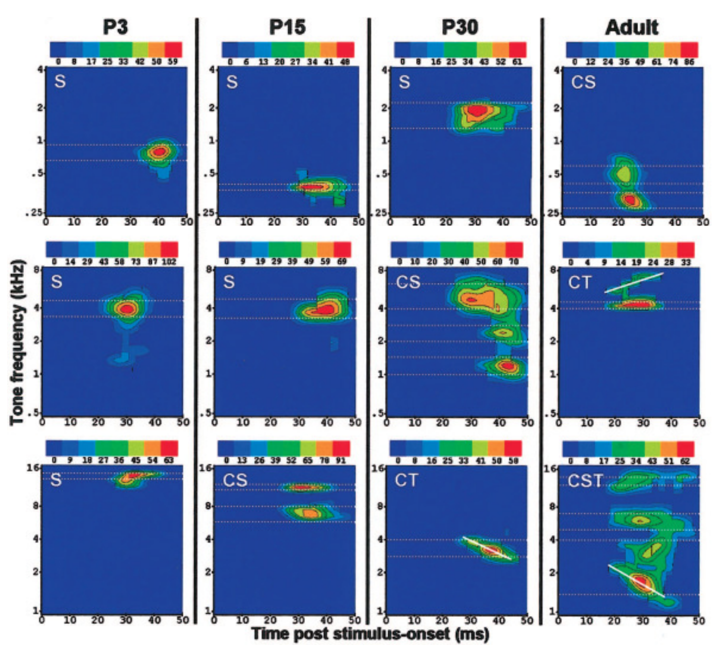
(nature vs. nurture)

Increase in complexity of neuron responses in auditory cortex with age



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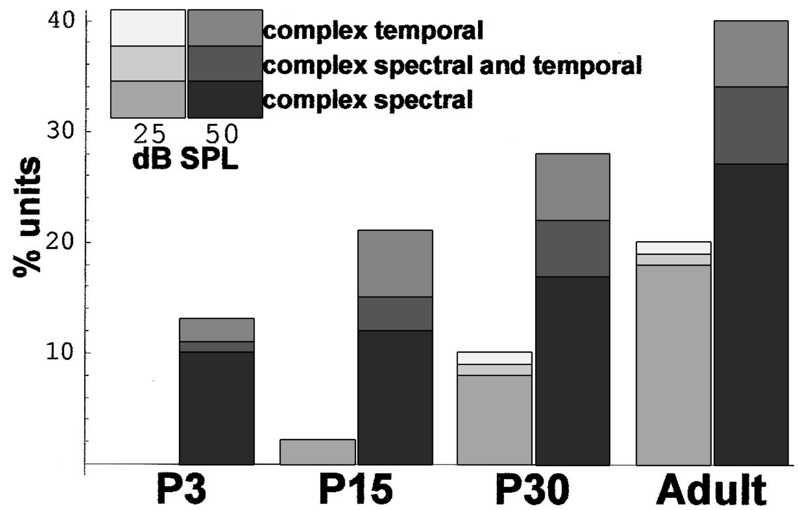
Proportion of “complex cells” in auditory cortex with age



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Increased complexity of auditory neuron responses reflects development of inter-neuronal connections

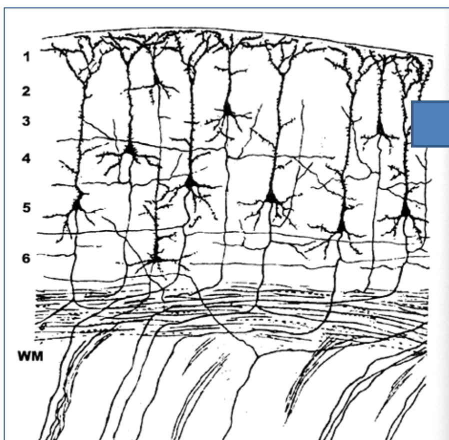
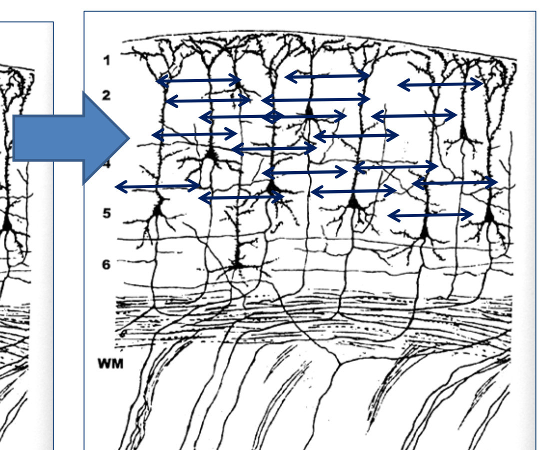


Fig 2. Illustration of laminar organization of cortex. Numerals 1 to 6 indicate cortical layers. WM — deep white matter. Adapted from Ramon y Cajal.[6]

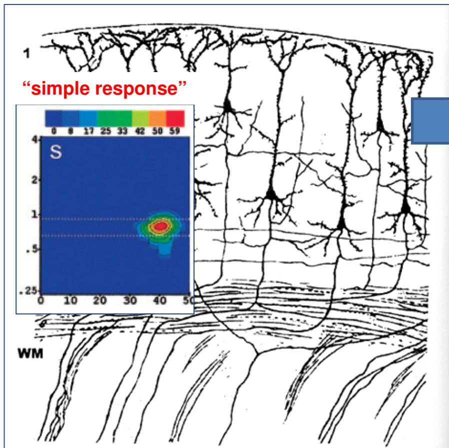
Cortex in early development



Mature cortex

(highly schematic)

Increased complexity of auditory neuron responses reflects development of inter-neuronal connections



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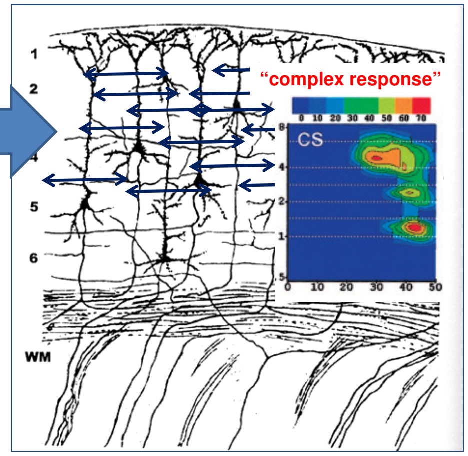
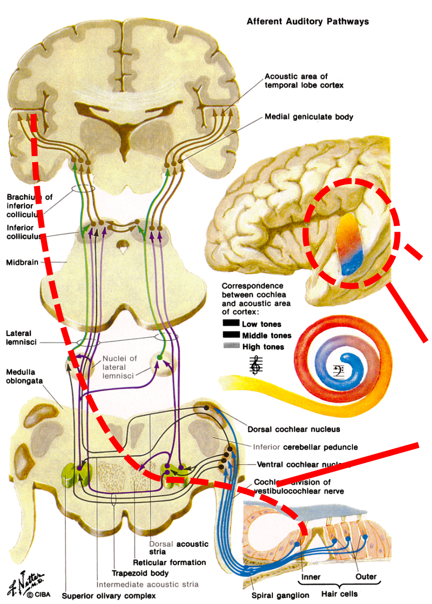


Mature cortex

(highly schematic)

Developmental refinements of the auditory pathways



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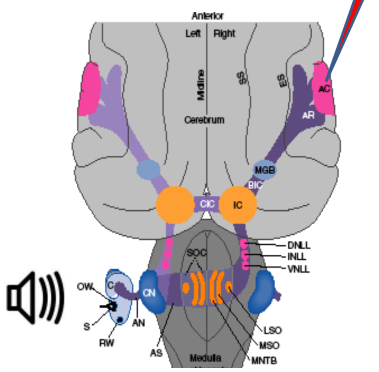
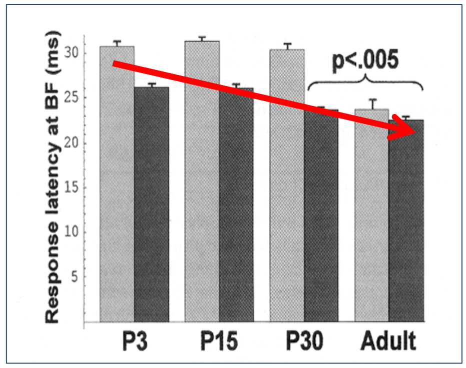
Neural “connectivity” improves with age

cortical neuron onset response latencies (chinchilla) at different ages





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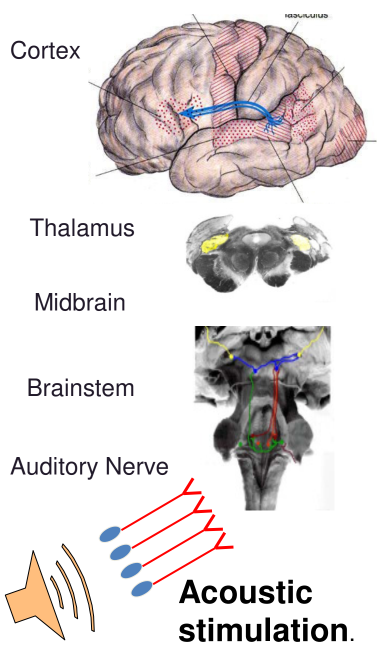
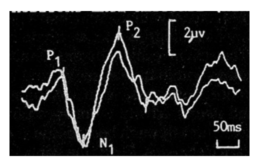
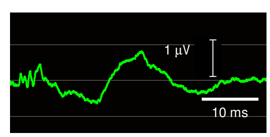
Acoustically evoked auditory potentials



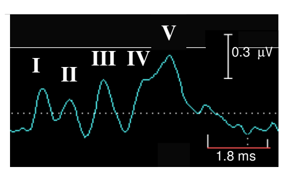
Cortical AEP



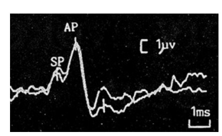
MLR



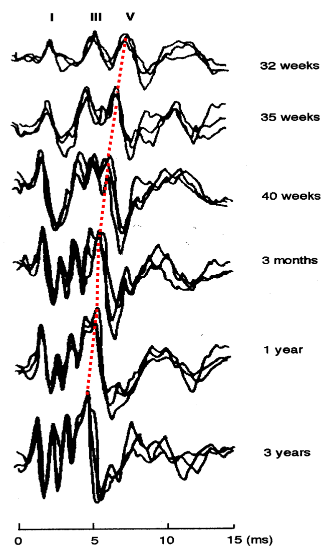
ABR

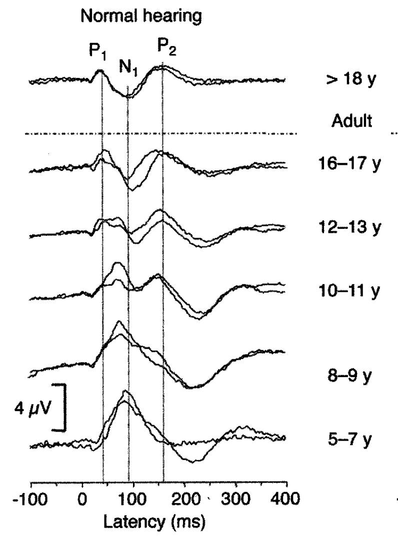


CAP



Evoked potential studies of human auditory system development



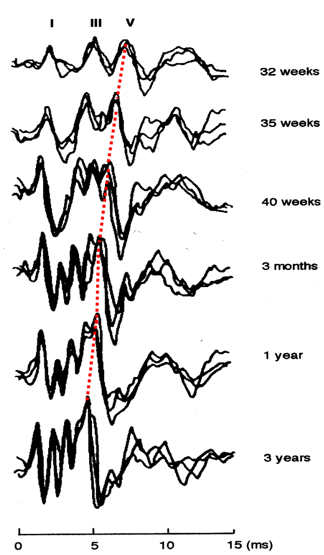


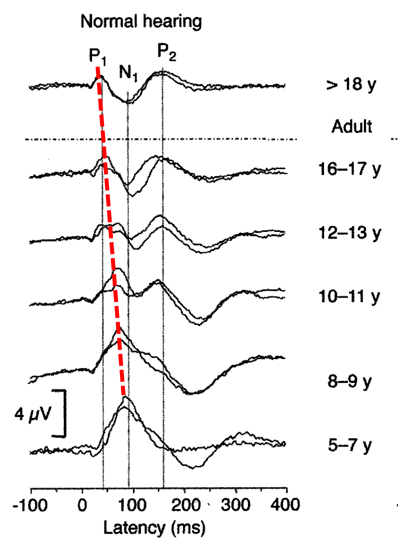
Auditory Cortex, Evoked Potentials

Auditory Brainstem evoked Responses ABR

Data from various works by Jos Eggermont

Evoked potential studies of human auditory system development





Auditory Cortex, Evoked Potentials

Auditory Brainstem evoked Responses ABR

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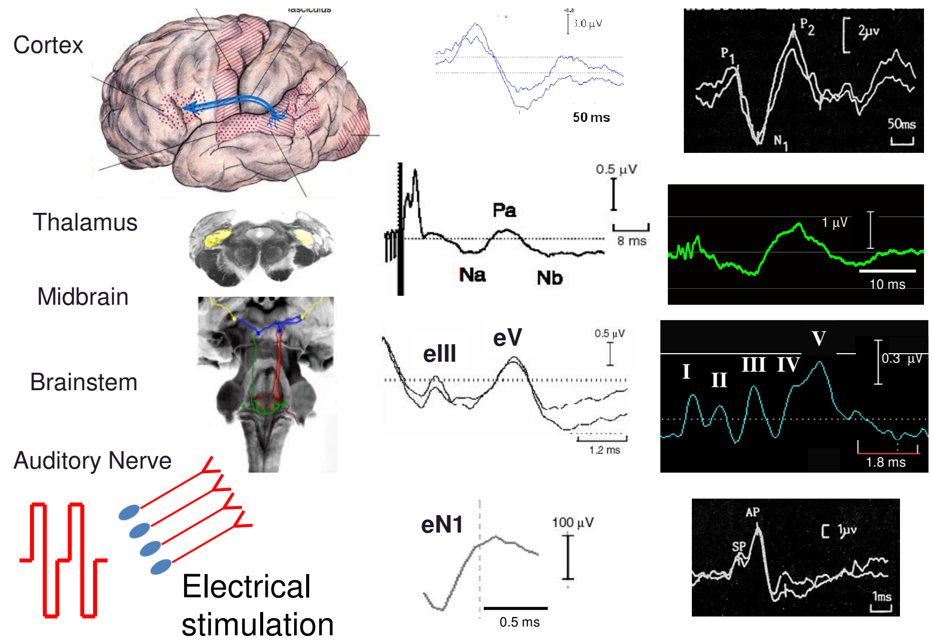
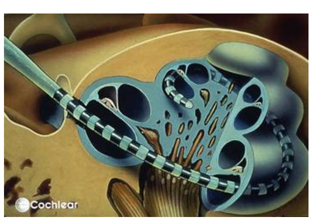
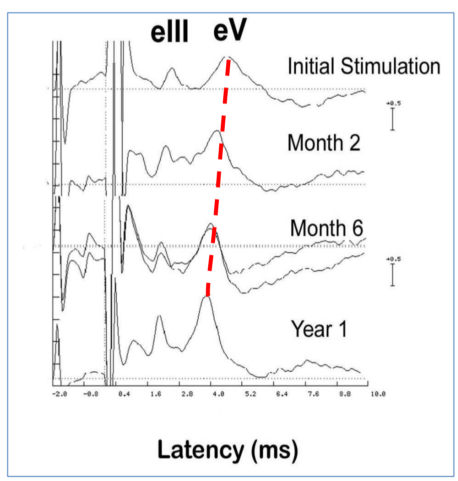
Electrically evoked auditory potentials in children with cochlear implants

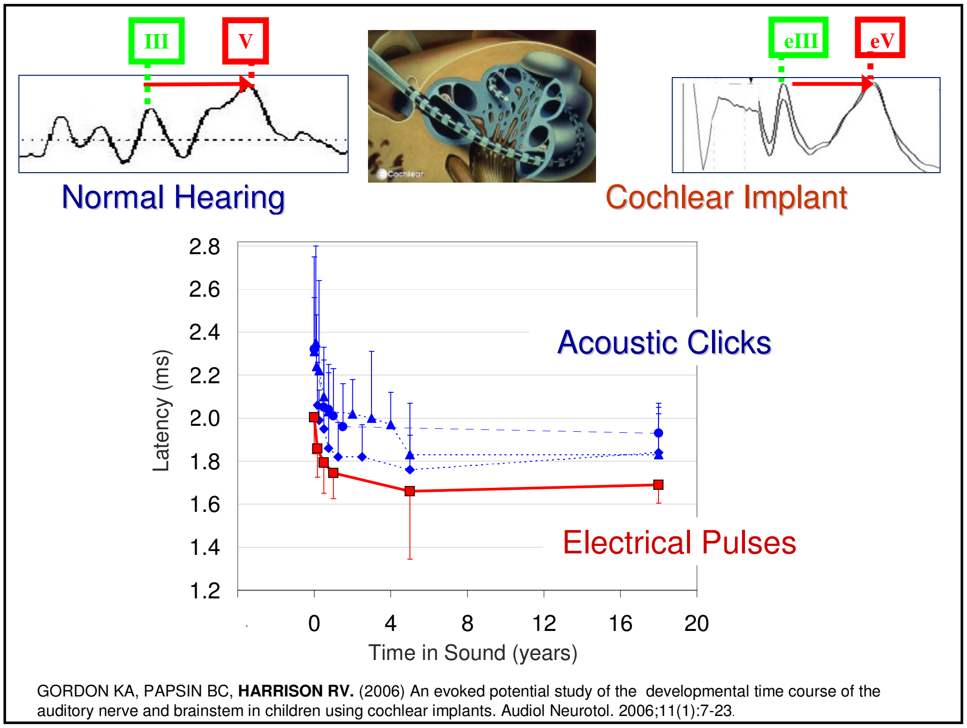


Auditory development through cochlear implant use





GORDON KA, PAPSIN BC, **HARRISON RV**. (2003) Activity dependent developmental plasticity of the auditory brainstem in children who use cochlear implants. Ear Hear. 24: 485-500


III
V
eIII
eV
Normal Hearing
Cochlear Implant
Acoustic Clicks
Electrical Pulses
Latency (ms)
2.8
2.6
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2.2
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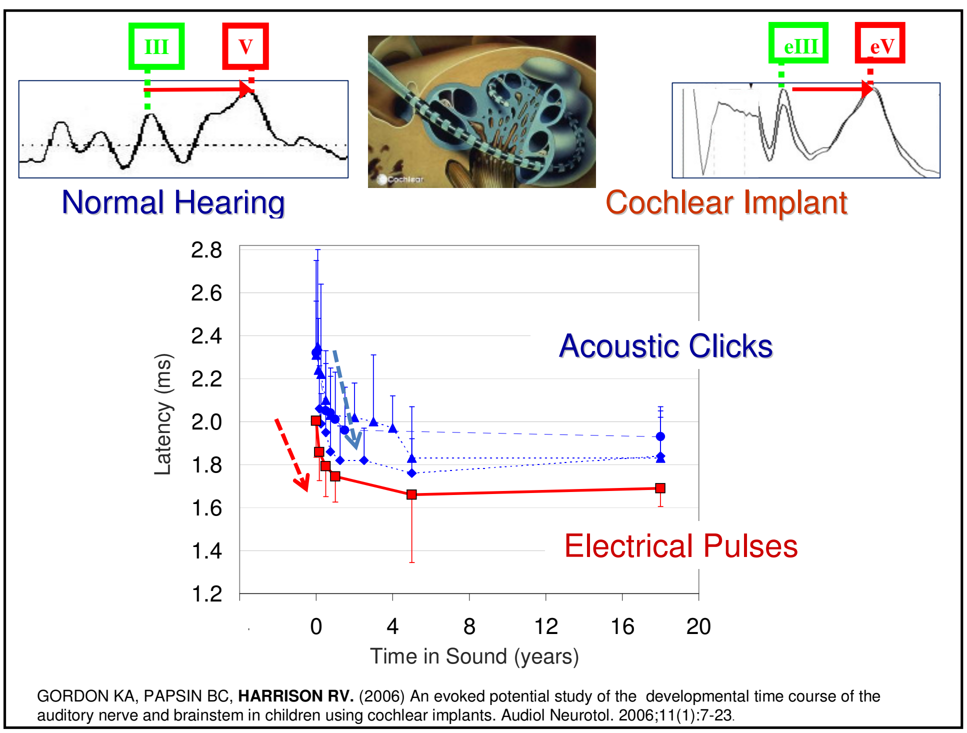
1.8
1.6
1.4
1.2
0
4
8
12
16
20
Time in Sound (years)
GORDON KA, PAPSIN BC, HARRISON RV. (2006) An evoked potential study of the developmental time course of the auditory nerve and brainstem in children using cochlear implants. Audiol Neurotol. 2006;11(1):7-23.


III
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2.0
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1.2
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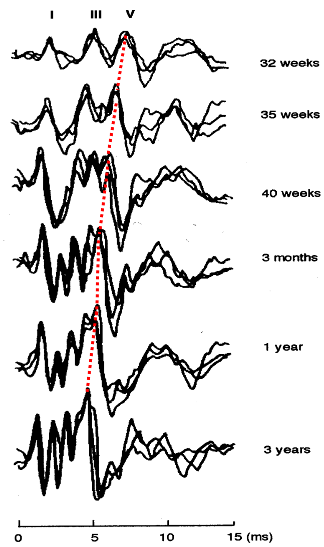
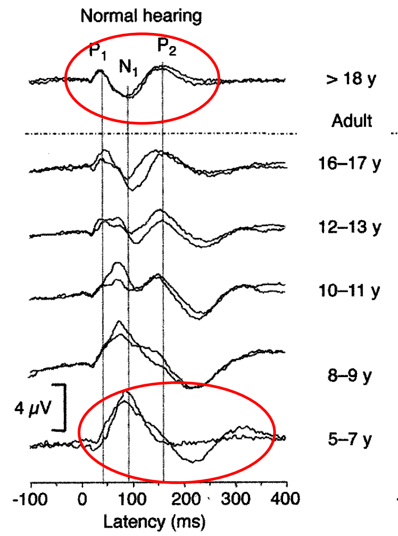
Evoked potential studies of human auditory system development



Auditory Brainstem evoked Responses ABR



Auditory Cortex, Evoked Potentials

Data from various works by Jos Eggermont

Post natal development of auditory cortex takes many years

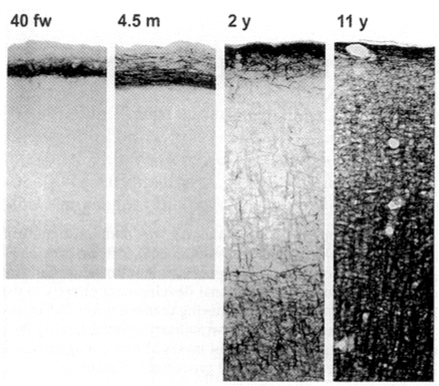


Fig 1. Neurofilament-immunostained sections of cortical tissue. At 40th fetal week (fw) and at 4.5 months' postnatal age, mature axons are present only in marginal layer. By 2 years of age, mature neurofilament-expressing axons are entering deeper cortical layers. By 11 years, mature axons are present with adult-like density in all cortical layers.

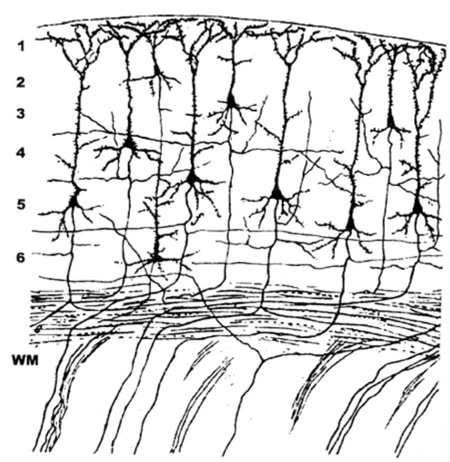


Fig 2. Illustration of laminar organization of cortex. Numerals 1 to 6 indicate cortical layers. WM — deep white matter. Adapted from Ramon y Cajal.[6]

Reference: Moore J.K 2002 ann otol rhinol laryngol 111, 7-10

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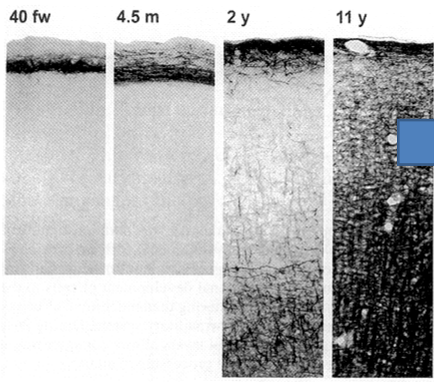

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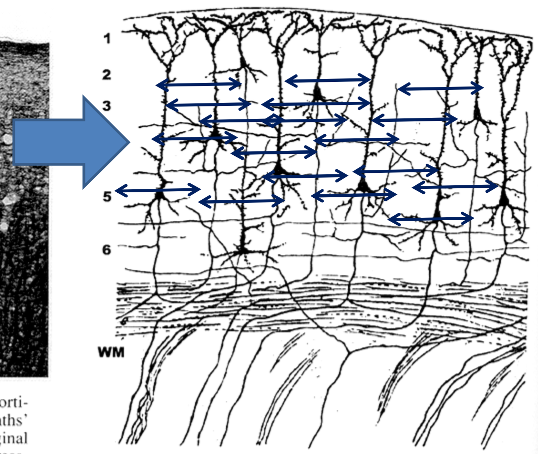

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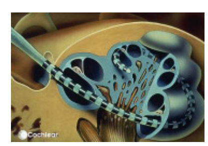
Developmental issues related to bi-lateral cochlear implantation in children

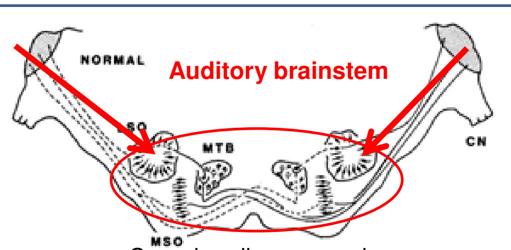
What are the effects on auditory system development of having input from only one side (single CI)?

Does a second, later implanted, contralateral cochlear implant work?

Simultaneous versus sequential bilateral cochlear implantation.

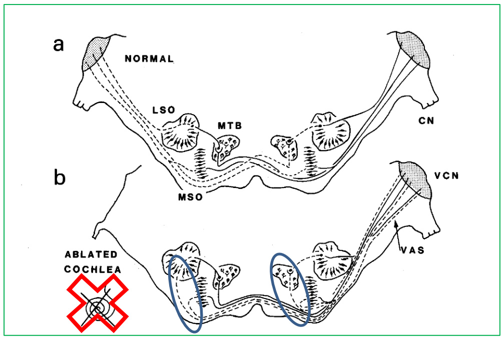


Normal neural substrate for binaural processing

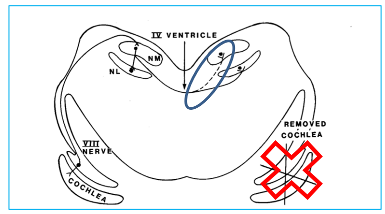


Developmental plasticity of the binaural system

Effects of early input from only one ear (one cochlea ablated)

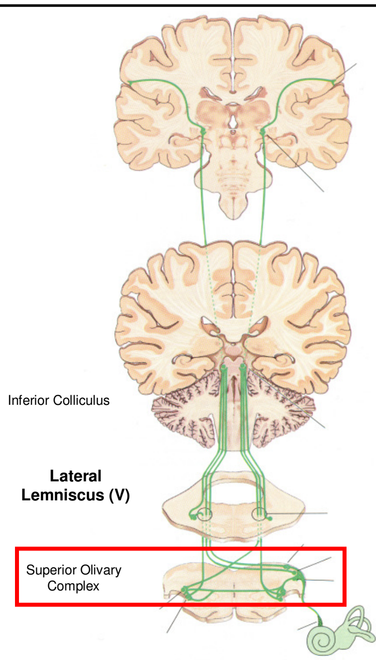


Effects on neonatal cochlear damage on the development of auditory pathways (in gerbil). (Kitzes L.M 1986)



Aberrant axonal branching in brainstem after unilateral otocyst removal (Parks and Jackson, 1986)

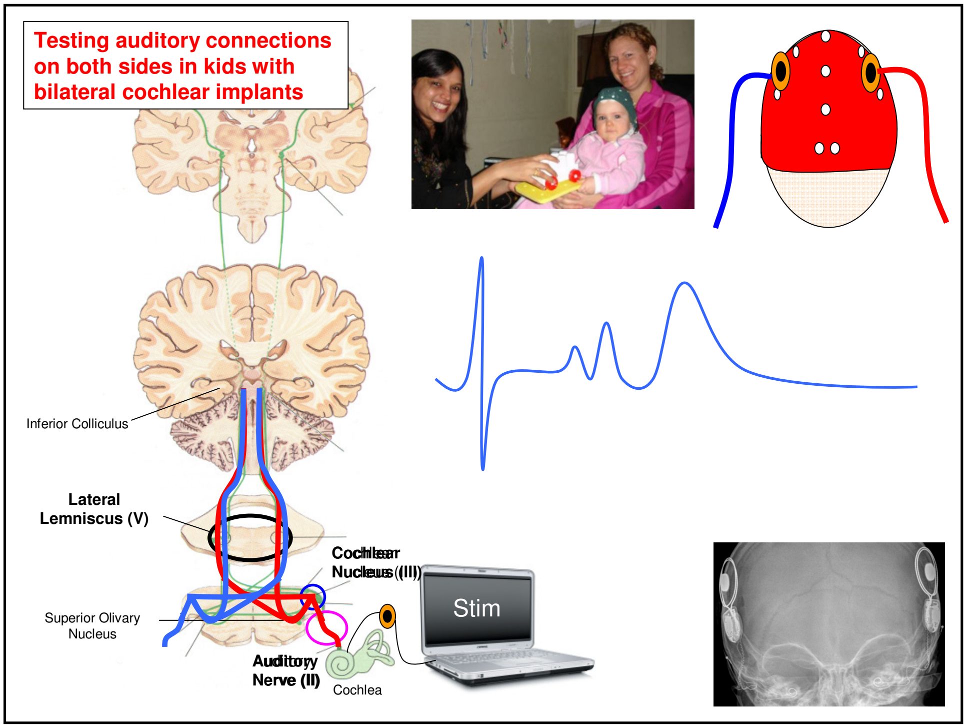
Question: - how is this different from a congenitally deaf child with one cochlear implant?

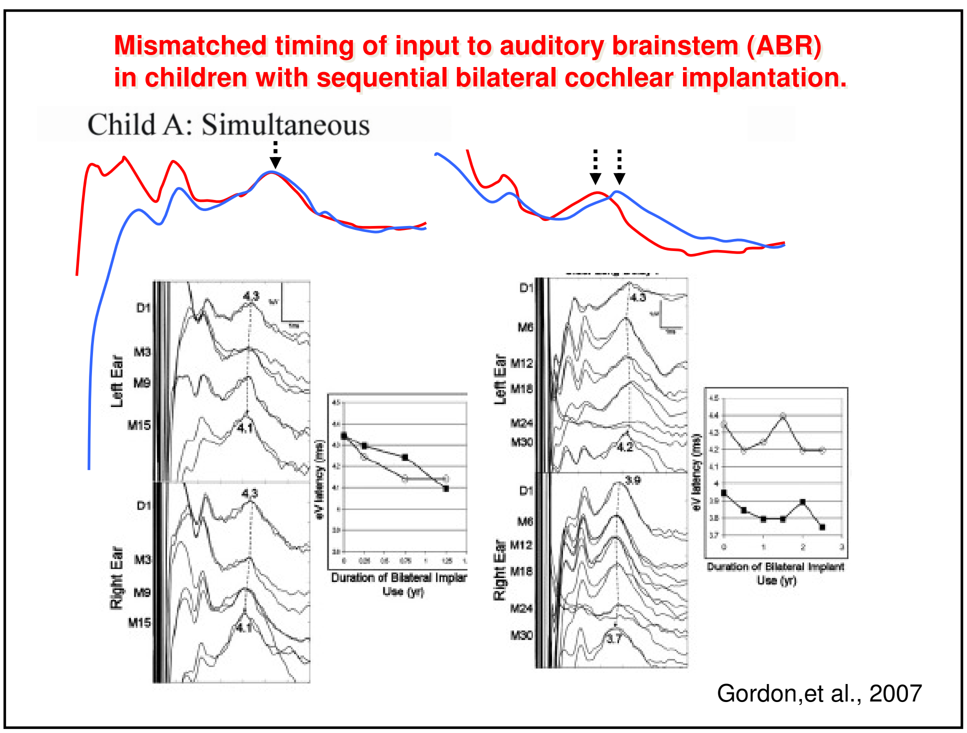


Using objective measures (ABRs) to assess binaural processing in kids with bilateral cochlear implants

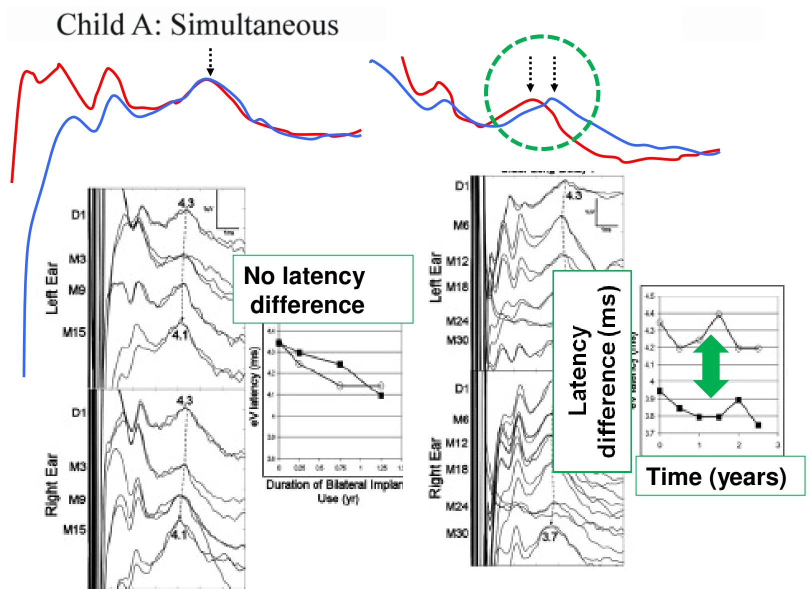
- Binaural processes are first established at the level of the brainstem
- Timing and level differences between the ears are compared for sound localization

THE HOSPITAL FOR SICK CHILDREN


Testing auditory connections on both sides in kids with bilateral cochlear implants
Inferior Colliculus
Lateral Lemniscus (V)
Cochlear Nucleus (III)
Superior Olivary Nucleus
Auditory Nerve (II)
Cochlea
Stim

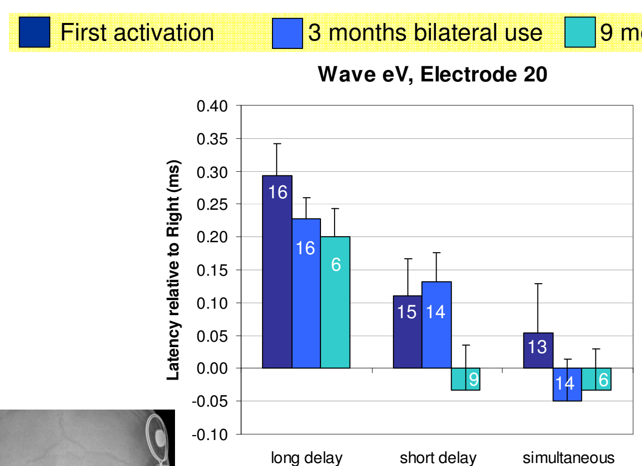

Mismatched timing of input to auditory brainstem (ABR) in children with sequential bilateral cochlear implantation.
Child A: Simultaneous
Left Ear
Right Ear
D1
M3
M9
M15
4.3
4.1
eV latency (ms)
Duration of Bilateral Implar Use (yr)
D1
M6
M12
M18
M24
M30
4.3
4.2
3.9
3.7
eV latency (ms)
Duration of Bilateral Implant Use (yr)
Gordon,et al., 2007

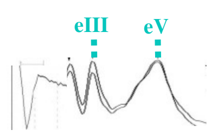
Mismatched timing of input to auditory brainstem (ABR) in children with sequential bilateral cochlear implantation.



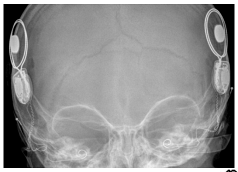
Gordon,et al., 2007

Right to left side difference in eABR (V) latency



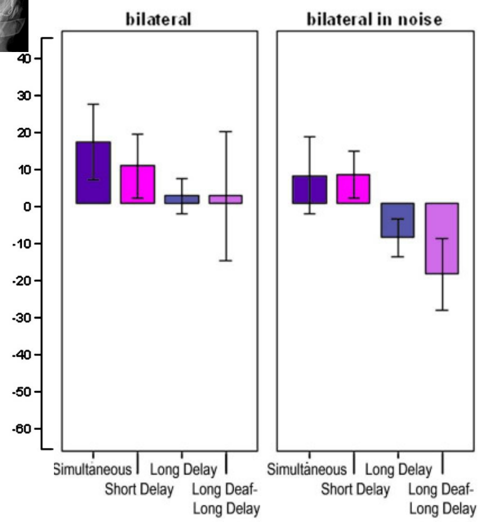


Gordon, et al., Otology & NeuroOtology, 2007

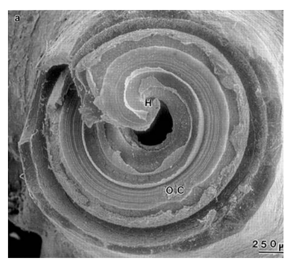


Speech perception in children using bilateral cochlear implants

% improvement in speech perception using both implants versus only one



Auditory Development and Brain Plasticity



Some clinically relevant "take home messages":

The pattern of cochlear nerve activity in the neonatal subject influences central auditory system organization.

Sensorineural hearing loss from an early age will result in cortical frequency map reorganization as well as many other aspects of auditory brain "programming".

Stimulation of the cochlear nerve by electrical stimulation with a cochlear implant drives the formation of auditory pathways in a rather "unusual" way.

The timing of binaural cochlear implantation is important.

A cochlear implant in a congenitally deaf infant serves two functions hearing AND development.

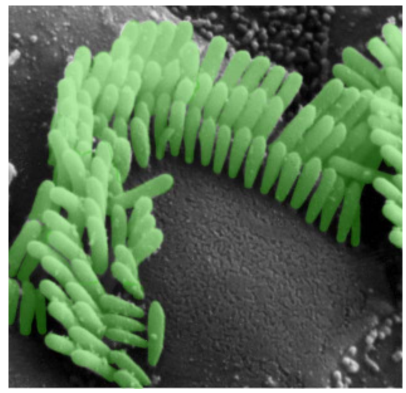
The auditory system has age related plasticity (especially in sub-cortical areas) and this has important implications for early hearing loss detection and intervention (next talk).

Sounds for a Young Generation, 2nd Latin American Pediatric Conference, Santiago, Chile.
25-27 November 2020

Auditory Development and Brain Plasticity

My thanks to collaborators:

Susan Stanton
Karen Gordon
Blake Papsin
Richard Mount
Trecia Brown
Akinobu Kakigi
Noam Harel
David Smith
Sachio Takeno
Daniel Ibrahim
Akira Nagasawa
Haruo Hirakawa



Funding from: CIHR and
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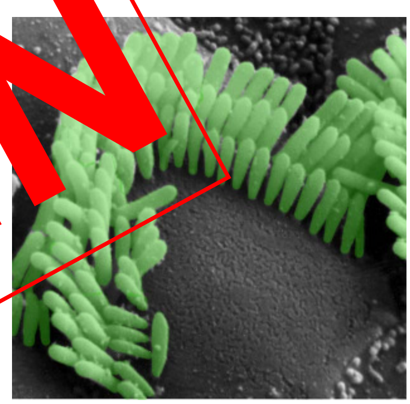
FIN



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