Exploring the capabilities of modern cochlear implants : from electrophysiology to quality of life

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Chapter 5

A new method for dealing with the stimulus artefact in electrically evoked compound action potential measurements

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Abstract

Objective: Residual charge on recording electrodes leads to elevated potentials after the end of the stimulus, which can easily overload the electrically evoked compound action potential (eCAP) recording systems (neural response imaging or neural response telemetry). A new method for dealing with this problem was tested in a series of animal experiments.

Material and Methods: We developed an amplifier with a compensation circuit that reduces the effect of the residual charge by electrical subtraction at the input. Using this amplifier we compared different artefact rejection protocols simultaneously in chronically implanted guinea pigs. A new, systematic nomenclature for the various forward masking schemes, based on the number of frames involved, is proposed.

Results: Proper adjustment of the compensation circuit reduces the overload time from >200 μs to <30 μs, but the compensation signals influence the final output signal considerably. To eliminate this deliberately introduced, reproducible artefact, an additional artefact rejection scheme is necessary. With alternating polarity (AP) and forward masking paradigms we could reliably record the N_1 peak. Forward masking responses reveal shorter latencies for cathodic-first biphasic stimuli than for anodic-first pulses. The average of these two closely resembles the response obtained with the AP paradigm.

Conclusions: It is worthwhile implementing the electrical compensation method proposed herein in clinical neural response imaging or neural response telemetry systems, as it represents a more robust way of assessing the eCAP.

Introduction

Nowadays, the fitting of cochlear implants is mainly based on subjective patient responses, putting serious constraints on the procedure, especially when it involves children. Therefore there is a need for objective measures that can provide information about implant performance. One such measure is the electrically evoked compound action potential (eCAP).[1] After injection of current pulses the eCAP can be recorded with a recording electrode positioned close to the cochlear nerve or intracochlearly. However, the stimulus artefact will be recorded as well as the response. Its amplitude is:/1000 times larger than that of the neural response, which immediately follows the artefact.

The latest cochlear implant models allow recording of the neural response to electrical stimulation from inside the cochlea through the implant itself, and this procedure is known as neural response telemetry (NRT)[2] or neural response imaging (NRI).[3]

The clinical potential of this first step towards easily accessible objective measurements is promising.[2] Recently, the use of profile-derived eCAP thresholds across the electrode array, followed by adjustment of the overall level of the profile to the hearing threshold and maximum comfortable loudness level using live voice has been proposed as a new possibility for processor adjustment.[4] However, with higher current levels the first negative peak of the eCAP (N_1) is often not recordable due to its short latency, making this part of the response waveform either distorted or even fully obscured by the stimulus.

Three different methods have been proposed to deal with the problem of the stimulus artefact, each having their specific strengths and weaknesses (figure 5.1).

The first method is electrical or digital subtraction[5], which implies the use of a ''template'' of the stimulus artefact without a neural response (figure 5.1A). When a recorded subthreshold artefact (without neural responses) is scaled to match the amplitude of a suprathreshold stimulus it can be subtracted from the latter recording and the neural response will remain. One of the limitations of this technique is the requirement to obtain a subthreshold recording that is truly free of responses. Furthermore, the method assumes linearity of the electrode-tissue interface, as well as of the stimulating and recording equipment. Finally, because

upscaling the subthreshold artefact also increases the noise, a substantial number of averaging sweeps are needed to ensure low noise in the artifact template.
The second paradigm[6] applies an alternating stimulus polarity (AP) (cathodic-first versus anodicfirst) (figure 5.1B), making use of the fact that the polarity of the eCAP response is equal for both stimuli. Averaging the recordings for the two stimulus types cancels the stimulus artefact and leaves the neural response. Although this technique is widely used both clinically[3] and experimentally, Miller et al.[7] showed that the polarity of the stimulus has an influence on latencies, threshold levels and the rate of growth of the eCAP amplitude. Therefore, it is likely that the response obtained using the AP method is the mixture of two different responses.

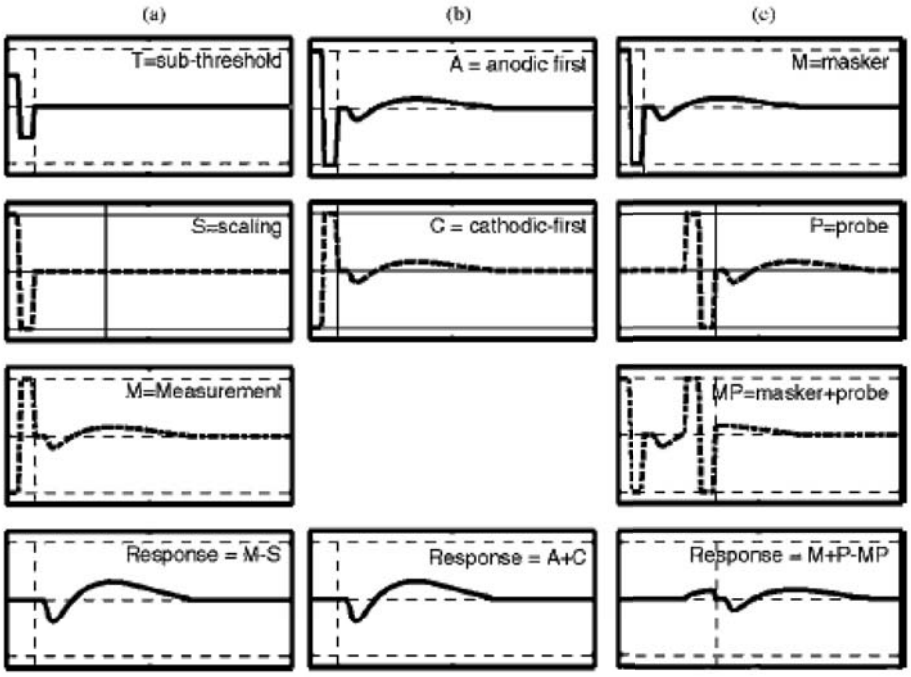

Figure 5.1: The three artefact rejection paradigms used in eCAP recordings. A: Template Scaling; B: Alternating Polarity (AP); C: Forward Masking (MP3).

The third technique is the forward masking technique (figure 5.1C), which takes advantage of the refractory properties of the cochlear nerve.[6] It is used in the NRT system of the Nucleus CI24M device[8]. The response is obtained by combining three different stimulus conditions, here referred to as frames. Therefore, we propose to call this forward masking paradigm the MP3 (masker-/probe 3) frame scheme. As we will explain in the Discussion, this results in a useful nomenclature which can incorporate numerous modifications of the forward masking scheme, each with their own application area (e.g. refractoriness and selectivity). The first frame, called the M (masker) frame, is a high-level, short-duration pulse presented at the start of the measurements. The second frame, called the P (probe) frame, is a high-level, short-duration pulse presented after a short delay. The third frame, called the MP (masker-/probe) frame, presents a high-level, short-duration masker pulse, before presenting a second, probe stimulus pulse. With the nerve in a refractory state due to the masker pulse, the response to the probe pulse consists only of the probe stimulus artefact. This template is subtracted from the original response to the probe pulse of the P frame.
The recorded response to the masker alone (M frame) is added to the previous subtraction to cancel the response to the masker in the MP frame. One of the main assumptions in this paradigm is that the MP interval is short enough (</0.5 ms) for all the nerves to be in their absolute refractory state[6]. If the MP interval is >0.5 ms, there is a relative refractory component at the moment of the probe stimulus in the MP frame. This is caused by some of the nerves that have recovered from their refractory state. These results in an unwanted neural response to this probe, which influences the final response calculated. Another potential problem is the fact that the masker in the MP frame not only excites a certain area around the electrode, but also charges the membranes of the nerve fibres in surrounding areas. These nerve fibres, although not depolarized by the masker, approach their threshold due to their proximity to the stimulating electrode. Then, the probe stimulus in the MP frame can excite these fibres, adding a neural response to the frame intended to record just the probe stimulus artefact.
In this study we compare these protocols in an attempt to eliminate the stimulus artefact in a series of experiments performed in chronically implanted guinea pigs and analyse their differences and shortcomings. Firstly, we examine the artefact itself and demonstrate the existence of a prolonged potential due to the electrical

properties of the electrode-/tissue complex. Then we introduce the use of a new amplifier with a compensation circuit that reduces the effect of this prolonged potential. With this newly designed amplifier we compare the different protocols using an experimental set-up in which all protocols run simultaneously in each animal.

Materials and Methods

Animals and preparation

Five unpigmented, female guinea pigs (200-600 g) were used. Subjects were anaesthetized with i.m. injections of a ketamine-xylazine compound (20 and 14 mg/kg, respectively). A maintenance dose of 50% of the initial amount was given as needed. Core temperature was kept stable with a heating pad. After general anaesthesia was induced, a local anaesthetic (2% lidocaine and 1:80 000 adrenaline) was injected at the incision site. A retro-auricular incision was performed and fat and muscle overlying the bulla were removed. Next, the bulla was opened to get a proper view of the base of the cochlea and the round window. For stimulation, a platinum_/iridium (90% Pt, 10% Ir) ball electrode (diameter 180 µm) was inserted through the cochlear wall after drilling a hole (diameter 280 µm) in the scala tympani of the basal turn. The recording silver (Ag) ball electrode (diameter 250 µm) was placed on the round window. One additional stimulating and one additional recording Ag electrode were inserted into the muscular tissue of the neck. All electrodes were connected to a DB9 connector that was fixed to the skull using dental acrylic. Additional contacts used as reference electrodes for differential recording were created using stainless-steel screws fixated transcranially at the sutura frontonasalis and bilaterally at the bregma. Finally, the skin was closed in layers with vicryl (5x0) sutures. After surgery the animals were transported back to the animal care unit and stayed there for a minimum of 7 days before the electrophysiological experiments started. For the experiments, the animals were anaesthetized for a maximum of 3 h with the same combination of ketamine and xylazine as described above. The care and use of the animals was approved by the Leiden University animal and ethics committee (registration number 99064).

Stimulation and recording

The intra-cochlear Pt-Ir electrode was stimulated by biphasic rectangular current pulses (50 μs/phase) generated by a custom-built, multichannel waveform generator[9] connected to a custom-built, optically insulated voltage-to-current converter with a high impedance (>10 MΩ).

Recordings were made differentially with the round window electrode as the positive pole, a retro-auricular Ag ball electrode as the negative pole and the frontal screw as the reference contact, connected with a custom-designed, optically insulated, battery-operated differential amplifier. This amplifier combines a wide bandwidth (2 Hz-65 kHz) and high input impedance (>/100 MΩ) with a low noise level (3 μVeff at the input; input range -5 to +5 mV). A limiter circuit in the input stage and clamping at the second stage controls the overload characteristics of the amplifier. Irrespective of the input voltage, the amplifier returns to its normal state within 10 μs after each pulse with resistive loads. For all recordings an amplification factor of x1000 was used. After anti-aliasing, eCAP waveforms were sampled at a rate of 100 kHz, digitized and analysed with a PC using custom-made software. Typically, averaging 32 sweeps improved the signal-to-noise ratio in the recordings sufficiently.

Results

Artefact

Figure 5.2 shows artefacts recorded for charge-balanced biphasic current pulses of 100-1000 μA. In accordance with the specifications of our amplifier, the recorded stimulus signal is clipped at a level of ±5 V. This first artefact is followed by a constant potential with a longer duration for higher stimulus levels (up to 200 μs for 1 mA). With purely resistive loads we did not find any such prolonged potentials and concluded that the electrical capacitive properties of the electrode-/tissue complex are mainly responsible for this phenomenon rather than the amplifier itself. Evidently, such prolonged artefacts, which persist during the period that the eCAP is generated, prohibit a reliable recording. One of the ways to circumvent this problem would have been to reduce the amplification factor, at the price of a lower signal-to-noise ratio and an increased number of sweeps in each average.

Here we will describe an alternative approach, which allows recordings with an amplification set to x 1000, even with large stimulus currents.

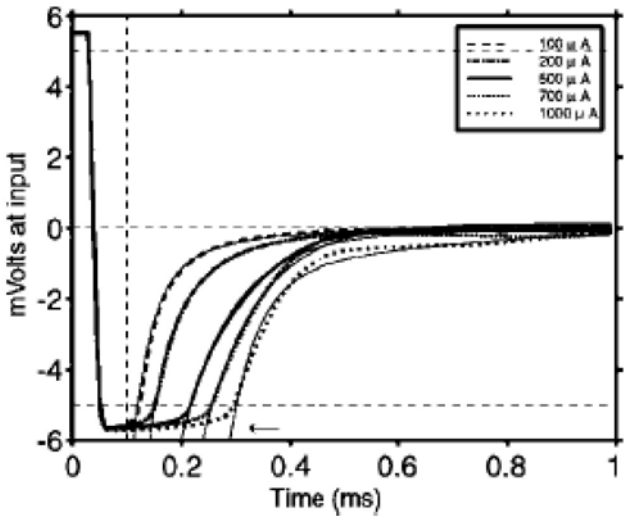

figure 5.2: eCAP measurement in guinea pig (GP) number 0417 made using anodic-first biphasic stimuli (50 ms/phase) of varying strength. The injected current drives the amplifier (x1000) into overload and leaves a residual charge on the electrodes, which obscures the neural response. This effect is more prolonged for higher stimulus levels, yielding latencies of up to 200 µs. The thin curves (indicated by the arrow) illustrate the adequacy of the fit of the double exponential function used for artefact rejection. The broken vertical line indicates the end of the stimulus.

Improved amplifier

Having concluded that the first part of the response is obscured by the residual charge in the electrode-/tissue interface, it occurred to us that it is advantageous to subtract the artefact electrically in the input stage of the mixing amplifier, rather than digitally subtracting a scaled artefact from the response. In this way, the saturation of the amplifier can be restricted to the time of stimulus delivery, in spite of the high (x/1000) overall gain of the amplifier. Analysis led to the conclusion that the residual potential due to a stimulus can be approximated by a

superposition of two exponential functions. The adequacy of the fit is illustrated in figure 5.2. Both time constants and the amplitude scaling factors describing this function depend upon the stimulus level. An electrical circuit that can generate such a potential was created and incorporated at the input stage of our amplifier. The artefact rejection circuit is triggered by a separate trigger generated by the waveform generator, in this way synchronizing the trigger to the end of the last stimulus pulse.

Removal of the compensation artefact

Figure 5.3 shows a typical eCAP recording with and without compensation, acquired using the MP3 method. Without compensation, the amplitude of the N_1 peak is hidden, while its latency is overestimated as 0.23 instead of 0.17 ms after stimulus onset, as found with compensation.

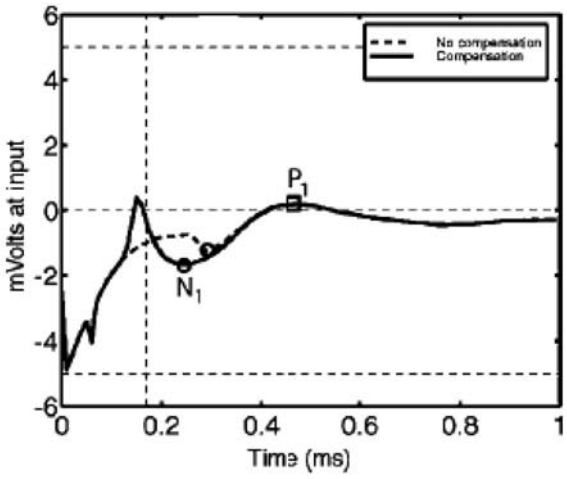

Figure 5.3: eCAP recordings with the MP3 method in GP 0417 with and without compensation, showing that the observed latency of the N1 peak is reduced from 0.23 to 0.17 ms after stimulus onset (anodic-first stimuli; 450 μA; 50 ms/phase; 32 sweeps). The broken vertical line indicates the end of the stimulus.

Figure 5.4a shows that the raw eCAP as recorded with the compensation method is heavily influenced by the actual settings of the circuitry. Independent of the setting, the latency due to saturation of the amplifier is reduced to </30 µs.

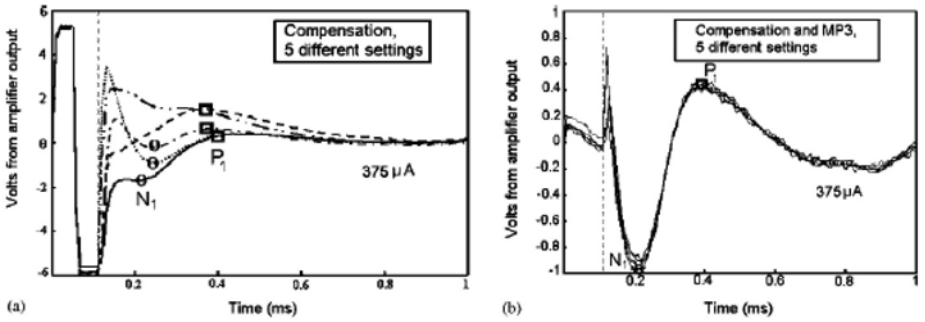

Figure 5.4: The effect of adding a stimulus artefact rejection scheme. (A) The effect of 5 different compensation settings on the directly recorded eCAP with a biphasic, anodic- first stimulus of 375 µA (GP 0419; 32 sweeps). Coarsely adjusting the parameters of the compensation signal is sufficient to reduce the time for which the amplifier is in overload to <30 ms after the end of the stimulus. The true waveform of the eCAP is unresolved because of the artefact introduced by the compensation circuit. The broken vertical line indicates the end of the stimulus. (B) Adding the MP3 paradigm to the compensation method reveals reliable and reproducible eCAP waveforms for all five compensation settings shown in (A). The broken vertical line indicates the end of the stimulus.

However, combining the compensation method with the MP3 paradigm yields an eCAP that is virtually unaltered by the exact setting, provided that the compensation keeps the amplifier within its linear operating range (figure 5.4b). The resulting signals have a consistent waveform, with a distinct and apparently undistorted N_1 peak at 0.18 ms after stimulus onset.

Comparison of the artefact rejection schemes

With the AP paradigm, the responses to anodic- and cathodic-first pulses are averaged. Figure 5.5 shows the results of combining the compensation method

and the AP paradigm. The setting of the compensation circuitry was the same for both stimulus polarities. As shown, it limited the prolonged potential after the end of the stimulus to <30 µs. With these settings, the latency of the N_1 peak and the amplitude of the recorded eCAP differ for the anodic- and cathodic-first stimuli.

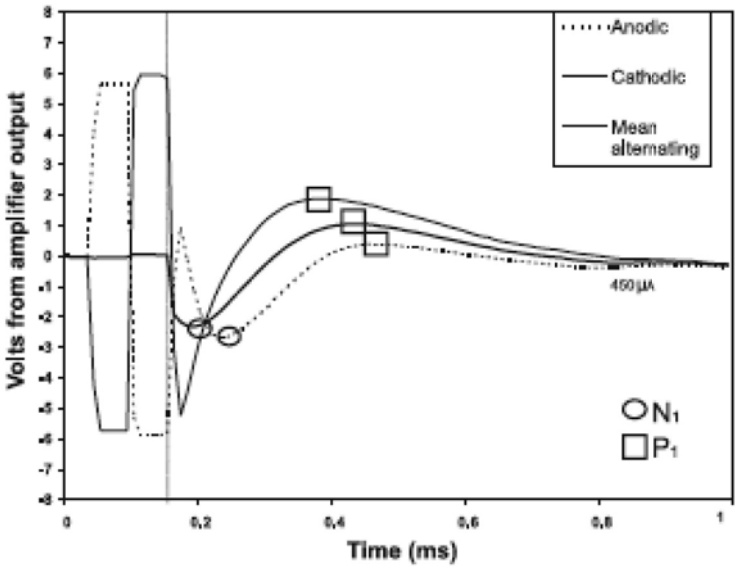

Figure 5.5: GP 0304, using 32 sweeps with biphasic stimuli of 450 µA with the AP paradigm and compensation. Recovery of the amplifier from saturation takes: ~30 µs. The average of the combination of the AP paradigm and compensation reveals a N_1 peak of 0.14 ms after stimulus onset. Both cathodic- and anodic-first stimuli are influenced by the compensation signals, but are cancelled due to the averaging of the AP paradigm. The vertical line indicates the end of the stimulus.

Obviously, these direct measurements are not reliable due to the compensation artefact, but the eCAP obtained by averaging both curves is likely to be free of such an effect. The latency of the N_1 peak of the average signal is 0.14 ms and that of the P_1 peak 0.36 ms.
In order to analyze the eCAP latency differences between cathodic- and anodic-first stimuli in more detail, eCAPs were recorded with the MP3 paradigm with artefact compensation using both anodic- and cathodic-first pulses (figure 5.6). It

turned out that the N_1 and P_1 latencies are shorter for cathodic- (</0.13 and 0.32 ms, respectively) than for anodic-first stimuli (0.16 and 0.38 ms, respectively).

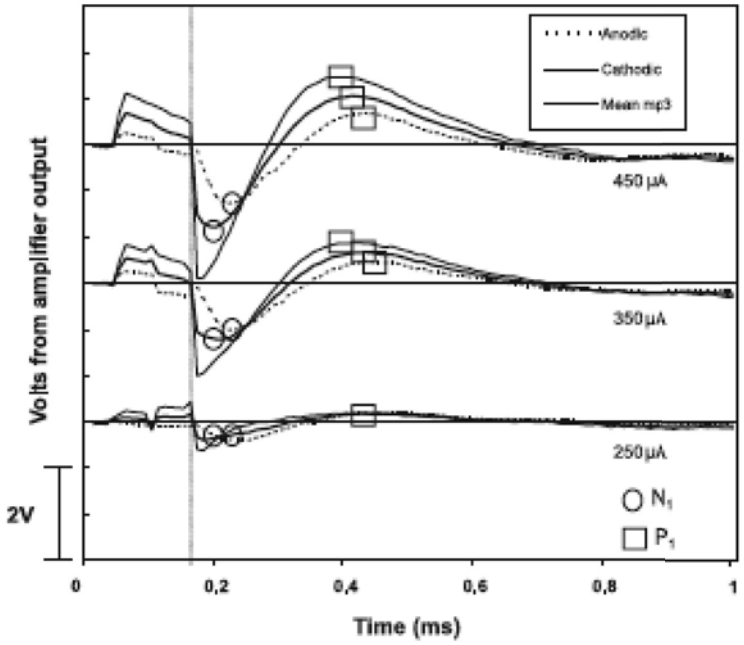

Figure 5.6: The MP3 paradigm with compensation for anodic- and cathodic-first biphasic stimuli of 250, 350 and 450 µA (50 µs/phase; 32 sweeps; GP 0304), and the average of the recordings for the two polarities. The vertical line indicates the end of the stimulus.

The current level used does not influence this effect. For cathodic-first stimuli the true latency of the N_1 peak is probably even shorter, as the N_1 peak is truncated by the stimulus artefact in these cases. The data in figure 5.6 allow another interesting way of comparing the artifact rejection schemes. If the MP3 method yields the true and undistorted eCAP, averaging the MP3 results for both stimulus polarities should give the same outcome as the direct averaging done with the AP paradigm. This comparison was performed in all animals for varying stimulus levels. A typical result is shown in figure 5.7. Generally, there is not a

perfect match between the N_1P_1 amplitudes obtained with both paradigms, but the waveforms are largely similar, as are the peak latencies.

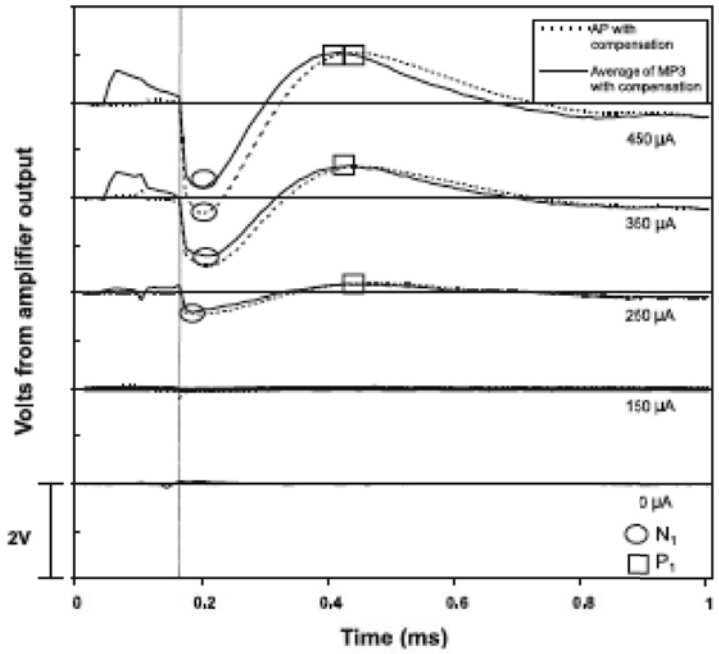

Figure 5.7: Comparison of the average of the cathodic- and anodic-first stimuli (MP3) and the AP paradigm signals in GP 0304 (0, 150, 250, 350 and 450 µA). The waveforms are largely similar, with comparable latencies and amplitudes. The vertical line indicates the end of the stimulus.

Discussion

We have introduced a new method to deal with saturation of the amplifier due to the stimulus artifact in eCAP recordings. This method allows the use of large amplification factors, thereby reducing the number of sweeps that have to be included in the average. An evaluation of the artefact that is measured with the neural response identified two main components: the recorded stimulus

and a prolonged potential due to the electrode-tissue interface. This prolonged potential hampers proper functioning of the amplifier for a considerable period after the stimulus and prevents proper recording of the N_1 peak.

Subtraction of an equivalent electrical signal at the input stage of the amplifier forced the input signal within its linear operating range and prevented saturation. The exact parameters of the subtraction network were shown to influence the shape of the measured response, but this newly introduced artifact could be removed using any of the known artifact rejection schemes in a reproducible way (see figure 5.4).

As shown in figures. 5.3 and 5.4, the method allows reliable recording of the N_1 peak for anodic-first stimuli, while figure 5.6 shows that the latency of this peak is considerably shorter for cathodic-first stimuli. This observation is in line with simulations performed with our computational model of the electrically stimulated cochlea.[10] As discussed by Frijns et al.[11], the excitation is dominated by the negative phase of the stimulus due to the so-called polarity selectivity ratio, which leads to four to eight times lower thresholds for cathodic than anodic stimuli. This phenomenon in itself can only explain part of the observed latency differences (up to the duration of 1 stimulus phase, i.e. 50 μs). Recent simulations in our laboratory revealed that the even longer latency differences observed in the experiments are probably due to temporal integration effects occurring in the neural membrane, which prohibit excitation of the nerves during the first part of the second (cathodic) phase in anodic-first stimuli.

In the light of these observations it is clear that the AP paradigm is likely to result in a response that is the average of two different outcomes: one for anodic- and one for cathodic-first stimuli. This conclusion is further corroborated by the experiment illustrated in figure 5.7, which yielded a close resemblance between the outcome of the AP paradigm and the average of the outcomes for anodic- and cathodic-first stimuli with the forward masking paradigm.

Recently, forward masking has been used in a number of different ways in the literature, each with its specific application area. The details of the recording (e.g. the number of frames involved and the choice of the M and P electrodes) are also specific for each application. In our laboratory the need was felt to develop a uniform and unambiguous nomenclature for the whole class of paradigms involving

M and P stimuli. The ''standard'' artefact rejection method as used since the early 1990s[6] involves three frames and is called the MP3 method. The ''modified forward masking artefact reduction scheme'', as proposed by Miller et al.[12] to determine the refractory properties of the auditory nerve, involves four frames and is called the MP4 method in our nomenclature. Selectivity measurements with the M and P on different electrodes[13,14] currently implemented in the NRT3 software (Cochlear Corp., Sydney, N.S.W.) are designated sMP3, reflecting the three frames involved. The compensation method used in the present study is applicable to each of the artefact rejection schemes discussed above. Theoretically, it has an additional advantage at higher stimulus levels, where recording of the N_1 peak is apparently difficult with current clinical implants. With both the CII Bionic Ear (Advanced Bionics Corp., Sylmar, CA)[3] and the CI24M (Cochlear Corp.)[8] the MP3 paradigm yielded responses with a steep slope and a barely discernible N_1 peak at higher stimulus levels. With our compensation method the shape of the N_1 peak was not influenced by the stimulus level, even with stronger stimuli. Of course this observation in guinea pigs has to be verified in humans.

Similarly, the new method has advantages for recording electrodes in the vicinity of the stimulating electrodes. In the CII Bionic Ear there has to be at least one unstimulated contact between the stimulating and recording ones to prevent saturation of the amplifier[3], while a similar observation holds for the CI24M.[8] Closer proximity of the recording electrode to the stimulated neural population is likely to yield larger response amplitudes, but this is precluded by the stimulus artefact. Adding a compensation circuit to the input stage of the amplifier will eliminate this problem. We conclude that it is worthwhile to implement the compensation method proposed here in future NRT/NRI systems, as it has the potential to broaden the clinical applicability and reliability of eCAP measurements.

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