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Physiological Mechanisms in Combined Electric–Acoustic Stimulation

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Objective: Electrical stimulation is normally performed on ears that have no hearing function, i.e., lack functional hair cells. The properties of electrically-evoked responses in these cochleae were investigated in several previous studies. Recent clinical developments have introduced cochlear implantation (CI) in residually-hearing ears to improve speech understanding in noise. The present study documents the known physiological differences between electrical stimulation of hair cells and of spiral ganglion cells, respectively, and reviews the mechanisms of combined electric and acoustic stimulation in the hearing ears.
Data Sources: Literature review from 1971 to 2016.
Conclusions: Compared with pure electrical stimulation the combined electroacoustic stimulation provides additional low-frequency information and expands the dynamic range of the input. Physiological studies document a weaker synchronization of the evoked activity in electrically stimulated hearing ears compared with deaf ears that reduces the hypersynchronization of electrically-evoked activity. The findings suggest the possibility of balancing the information provided by acoustic and electric input using stimulus intensity. Absence of distorting acoustic–electric interactions allows exploiting these clinical benefits of electroacoustic stimulation. **Key Words:** Cochlear implant—Electrophony—Hearing loss—Masking—Residual hearing.

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Criteria for cochlear implantation (CI) have been expanded to include subjects with significant residual hearing (1,2). Refined implantation techniques (3–5), round window implantation (6,7), combined with expanded knowledge of cochlear anatomy (8,9) allowed improved outcomes. Residually hearing CI subjects achieve better speech understanding compared with subjects without residual hearing (3,10–13). The questions regarding the physiological basis for this benefit and the interactions between residual hearing and electrical stimulation through the cochlear implant are, however, still not fully understood.

Physiological studies addressed this question. Stimulation of a residually-hearing ear generates activity different from stimulation of the deaf ear. The initial physiological observation dates back to the Ph.D. thesis of Moxon (14), extended in subsequent studies (15–18) that documented lower electrical stimulation thresholds in hearing ears. This indicates that in hearing ears additional elements are electrically stimulated. Due to the assumed contribution of hair cells, such responses were called electrophonic in contrast to the electroneural responses observed in deaf ears.

Speech signals are characterized by a high dynamics in sound pressure changes. This represents a problem for CIs: compared with 40 to 80 dB dynamic range in acoustic stimulation in the individual auditory nerve fibers, the dynamic range for pulsatile electrical stimulation is as a rule less than 3 dB (19–21), and also in population (where individual fibers have different response thresholds) the dynamic range rarely covers 20 dB (22). In electrically-stimulated hearing ears an expanded dynamic range in individual auditory nerve fibers was observed (20,23,24). Results consistent with increased dynamic range in hearing condition have been provided (23,25), also at the population level (22,26). All together these findings document that responsiveness to electrical stimulation is different if the cochlea preserves some hearing sensitivity.

In the following we analyze where electrophonic stimulation may take place, which type of constraints exist for such bimodal stimulation, and finally we discuss the mechanisms of the benefit and the interactions between acoustic and electric stimulation.

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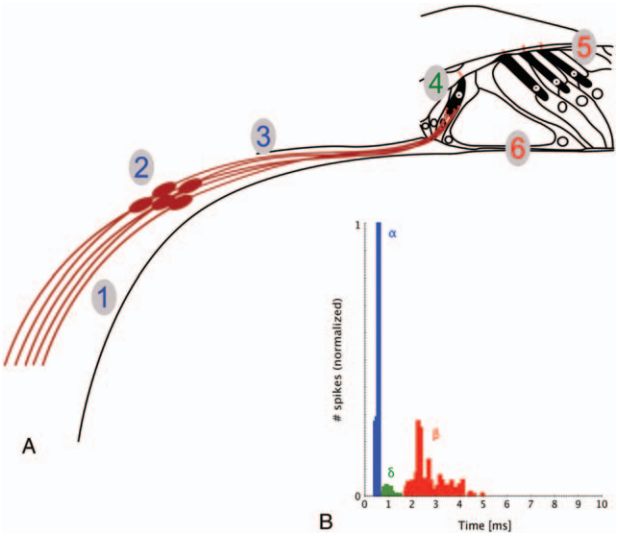

FIG. 1. *A*, Potential sites of electrical stimulation of a hearing ear. *B*, Sketch reflecting different responses (poststimulus time histograms) of single fiber responses with pulsatile electrical stimulation of hearing ear; based on Ref. (23), scaling of the ordinate is only approximate. Three different types of responses are marked by color. Numbers for sites of stimulation in *A* and responses in *B* are color-matched. For details, see text. Part *B* based on data from (23), similar results also in (20).

SITE OF STIMULATION

Combining the available evidence, electrical stimulation of the hearing cochlea may cause responses in different sites of the organ of Corti (Fig. 1A).

The Level of Central Axon of Spiral Ganglion Cells (SGC)

There is sufficient evidence documenting that electrical stimulation at higher currents takes place at the central process of the SGCs (Fig. 1, label 1). The strongest evidence comes from direct comparison of the response latencies in single fiber responses that demonstrate that anodic stimulation has higher threshold but shorter latencies than cathodic stimulation (20,27). The higher threshold indicates that the site of stimulation is further distant from the electrode, shorter latency indicates that the stimulation site is closer to the recording electrode. Both these observations consistently indicate a more central stimulation site for the anodic stimulation. The value of latencies combined with the propagation velocity of auditory nerve fibers in the range of ~12 m/s (28) supports the stimulation in the central axon using anodic stimulation. Due to axonal myelination, stimulation sites are likely the first nodes of Ranvier on the central axon.

Soma

There is few evidence for electrical stimulation at the soma of SGC (Fig. 1, label 2). While there is ongoing discussion whether the soma of SGC is completely devoid of myelin (29–31) or contains only few layers of Schwann cell membranes, the capacitance of the soma and the lower concentration of sodium channels makes the stimulation at this site rather unlikely, particularly at physiological stimulation levels.

Peripheral Process of SGCs

The evidence for electrical stimulation at the peripheral processes (Fig. 1, label 3) comes from the same studies as discussed in point ''The Level of Central Axon of Spiral Ganglion Cells'' above: the same evidence supports also that cathodic stimulation may activate surviving primary afferents (20,27). At which node of Ranvier this happens and whether it also happens in chronically deaf cochlea remains to be investigated. Human CI users demonstrate a better threshold for anodic compared with cathodic stimulation (32,33), consistent with the concept that in the clinical condition, with implantations after years of hearing loss, the majority of peripheral processes of SGC have already degenerated and stimulation can only take place at the central axon.

Inner Hair Cells (IHCs)

The evidence for the stimulation at IHC is only indirect and not very strong (Fig. 1, label 4). That IHC might get stimulated directly is extrapolated from long response latencies that are observed in hearing cochleae only, in absence of the ringing typical for mechanical responses (20,23,24,27). Consistently throughout all studies such responses were identified only in few % of the recorded fibers.

Outer Hair Cells (OHCs)

At present it appears well substantiated that OHCs are targeted by the electrical stimulation directly, causing mechanical responses that lead to a travelling wave on the basilar membrane (Fig. 1, label 5). On one hand, otoacoustic emissions were recorded in response to electrical stimulation, clearly demonstrating that electrical stimulation induces movement of the basilar membrane (34,35). On the other hand, single fiber recordings demonstrate that the responses to electrical stimulation in a hearing cochlea resemble click responses (23). The latencies correspond to excitation at the level of hair cells.

Mechanical Movement

Finally, another mechanism of stimulation could be the basilar membrane by the interaction of the electrical field generated by the implant with the electrical field that is caused by the endocochlear potential (Fig. 1, label 6). This may result in mechanical forces that can cause the movement of the basilar membrane (20,22). The endocochlear potential requires an electrical separation of the scala media from the scala tympani. Loss of hair cells would make the barrier leaky. However, such effect, even though described previously, is likely to exist only for a brief period of time around the loss of hair cells, after which reparation processes likely restore endocochlear potential (36,37). As will be shown below, direct mechanical effects appear less likely than direct OHC stimulation, but need to be investigated in the future.

In the present context the deaf cochlea will refer to profoundly deaf cochlea with no residual hearing. In such deaf cochlea (38,39), only sites ''The Level of Central Axon of Spiral Ganglion Cells,'' ''Soma,'' and ''Peripheral Process of SGCs'' remain available for stimulation, since hair cells are absent. Furthermore, due to loss of primary afferents with time, with increasing duration of deafness the site ''Peripheral Process of SGCs'' becomes a progressively less probable. Finally, as discussed above, ''Soma'' is also not very likely as a site of stimulation.

Based on this analysis it becomes clear that there are fundamental differences between electrical stimulation of a hearing ear and a profoundly deaf ear. A part of the electrical response observed in hearing ears is related to mechanical effects, with a probable mediation through outer hair cells (23). So called β responses (Fig. 1B) in the auditory nerve fibers were very similar to responses evoked by acoustic clicks. In comparison to the direct electrical stimulation of spiral ganglion cells (α response), the β response shows a longer response window, lower threshold, and longer latency, as expected for stimulation at the hair cell level. Detailed analysis of response latencies and jitter in hearing and deafened cochleae were again consistent with OHC stimulation (20,24,25). Additionally, there is also a direct IHC stimulation (23, long latencies, but no ringing, so-called δ response; comp. 20). Such responses are, however, very rare. Very likely they are of limited functional significance for the clinical condition.

CHARACTERISTICS OF THE ELECTROPHONIC EXCITATION

The electrophonic stimulation, defined as electrical stimulation mediated by hair cells, differs from electroneural stimulation (direct stimulation of SGCs) by

1) Lower threshold;
2) Larger dynamic range;
3) Longer response latency (∼1 ms).

Using these differences it is possible to identify and differentiate characteristics of electrically-stimulated hearing ears caused either by electrophonic or electroneural stimulation.

Signs of β-response were found throughout the whole cochlea, although at high currents in the mA range (14,20). Response latencies (20) identified a temporal gradient with shortest latencies at high frequencies and longest at low frequencies, whereas the short latencies at frequencies above 10 kHz in the cat where close to the range of peripheral axon stimulation (at the level of primary afferents). This may be caused by a travelling wave initiated by the electrical stimulus.

Multielectrode arrays allow recording from a broad tonotopic in the auditory midbrain simultaneously. Such an approach, while adding response complexity due to parallel centripetal pathways within the auditory system, provides a much higher yield, allows paired comparisons before and after deafening and allows inference where in the cochlea electrophonic responses appear. By that the differences between responses of a hearing and deaf ear can be directly observed within the same animal. Thus, it was possible to double-dissociate the effects of electrophonic and electroneural responses in the same animals (22). The electrophonic response was observed at characteristic frequencies (CFs) corresponding to the frequency spectrum of the time function of the electric signal (Fig. 2), whereas the electroneural response was observed at the cochlear location corresponding to the cochleotopic position of the active stimulation electrodes. This indicates that the temporal property of the electrical signal drives the electrophonic response (hair cells).

There was a gradient in the electrophonic effect (Fig. 3). It was strongest if the place of electrophonic response was close to the 8 to 9 kHz region, the place of best hearing in guinea pigs. The more distant the electrophonic site was from this position, the more current was necessary to generate the electrophonic response. The electrophonic response had high thresholds for frequencies above 12 kHz, but previous studies observed also there electrophonic responses (14,20).

From all these observations, three alternatives for physiological mechanisms are possible:

1) Selective stimulation of OHCs at the cochlear place with CF corresponding to the frequency of the electrical time function. Differences in threshold would be here the consequence of the distance between stimulated OHCs and the active electrode. This would imply that the membrane of the OHC acts like an electrical filter, so that only the electrical stimulus corresponding to the tonotopic place of the OHC will activate it. This alternative is not really probable, since such large variation in electrical properties of the outer hair cell membranes was not observed.
2) The electrical field generated by the cochlear implant interacts with the endocochlear potential, causing a mechanical movement at the basilar membrane that travels to the corresponding place in the cochlea.
3) Electrical stimulation activates the OHCs in the proximity of the active electrode. This initiates a ''local'' travelling wave (see below).

The local travelling waves spreads toward the apex and likely cause the time delays observed in (20). As suggested in (22), high frequencies (>12 kHz) may be less effective in activating hair cells due to the capacitive properties of the membranes involved, causing a short circuit of the membrane at these frequencies. This may explain why electrophonic responses at high frequencies may require higher stimulation currents. The dependence of electrophonic threshold on site of the cochlea, as expressed in the probability function (Fig. 3), could be

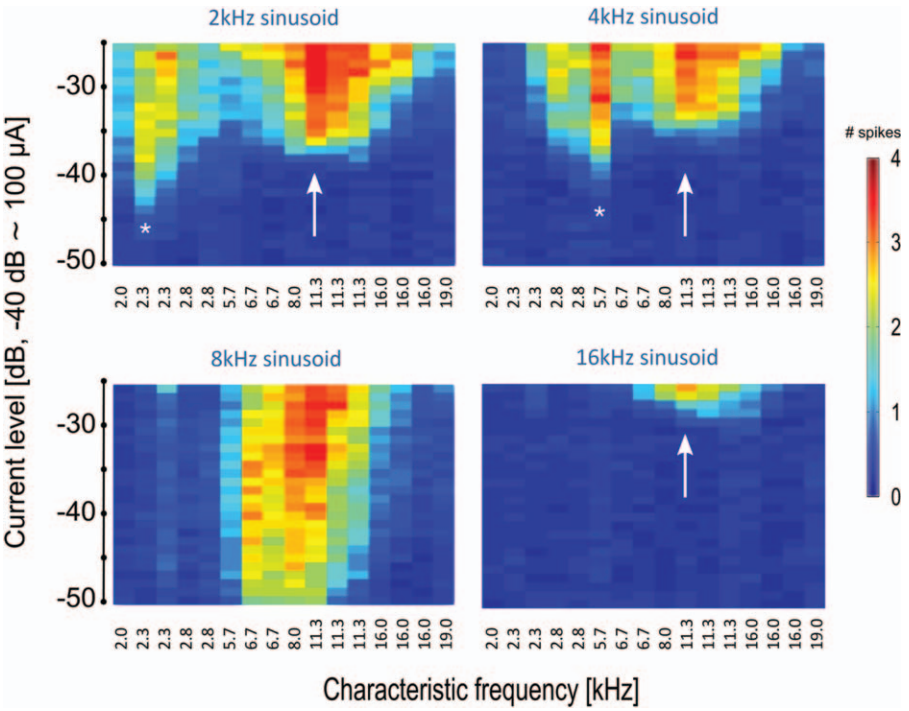

FIG. 2. Electrophonic response in a hearing ear takes place at the cochlear position that corresponds to the frequency of the stimulus. Recordings are shown along the tonotopic axis of the central nucleus of the inferior colliculus of a guinea pig using a multielectrode array. The abscissa shows the characteristic frequency of the unit recorded at a given contact, the ordinate the current level of the electrical stimulus. The color denotes the firing rate of the unit. The stimulus was an electrical sinusoid, frequency is shown in the panel title. Stimulation was bipolar with the apical most pair of contacts near a CF of 9.5 kHz. The responses show two sites: one (electroneural, *white arrow*) corresponding to the position of the active electrode (apical near CF = 9.5 kHz), the other (electrophonic, *white asterisk*) corresponding to the frequency of the electrical stimulus. With 8 kHz stimulation, both responses are fused. In 16 kHz stimulation, no electrophonic response was found (with currents below 500 µA). Data from (22).

related to intrinsic differences of the sensitivity of the organ of Corti to the mechanical movement. It is notable that the probability function of electrophonic responses (Fig. 3) shows the highest sensitivity at the place of best hearing of the guinea pig (22,40). It has to be considered that this travelling wave is generated by local effects near the active electrode, and not globally in the whole cochlea (as caused by the stapes footplate movement), and therefore the propagation properties can differ from the acoustically-evoked travelling waves. We suggest that the probability function of electrophonic responses is the consequence of two processes: mechanical sensitivity of the organ of Corti and capacitive effects at high frequencies.

The clinically available stimulation strategies use monopolar configuration with current spread throughout the whole cochlea. While electrophonic stimulation may, thus, be more spread-out in clinical conditions, the severely compromised high-frequency hearing in most implanted subjects limits the possibility of their occurrence in the basal cochlea.

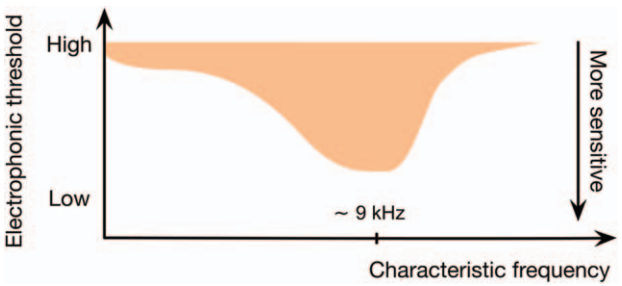

FIG. 3. Electrophonic spread function with bipolar configuration. The orange area schematically encompasses the region of thresholds for electrophonic responses using bipolar stimulation in guinea pigs. Lowest thresholds were observed near the position of the best hearing for guinea pigs. Based on results from (22).

BENEFICIAL EFFECTS OF ELECTROACOUSTIC STIMULATION (EAS)

Combining psychophysical and physiological evidence, the beneficial effect of EAS likely rests on several physiological mechanisms:

1) The presence of reliable low-frequency information that is required for temporal pitch perception and fundamental frequency of speech. Most cochlear implant stimulation strategies either do not convey this kind of information or present them at an incorrect cochlear place. Studies with intraneural stimulation indicate that a dedicated

low-frequency pathway may exist that is not sufficiently activated by CIs (41). While some CI stimulation strategies are aimed at stimulation of the apical portion of the cochlea, either by use of deeply penetrating electrodes (42) or by using other techniques activating the apical cochlea (43), it is likely that most of the clinically used strategies are not very effective in this regard. Adding low frequency acoustic hearing, even if not alone sufficient for speech understanding, may complement electric hearing by providing stronger representation of the fundamental frequency of many signals, including speech (13,44–46). This may not only be essential for pitch perception in implanted subjects, but also helpful for speech understanding in stream segregation (cocktail-party) conditions by the use of low-frequency interaural time difference cues.

2) Expand dynamic range by acoustic input. Modulation detection is one key factor in speech understanding with CIs (47). Limited dynamic range affects the coding of modulations. The narrow dynamic range in single fibers (1 to 3 dB, review in (48)) is effectively complemented by residual hearing that allows larger dynamic ranges in the hearing region for acoustic stimulation. Additionally, an expanded electrical dynamic range is observed in electrophonic responses (Fig. 4).
3) Expanded dynamic range by reduced synchronization to the electrical stimulus. The high synchrony of single fiber responses to electrical stimuli (Fig. 5A), the ''hypersynchronization'' (48), is the cause for the small dynamic range of electrically-stimulated deaf ears. On the other hand, with intact hair cells and extracochlear stimulation, the phase locking of auditory nerve fibers to electrical stimulation had in mean lower synchronization indices (SI) than for acoustical stimulation (50). Further analysis of this data set in fibers where both modalities could be tested (pairwise) demonstrates that SIs in hearing ears were, in contrast to deaf ears, not larger for electric than acoustic stimulation (Fig. 5B). This was despite of acoustic stimulation presented at CF, while electric stimulation at 125 Hz, and thus the comparison being biased in favor of the more effective low frequency electric stimulation (comp. Fig. 5A). In hearing condition, the synchronization to electric stimulus consequently appears weaker than in the deaf condition. While this suggestion requires a direct study with intracochlear stimulation and direct comparisons, it is consistent with the observation that evoked firing rates to the same electric stimulus are higher in the deafened condition compared with hearing condition ((22), Fig. 4). The most likely explanation is the spontaneous firing of fibers connected to functional hair cells that cause refractory periods in which the fibers cannot be stimulated by electric fields. This has twofold consequences: 1) the spontaneous firing inherently reduces the synchronization index by introducing spikes that are not synchronized to the stimulus, and 2) spontaneous firing prevents spikes evoked by the electrical stimulus during refractory period, i.e., prevents spikes that are synchronized to the electrical stimulus. These two factors together reduce the phase locking of the responses to electrical stimulation in the hearing ears. Another option is a different current path in the hearing cochleae compared with deaf cochleae due to intact cuticular plate in the hearing condition. A different current path may explain the lower maximum evoked firing rates in hearing condition (Fig. 4). In conclusion, hearing portions of the cochlea are more difficult to drive by electric fields than the deaf portions of the cochlea, and this naturally balances the stimulation depending on hearing status. The situation is even more impeded in combined EAS stimulation at low current levels, when the SI to electric stimulation is further reduced (Fig. 5B).

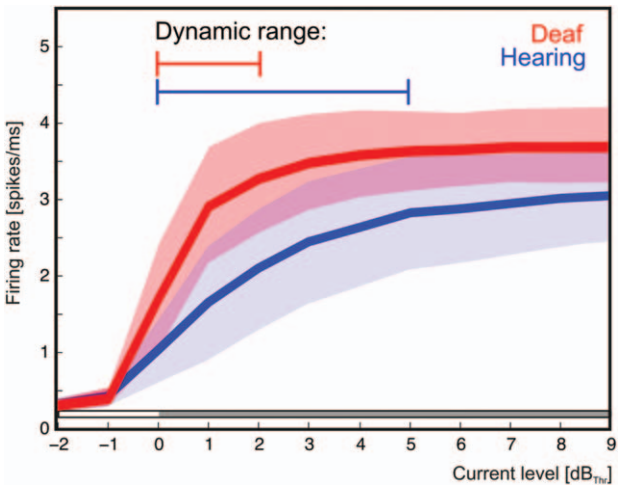

FIG. 4. Dynamic range in hearing cochleae is larger than the dynamic range in deafened cochleae. Shown are mean rate-level functions of responses in the central nucleus of the inferior colliculus recorded in response to a biphasic, charge-balanced pulse (100 μs/phase); the data from all characteristic frequencies were pooled. Shaded areas represent ±1 standard deviation. Gray bar below shows levels with statistical significance (paired Wilcoxon test, $\alpha = 5\%$, corrected for multiple comparisons by false discovery rate detection procedure, (49)). Data from (22).

This is, however, only part of the benefit of EAS. To understand the full picture of consequences of residual hearing for CI, we need to consider potential interactions between acoustic and electric stimulation in residually-hearing ears.

ELECTRO–ACOUSTIC INTERACTIONS

When providing two stimuli to hearing ears, masking phenomena are well established in the auditory

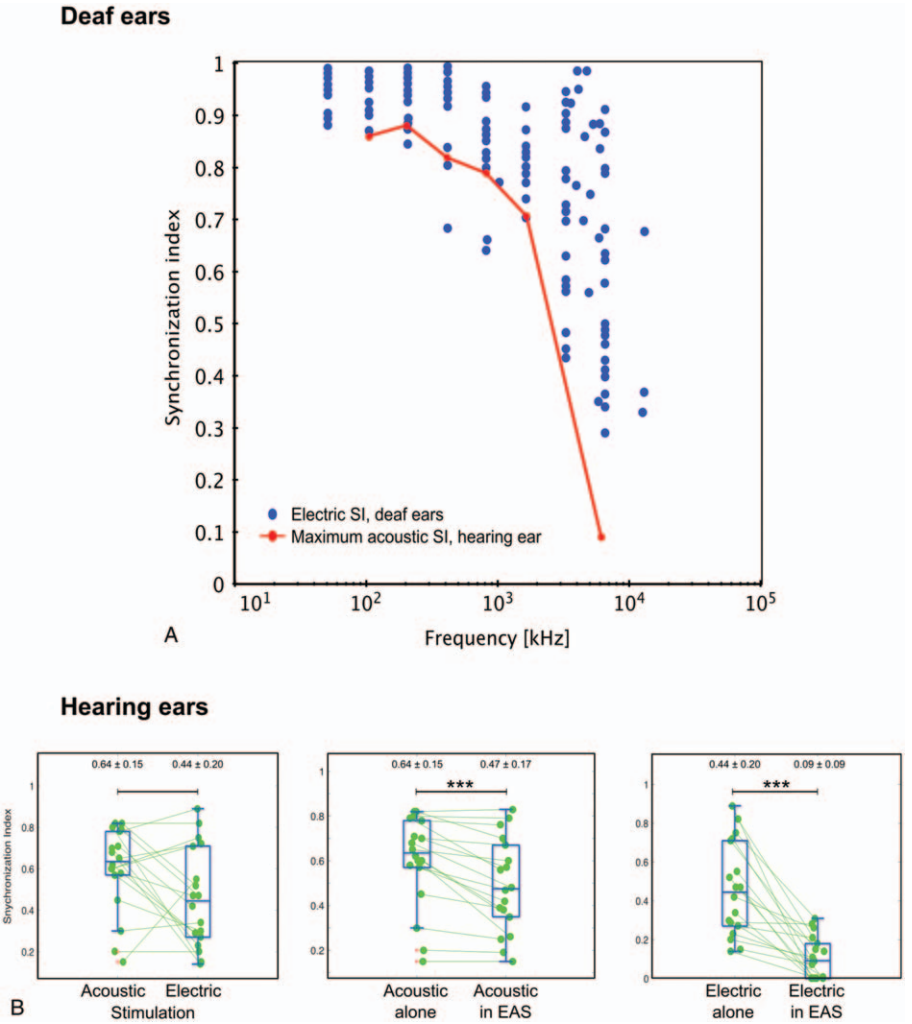

FIG. 5. Synchronization to electric stimulus is weaker in the hearing ear compared with a deaf ear. *A*, Comparing the synchronization index (vector strength) of auditory nerve fiber responses to acoustic stimulation in a hearing cochlea to that of electric stimulation in a deafened cat cochlea reveals that electrical synchronization indices (SI) are higher for electric stimulation in the deaf ear. Figure redrawn from (48). *B*, Using extracochlear sinusoidal 125 Hz electric stimulation at 6 dB above the threshold of the fiber in a normal hearing ear, the synchronization index is no longer higher than in acoustic stimulation (*left panel*, paired Wilcoxon test, $\alpha = 5\%$), which is different to (*A*) Adding simultaneous electric stimulation to the acoustic stimulation (electroacoustic condition, EAS) decreases the synchronization to the acoustic stimulus significantly (*middle panel*). Similarly, adding acoustic stimulation decreases the synchronization to the electric stimulus significantly (*right panel*). These data demonstrate that for moderate electric stimulation (6 dB above threshold), the stimuli interfere and that the acoustic stimulus may dominate the electric stimulus. Data from (50). EAS indicates electroacoustic stimulation.

psychophysics applicable to EAS. Physiologically, three types of interactions are possible:

1) Hair cell interactions, caused by interactions of mechanical movements of the basilar membrane and/or excitation of the hair cells between electrophonic and acoustical stimulation. They may share the characteristics of acoustic masking phenomena. Depending on stimulation intensity, acoustic stimuli may dominate over electrophonic (electric) stimulation and vice versa. The regions where such interactions will occur will depend on the probability of the electrophonic response (Fig. 3; (22)). However, future experiments are required to describe the electrophonic probability function for monopolar configuration.
2) Neural interactions, caused by interactions between the acoustically-evoked spike train and the electroneural stimulation patterns at the level of the auditory nerve. They result from refractory period of the auditory nerve fibers that may block responses both to electric as well as to acoustic stimulation, depending on which stimulus is leading. Furthermore, electric stimulation may also cause hyperpolarization of the neuronal membranes under some conditions (as in the example of anodic surround). Such neural interactions will be additive or subtractive (i.e., linear) in nature (Fig. 6). Indeed, no

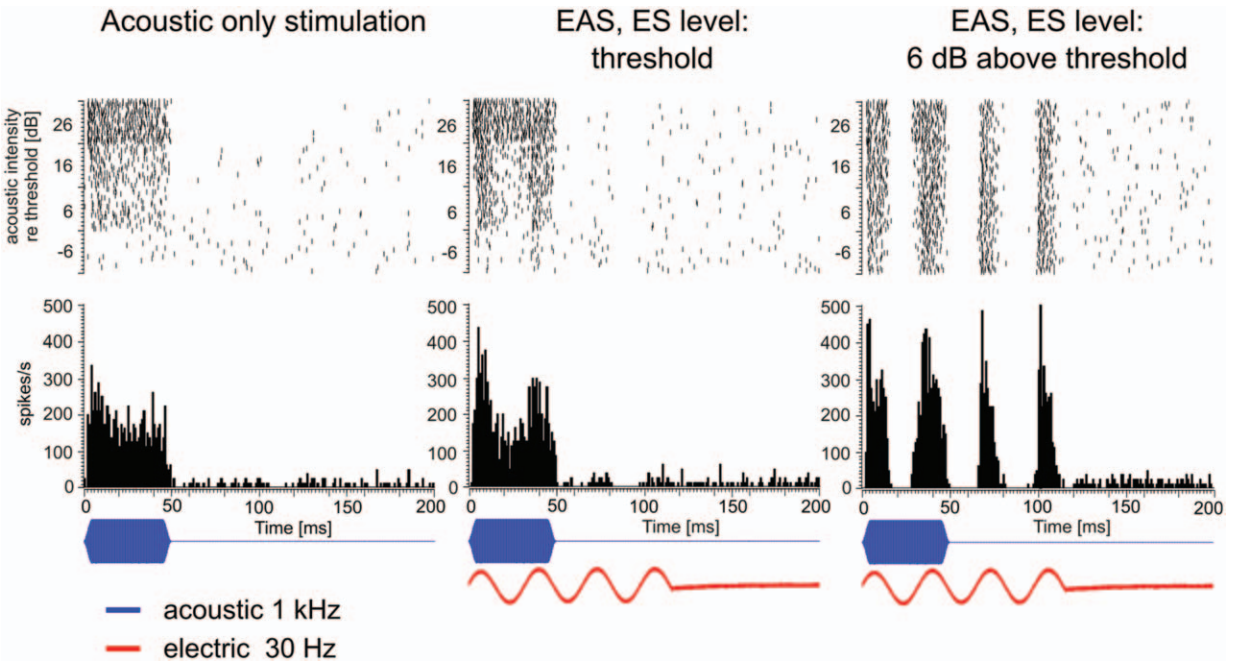

FIG. 6. Auditory nerve fiber responses to acoustic and combined electroacoustic stimulation (EAS) for a fiber with characteristic frequency of 1 kHz and extracochlear (round window) electric stimulation. Shown are raster plots (*top*) and poststimulus time histograms (*bottom*) for acoustic stimulation (*left*), EAS with electric stimulation level at threshold (*middle*) and EAS with stimulation at 6 dB above threshold of the given fiber for the given electric stimulus. In the EAS condition at threshold of both stimuli (*middle*), electric responses appear more prominent, but at higher acoustic stimulation of 20 dB above threshold, the acoustic response dominates. At 6 dB above electric threshold, the electric stimulus dominates (*right*). For low frequency electric stimulation, phase-dependent suppressions of firing were observed, as in the present case at 6 dB above threshold. All observed phenomena were consisting of activations or suppressions, in absence of distortions or other nonlinear phenomena. Data from (50).

evidence for true (nonlinear) distortions between both inputs has been observed so far (40,50). With long-lasting stimuli, the interaction between the temporal properties may vary over time depending on mutual temporal relations of the two stimuli (51,52) and the mutual phase relation of the stimuli (53). Neural interactions can occur at all cochlear positions where the electric stimulus drives the nerve fibers. In monopolar stimulation this likely covers large regions of the cochlea. Which stimulus dominates will depend on which causes more action potentials in the auditory nerve. This may well be the acoustic stimulus for low electrical levels (Fig. 5, (50)). At low acoustic and high electric levels the electric stimulation can dominate, too (Fig. 6, compare 52), further emphasized by high stimulation rates, pulsatile stimulation, and monopolar configuration. Despite the absence of a comprehensive study truly quantifying these effects, at this point there is sufficient evidence for both types of phenomena: acoustic dominance at low current levels and electric dominance at high current levels. Reducing the electrical stimulation level for stimuli where interactions are expected provides an excellent opportunity to shift the functional effects in favor of the acoustic input. The fact that such trading occurs in both directions (acoustic and electric) and the absence of distortions explains why reducing the overlap between electric and acoustic input does not always improve outcomes (54) and documents the robustness and complementarity of both information.

3) Central interactions, caused by interactions at the level of the central auditory system. Examples of such phenomena may include informational masking, but also some forms of energetic masking that are generated in the central auditory system.

In total, the interactions will depend on the number of phenomena: probability function of electrophony (Figs. 2 and 3), mutual relations of stimulation intensities, extent of residual hearing including preservation of outer and inner hair cells. Defining where an electrophonic response is likely to appear requires identification of the site of the cochlear response and comparison with the electrophonic probability function (Fig. 7). The known probability function comes from bipolar stimulation (22); for other conditions the spread functions require further definition. Finally, the preservation of the hair cells is likely very variable in human subjects. For this reason, a clinical approach is required that defines all relevant factors in the individual subject before one can interpret the effects of electrical stimulation. This will help to maximize the benefit of EAS.

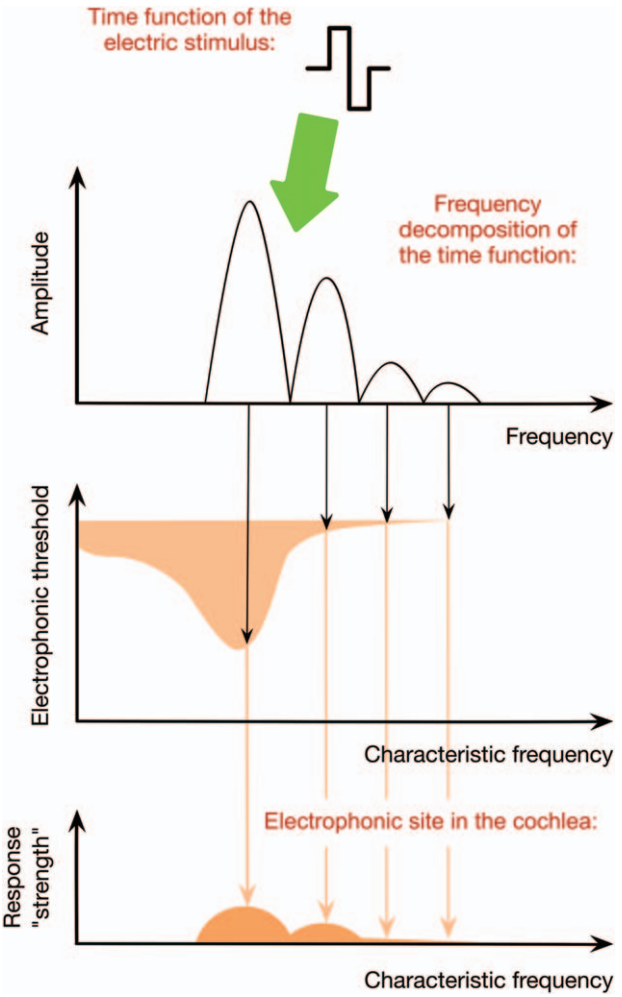

FIG. 7. Simplified model predicting electrophonic responses. To predict the cochlear place of the electrophonic response, the time function of the electrical stimulus is used. Frequency analysis reveals its dominant frequency components. Comparing their frequency to the place of electrical stimulation and its spread function reveals where in the cochlea (at which characteristic frequency) the largest response will be observed.

We assume that the most frequent interactions observed in human subjects will be the additive/subtractive auditory nerve interactions. We assume that the clinically-used short pulses are unlikely to generate strong electrophonic effects in implanted humans (22), partly also because the subjects have impaired high-frequency hearing and thus a non-intact population of hair cells. It remains to be shown how many outer hair cells can be recruited to generate electrophonic responses in the apex of implanted humans. At higher frequencies the loss of outer hair cells in these subjects is extensive. Consequently, hair cell interactions appear unlikely for high stimulation frequencies in humans. Only detailed evaluation of these effects in human subjects will provide final evidence. We propose that neural interactions will be the predominant type of interactions observed in implanted humans. Since these are mainly of linear nature, they should not provide distortions in the perceived stimulus.

In conclusion, the existing data on the neurophysiological aspects of EAS suggest that the use of electrical stimulation is in wide range complementary and not competitive or distorting to residual hearing. Electrical stimulation provides meaningful additive information to the acoustic input. Although many physiological mechanisms in EAS remain open, the existing physiological evidence supports the extensive beneficial effects of EAS.

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