The Sources of Auditory Evoked Responses
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This talk presents results from my research at the Max-Planck-Institute for Psychiatry in Munich (with Ives von Cramon), at the Universities of Ottawa and Toronto (with Terry Picton), at the Helsinki University of Technology (with Riitta Hari) und from the Section of Biomagnetism at the University Clinic Heidelberg (with André Rupp, Alexander Gutschalk and Peter Schneider).
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Brief sounds elicit a series of deflections in the auditory evoked response that are classified into fast, middle and slow components, as done by Terry Picton, or into early, middle and late components, depending on their latency.

The early components require a sharp brief onset sound, e.g. a click or plop, and thousands of averages to be extracted from the ongoing EEG. The slow components can be evoked in the EEG or MEG also by tone bursts or speech sounds, for example.

The most prominent peaks of the early components, also called auditory brainstem response (ABR) or brainstem auditory evoked potentials (BAEP), are the so-called waves I to V occuring in the first 10 ms. Na and Pa peak at middle latencies around 19 and 30 ms and the slow components P1, N1 and P2 occur later between 50 and 200 ms.



Early and middle latency components are conveniently measured using the voltage difference between an electrode at the vertex, for example at FCz, and an electrode at the earlobe or mastoid.

The prominent pattern of waves I-V is observed using the earlobe ipsilateral to the side of stimulation. In the contralateral derivation, prominent negative peaks (I- / III-) appear prior to a large but slightly delayed wave V.

The middle latency waves Na and Pa appear more symmetric indicating vertical current flow similar to wave V.

At a lower sound intensity (20 dB) the fast early waves are delayed and quite diminished while the slow activity underlying waves V, Na and Pa is also delayed but reduced less.

The typical low cut-off filter setting of 100 Hz in an ABR recording reduces these slow activities and distorts the ABR waveshape, if the low cut-off filter characteristic is too steep.

The main sites and orientations of the current flow in the ascending auditory pathway contributing to these scalp signals are illustrated by red arrows.



Such filter-distored BAEP is shown in many textbooks along with the roman numerals of waves I-V. These are attributed in a simple sequential manner to the waystations and nuclei of the auditory pathway starting from the auditory nerve up to the inferior colliculus.

Yet, as will be shown in the next few slides, the main orientations of waves III, III- and V indicate a different origin of the far-field potentials recorded at the scalp. We need to consider the zones of the depolarizing currents entering into the neurons at each nucleus (-) and of the return currents exiting along the ascending axons (+) to understand the generation of the dipolar potentials underlying the BAEP.



When trying to model the scalp-distribution of the BAEP by 5 simple monophasic waves, the activities cannot be explained sufficiently, particularly in the contralateral derivation Cz-Ac. However, if we use a model of summed action potentials with double firing – as known from auditory nerve recordings, the BAEP can be explained by 6 equivalent generators with similar waveshapes reflecting the propagation along the ascending auditory pathway (Scherg and von Cramon 1985. Electroenceph. clin. Neurophysiol. 62: 290-299).



The location and orientation of the 6 equivalent dipole fields leads to an interpretation that is consistent with the propagation times along the ascending fibre tracts and the synaptic transmission times at the nuclei (VCN / MSO):

Wave I and a part of wave II reflect the double firing of the distal auditory nerve.

When the action potential volley enters the brain, wave I- is generated by volume conduction effects since the petrous bone acts like an insulator.

Considering the conduction velocity of 20 m/s and the length of the auditory nerve as well as one synaptic transmission time (0.6 ms), wave III reflects the volley leaving the ipsilateral cochlear nucleus (VCN).

Wave III- is due to the change in orientation of the fibres crossing the brainstem. Before crossing they tend more upwards. The delay of ~0.5 ms relative to wave III reflects that the volley has crossed the brainstem halfway.

The dipoles of waves I to III- are predominantly oriented horizontally whereas the following equivalent dipoles of waves IV and V are oriented more vertically. They reflect the volleys leaving the ispilateral (IV) and contralateral olivary complexes (V). The currents entering the olivary nuclei are the sinks and the ascending fibres in the lateral lemnisci are the sources forming the resulting vertical dipole fields. The latency difference of waves IV and V reflects the time the volley needs to cross the brainstem from ipsilateral to contralateral.

Thus, wave V cannot be generated by the inferior colliculus (Scherg and von Cramon 1985. Electroenceph. clin. Neurophysiol. 62: 290-299).



This slide illustrates the interpretation based on the spatio-temporal 6 dipole model of the BAEP and the timing of the ascending action potential volleys considering a nerve fibre velocity of 20 m/s and a synaptic transmission time of 0.6 ms).

Wave I to III- have a predominantly horizontal orientation and reflect the activities of the auditory nerve, distally (I) and when entering the brainstem (I_N), leaving the ventral cochlear nucleus (VCN, III) and crossing the brainstem (III_N).

Wave IV and V predominantly reflect the ispi- and contralateral volleys ascending from the superior olivary complex (SOC) into the lateral lemniscus (LL).

Activity of the bilateral volleys leaving the IC and CGN cannot be clearly associated with the later, smaller and less consistent peaks of the BAEP, possibly because their relatively symmetric dipole fields tend to cancel.

The next reliably recordable AEP activity is the N19/P30 complex of the MAEP. It originates bilaterally in the primary auditory cortex whereas the P50 of the MAEP (P1 in LAEP) originates more laterally along the Heschl's gyrus (Scherg and von Cramon 1986. Electroenceph. Clin. Neurophysiol. 65: 344-360; Schneider et al. 2005. Nat. Neurosci. 8: 1241-1247).



The depth recordings in a patient with a left pontine tumor showed abolition of the ipsilateral wave I- and later waves while waves I and II were preserved. These findings supported the peripheral origin of wave II as second peak of the volley of the distal auditory nerve. When stimulating the right ear, scalp wave V was delayed. This indicated an impairment of the output from SOC on the lesioned side and supported the contralateral origin of wave V (Curio, Oppel & Scherg 1987. Electroenceph. clin. Neurophysiol. 66: 29-33).

A lesion of fibre tracts, e.g. in multiple sclerosis, stops the propagation of the volley and produces a dipole field with opposite orientation that counteracts and annihilates the dipole field of the outgoing volley, e.g. of wave III in the case of a pontine lesion. Similarly, a lesion of the inferior colliculus (IC) can stop the volley ascending along the lateral lemniscus and thus diminish wave V – this giving the wrong impression that IC were the generator of wave V.

Lesions of the auditory radiation can disconnect the primary auditory cortex and abolish the ipsilateral waves N19-P30 of the MAEP while a delayed LAEP can be recorded due to cortical connections from the ipsilateral, intact side (Scherg and von Cramon 1986. Electroenceph. Clin. Neurophysiol. 65: 344-360; Eur. Arch. Psychiatr. Neurol. Sci. 236: 56-60).



The current sinks (-) at the nuclei and sources (+) along the exiting fibre tracts are illustrated below the ipsilateral cochlear nucleus (III) and next to the contralateral olivary compley and lateral lemniscus (V). The change in orientation of the crossing fibre tracts creates wave III-.

Waves IV and V predominantly reflect the upward oriented current flow along the lateral lemnisci ipsi- and contralaterally.



When modeling the middle latency auditory evoked potential (MAEP) recorded along a coronal chain of 12 electrodes by equivalent regional sources bilaterally in the Heschl's gyrus, the N19-P30 complex can be seen to be generated by vertical dipole currents.

If one side is deafferented due to a lesion (left side), no primary current is seen on the affected side whereas the intact right side shows the vertically oriented N19-P30 complex (case illustrated above).

Based on the hypothesis that we can have vertical and lateral source currents bilaterally in the auditory cortex, 4 fixed dipoles are placed within the head model to estimate the bilateral currents in the coronal plane. Thus, the 12 recorded scalp signals (data matrix D) are uniquely reduced to 4 source signals (S) by applying the fixed inverse operator L⁻¹ to the recorded data matrix D.

In other words, the dipoles act like probe sources showing the abolition of N19-P30 on the deafferented side and the unilateral origin of the scalp-recorded N19-P30 in this patient despite its wide scalp distribution (Scherg and von Cramon 1986. Electroenceph. Clin. Neurophysiol. 65: 344-360; Eur. Arch. Psychiatr. Neurol. Sci. 236: 56-60).



In normal subjects, both MAEP and LAEP have bilateral sources in the Heschl's gyrus. N19t-P30t and N100t-P180t are rendered by nearly vertical dipoles (t: tangential) whereas the radial currents reflect the radial waves N27r-P39r and the lateral T-complex N150r.

When the auditory stimulus was applied unilalerally without masking, the contralateral activity of the auditory cortex was about 6% larger in the MAEP and 11% larger in the LAEP than the ipsilateral activity (Scherg and von Cramon 1986. Electroenceph. Clin. Neurophysiol. 65: 344-360).

The localization in normals using bilateral symmetric sources in the coronal plane was supported by the localization of the sources in the intact hemisphere in the cases with unilateral lesions.



The cortical origin of MAEP and LAEP was supported by the findings in a case with bilateral lesions of the auditory cortex.

Here, the source model included an additional vertical dipole in the brainstem to account for the slow activity underlying the BAEP. No primary N19-P30 activity was seen on either side, nor was there any LAEP. In the MAEP only the post-auricular muscle reflex (PAM) could be seen apart from a questionable, weak radial component N27r.

Peripheral hearing appeared normal, since the BAEP could be recorded from 70 down to 15 dB HL (Mathis, A., Bucher, P.O., Arnold, W. and Scherg, M. Schwere zentrale Hörstörung oder akustische Agnosie? - Eine Fallbeschreibung. Sprache-Stimme-Gehör 1988, 12: 137-144).



The typical pattern of the source activities of the MAEP (vertical tangental: N19t-P30t; radial: N27r-P39r) and of the LAEP (N100t and N150r) is observed bilaterally in normal subjects (left).

However, if a lesion affects the Heschl's gyrus unilaterally, both MAEP and LAEP appear abolished or largely reduced in the reconstructed source activity on the lesioned side. The source activity of the healthy side appears normal and can fully explain the scalp-recorded AEP (right).



In a case with a lesion of the left auditory radiation, the MAEP source activity was abolished on the left side (the early transient at the left side of the red cicle is related to the PAM) and normal in the right auditory cortex (AC). LAEP source activity of the left AC was of normal amplitude but appeared delayed by ~20 ms, indicating activation of the deafferented left AC by cortical connections crossing from the right AC.



In 1989, we published the first recordings of middle latency auditory evoked fields (MAEF: N19m, P30m, P50m). Using a masking technique, high frequency sounds could be shown to evoke an earlier N19m-P30m complex. These MEG findings confirmed the cortical origin of the middle latency auditory evoked response shown previously by source analysis of the EEG and lesion studies of the MAEP.



Using 2 sources with different orientations, the primary N19m-P30m complex could be separated from the P50m, originating more laterally in secondary areas of the Heschl's gyrus.



In MEG recordings, the primary P30m was shown to be larger in professional musicians and amateurs as compared to non-musicians (Schneider, Scherg, Dosch et al.: Morphology of Heschl's gyrus reflects enhanced activation in the auditory cortex of musicians. Nat. Neurosci. 2002, 5: 688-694). The enhancement was related to better discrimination of pitch and increased cortical thickness in musicians.

In contrast, the P50m was greatly enhanced only in professional musicians. The enhancement correlated with the daily time of practice in the past 10 years (Schneider, Sluming, Roberts et al.: Structural and functional asymmetry of lateral Heschl's gyrus reflects pitch perception preference. Nat. Neurosci. 2005, 8: 1241-1247).



Tonebursts of 400 ms duration evoke several slow components of the LAEP:

The onset N100, a lateral N150 (T-complex), and a sustained DC-potential persisting while the stimulus is present. By collapsing data of 10 subject over right and left ear stimulation, we obtained a clean grand average data set that could be separated into 3 components on each side having different orientations in space (Scherg and Picton. Event-Related Brain Research, EEG Suppl. 1991, 40:24-37):

- 1. The onset transient of N100-P180, predominantly originating in the primary koniocortex.
- 2. The lateral onset component N150.
- 3. The P50 and sustained potential (SP) originating in the more anterio-lateral parakoniocortex of the auditory cortex.



The so-called mismatch negativity (MMN) is created by subtracting the standard response from the response to a deviant tone. Using 2 dipoles on each side, we were able to separate the bilateral activity into a true, later mismatch activity (MMNb) and an earlier mismatch component (MMNa) that was only present when the pitch difference was large (1000 Hz). In this case, a newly activated pool of neurons creates an N100 component in the primary auditory cortex (MMNa). The true, later component MMNb is related to the more anterior parakoniokortex where pitch is predominantly processed (Scherg, Vajsar, Picton. A source analysis of the human auditory evoked potentials. J. Cogn. Neurosci. 1989, 1: 336-355).



Brief stimuli as well as the onsets and offsets of tonebursts, for example, produce transient responses. When modulating a continuous tone with a lower frequency or by using trains of brief stimuli, the so-called frequency following responses can be evoked.

With click trains of 80 Hz mainly the brainstem activity underlying the BAEP is evoked. Modulation with 40 Hz leads to a particulary large frequency-following response (FFR) – the so-called 40Hz-response, because the slow component underlying the BAEP (5-6 ms) and the P30 component of the MAEP overlap favourably.

At slower frequencies, EEG rhythms dominate and make the recording of an FFR difficult (from Picton T. Hearing in time: Evoked potential studies of temporal processing. Ear Hear. 2013, 34: 385-401).



By performing an analysis with sources in the brainstem (1: vertical orientation, 2: horizontal) and bilaterally in the auditory cortex (3,4: tangential, 5,6: radial), we were able to separate the major components of the FFR (Herdman et al. Intracerebral sources of human auditory steady-state responses. Brain Topogr. 2002, 15: 69-86) into:

- 1. The vertical brainstem response (BS), present both at 88 and 39 Hz.
- The right and left vertical components of the auditory cortex, only present at 39 Hz but not clearly seen at 88 Hz (ACvR / ACvL).
- 3. Small radial cortical components, seen only at 39 Hz.

This demonstrated that the evoked auditory cortical activity can hardly follow at very fast modulation rates. In contrast, both brainstem and cortex contribute and summate positively at modulation frequencies around 40 Hz.



When presenting a click train of 200 Hz, an onset response and a sustained field were recorded in the MEG. If the interstimulus interval was regular (fixed interval of 5 ms), the sustained field was larger as compared to a train with a randomly varying interval between the clicks (irregular stimulus with the same number of clicks per second).

Using source analysis, we were able to separate two sources, i.e. :

- 1. a specific source coding regularity in the more anterior pitch area, and
- 2. a posterior source in the planum temporale coding the energy onset of N100 and a smaller part of the sustained field that did no depend on regularity

Thus, the anterior source region appears to be involved in pitch perception and the posterior in loudness (Gutschalk A, Patterson RD, Rupp A, Uppenkamp S, Scherg M. Sustained magnetic fields reveal separate sites for sound level and temporal regularity in human auditory cortex. Neuroimage 2002, 15: 207-216).



An energy onset response is elicited whenever there is an onset of a sound, i.e. a sudden increase of loudness. Here, the noise onset elicited a P50m-N100m complex in the MEG. The following changes from noise to pitch 1 and then on to pitch 2 were without changes in loudness (Rupp A et al. Acta Acoustica 2018).

The energy onset response (EOR) is generated predominantly in the planum temporale which was found to code loudness in our previous MEG studies.



When the noise changed into a sound with pitch 1 the so-called pitch onset response (POR) was elicited in a more anterior area of Heschl's gyrus (Rupp A et al. Acta Acoustica 2018).



When the pitch changed from pitch 1 into pitch 2 the so-called pitch change response (PCR) was elicited in a still more anterior area of Heschl's gyrus (Rupp A et al. Acta Acoustica 2018).



Similarly, MEG revealed that the different aspects of a vowel stimulus activate different substrates in auditory cortex. The glottal puls rate (GPR) was represented in the most anterior area related to pitch perception, whereas the mean formant frequency (MFF) was represented more posteriorly in the vicinity of vowel type change (VT). Again, the energy onset reponse (EOR) localized most posteriorly and laterally (Andermann M, Patterson R, Vogt C, Wintersteller L, Rupp A. Neuroimage 2017).



Using distributed source imaging, Taddeo et al. (2020) were able to show that the MEG responses to melodies involved the more anterior auditory cortex. As compared to the first tone onset which is clearly lateralized to the contralateral cortex, melodies are also processed more bilaterally and in the more anterior secondary areas of the auditory cortex.



In 2022, the group of André Rupp published a study of the late AEP elicited by pitch stimuli presented to the normal hearing (NH) ear and to the other ear with a fitted cochlear implant (CI) in 20 subjects with unilateral hearing loss. This allowed for a direct comparison of the LAEP in normal and CI-fitted ears. The P2 component was larger when the normal ear was stimulated, whereas the CI response exhibited a larger pitch related P2 when the prosody of the pitch stimuli was varied. This finding demonstrated that prosody can be well perceived with cochlear implants.

Sound Property	Component	Region of AC
Peripheral Synchronization	P30m	Primary AC, koniocortex
Masking Period Patterns	P50m	Lateral Heschl's, para-kc
Energy Onset Response	N100m	Lateral Planum temporale
Pitch & Salience	N100m	Lateral Heschl's, para-kc
Melody	N100m	Antero-lateral Heschl's
Timbre - Hissiness	P200m	Medial Heschl's
Vowel - Spectral Shape	N100m	Planum temporale
Size of a Speaker/Instrument	N100m	Planum temporale
Binaural Hearing	N100m	Planum temporale
Size of a Speaker/Instrument Binaural Hearing	N100m N100m	Planum temporale

Primary auditory cortex (koniokortex) processes the first input as well as highfrequency features like timbre and hissiness. Pitch and melody are mainly processed in the more antero-lateral structures of Heschl's gyrus. Other features like loudness and binaural hearing are processed more in the planum temporale. The summary has been compiled by André Rupp based on the research of his group from 2002 - 2022.



Auditory stimuli can also activate other cortical structures, depending on the task involved (see following example). However, the first cortical processing occurs in primary auditory cortex and is reflected in the middle latency components.



In this reaction time experiment, 128 EEG channels and fMRI were recorded in a single subject in separate sessions. The subject was asked to press a button as fast as possible after hearing a sound presented in random sequence.

The averaged AEP appears widespread over the scalp, however with varying waveshapes. In addition to averaging the EEG-responses to the sound stimulus, averaging was also done using the button press as a trigger to synchronize the EEG activities related to the finger movement.

Thus, we needed multiple source analysis to separate the components and identify their origins using both averages. Activity spots in the fMRI could be used as control and/or seeds to extract the activity of the active regions.



By placing (or fitting) a symmetric pair of regional sources (1,2) into the left (1) and right (2) primary auditory cortex, the vertical N100 and laterally oriented N150 are reflected in the red and blue source waveforms.



Prior to N100, a central activity can be seen peaking at 84 ms in the vicinity of the SMA (source 3, green). Activation of SMA is also evident from fMRI. Without this decomposition of the scalp EEG by multiple source analysis, this activity can neither be seen nor separated from the arising onset of the AEP in the bilateral auditory cortex. The voltage map shows clearly that the anterior-frontal negativity due to the earlier activation of SMA is hidden in the widespread negativity of the rising primary N100.



When synchronizing the average to the button press, the activation of the contralateral motor cortex 40 ms prior to the key closure becomes evident (source 4, pink). This activation is confirmed by fMRI as well. Similarly to the SMA activity, the dipolar pattern of the activated motor cortex is completely covered by and hidden in the large, widespread negativity of the primary N100 on the scalp.



In the whole-head recording of the EEG, a strong vertical dipole pattern is seen over the lower back of the head. This activity is well modeled by a source in the cerebellum (source 5, brown).

Another, later activation (source 6, blue) appears in visual cortex, problably due to the requirement of the subject to hold his eyes steady and fixate a screen while performing the task.

Both localizations were also supported by fMRI.

Thus, if a task like a button press is linked to the presentation of a tone, we must be aware that more brain regions become involved in the processing of and the reaction to the tone.