



**PETER PAZMANY
CATHOLIC UNIVERSITY**



**SEMMELWEIS
UNIVERSITY**



Development of Complex Curricula for Molecular Bionics and Infobionics Programs within a consortial* framework**

Consortium leader

PETER PAZMANY CATHOLIC UNIVERSITY

Consortium members

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Nemzeti Fejlesztési Ügynökség

ÚMFT infóvonal: 06 40 638 638

nfu@nfu.gov.hu • www.nfu.hu

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ELECTROPHYSIOLOGICAL METHODS FOR THE STUDY OF THE NERVOUS- AND MUSCULAR-SYSTEMS

Az ideg- és izom- rendszer elektrofiziológiai vizsgálómódszerei

LECTURE 7

EVENT-RELATED POTENTIALS

(Eseményhez kötött potenciálok)

BALÁZS DOMBOVÁRI and GYÖRGY KARMOS

AIMS:

In this lecture, the student will become familiar with the different categories of the event related potentials, characteristics of ERP components, the recording techniques, and with the relevance of ERP method in the clinical practice.

- ***Event-related Potential (ERP):***

Any potential elicited by and time locked to a sensory stimulus, or associated with an event, execution of a motor, cognitive, or psychophysical task.

- ***Evoked potential (EP):***

Wave or complex elicited by and time-locked to a sensory or other stimulus, for instance an electrical stimulus, delivered to a sensory receptor or nerve, or applied directly to a discrete area of the brain.

GENERAL CHARACTERISTICS OF THE ERPs

ERPs are usually composed of several deflections of positive or negative polarity. Deflections having a functional relevance are called components. They are described by their scalp distribution, polarity and peak latency. N100 refers to a negative peak with a latency around 100 ms. Earlier ERP components were numbered according to their temporal appearance (e.g. P1, P2, P3).

Parameters of the short latency, *early components* are usually depend on the physical parameters of the evoking stimulus therefore they are called „**exogenous components**”. *Longer latency components* are determined more by the relevance of the stimulus in the given situation. The same stimulus depending its significance may or may not elicit a component. They are called „**endogenous components**”. Some components can be influenced both by the physical parameters of the stimulus and by its relevance, they are named „**mesogenous**”.

CLASSIFICATION OF ERPS:

■ Type of event:

- Sensory evoked potential
- Motor potential
- Event-related synchronization /desynchronization
- Induced response
- Etc.

Exogenous components of the sensory evoked potentials are used in clinical practice to test the function of the sensory pathways.

CLASSIFICATION OF THE COMPONENTS OF ERP:

■ By latency:

- Early components
- Mid latency components
- Late components

■ By nature of the evoking effect:

- Exogenous components
- Mesogenous components
- Endogenous components

The endogenous components may change depending on the subjects prior experience, decisions and intentions; are modulated by the task parameters and the instructions. They are used in cognitive psychophysiology and clinical psychology.

THE CORRECTIVE EFFECT OF AVERAGING ON SIGNAL TO NOISE RATIO

EEG epochs containing a given type of event (mostly a stimulus) are extracted from EEG. These are aligned with respect to the event and averaged together. A single epoch consist of an ERP plus the spontaneous EEG, regarded as random noise. The amplitude of the ERPs is usually small ($0.1\text{-}5\text{ }\mu\text{V}$) compared to the spontaneous EEG activity (up to several hundred μV). Basically every ERP waveform is assumed to be identical whereas the noise assumed to be completely unrelated to the event. The task is to extract ERP waveforms from epochs. If every ERP waveform look exactly the same on every trial, averaging together several trials will yield the same waveform that was present on the individual trials. In contrast the noise whioch is random on every trial, so the average of a large number of trials will be a zero. In summary, the average of many trials containing both ERP waveforms and random noise will consist of reduced noise and amplified ERP waveform.

THE CORRECTIVE EFFECT OF AVERAGING ON SIGNAL TO NOISE RATIO (CONT.)

More precisely:

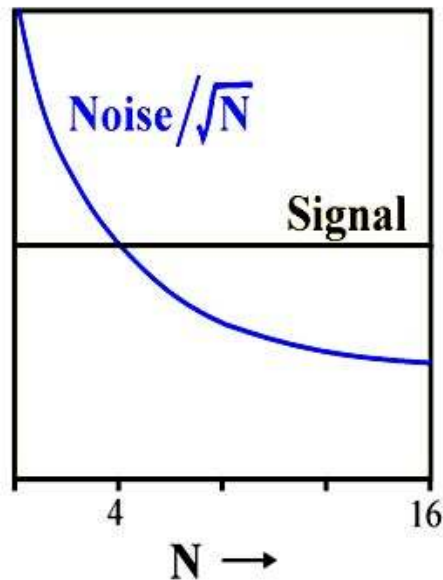
If R is the amount of noise on a trial, N is the number of trials, then the size of noise in an average of the N trials will be:

$$(1/\sqrt{N}) \cdot R$$

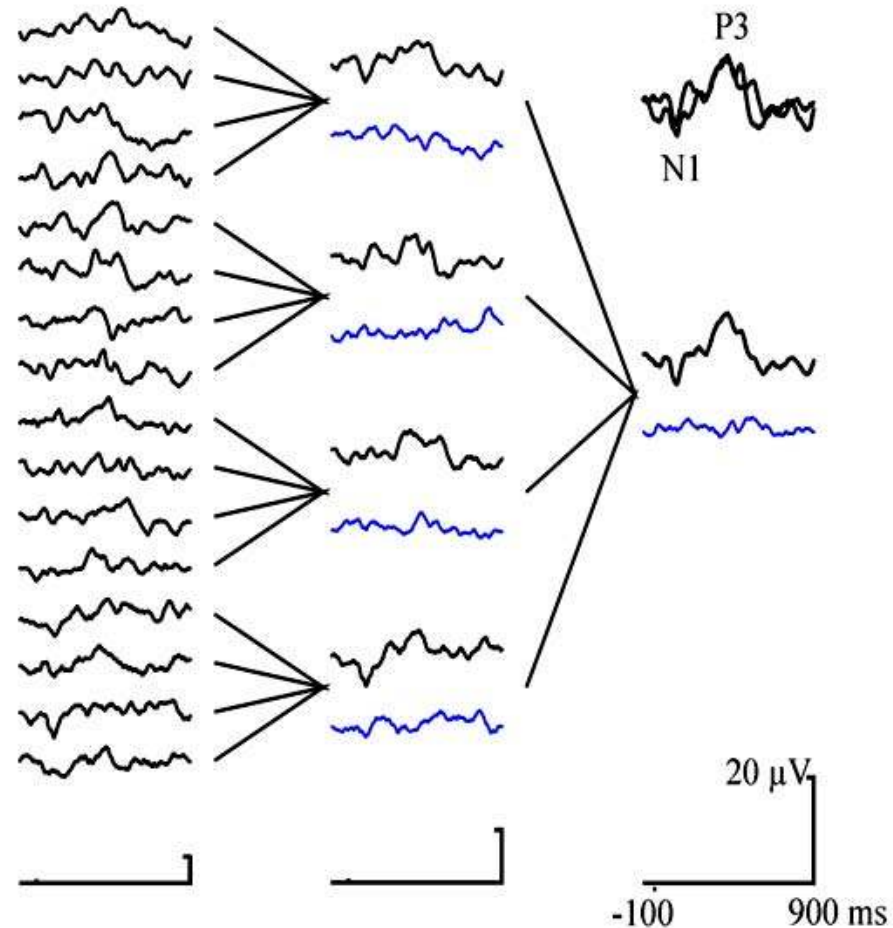
Example:

In an experiment if we are measuring acoustic evoked potentials with an amplitude of $10 \mu\text{V}$ and the actual noise is $40 \mu\text{V}$ on a single trial, then the signal to noise ratio (SNR) will be $10/40=0.25$, which is not very good. To increase SNR from 0.25 to 2 it is necessary to average 64 trials, because $\sqrt{64}=8$. (SNR increases as a function of the square root of the number of trials.)

Averaging



It will take 4 times as many trials to make it look 2 times better.

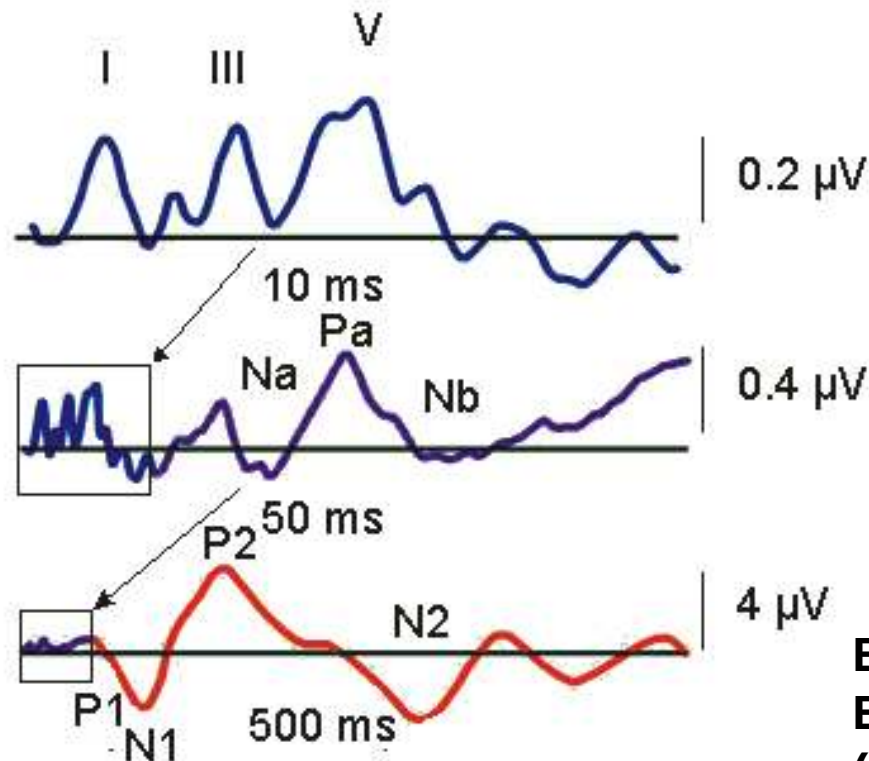


CHARACTERISTICS OF EVENT RELATED POTENTIALS SHOWN ON THE AUDITORY ERP

Early components e.g.
auditory brainstem
potential (BAEP)

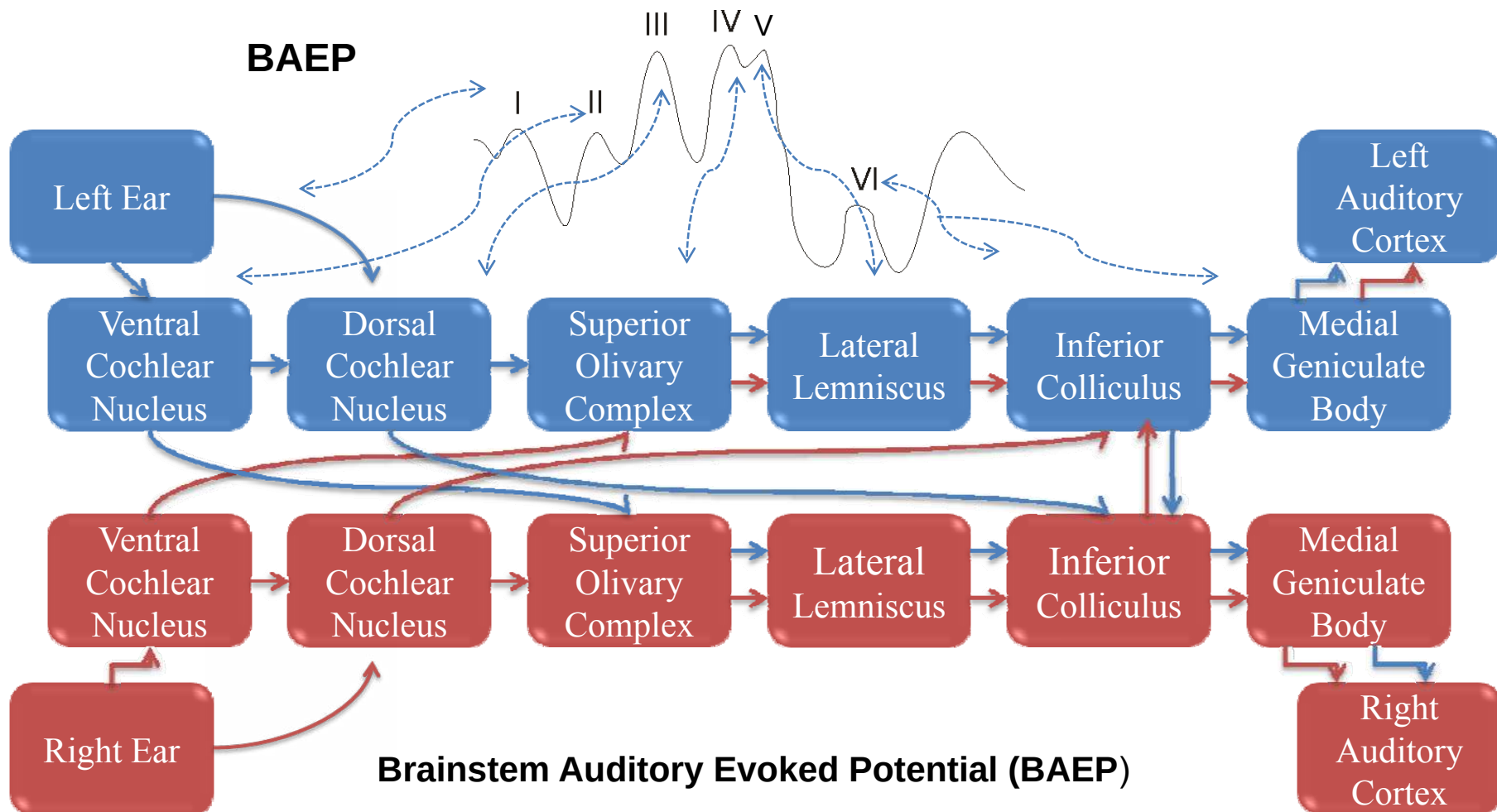
Middle latency components

Late components (e.g.
slow auditory response)



Exogenous-
Endogenous-
(Mezogenous)-
components

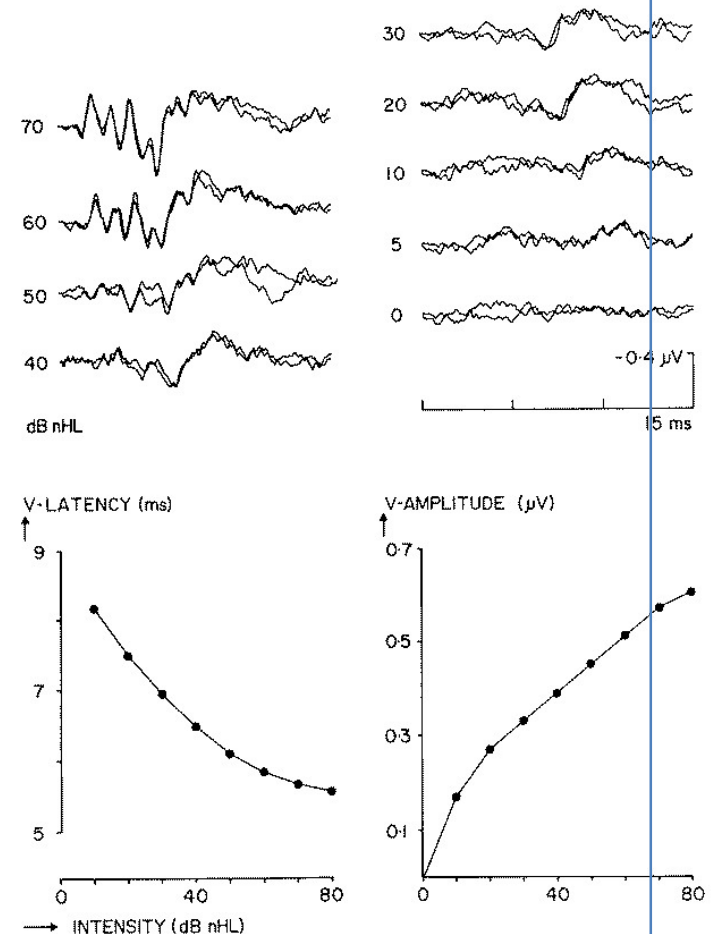
EXAMINATION OF THE AUDITORY PATHWAY BY ERP



EFFECT OF STIMULUS INTENSITY ON THE BAEP

The traditional audiometry is subjective technique to measure hearing threshold. The BAEP as an exogenous response can be used to determine the hearing threshold (objective audiometry). Usually the amplitude and latency of component V is measured. Its *latency* is inversely while its *amplitude* is nearly linearly related to the stimulus intensity (dB). The advantage of *brainstem audiometry* is that the hearing threshold can be tested even in unconscious subjects or in newborn babies.

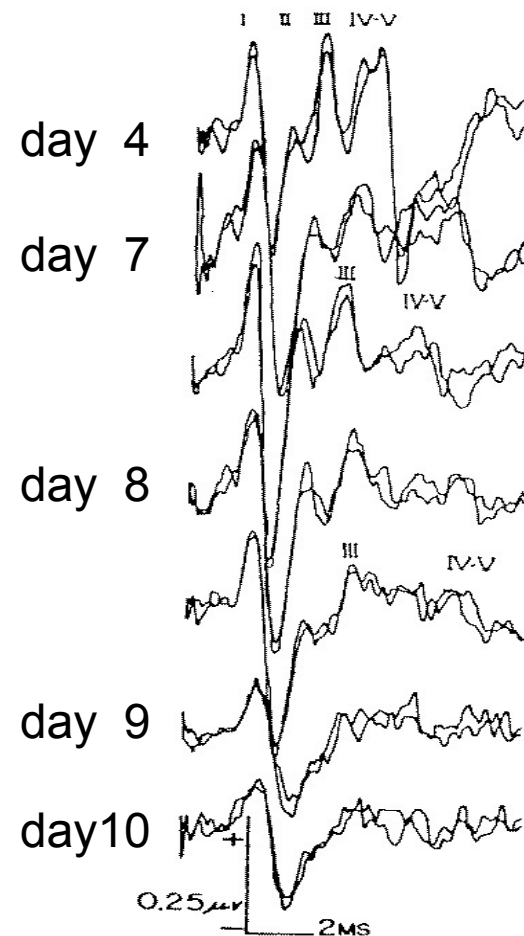
Because of its short latency the BAEP can be elicited by high rate repetitive stimuli.



BRAINSTEM RESPONSES IN COMA

EEG is widely used in the diagnosing of the cerebral death. In coma patients the BAEP may show the gradual deterioration of the brain stem functions. This way the loss of BAEP components is also confirmatory for brain death.

The figure shows the changes of the BAEP components in a serious coma patient. The days indicate the days after an anoxic event. On day 4 the patients displayed withdrawal responses to noxious stimuli and the cephalic reflexes were preserved. These reflexes were no longer present at day 8 and the EEG became flat. From day 10 the responses to noxious stimuli were absent, the patient deceased on day 14. The gradual loss of the BAEP components indicate the worsening of the status of the patient.



MIDDLE LATENCY ERP COMPONENTS

The latency range of the middle latency auditory evoked potentials (MLP) is 12-80 ms. They are multiple negative-positive waves named: N_0 , P_0 , N_a , P_a , N_b . These components reflect the neural processes appearing when the sensory input enters the sensory cortex. The MLPs are primarily exogenous but there are data indicating that they may be modulated by behavioral factors like awareness and attention. They are recorded with highest amplitude above the frontal area of the scalp. The reason is that the auditory cortex is located in the depth of the Sylvian fissure in the temporal lobe and the generators of the MLP project towards the frontal area (See L. 9.).

COGNITIVE PSYCHOPHYSIOLOGY

Cognitive psychophysiology concerned with the scientific study of biological substrates underlying cognition. It addresses the questions of how psychological/cognitive functions are produced by the brain. Physiological measures like ERP and brain imaging techniques are used to reveal processes of brain information processing.

In the following slides ERP paradigms and components studied by cognitive psychophysiology are discussed.

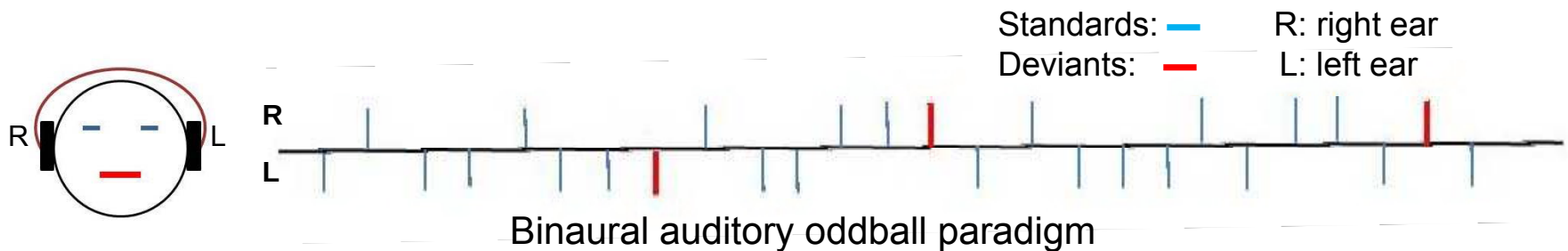
The most often used ERP paradigm in cognitive psychophysiology is the „oddball paradigm”.

ODDBALL PARADIGM

The subject is presented with two types of stimuli. One is a frequently occurring, more common stimulus (called standard or non-target) interleaved by infrequently, rare ('oddball') stimuli. The ERPs elicited by the standard and deviant stimuli are compared.

The oddball paradigm can be *passive*, if the subject has no task to respond to either of the stimuli. In *active* oddball paradigm the subject is asked to indicate the occurrence of the rare (target) stimuli by counting or by pressing a button.

Auditory stimuli can be presented monaurally, into one ear or binaurally, to both ear. At dichotic stimulation different stimuli are given to the two ears.



MISMATCH NEGATIVITY

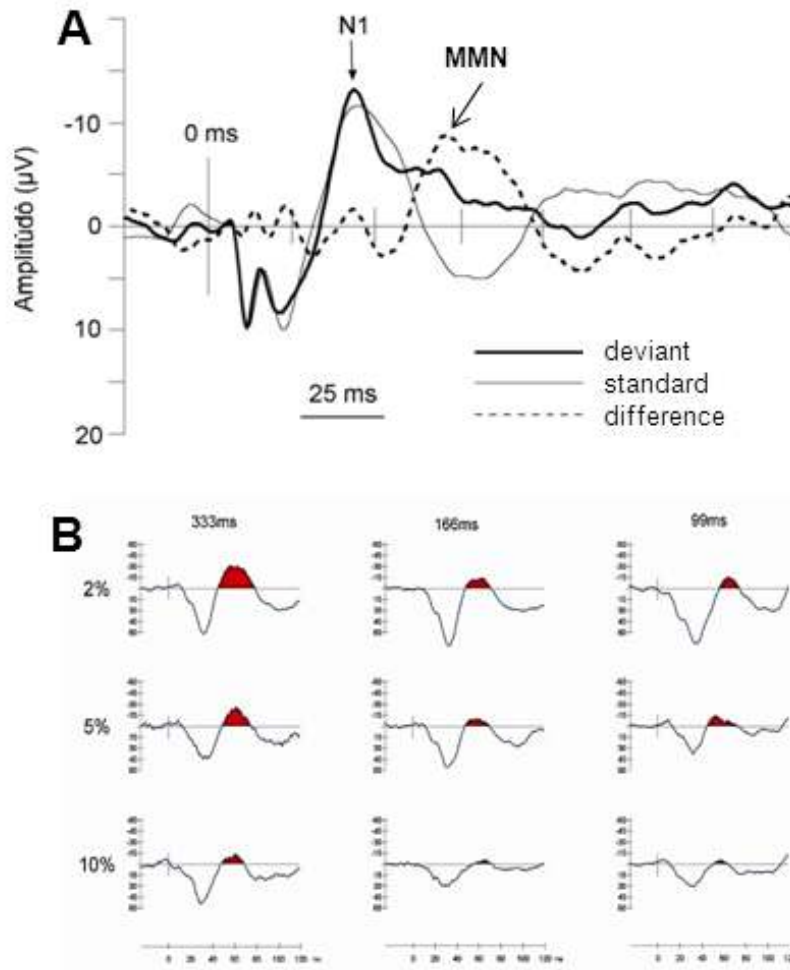
The mismatch negativity (MMN) is an ERP component to a deviant stimulus in a sequence of standard stimuli in a passive oddball paradigm.

It can occur in any sensory system, but it has most frequently been studied in the auditory modality. The MMN can be elicited regardless of whether the subject is paying attention to the stimuli. During auditory sequences, a person can be reading or watching a silent subtitled movie. The MMN may be elicited whenever the standard and deviant auditory stimuli are discriminable on any of their features (pitch, intensity, duration).

MMN is a negative component in the difference curve (deviant response – standard response). Its peak latency varies between 100-200 ms. The lower is the probability of the deviant, the higher amplitude MMN appear.

MMN reflects the operation of an automatic, „preattentive” change detector process in the auditory cortex related to early (echoic) memory.

ANIMAL MODEL OF MMN



MMN can be demonstrated in animals where electrodes can be implanted into the auditory cortex.

In Fig. A auditory evoked potentials recorded from the auditory cortex of a cat are shown. The standard stimuli were short 1 kHz tone bursts while the deviant stimuli were 2 kHz tone bursts. The MMN can be seen in the difference curve.

In Fig. B the effects of repetition rate (interstimulus interval) and the deviant probability of the stimuli on the MMN is depicted.

EFFECT OF DEVIATION OF STIMULI ON MMN

A

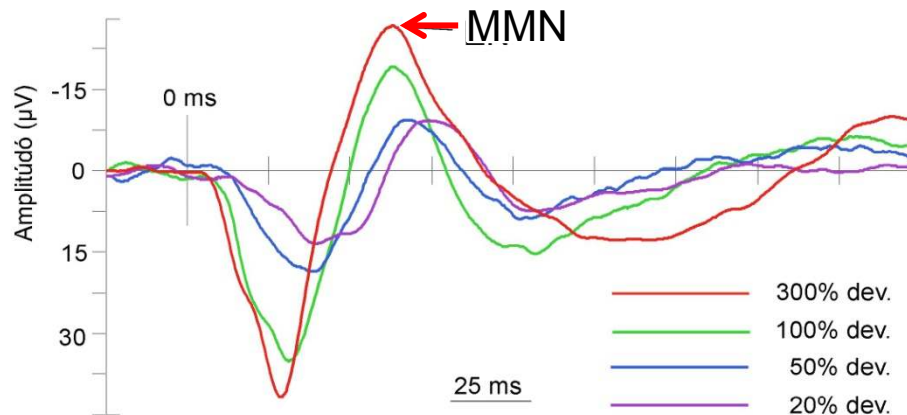
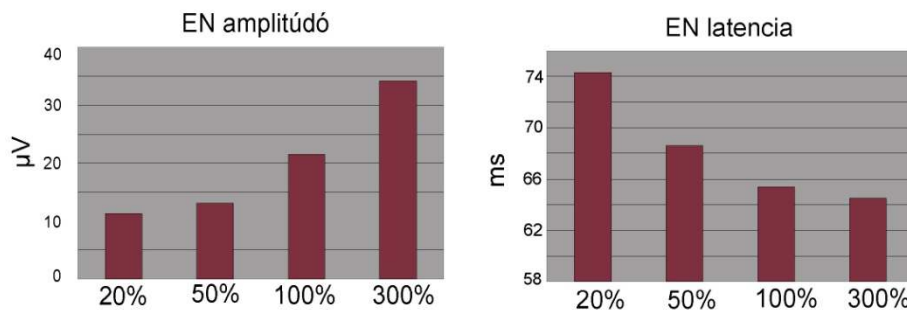


Figure A shows the difference curve of a frequency MMN recorded from the surface of the auditory cortex of cat.

Short tone bursts of 1 kHz were given as standard stimulus. The frequency of deviant stimuli differed from the standard by 20 to 300%.

The amplitude and peak latency changes of MMN is depicted in graphs of figure B.

B



N100 COMPONENT

N100 or N1 is a negative-going component of the auditory evoked potential. It peaks in adults between 80 and 120 milliseconds after the onset of a stimulus, and distributed mostly over the fronto-central region of the scalp.

The auditory N100 is generated by a network of neural populations in the primary and association auditory cortices in the superior temporal gyrus in Heschl's gyrus and planum temporale. Some generators are located in the frontal areas.

The N100 component is a typical „mesogenous” component, because it is elicited by any unpredictable stimulus in the absence of task demands. It can be used for objective audiometry because its amplitude depends on the intensity of the stimulus (may test the function of the auditory cortex).

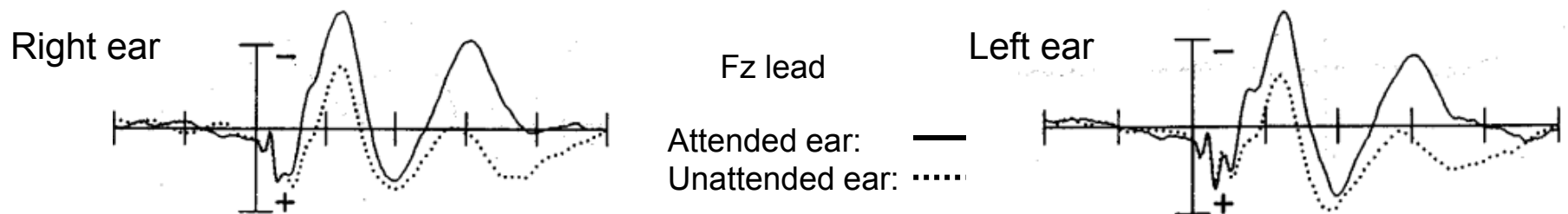
The N100 also is endogenous because it is characteristically influenced by selective attention.

EFFECT OF SELECTIVE ATTENTION ON N100 COMPONENT

Active oddball paradigm, dichotic listening task (see S. 14.). Standard stimuli are short tones given randomly to the right and left ears (e.g. 1000 and 2000 Hz) with short interstimulus interval (~300 ms.). The subject has to count the higher intensity deviant stimuli given to the selected ear.

ERPs elicited by stimuli given to each ear are selectively averaged. Responses were compared whether the ear was attended or unattended. Responses to stimuli given to the attended ear the N100 component appeared with higher amplitude.

Conclusion: *Enhanced response at the attended channel!*



P300 COMPONENT

Endogenous components appearing to deviant stimuli in active oddball paradigm with latency around 300 ms are called P300.

Amplitude of P300 is sensitive to stimulus probability, meaning of the stimulus, and the psychological resources allocated to its processing of it. The more complex are the stimuli to be processed the latency of the P300 is longer.

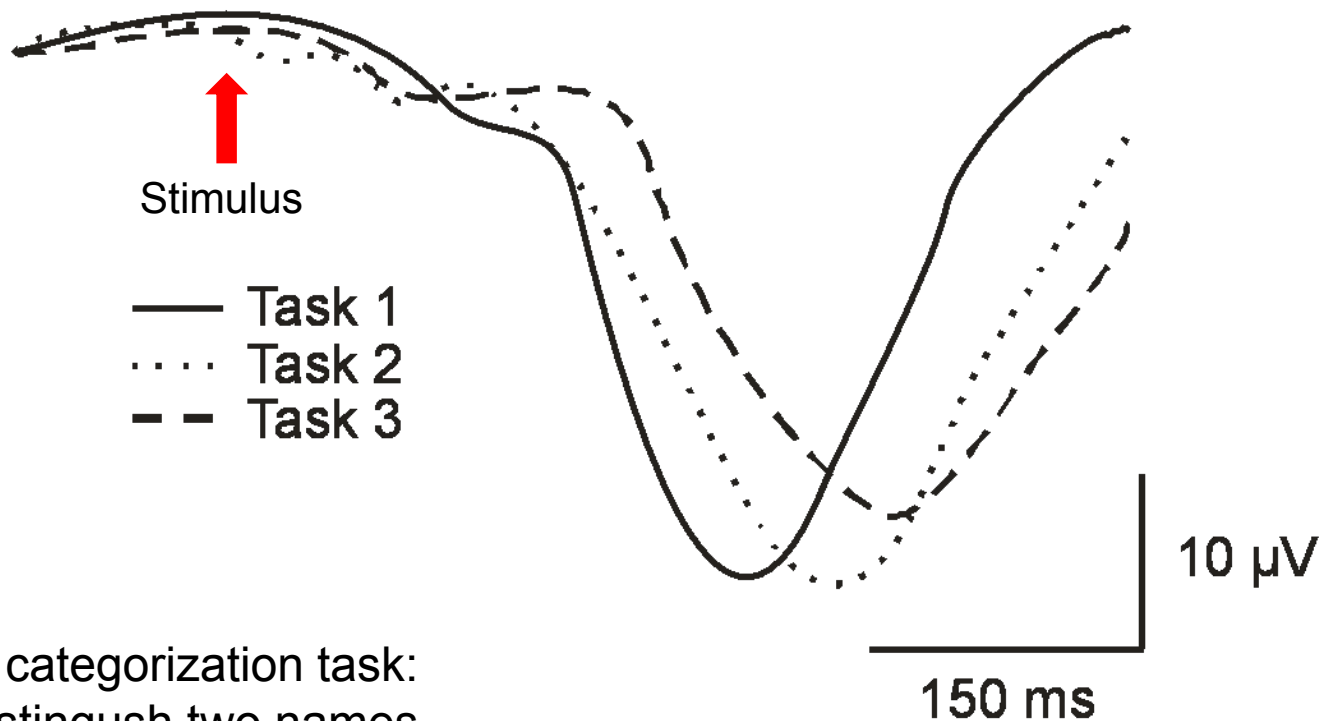
Mental chronometry: P300 latency may reflect the stimulus evaluation or categorization time.

In dual-task paradigms P300 amplitude to the concurrent secondary task decreases depending on the perceptual/cognitive demand of the primary task.

The P300 may be related to the *closure of the perceptual processing* or to the *memory update* after processing of the deviant stimulus.

Recently P300 component is successfully used in *brain-computer interface* studies. In psychopathological cases (e.g. dementia) characteristic P300 changes appear.

MENTAL CHRONOMETRY



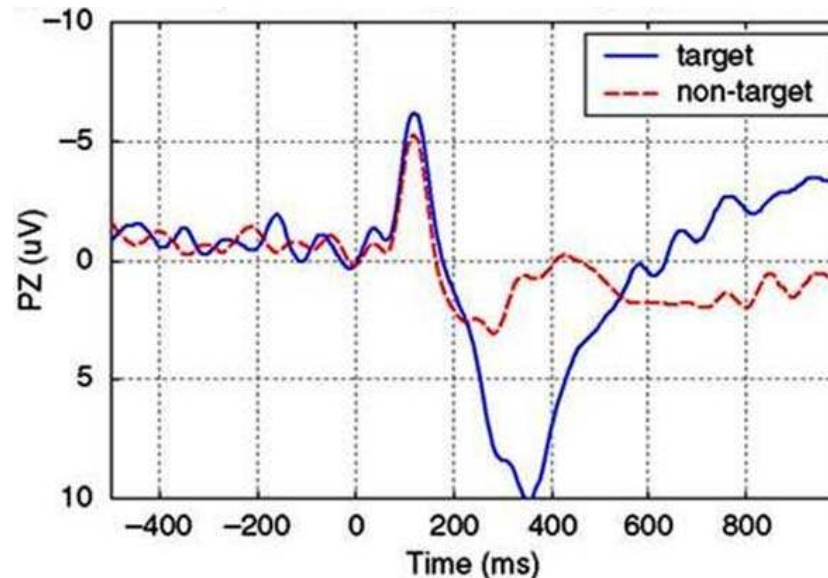
Semantic categorization task:

Task 1: distinguish two names

Task 2: distinguish female and male names

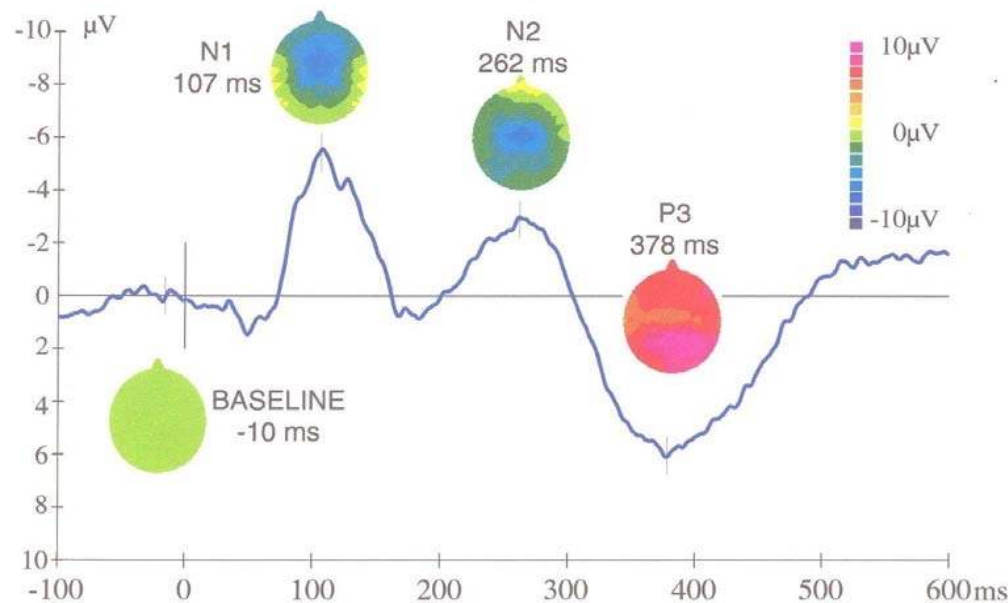
Task 3: recognize the synonyms of a name

NOVELTY P300 IN ACOUSTIC TASK PARADIGM



If in an active acoustic oddball paradigm additional unexpected novel stimuli are rarely interspersed a positive deflection similar to „classical” P300 appear. It is called „*Novelty P300*”. It appears with frontal scalp distribution while the classical P300 has a centro-parietal maximum.

SCALP DISTRIBUTION OF ACOUSTIC ERP BRAIN MAPPING

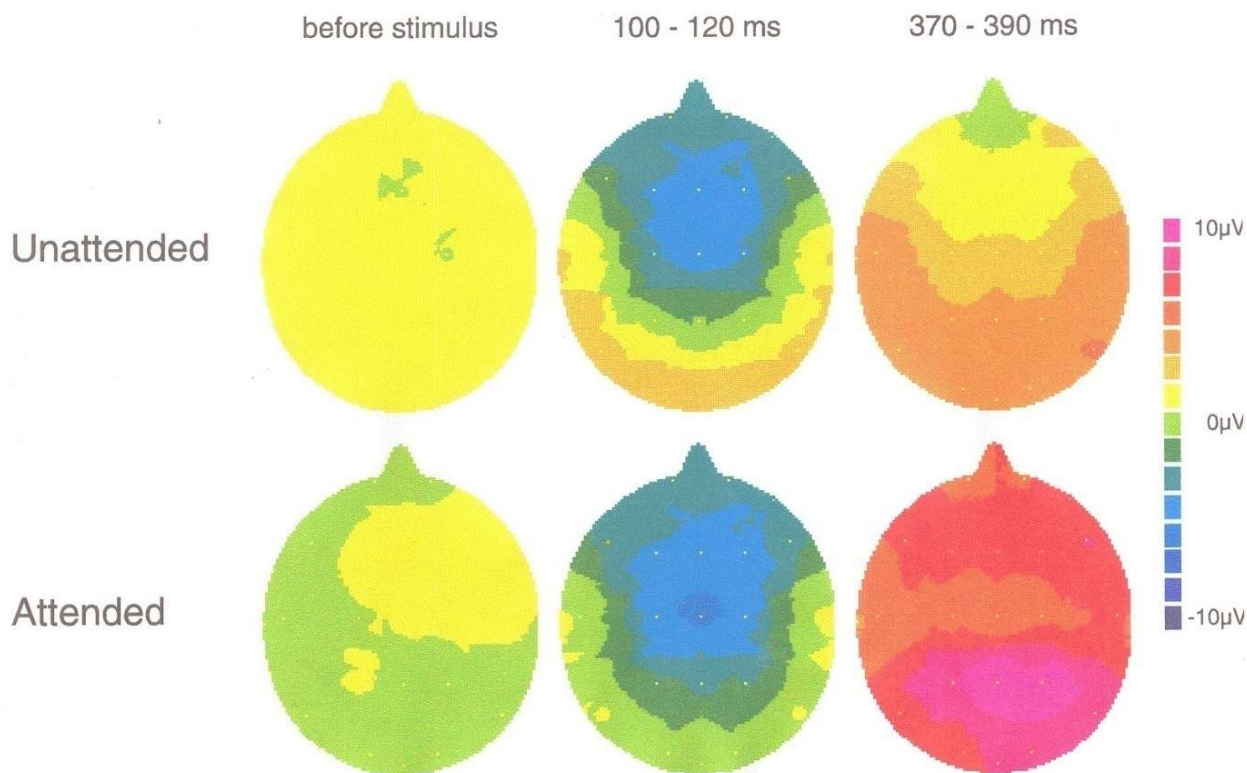


Scalp distribution of the ERPs can be displayed in „EEG brain maps”. The topography of ERP amplitude is color coded. These maps are stylized representations, not anatomically accurate rendering. Brain maps are used to display EEG frequency distribution and compare ERP component distributions in task situations.

DISTRIBUTION OF ACOUSTIC ERP DURING TASK

N1, P300

Latency



LANGUAGE RELATED ERP COMPONENTS N400

Semantic processing are reflected in cognitive ERP. A typical experiment is the *sentence reading task*. It usually involves computer presentation of words one-by-one to form a sentence. If a sentence is ending with a semantically incongruous word a negative late component with latency around 400 ms called *N400* appears. The amplitude of the N400 is proportional with the degree of incongruity.

N400 component is specifically sensitive to violation of semantic expectancies.

In the same experiment morphosyntactic change of the words (letter size, capital letters) induce a late positive wave called *P600*. See: Kutas and Hillyard: Science, 1980, 207: 203-205 fig.1.

MOVEMENT RELATED POTENTIALS

A characteristic ERP is the slow potential change that can be recorded on the scalp above the motor cortex before the self-paced movements. The paradigm is that the subject is instructed to initiate flexion of the index finger repetitively every 10 s. The EMG signal is used as trigger and the EEG activity is averaged backward recording the ERP before the movement. A negative deflection beginning about 800 ms before the movement is called „*readiness potential*” or „*Bereitschaftspotential*” (the German Kornhuber and Deecke described first the phenomenon).

The readiness potential is related to the preparation of the movement. During the movement execution further components of the movement related ERP appear called „*reafferent potentials*” they are evoked by the afferents from the moving muscle.

The readiness potential has higher amplitude contralateral to the given movement.

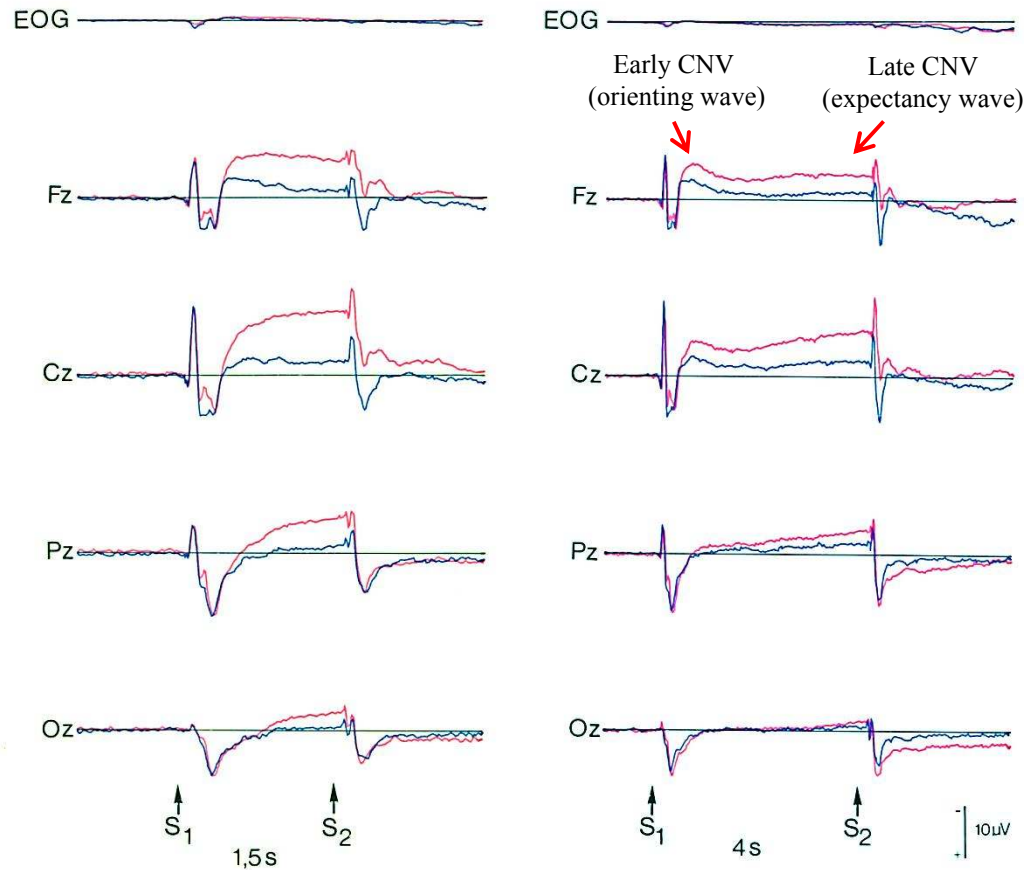
CONTINGENT NEGATIVE VARIATION (CNV)

CNV is a slow ERP that can be recorded in the so called fore period of a *warned reaction-time task*. This means that a warning stimulus (S_1) is given before the imperative stimulus (S_2) to which the subject has to respond. The warning stimulus elicits first the modality specific evoked response. After it during the time between S_1 and S_2 (0.5-4 s) a slow negative shift develops over the central and frontal areas until the S_2 . This negative wave is called CNV.

Often in the CNV an early and late phase can be distinguished. It is supposed that early CNV reflects orientation (O-wave) while the late is related to expectancy (E-wave). The idea that the E-wave is not just a motor potential (readiness potential) was proved by the fact that it appears without movement response too.

Changes in CNV can be observed in such psychopathologic cases when attention and stress responses are modified (depression etc.)

CNV WITH SHORT AND LONG S_1 - S_2 DELAY



S_1 : auditory click

S_2 : flash stimulus

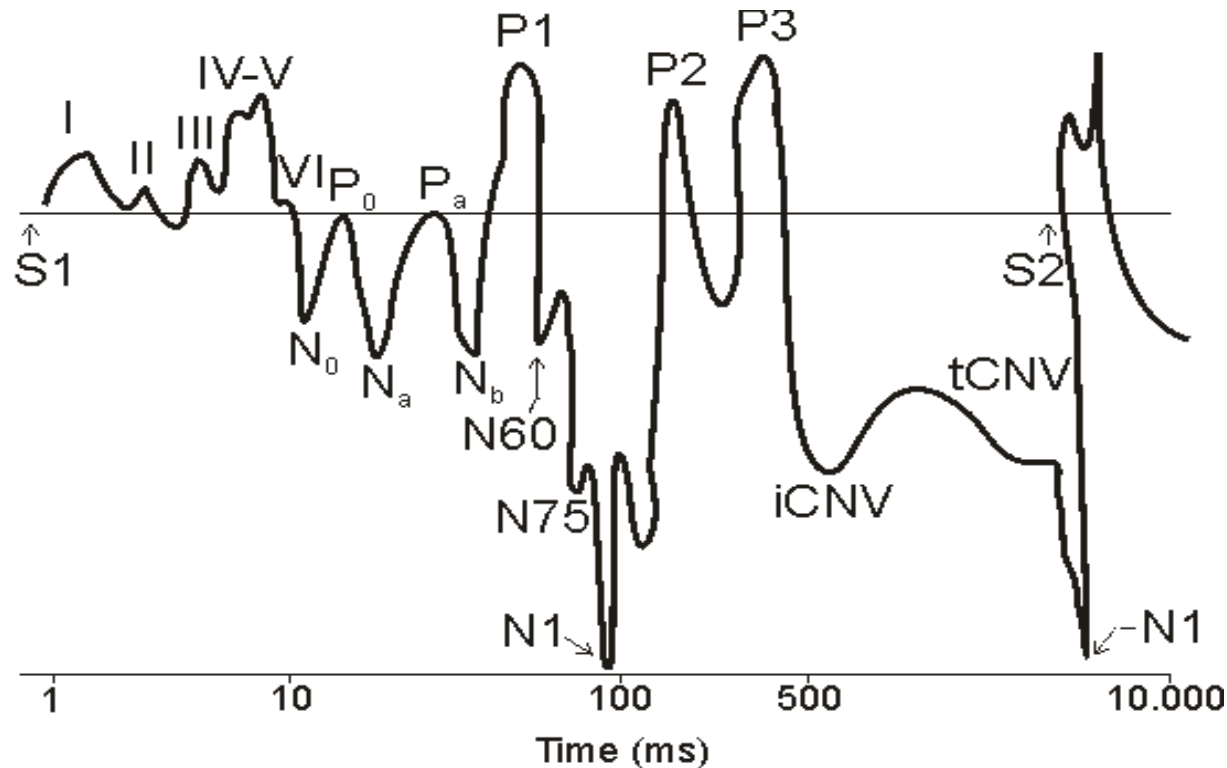
— Task to S_2 : fast button press

— Control: no task

At 4s S_1 - S_2 delay the early and late components of CNV can be recognized.

The flat EOG indicate that the CNV is not an eye movement artefact.

SUMMARY OF THE COMPONENTS OF THE AUDITORY EVENT RELATED POTENTIALS



logarithmic time scale !!!

AUDITORY STEADY-STATE RESPONSE (ASSR)

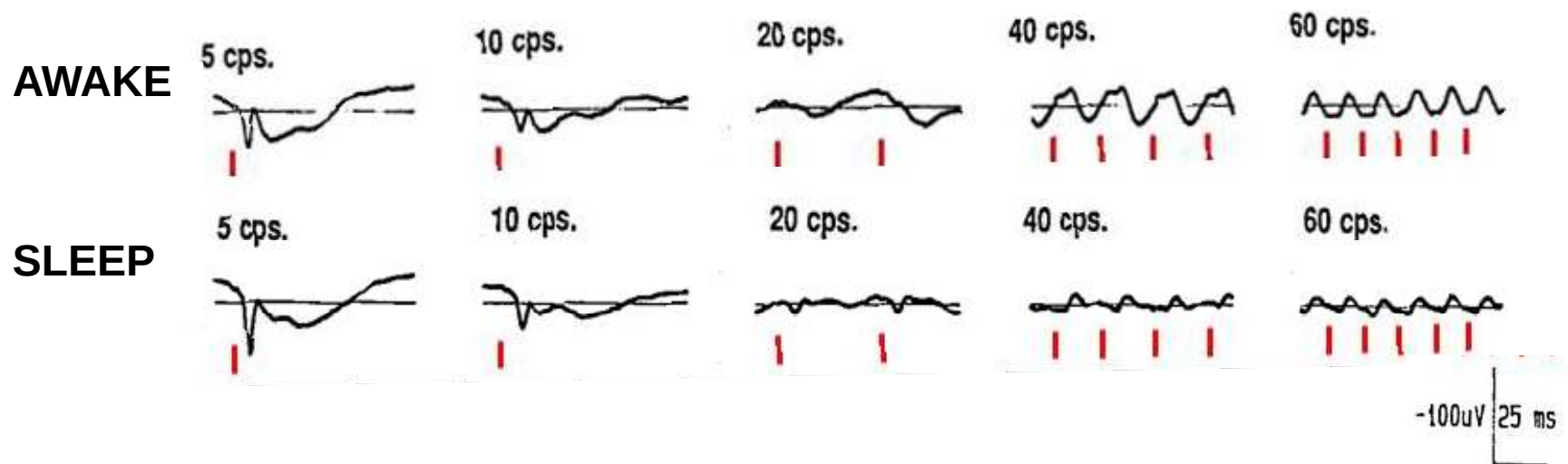
Steady-state responses (SSR) are produced when stimuli are presented at a rate sufficiently rapid that the response to any one stimulus overlaps the responses to preceding stimuli. After the first few stimuli, the recorded potentials assume the periodic waveform of the steady-state response.

Steady-state responses in most cases have sinus wave like pattern. Because of this they can be analysed in the frequency domain. In the auditory modality SSR appears from around 40/s repetition rate (often called „40 Hz response”) but it can be elicited by repetitive stimuli at 80-120/s. The 40Hz response is generated in the auditory cortex while it is supposed that the higher frequency ASSR may be generated in the brainstem. 40 Hz SSR is sensitive to sleep the while higher frequency SSRs are not.

Auditory steady state responses are widely studied in the clinical audiology because this type of ERP can be used for objective audiometry.

DEVELOPMENT OF ASSR IN CAT AUDITORY CORTEX

ASSR similar to human one can be recorded in the auditory cortex of behaving cat with chronically implanted electrodes. Increasing of the rate of the click stimuli above 10/s the complex pattern of the evoked potential changes to a sinus like wave shape that has highest amplitude at 40/s rate. The 40 Hz ASSR is highly attenuated during slow wave sleep.





CLINICAL APPLICATION OF THE ASSR

In the following slides a technique called „MASTER” (**M**ultiple **A**uditory **S**teady-State **R**esponses) will be shown that was developed by *T.W. Picton* and *M.S. John* (Rotman Research Institute, Baycrest, Ontario, Canada) for clinical audiometry purposes. This is a good example how the computer methods can be used in clinical diagnosis.

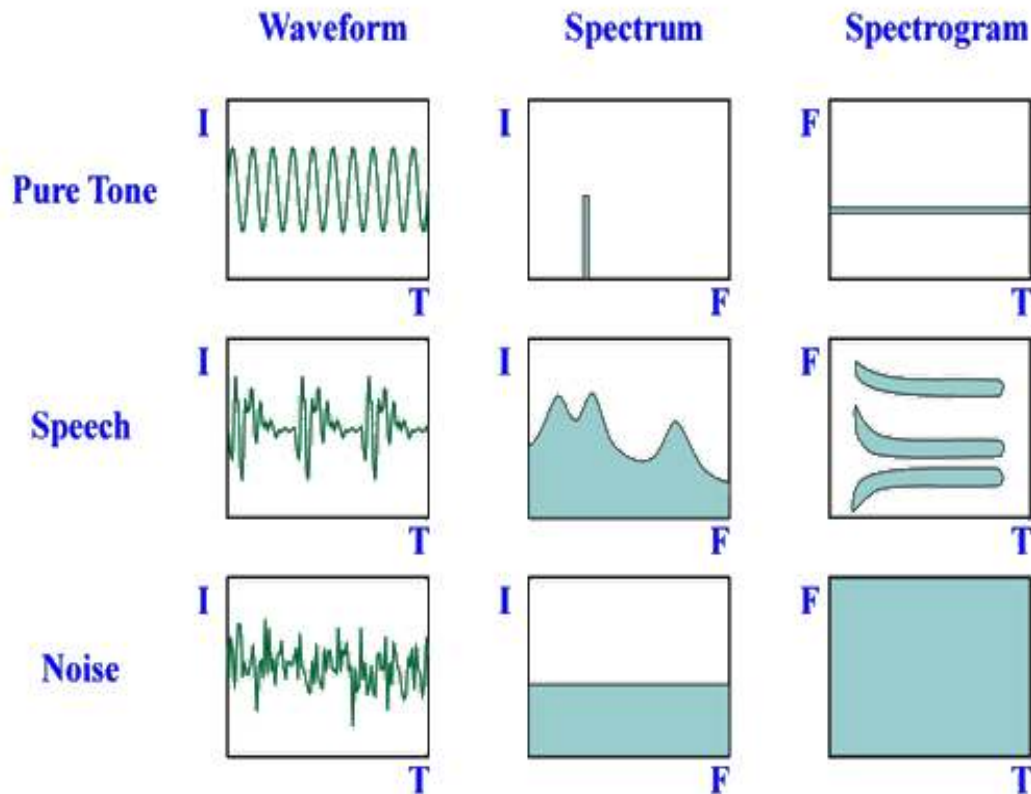


Prof. Terence (Terry) W. Picton
Univ. of Toronto
Rotman Research Institute



Dr. Sasha John
Univ. of Toronto
Inst. Biomat & Biomed Engin.

CHARACTERISTICS OF ACOUSTIC SIGNALS

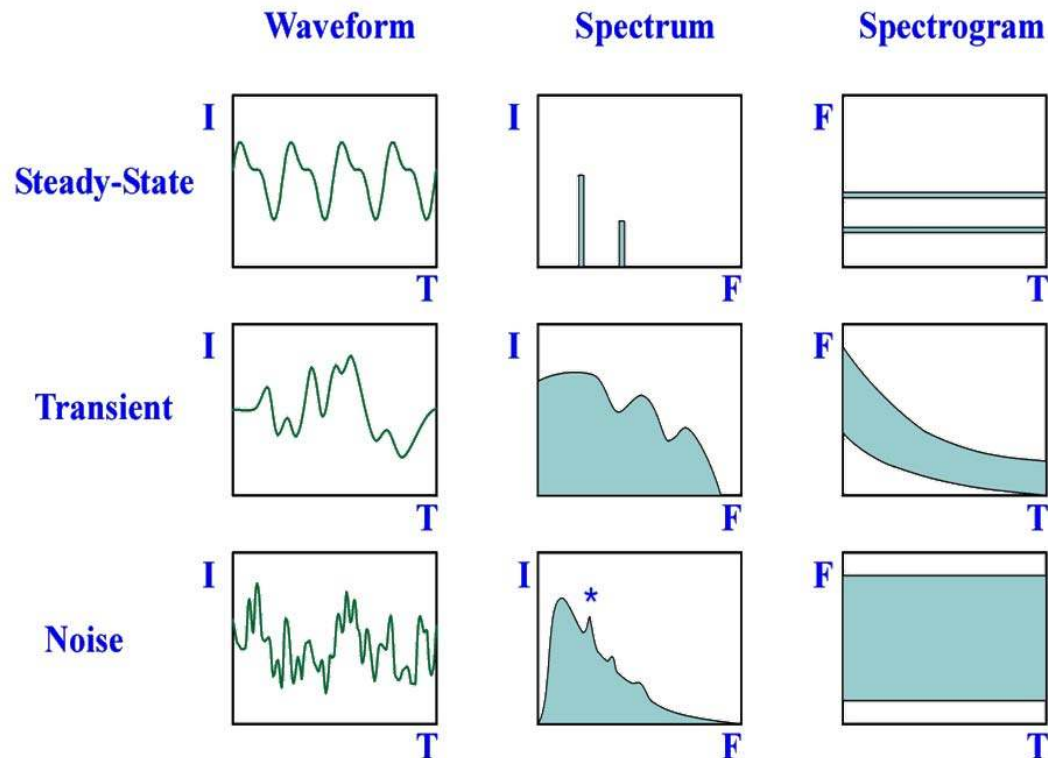


The characteristic of the acoustic signal can be described by the FFT spectrum and the temporal pattern by the spectrogram.

In the schematic figures characteristics of a *pure tone*, *speech signal* and *noise signal* are shown.

This and the following figures by courtesy of T.W. Picton and M.S. John

CHARACTERISTICS OF BRAIN ELECTRICAL RESPONSES



The spectro-temporal characteristics of the brain signals can also be depicted. The SSR can be well described by the FFT. The first and second harmonics of the SSR is shown on the figure.

ASSR can be elicited by repetitive clicks but for audiometric purpose amplitude modulated pure tone stimuli are the best.

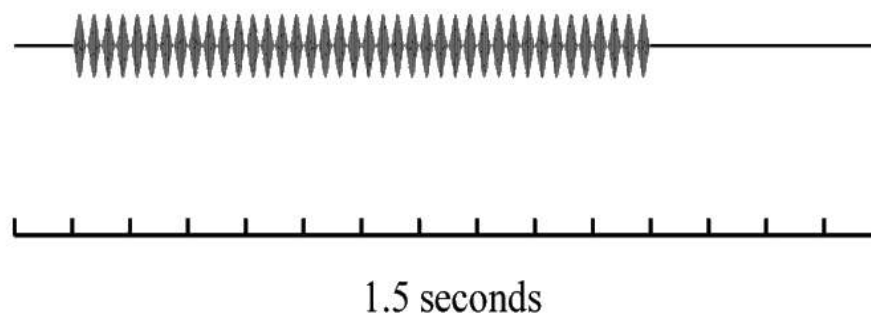
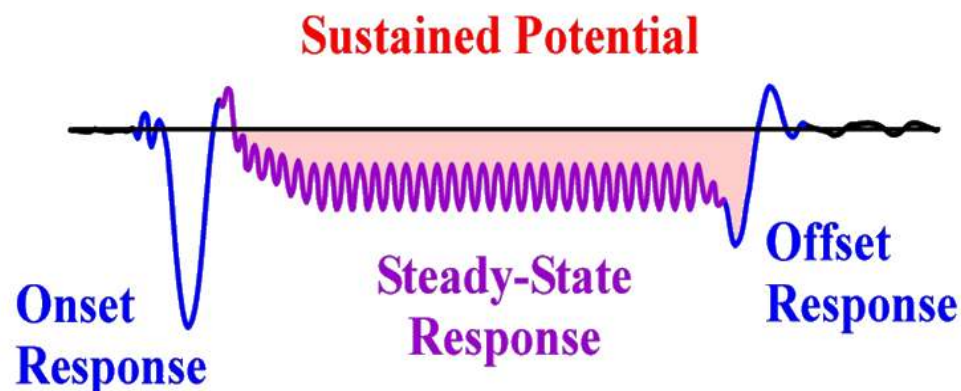
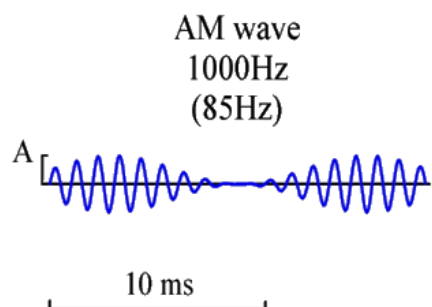
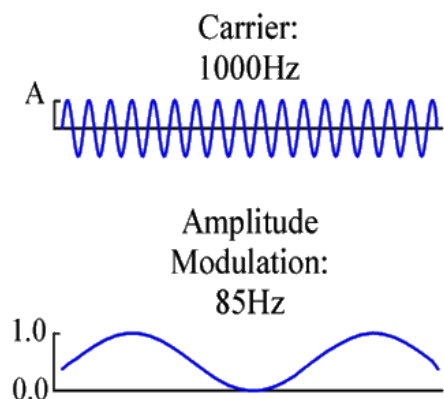
AMPLITUDE MODULATED TONE STIMULUS

The left side of the next slide shows how an amplitude modulated tone stimulus is generated. 1000 Hz tone (called carrier frequency) is amplitude modulated by a lower frequency sine wave (85 Hz). The result will be an amplitude modulated (100%) 100 Hz stimulus.

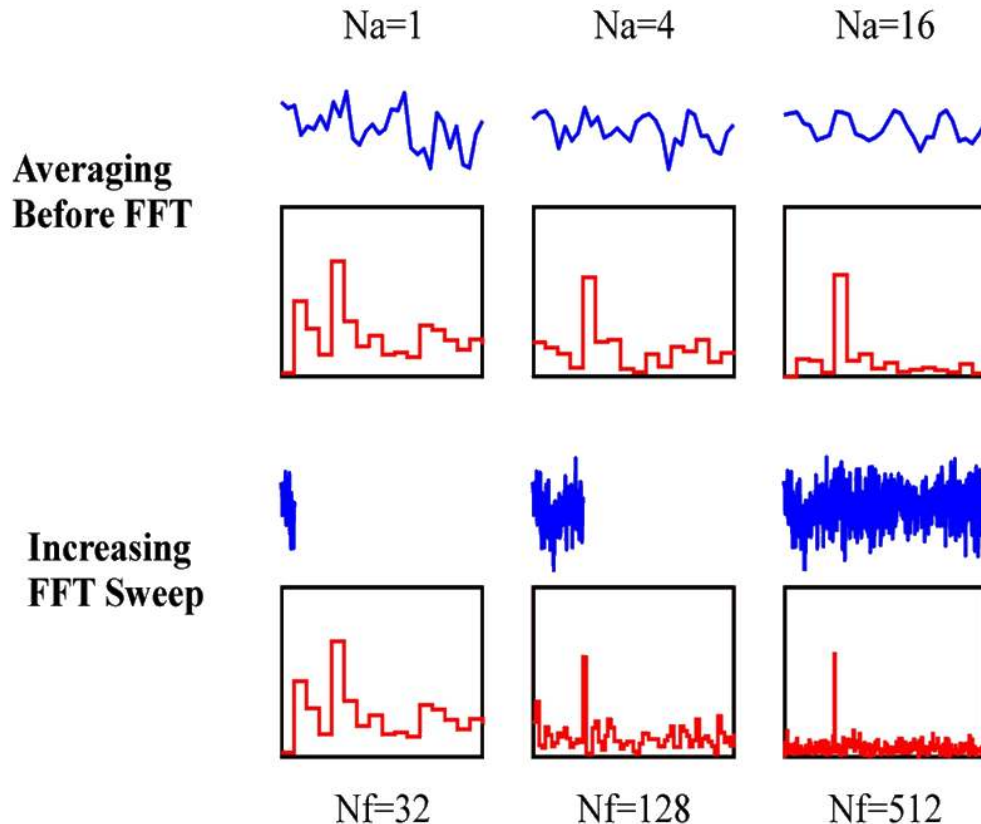
The ASSR elicited by a burst of such stimulus is shown on the right side of the figure. At the beginning of the stimulus a transient „*on response*” is elicited. Similarly at the end a transient „*off response*” appears. The SSR contains a DC type „*sustained response*” and the real „*steady-state response*” that corresponds to the modulation frequency.

In the *ASSR audiometry* the amplitude and phase characteristics of the SSR part of the response is measured.

ASSR ELICITED BY AMPLITUDE MODULATED TONE STIMULI



EVALUATION OF THE SSR



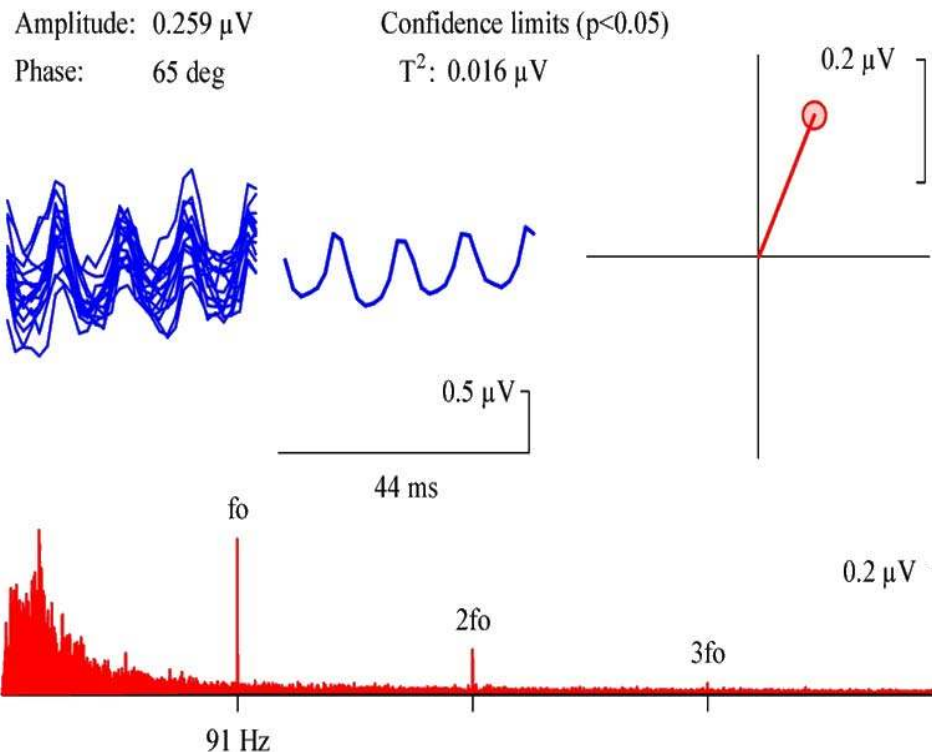
SSR can be evaluated both in time domain (averaging) and in frequency domain (FFT).

In the upper rows averaged responses (n: 1, 4, 16) and the FFTs calculated from the averages are shown.

In the lower rows different trains of SSR and their FFTs can be seen. The frequency domain analysis gives better quantitative result.

ASSR EVALUATION IN FREQUENCY DOMAIN

Intensity: 80 dB SPL Carrier: 1000 Hz Modulation: 91 Hz



Upper row shows original and averaged SSR (blue) and the phase and amplitude value of f_0 harmonic of the FFT, depicted below.

The phase and amplitude can be detected automatically and the stimulus presentation and averaging can be stopped when the amplitude exceeds a given confidence limit.

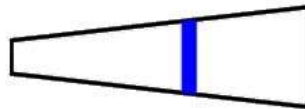
REPRESENTATION OF STIMULUS IN THE COCHLEA AND IN THE AUDITORY CORTEX

Carrier of 1 kHz
100% AM
25% FM
Modulation at 81 Hz



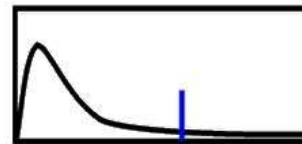
Sound

Activation at 1 kHz
Region of Basilar
Membrane



Cochlea

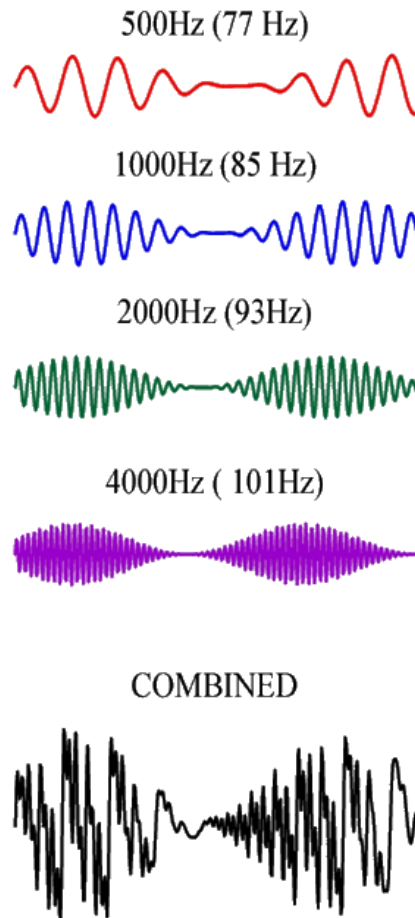
Steady-State
Response at 81 Hz



Brain

The figures show that the amplitude modulated sound stimulus activates the basilar membrane at the site of the carrier frequency while in the brain stem and in the auditory cortex the ASSR is determined by the modulation frequency and the energy of envelope.

MIXING OF SOUNDS

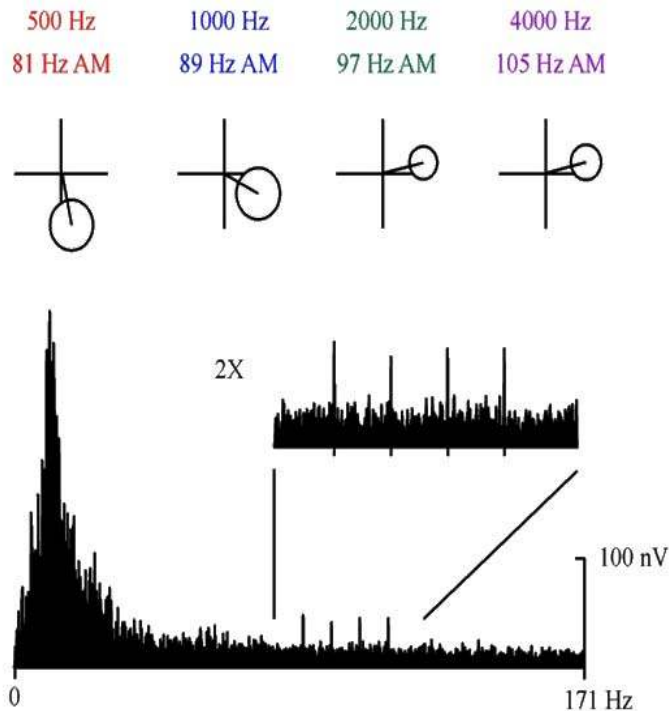


Different frequency and differently modulated sound stimuli can be mixed together. By frequency analysis the original patterns can be recovered. The cochlea is doing frequency analysis and the ASSR frequency corresponds to the modulation frequency but its amplitude reflects the perceived stimulus intensity.

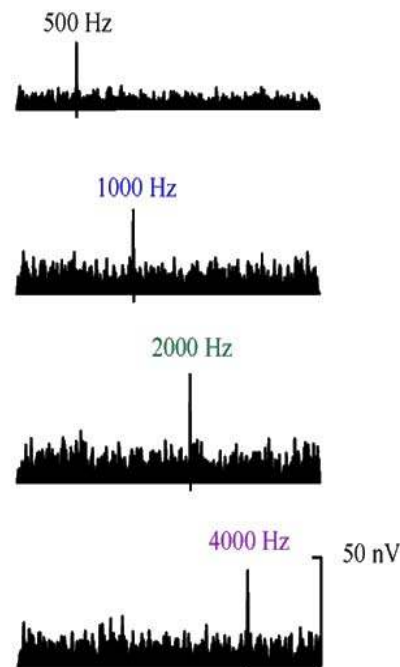
This way with different intensity stimuli objective audiometry can be done if the the evoked ASSR-s are evaluated.

ASSR RESPONSES ELICITED BY MIXED STIMULI

Four Stimuli Simultaneously



Single Stimuli



The mixed four stimuli given through earphone to the ear elicit four ASSR corresponding to the modulation frequencies. The phase amplitude of the responses reflect the perceived tone intensities.

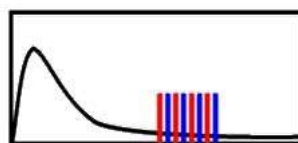
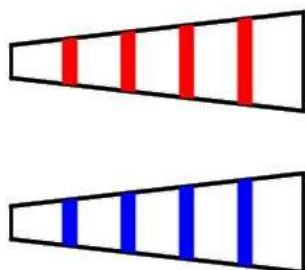
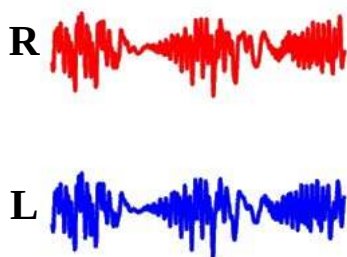
The ASSR can be used to estimate the audiogram of subjects who cannot respond accurately on behavioral testing, such as newborn babies or adults with a functional hearing loss.

AUDIOMETRY BY ASSR WITH STIMULI TO BOTH EARS

Carrier Modulation

0.5	77	81
1	85	89
2	93	97
4	101	105
kHz	Hz	Hz

Four stimuli to the left ear and
four stimuli to the right ear



Sound

Cochlea

Brain

Mixed stimuli can be given to both ears simultaneously if the modulating frequencies are different.

In everyday audiometry the usually tested frequencies are 500 Hz, 1, 2, and 4 kHz. At a given intensity level all these frequencies can be tested in both ears simultaneously and automatically.

This way ASSR audiometry makes possible a fast and effective screening.

MASTER APPLICATIONS

Auditory Steady State Response has been scientifically proven to provide valuable information on hearing thresholds, particularly in babies.

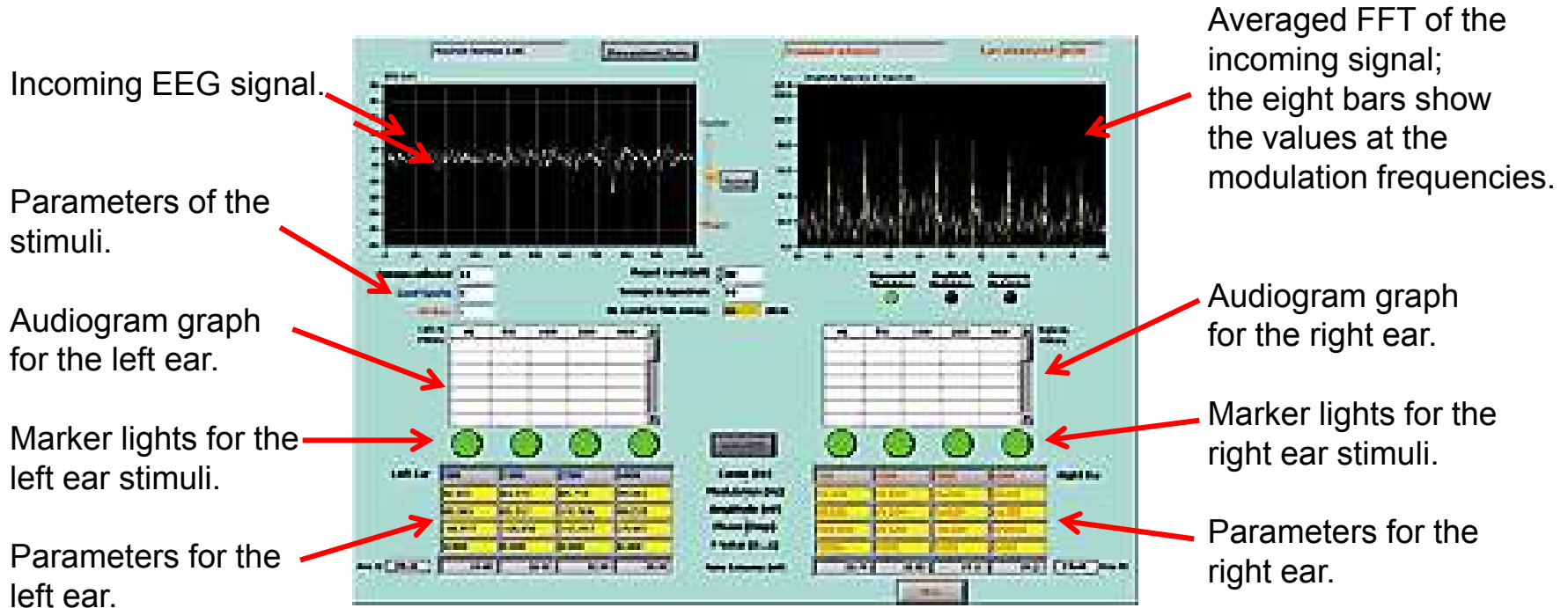
On the principle shown above laptop based ASSR audiometers were introduced by different companies primarily for newborn hearing test. The ASSR is a good complement to the BAEP test. Its advantage that signal intensity can be as high as 120 dB HL.

Electrodes are placed to C_z and to the nape or to C_z and the mastoid.

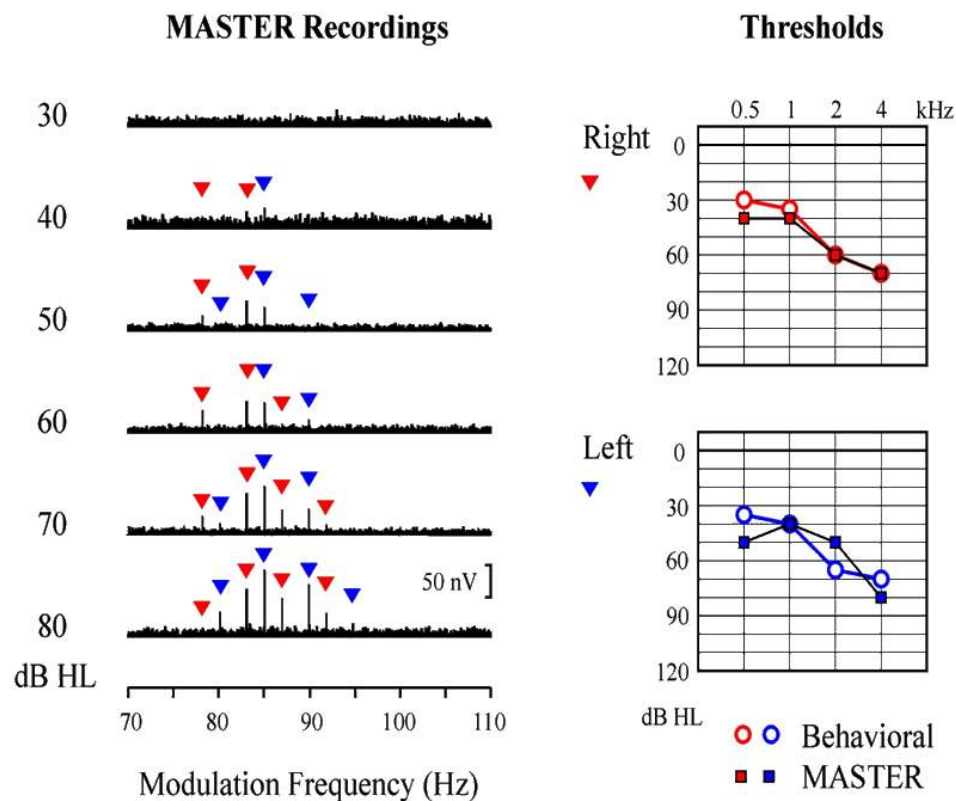
The system automatically delivers the stimuli, makes the averaging and measures the signal to noise ratio at the modulation frequencies. As the S/N reaches a certain level the marker lights change from red (F-ratio of significance= >0.101) first to yellow (F-ratio of Significance= $0.051 - 0.101$), then to green (F-ratio of Significance= <0.050) and the stimulation stops.

The total test can be performed in 45-60 min.

ONE OF THE DISPLAY SCREENS OF MASTER II



COMPARISON OF THE BEHAVIORAL AND ASSR AUDIOMETRY



On the left side of the figure FFT harmonics of the ASSR is shown at different sound intensities. On the right side behavioral audiometry curves are compared with the result of the MASTER ASSR audiometry.

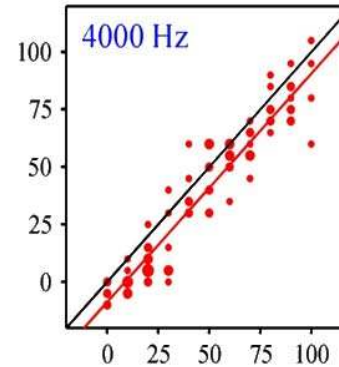
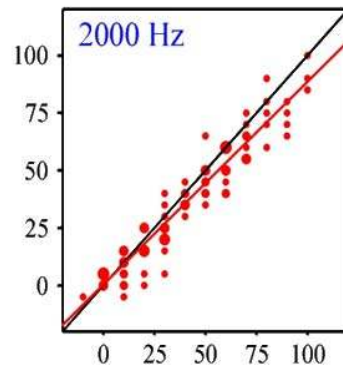
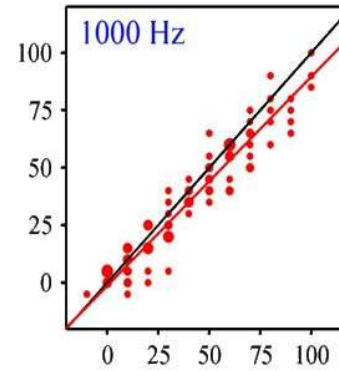
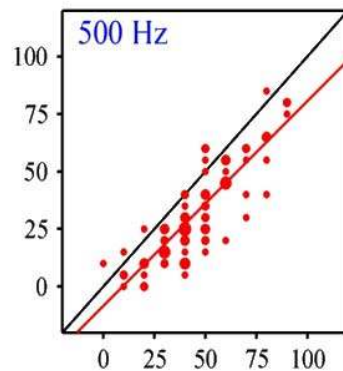
COMPARISON OF THE BEHAVIORAL AND ASSR AUDIOMETRY

Estimating
Behavioral
Thresholds

Thresholds

Behavioral
(dB HL)

Physiological
(dB HL)



The good correlation between the behavioral and physiological (ASSR) thresholds proved that the ASSR objective audiometry can be used for testing hearing of newborns.

Recently commercial systems were introduced for this purpose.

COMMERCIALLY AVAILABLE ASSR SYSTEMS



REVIEW QUESTIONS

- What is the difference between the evoked potentials and the event related potentials?
- Which components of the evoked potentials are called exogenous?
- What is the difference between the exogenous and endogenous components?
- Why and how is averaging used for the study of human event related potentials?
- What is the clinical relevance of the brainstem auditory evoked potential?
- List the examples of the use of ERPs in cognitive psychophysiology.
- What is the „mismatch negativity” ERP component?
- How is selective attention reflected in N100 component?
- What is P300 component?
- Which are the language related ERP components?
- How is motor preparation reflected in the brain electrical activity?
- What is „contingent negative variation”?
- How is the auditory steady state response used in the clinical practice?

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