Clinical Physiology of the Auditory Cortex

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Auditory Cortex

How do we define it?

Lateral Sulcus
Temporal Lobe
Superior Temporal Gyrus
Superior Temporal Sulcus

Anatomically
The auditory cortex...appears to perform sound analysis by synthesis, i.e. by combining spatially distributed coincident or time-coordinated neuronal responses.

Guenter Ehret, 1997
Auditory Cortex

- Ultimate destination for ascending auditory input, **tonotopically organized** with full frequency representation.

- Much larger than brainstem and thalamic nuclei, has several "secondary" areas with full tonotopic organization.

- Divided into six layers - **afferents terminate primarily in layers III-IV**.

  - "Auditory Perception"
    - A primary site of functional reorganization – **auditory plasticity**
    - Projects down to MGB and IC - modifies input!
    - Projects to sensory association areas, **sensory integration**!
    - Projects to Broca’s and Wernicke’s areas.

Where is AI?

Where is AI?
What puts the “Auditory” in Auditory Cortex?

- Functional specificity of various auditory cortical fields in mammals can be determined by input from thalamic nuclei from MGB and other thalamic and extra-thalamic inputs (Winer, 1992, Rouiller, 1997).
- Thus AI organization can only be understood by considering thalamic input and thalamocortical and cortico-thalamic loops.

Auditory Cortex (Human)

- Three subjects shown.
- Heschel’s area outlined in purple.
- Highlighted areas are averaged responses for each subject to all stimuli.
- Yellow most robust response, then red, then purple.
- Much variability in auditory areas between ears and between subjects.
**Auditory Maps, AI**

- Most clearly defined maps are in the central area of AI

- In this area are patches or clusters of neurons with:
  - Lowest response thresholds to tonebursts (Schreiner et al., 1992; Sutter & Schreiner, 1995)
  - Very non-monotonic (peaked) rate-intensity functions (Schreiner et al., 1992; Clarey et al., 1994; Sutter & Schreiner, 1995)
  - Smallest dynamic range of rate-intensity functions (Schreiner et al., 1992)
  - Shortest response latencies (Mendelson et al., 1997)
  - Preferences to downward frequency sweeps and slow FM rates (Heil et al., 1992; Mendelson et al., 1993)
  - Sharpest frequency tuning (Heil et al., 1993)

**Neuronal Code for Sound in Auditory Cortex**

- Aspects of Plasticity:
  - Behavioral states can change response patterns in AI.
  - Learning can change the significance of a sound pattern.
  - Stimulation of basal forebrain (major cholinergic output source in CNS, facilitates learning & Attention) facilitates response of neurons in AI (rat, Harms et al., 1993).
  - Cholinergic influence on neurons in cat AI results in plasticity of frequency response areas and sharpness of tuning (Ashe et al., 1989).
  - Topographies of neuronal response characteristics in AI such as the widths of tuning curves, degrees of monotonicity, and dynamic ranges can change by the action of the brain cholinergic system.
  - Summary: The neuronal code for a given sound pattern in AI can be expected to change as a function of the animal’s attention to and experience with a certain sound.

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Dr. Hallowell Davis

"Father" of evoked response audiometry

Dr. Pauline Davis was the first to report CAEP in humans.
Women and CAEPs:
Leaders in Translational Research

- 1990’s-2000-
  - ERPs: Kraus, Sharma, Tremblay, Martin, Oates, Purdy, Wunderlich, Firszt, Brown

CAEP

- Slow, Late, Vertex, Corticals, ERPs.
- Sensory: Obligatory (exogenous)
  - response parameters are highly dependent upon stimulus characteristics
  - P1-N1-P2;
  - MMN
- Processing-contingent: Cognitive (endogenous)
  - response parameters are dependent upon the listener’s perception, attention and other cognitive processes.
  - N2, P300 (P3a), late processing negativity
Cortical Auditory Evoked Potentials (CAEPs)

- Primary auditory cortex & auditory association areas

Obligatory ERPs: P1-N1-P2

- Multiple generators
  - Bilateral superior aspect of temporal lobe (auditory cortex) generators plus
  - Auditory association area of superior temporal gyrus.
  - Some contribution from pre-motor cortex under influence of reticular formation

Subject Factors

- Infancy and early childhood:
  - CAEP can be recorded from premature infants at 26 weeks.
  - CAEP in infants has low amplitude, long latency, simple morphology, different scalp distribution
  - This suggests differences in underlying neural generators.

- Maturation
  - Substantial changes with maturation, through late teen-age years.
  - Latency, amplitude, scalp distribution, morphology vary with development
### Sleep and Arousal

- CAEPs can be recorded during sleep (in adults).
- Thresholds are elevated (20-30 dB).
- Latencies are longer.
- Amplitudes vary: P2 and N2 may be bigger, P1 and N1 smaller.
- More variability in latency and amplitude during sleep.

### Attention

- Amplitudes are generally larger in an "attend" listening condition compared to "ignore".
- N2 may be particularly increased.
  - Increase in N2 may "pull down" P2 amplitude.
- Sedatives, tranquilizers and psychotherapeutic agents have complex effects on CAEP, usually reducing amplitude and increasing latency.

### Functional Significance of N1

- An index of change
  - silence to sound
  - change in intensity
  - change in frequency
  - "attention triggering" process of cortex?
- N1 amplitude will be affected by stimulus parameters:
  - level, frequency, spatial location, phonetic content of speech, ISI, rise-time
Stimulus change and N1-P2

- **Rise-time:**
  - Amplitude increases as RT increases to 30 ms, but decreases when RT > 50 ms.

- **ISI:**
  - Amplitude increases as ISI increases from 1-10 s.

- **Level**
  - Amplitude increases over about a 40 dB SL range in normally hearing ears.
  - Latency is fairly stable until within 15-20 dB of threshold.
  - N1 can be recorded at 5-10 dB SL in awake adults.

Clinical Applications

- Presence of CAEP indicates that auditory cortices have been stimulated.
  - Frequency specific threshold estimation

- Malingered
  - Demonstrate cortical responsivity to sound.
  - Especially when ABR or MLR are absent.

- Excellent tool to use for the passively cooperative child or adult.
Recording CAEPs

- Stimulus: click, toneburst, tone, speech sound.
  - For tonebursts, use a 20 ms RF time
  - Larger amplitudes for low frequency tones (<1 kHz).
- ISI: 1/s or 1/2 s
  - Use "intermittent" stimulus
    - Consider "oddball" paradigm with periods of silence.

Recording CAEPs

- Epoch: 500 ms with 50 ms pre-stimulus interval
- Filters: 1-30 Hz or 1-15 Hz.
- Montage: Vertex-Earlobe
- Number of Sweeps: 50-100
  - Increase sweeps closer to threshold
- Subject: awake, alert, quiet.
  - Children may watch a silent carton.
  - Younger children may be engaged in quiet play, look at books, manipulate toys.

Electrode Sites/Topography

- N1-P2 is largest at vertex.
- N1-P2 can be recorded from (almost anywhere) the frontal scalp.
- "Inversion" of waveforms over a coronal array.
- Use of a non-cephalic reference (inverting) electrode.
Filter settings

- Use high pass edge at 0.1 to 1 Hz
- Use low pass edge at 30 to 100 Hz.
- For P1-N1-P2, 1-30 Hz works very well

Research Applications

- Maturation of auditory system.
- Evaluation of neural substrates of speech perception.
- Perception of sound in new and experienced CI users.

CAEPs to tones or speech sounds can be obtained in infants and young children (Wunderlich, Cone-Wesson, and Shepherd, 2006).

These responses were obtained at suprathreshold levels in subjects who were awake.
RESULTS: Newborns

Morphology
- Characterised by P2 (~250 ms) followed by N2 (~400-500 ms).

Effect of stimulus type
- Slow tones evoked larger P2 and N2 than high tones.
- Words evoked P1 and N1 more often than tones.
- Words evoked larger P2 and N2 than tones.

<table>
<thead>
<tr>
<th>Word</th>
<th>Low</th>
<th>High</th>
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<tr>
<td>Cz</td>
<td>P2</td>
<td>N2</td>
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<td>P1</td>
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<td>N1</td>
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<td>C3</td>
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<td>N1</td>
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RESULTS: Newborns

- Words evoked larger P2 and N2 than tones.

P1 latency change with age.

Ponton et al, 1996

\[ y = -32.746 \ln(x) + 155.5 \]

\[ R^2 = 0.78 \]
Early component of CAEP reaches normal latency in children who have auditory experience with electrical stimulation.

P1 latencies show a dramatic shift in latency within several months of hearing experience with a cochlear implant.
Electrophysiology of Auditory Neuropathy

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Identification

• The identification of auditory neuropathy is based upon electrophysiology:
  – Presence of EOAE and/or CM
  – Absence or “gross abnormality” of neural potentials (CAP and/or ABR)

• Where to from here?

Site-of-lesion and treatment decisions

• This review was undertaken in order to determine if AEPs could provide:
  – Site-of-lesion information
  – Knowledge to inform rehabilitation and treatment decisions
Types of AEPs

- **Cochlear receptor potentials**
  - CM
  - SP

- **Auditory nerve potentials**
  - CAP

- **Brainstem potentials**
  - ABR
  - ASSR (fast rate)
  - FFR

- **Thalamo-cortical potentials**
  - AMLR
  - ASSR (40 Hz)

- **Cortical potentials**
  - ASSR (<40 Hz)
  - Obligatory
    - P1-N1-P2
    - MMN
  - Cognitive
    - N2
    - P300

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  - P1 - N1 - P2
  - MMN

- **Cognitive**
  - N2
  - P300

**Preview of conclusions:**
- We may need to use them all to accomplish the goals of SOL and informed treatment.

**Caudal-to-rostral view of ANS and AEPs**
- Review of mechanisms
- Applications to ANHL and SNHL

**CM present ABR absent**

- Chisin et al, 1979 reported this result in a group of children deafened by hyperbilirubinemia/kernicterus.
- Speculated that this finding may indicate a lesion of the cochlear nucleus.
- This might be now recognized as auditory neuropathy.
  - Association with ANHL and hyperbilirubinemia is now established.
The normal (transtympanic) ECoG

- Recording electrode at or near RW
- Click and tonebursts
- Components:
  - Cochlear microphonic (CM)
  - Summating potential (SP)
  - CAP (compound nerve action potential)

CM and SP

- CM is an extra-cellular, alternating current, receptor potential that follows stimulating waveform.
  - Derived from the currents flowing through OHCs as they are polarized and depolarized when transducer channels are opened by stereocilia bending.
- SP is a DC receptor potential generated by OHCs and IHCs.
  - Polarity and distribution of OHC/IHC components depends on level and stimulus frequency.
  - SP generated by IHCs for high frequencies.

RW ECoChG, normal hearing

P Chalmers and McMahon et al., 2008
Growth of DC component (SP) with stimulus frequency.

Palmer and Russell, 1986

SP and CAP (clicks): Normal

Santarelli et al, 2008

CM in ANHL

- CM can be present when EOAEs are absent.
  - CMs do not require “active process” for generation.
- CM reported to be enlarged in ANHL (Starr et al, 2001)
  - Those with enlarged CM were young
  - Normal neonates have large CMs (Young, 1999)
    - 0.12-0.57 uV @ 60-90 dB nHL
- CM amplitude may be modulated by efferent system including MOCB and acoustic reflexes.
  - Both are absent in ANHL
- Persistence of large CMs may indicate lack of efferent suppression.
Abnormal “Positive Potential” (APP)

- Amplitude is 2-3X that of normal SP.
- Duration is 3-4 times longer than normal SP.
- Found in 8% (n=34) of 431 children suspected of having severe-profound HL.
- Recorded using RW ECoG and high frequency (8 kHz) toneburst.

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**APP (enlarged SP)**

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**Examples of APP (8 kHz tone burst)**

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Fig. 1. RW ECoG recordings from 5 different subjects showing APP aftertading 8 kHz tone burst at 100 dBnHL.
APP and ANHL

- In O’Leary et al report, no child with APP had an ABR.
- All but two with APP had profound HL.
- Clinical histories of those with APP were typical of those with ANHL:
  - Rocky perinatal course owing to prematurity
  - Hyperbilirubinemia
  - Birth hypoxia

APP and Outcomes

- 26 children with APP
  - 12 had adequate speech and language development with a hearing aid
  - 12 did not receive benefit from hearing aid
    - 8 received a cochlear implant

Santarelli et al, 2008

- CM, SP and CAP recorded using transtympanic ECoG and click stimuli
- CMs found in 16/16 subjects, some enlarged
- SPs apparent in only 8/16
- CAPs found in 5/16 ears
- A broad low amplitude, delayed latency, long duration potential found in 7 others
SP and CAP (clicks): Normal and ANHL

Adaptation paradigm used to identify pre-from post-neural components

3 types of results in adaptation paradigm:

- 2/5 with SP showed no adaptation of CM or SP component
- 3/5 showed SP/CAP complex attenuated with adaptation, similar to control subjects.
- 2 subjects without identifiable SP or AP showed effects of adaptation, suggesting the low broad wave was of neural origin.
  - Dendritic potential reflecting sustained depolarization (and negative extracellular field) of unmyelinated 8th nerve fibers at proximal portion

SP, CAP and ABR, normal and ANHL

- SP and CAP (clicks): Normal and ANHL
- Santarelli et al, 2008

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Santarelli et al, 2008
Dendritic Potentials

- McMahon et al (2008) describe APP and dendritic potentials in ANHL
- 14 subjects
- SP and CAP absent in 2/28 ears
- 15 ears with APP
- 11 ears with “broad” long duration negative potential identified as DP

APPs and DPs

- APPs interpreted as a pre-synaptic disorder
  - Could be due to disruption of neurotransmitter release
  - Should be amenable to electrical stimulation

- DPs interpreted as post-synaptic disorder
  - Abnormal build-up of depolarizing current
  - DP may indicate dysfunction at level of proximal portion of 8th nerve
    - Stimulation of 8th nerve distal process by cochlear implant may not be effective
ECoG

- RW ECoG yields excellent definition of SP and CAP compared to peri-tymppanic or far-field (scalp) recordings
  - Use of “golf club” electrode on RW
- More common in Australia and Europe
- What is cost-benefit ratio for RW ECoG in auditory neuropathy?

E-CAP

Cochlear Implantation in Children with Auditory Neuropathy Spectrum Disorder

Holly E. B. Tegge, Patricia A. Roush, Jennifer S. Woodard, Debra R. Hatch, Carbon J. Zelnick, Emily Bass, and Craig A. Buchman
Brainstem Responses

- Kraus et al (1984) reported ABRs absent in some cases of mild or moderate hearing loss.
  - Recognized this as a “neural” or auditory brainstem dysfunction
- ABRs may be absent (70%) or abnormal in ANHL
  - Little quantitative knowledge of “abnormal”
  - Those with abnormal ABRs have better PTAs
    - But PTA is unrelated to speech perception performance
- ABR used to identify ANHL only in conjunction with EOAEs, CM and SP
E-ABR

- Shallop et al were first to demonstrate “normal” E-ABRs in ANHL patients with implants.

- Gibson and Sanli (2007) reported E-ABR findings in 39 patients with ANHL who received implants.
Gibson and Sanli (2007)

- 2 types of findings from RW ECoG and subsequent E-ABR (after implantation)
  - APP, normal E-ABR (N=32)
  - APP abnormal E-ABR (N=7)
- Those with normal E-ABR had significantly higher rating on a scale of speech perception abilities than did those without E-ABR.
  - McMahon et al (2008) also found that SP+DP finding was associated with abnormal E-ABR and poorer outcomes with CI.

Runge-Samuelson et al, 2008

- E-ABRs quantified
- Small sample (N=5) compared to E-ABR in 27 with SNHL
- E-ABR in ANHL
  - Tend to have lower amplitude than in SNHL
  - Some have prolonged latencies at near threshold levels.
- No follow-up/outcomes data provided.

Runge-Samuelson et al, 2008

![E-ABR in ANHL](image)
Examples of E-ABRs
Adults, SNHL (post-lingual)
Considerable variability.
E-ABR not strongly related to speech perception outcomes. But 2/3 with no E-ABR had poorest speech perception results. This finding signals a poorly synchronized neural response.
Firszt et al, 2002

E-CAP and E-ABR
• E-CAP (NRT/NRI) is now routinely measured to monitor cochlear implant integrity.
• E-CAP + E-ABR would allow evaluation of neural synchrony at 8th nerve and brainstem levels.
  – Results would indicate those with 8th nerve versus brainstem disorder.
    • Pre- vs. post-synaptic disorder?

ASSR and ANHL
• ASSRs at >70 Hz have brainstem (and cortical) sources.
  – Reflect ability of 8th nerve and brainstem generators to follow rate of modulation.
• ASSRs may be present when ABR is absent
  – Differences in stimulus calibration
  – Differences in filtering?
    • not enough synchrony for wave V, but enough for rate following (energy below 100 Hz)
• Presence of ASSR when ABR is absent raises suspicion of ANHL.
  – Some measure of pre-neural response must be obtained to confirm diagnosis.
• ASSR “threshold” should not be used to judge “severity” of ANHL.
• No studies utilizing ASSR for lower MF (i.e., 40 Hz or lower).

Speech Evoked Brainstem Responses
• Kraus and colleagues
• Onset response to consonant, frequency-following responses (FFR) to F0, F1 and F2
• Absence of onset response likely in ANHL
• FFR depends on sub-population of brainstem (SOC) neurons with exquisite sensitivity to phase of low frequency stimuli.
  – Lack of timing/synchrony at 8th nerve in ANHL likely precludes an FFR
Auditory Middle Latency Responses (MLR)
• Kraus et al (1984) tested MLR in 5/7 subjects with “brainstem dysfunction”.
• MLR present in 1/5
  – Subjects tested while sleeping, all but one were <12 years of age
  – Starr et al (1996) reported MLR present in 2/6 adults tested
• MLR dependent upon integrity (and neuromaturation) of auditory thalamus, auditory radiation and primary auditory cortex.

Examples of E-MLR
Adults, SNHL (post-lingual)
Firszt et al found that E-MLR had highest correlation with speech perception results.

Cortical Auditory Evoked Potentials (CAEP)
• “Obligatory” (exogenous) CAEP are dependent upon stimulus parameters
  – P1, N1, P2
  – MMN
• Generators/sources
  – Primary auditory cortex (Heschl’s gyrus) for P1-N1-P2
  – Contributions from hippocampus, planum temporale, lateral temporal cortex, superior portion of temporal lobe, association areas, mesencephalic reticular activating system, lateral posterior temporal gyrus
CAEP in Adults with ANHL

- Comprehensive psychophysical and CAEP measures in a young adult with ANHL
- CAEPs present

CAEP, VOT contrast

Adult with ANHL

P1-N1 latencies are prolonged

MMN for duration and direction of formant change.

MMN present for /ba-wa/ only.

Kraus et al, 2000
CAEP in Infants and Children

- Presence of CAEP in children with ANHL associated with significantly better speech perception scores and benefit from amplification
  - 60% of children with ANHL had CAEP for tonal and/or speech tokens

MMN in children with ANHL

- Subjects were those from Rance et al, 2002
  - Tested with an odd-ball paradigm contrasting tones (400 vs. 440 Hz) and speech (bad vs. dad).
  - Only those with CAEP present were included
    - Had better speech perception scores
MMN in children with ANHL

- MMN present in >90% of children with SNHL
- MMN present in <50% of children with ANHL
  - 4/9 for tone contrast
  - 2/7 for speech contrast
- Speech perception scores of those with MMN present = 84%
  - Absent MMN scores=42%
- Children with SNHL had MMN present when speech perception scores were <60%.
- No relationship with severity of pure tone loss.
• Obligatory CAEPs, including MMN, are associated with better speech perception abilities in children with ANHL.

• CAEPs indicate that neural representation of acoustic features of stimulus are encoded at cortical levels and enable speech perception.

CAEP for speech token (infant)

Pearce et al, 2007
Cortical maturation and behavioral outcomes in children with auditory neuropathy spectrum disorder

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Figure 2. PK waveforms for each participant with normal (A), delayed (B), and abnormal (C) PK impulses, respectively. Waveforms are lined from oldest to youngest on horizontal axis.
E-CAEP

- Sharma et al (2005) provided a case-report of E-CAEP for child with ANHL

- Would electrical stimulation (via cochlear implant) result in a “normal” CAEP for 40% of children without CAEP?

McMahon et al
Present EABR & present ECAEP
(n=4 ears)
Absent /poor morphology EABR & present ECAEP (n=3 ears)

McMahon E-ABR + E-CAEP

- 4 ears with absent/poor morphology E-ABR
  - 3 / 4 had E-CAEP present
  - Average speech perception scores were 69-72%

- 3 ears with normal E-ABR and E-CAEP
  - Speech perception results were 75-87%

- 1 ear with E-ABR present, E-CAEP absent
  - Speech perception score was 29%
**Conclusions and Future Directions**

- AEPs from cochlea, 8th nerve, brainstem and cortex can be used to delineate site-of-lesion
  - Results are from small populations
  - Need to determine mechanism of generation of enlarged SP and the “dendritic potential”.
  - Much we need to know about sensitivity/specificity of AEPs in ANHL
  - Different from performance for SNHL
- Acoustic and E-CAEP show promise as a method for prognosis in ANHL
Needs

- Measurement of functional hearing abilities correlated with AEP findings
  - Conventional measures of speech perception require receptive language age of 2.6 years
  - Measurement of psychophysical abilities in young infants (with or without HL) are challenging
    - Infant speech feature discrimination
    - Gap detection tests

Recommendation

- Functional hearing scales: IT-MAIS, ELF
- Speech perception tests developed for pre-verbal implant candidates:
  - Early Speech Perception scales (Moog and Geers)
- AEPs, together with these should be used in ANHL research to quantify basic hearing abilities and to monitor treatment efficacy