

**Deconvolution of overlapping cortical auditory evoked potentials recorded
using short stimulus onset-asynchrony ranges**

Fabrice Bardy MClin Aud^{1,2,3}

Bram Van Dun PhD^{2,3}

Harvey Dillon PhD^{2,3}

Catherine M McMahon PhD^{1, 2}

¹ Department Linguistics, Macquarie University, NSW, Australia.

² HEARing Co-operative Research Centre, Australia

³ National Acoustic Laboratories, NSW, Australia

Correspondence to:

Fabrice Bardy

Australian Hearing Hub

16 University Avenue

Macquarie University NSW 2109 Australia

P +61 2 94 12 68 14

F +61 2 94 12 67 69

Email: Fabrice.Bardy@nal.gov.au

Highlights

- The Least-Squares (LS) deconvolution can effectively disentangle overlapping cortical auditory evoked potentials (CAEPs).
- The CAEP is sensitive to the frequency of the stimulus, the length of the stimulus onset-asynchrony (SOA), and the mode of presentation (fixed or alternating).
- The deconvolution of CAEPs using short SOAs in a paired paradigm provides information about the balance of cortical excitation and inhibition for rapidly presented stimuli.

Keywords

- Electroencephalography
- Least-squares Deconvolution
- Cortical auditory evoked potential
- Stimulus onset-asynchrony
- Alternating stimulus frequency

Abstract

Objective: The first aim of this study is to validate the theoretical framework of Least-Squares (LS) deconvolution on experimental data. The second is to investigate the waveform morphology of the cortical auditory evoked potential (CAEP) for five stimulus onset-asynchronies (SOAs) and effects of alternating stimulus frequency in normally hearing adults.

Methods: Eleven adults (19 - 55 years) with normal hearing were investigated using tone-burst stimuli of 500 and 2000 Hz with SOAs jittered around 150, 250, 450, and 850 ms in a paired-interval paradigm with fixed or alternating stimulus frequency.

Results: The LS deconvolution technique disentangled the overlapping responses, which then provided the following insights. The CAEP amplitude reached a minimum value for SOAs jittered around 450 ms, in contrast with significantly larger amplitudes for SOAs jittered around 150 and 850 ms. Despite this, longer latencies of N1 and P2 consistently occurred for decreasing SOAs. Alternating stimulus frequency significantly increased the amplitude of the CAEP response and decreased latencies for SOAs jittered around 150 ms. Effects of SOAs and alternating stimuli on CAEP amplitude can be modelled using a quantitative model of latent inhibition.

Conclusions: LS deconvolution allows correction for cortical response overlap. The amplitude of the CAEP is sensitive to SOA and stimulus frequency alternation.

Significance: CAEPs are emerging as an important tool in the objective evaluation of hearing aid and cochlear implant fittings. Responses to closely spaced stimuli provide objective information about integration and inhibition mechanisms in the auditory cortex.

Introduction

Cortical Auditory Evoked Potentials (CAEPs), also called “late latency AEPs” provide valuable information about the integrity of the auditory pathway up to the auditory cortex.

Measurement of CAEPs is increasingly used for objective clinical audiometry or to objectively assist with the fitting of hearing aids in infants and incapacitated adults (Billings et al., 2012, Dillon, 2005, Lightfoot et al., 2006, Ross et al., 2000).

The waveform morphology of CAEPs obtained for stimulus onset-asynchronies (SOAs) between 0.5 and 10 s is well reported in the literature. In normal hearing adults, this waveform morphology is characterised by the P1-N1-P2 complex occurring between 30 and 260 ms after stimulus onset (Alain et al., 2007). Many studies to date have focused on the effect of SOA change in the adult CAEP waveform, using a constant interval between stimuli (fixed SOA) and a single stimulus frequency (rather than interleaved stimuli). Generally, for SOAs greater than 500 ms, increased amplitude of the neural response is observed as the SOA extends to at least 10 s with minimal change to waveform latencies (Davis et al., 1966, Sussman et al., 2008, Tremblay et al., 2004, Zacharias et al., 2012a). Using a conventional averaging technique, only a few studies have investigated the CAEP characteristics for short SOAs. Down to 300 ms, these studies have generally shown reduced amplitudes and prolonged latencies with a decreased interval between stimuli (Davis et al., 1966, Sussman et al., 2008). Such changes are highlighted by Sussman et al. (2008). Using adult participants, it was shown that with an SOA decrease from 800 to 400 ms for tone bursts 50 ms in duration, a progressive suppression in N1 peak amplitude and increase in P1 and P2 latencies occurs. Likewise, based on data collected from younger adults, Tremblay et al. (2004) reported similar amplitude reductions of the P1-N1-P2 response and small N1 and P2 latency increases as the SOA was reduced from 1690 to 700 ms for a speech stimulus (/pa/) and tonal stimulus (1000 Hz) with 180 ms duration.

Interestingly, in a recent study focussing on the N1m recorded with magnetoencephalography (MEG), Zacharias et al. (2012a) report that stimulation history had a important influence on the amplitude of the auditory response. They indicate that the amplitude of the response in the random design was influenced by both the immediately preceding SOA and the time intervals between all other preceding stimuli. Further, the strength of the response was more affected if the SOA was fixed compared to a sequence where SOAs occurred in a pseudorandom order. In the fixed presentation mode, the response asymptoted to a value, whereas in the random design the response amplitude varied more widely. On the basis of these findings, the authors developed the “transient reduction of excitability” (TREX) model which accounts for the N1m amplitude changes after preceding stimuli.

The high temporal resolution of electroencephalography enables the neural processing of rapidly presented acoustic stimuli to be investigated. However, the recording of auditory evoked potentials (AEPs) at fast presentation rates is not commonly used as the neural responses overlap when the response length is longer than the interval between two stimuli (Ozdamar et al., 2006). For SOAs shorter than 300 ms, the utilisation of normal averaging techniques show that the CAEP waveform characteristics change dramatically due to the overlap of two cortical responses, thereby complicating the interpretation of results (Durrant, 2007, Sable et al., 2004, Sussman et al., 2008).

The few studies investigating CAEPs using a correction technique for overlapping responses for short SOAs, have used the level 1 Adjacent Response (ADJAR) technique (Woldorff, 1993). Level 1 of ADJAR is a non-iterative process which corrects for the immediately preceding or following response by subtracting the best estimate of the response to the first stimulus from the overlapped response (Fox et al., 2010, Sable et al., 2004, Wang et al., 2008). One of the main limitations of this method is the wide SOA range needed to make an

accurate estimation of the correct undistorted waveform. Budd et al. (1994) used this method in a design which included a large SOA jitter and derived the CAEP morphology for different SOA ranges. Another study using paired paradigms implemented ADJAR level 1 to investigate the cortical response elicited by the second stimulus of the pair using short SOAs (Fox et al., 2010). A consensus among the findings of these studies was that the N1 amplitude increased with SOAs shorter than 400 ms. Similar results using the same method have also been reported with the corresponding magnetic component, the N1m (Loveless et al., 1996).

When response overlap occurs, the goal of the deconvolution is to recreate the response as it existed before the convolution of the response and the stimulus timing took place. The deconvolution technique, which is described and validated in an accompanying paper, is based on a combination of mathematical concepts of deconvolution and least squares (LS). The LS deconvolution can only be performed if the stimulus sequence is jittered and known for processing of the continuous EEG file.

There are two main assumptions underlying the use of the LS deconvolution technique. The first assumption is that the overlapping responses correspond to the linear superimposition of the cortical responses time locked on the stimulus sequence (Burger et al., 2009). The second is that the morphology of the response to a succeeding sound is identical in one jitter range. In other words, the system is considered to be time-invariant within each SOA range tested. The ability to apply the LS deconvolution with a restricted jitter range is its major advantage over ADJAR.

In this study, we investigated the adaptation of the cortical response in adults with normal hearing, used a paired paradigm generated by tone-burst stimuli presented with short SOAs and alternating or non-alternating frequencies. The use of the Least-squares (LS) deconvolution optimizes the recovery of the overlapping CAEPs by minimizing residual

errors. Finally, we implemented a physiological model recently developed by Zacharias et al. (2012a) that supports a latent inhibition principle for the increase of the response amplitude for SOAs shorter than 450 ms.

Hypothesis

The first hypothesis is that the LS deconvolution technique can disentangle overlapping CAEPs recorded in normal hearing adults. The second hypothesis is that the CAEP generated by the second stimulus of the pair will be influenced by the SOA between the two stimuli of the pair. The third hypothesis is that pairs with changing stimulus frequencies will evoke CAEPs larger than pairs with the same stimulus frequencies, and that the increase will be largest for the shortest SOAs.

Methods

The theoretical framework developed and presented in an accompanying paper, which disentangles multiple overlapping responses, was applied to recover CAEPs recorded in a paired tone-burst paradigm including very short SOAs.

Subjects

Eleven healthy participants (6 females and 5 males; ages ranging from 19 to 55 years; mean 29 years 5 months; SD 10 years 3 months) with normal hearing, and no history of hearing difficulty or neurological disorder, participated in the study. Written informed consent was obtained from participants and the study was approved and conducted under the ethical supervision of the Australian Hearing Human Research Ethics Committee and the Macquarie University Ethics Review Committee.

Stimuli

The auditory stimuli used in this experiment were two tone-burst stimuli with frequencies of 500 and 2000 Hz with an intensity of 50 dB nHL presented binaurally. These tone-bursts were 50 ms in duration with a 10 ms rise-fall time to minimize spectral splatter. Stimuli were acoustically calibrated in an HA-2, 2-cc coupler using a Brüel & Kjaer 4230 sound level meter. MATLAB (Mathworks) was utilized to create the sequence file and Neuroscan Stim2 (Compumedics) to present the stimuli.

The auditory stimuli were presented in a paired-stimulus paradigm. The stimulus onset-asynchrony (SOA) of each stimulus pair was selected from four different ranges. These SOA ranges were labelled by their geometric SOA mean (SOA150 = 120-190 ms; SOA250 = 190-330 ms; SOA450 = 330-610 ms; SOA850 = 610-1170 ms). Sequence optimization was not required in this specific experimental design given that the investigated overlap is always only composed of two responses. Each stimulus pair was separated by an inter-pair interval randomly selected from 1120 to 2240 ms (SOA1650). As stated before, the introduced SOA jitter is a prerequisite to allow a solution for the matrix algebra of the LS deconvolution method.

Both a fixed and alternating presentation mode were investigated (see Figure 1). In the fixed presentation mode, the stimulus frequency was fixed at 500 Hz in Run 1 and at 2000 Hz in Run 2. In the alternating presentation mode, the two stimuli of the pair had different frequencies. In Run 3, the 500 Hz stimulus was in first position and the 2000 Hz stimulus in second position of the pair. In Run 4, the positions were reversed.

For the four runs of the experiment, the SOA distributions were rectangular within each SOA range with a SOA step size of 13.3 ms. All SOA ranges had the same time length of presentation which implies that the number of stimulus pairs depended on the SOA range. It allowed for:

- 110 stimulus pairs for SOA ranging between 610 and 1170 ms (SOA850);

- 132 stimulus pairs for SOA ranging between 330 and 610 ms (SOA450);
- 143 stimulus pairs for SOA ranging between 190 and 330 ms (SOA250);
- 152 stimulus pairs for SOA ranging between 120 and 190 ms (SOA150);

According to the properties of signal averaging, a larger number of presentations for the short SOA ranges lead to a slight signal-to-noise ratio (SNR) increase. These differences do not affect the results and conclusions of this study. The duration of each run was approximately 17 minutes. The run's order for each subject was quasi-random using a Latin square design (Bradley, 1958). Recordings were obtained over a period of approximately 2 hours each for the test and retest conditions, with a lunch break in between.

Data acquisition

The electroencephalograms were obtained with Neuroscan Synamps2 version 4.3 (Compumedics) by placing six gold-plated electrodes onto the subject's head. The International 10-20 system (Roger, 2007) was used with electrodes placed at vertex midline (Cz), the left (C3) and right (C4) hemispheres, at the right (M2) and left (M1) mastoids and one on the forehead (Fpz) to act as ground.

Prior to the placement of electrodes, the subject's skin was prepared using NuPrep EEG abrasive skin prepping gel. Water-soluble electrode paste was used to ensure a good connection between electrodes and skin and to achieve low impedance of less than 5 k Ω across all electrode sites. During testing, the subjects were sitting comfortably in a dimmed, sound attenuated booth, while the tone-burst stimuli were delivered through insert earphones (Etymotic ER-3A). The participants watched a muted close-captioned DVD of their choice and were instructed not to pay attention to the stimulus.

Data Analysis

For the purpose of this paper, latency and amplitude measurements were analyzed at the vertex midline (Cz) referenced to the right mastoid (M2) as the CAEP amplitude in this site is the largest (Hall, 2007).

All EEG channels were amplified with a gain of 2010, digitized at a sampling rate of 1000 Hz, and online bandpass filtered between 0.01 and 30 Hz. All epoched files were exported to MATLAB for off-line processing. The signal processing on the raw EEG files was partly conducted using EEGLAB (Delorme et al., 2003). For artefact rejection, epochs composed of a pair of stimuli with signal in excess of $\pm 50\mu\text{V}$ were excluded. The EEG files were offline bandpass filtered between 3 and 15 Hz using a zero-phase filter. An epoch of 500 ms (100 ms pre- and 400 ms post-stimulus onset) was used for the study. The CAEP generated by both the first and second stimulus of each pair, for SOAs jittered around 150 ms, 250 ms, 450 ms and 850 ms, were recovered using LS deconvolution

P1, N1 and P2 peak latencies and amplitudes were visually identified. These amplitudes and latencies were then averaged to obtain means and standard errors based on the eleven subjects. The overall magnitude of the CAEP was also expressed as the root mean square (RMS) in a response window from 0 to 300 ms after onset.

Statistical Analysis

Repeated measures ANOVAs were performed in a $5 \times 2 \times 2$ design on the recovered waveforms. The independent variables were 5 SOA conditions (150 ms, 250 ms, 450 ms, 850 ms, and 1650 ms), 2 stimulus frequencies (1000 Hz and 2000 Hz), and 2 modes of presentation (fixed or alternating). The ANOVAs were performed on the absolute amplitudes of peak P1, N1 and P2, the RMS amplitude, and the absolute latency of peak P1, N1 and P2. Greenhouse-Geisser corrections for sphericity were applied, as indicated by the cited ϵ value. Post-hoc comparisons were calculated using Tukey's test (Keselman, 1998, Park et al., 2009). All statistical analyses were conducted using Statistica 7.1 (StatSoft, Inc.).

The inter-class correlation coefficient (ICC)

Inter-class correlation coefficients (ICC) were calculated between waveforms elicited by the first stimulus of the pair for each SOA range. The ICC provides an objective global index of the similarity of amplitude and shape between the two waveforms. An ICC Case label 1 using an absolute agreement definition described by McGraw et al. (1996) was calculated. The ICC becomes 1 when there is perfect agreement whereas a smaller value represents lower similarity between two waveforms. This measure allows evaluation of the influence of the duration of the succeeding SOA on the morphology of the cortical response of the first stimulus of the pair (for the SOA ranges 150, 250, 450, and 850 ms).

Results

Overlapping cortical auditory evoked responses

Figure 2 presents the CAEP grand averages elicited by the two tone-bursts of the pair with SOAs jittered around 150 ms. This is shown for the 4 different runs, before correction (dashed line) and after correction (solid line) using LS deconvolution. The uncorrected waveform for each run illustrates the problem of overlapping responses when the time interval between the stimuli of the pair (i.e. SOA) is shorter than the CAEP response length. In the uncorrected waveform, averaging overlapping responses in the presence of 70 ms jitter (120-190 ms) works as a low-pass filter of about 14 Hz ($=1000/70$), reported previously by Woldorff (1993). Hence, jittering only cancels the high frequency components of the overlapping response. The frequency of the slowest dominant wave of the CAEP is smaller than 14 Hz. Therefore, clear overlapping responses are still observable. For example, the late portion of the uncorrected waveform of the 1st tone-burst of the pair still contains the response to the second tone-burst. Similarly, the baseline and early portion of the response to the second stimulus of the pair is contaminated by the late portion of the response of the 1st tone-burst. This example shows the

complications to label, characterise and interpret the amplitudes and latencies of the components of the response and the need to apply a correction technique. The difference between the uncorrected and corrected waveform shows the effect of the LS deconvolution. Waveform morphology and statistical analysis of the corrected waveform are reported later in this paper.

Intra-class correlation coefficient (ICC) analyses

For each subject, the similarity of the CAEP (evoked by the first stimulus of the pair) for each of the four different SOA ranges was investigated by calculating the ICC over the 0-350 ms time interval. The same calculation was then made on the waveform grand average over all subjects (again amongst those four SOA ranges). The subjects' ICC means and standard deviations, and the ICC of the waveform grand average are summarized in Table 1.

A general observation is that the high ICC for the grand mean waveform for all runs (≥ 0.95) are minimally affected by variation in the succeeding SOAs, which indicates that CAEPs were elicited in response to the first stimulus of the pair. The lower value of the ICC subject means is mainly due to a poor SNR within certain subjects. When the waveform contains significant random noise, the level of similarity is affected. These findings can also be visually confirmed in Figure 3, which shows similar responses to the first stimulus of a pair over all four SOA ranges plus the grand average, which includes all four runs. After application of the LS deconvolution to disentangle overlapping waveforms, the morphology of the cortical response of the first stimulus of the pair did not appear to be influenced by the presence of the second stimulus of the pair. For this reason, the CAEP average over the four SOA ranges in response to the first stimulus of the pair was used in the statistics as the 1650 ms preceding SOA condition.

Cortical components analysis after overlap correction using LS deconvolution

Figure 4 shows the grand averages from all 11 subjects for the four runs (500 and 2000 Hz, fixed and alternating), and five different SOA ranges (150 to 1650 ms). Results for the amplitudes and latencies of the 3 components P1, N1, and P2, as well as the CAEP RMS amplitudes are reported below in more detail. The statistics are reported in Table 2.

P1 component

It is important to note that of the three components, P1 has the lowest amplitude. The P1 peak can therefore more easily be contaminated by noise. Repeated measures ANOVA showed a significant main effect of the SOA on the amplitude of the P1 component (Table 2). Moreover, post-hoc comparisons revealed a trend of gradual growth of the amplitude of P1 while reducing the SOA from 1650 to 150 ms (see Figure 5, top).

Regarding the P1 latency, repeated measures ANOVA revealed a significant main effect of the SOA and stimulus (Table 2), as well as a significant interaction between the factor mode of presentation (fixed versus alternated) and the stimulus (500 Hz versus 2000 Hz) ($F(1,10) = 5.51$; $p = 0.04$; $\epsilon = 1$). No statistically significant differences between the different conditions were found in the post-hoc comparisons (Figure 6, top).

N1 and P2 components

The repeated measures ANOVA on the absolute amplitude and latency of N1 and P2 showed a significant main effect of the stimulus, the mode of presentation, and the SOA, except for P2 latency where the effect of the stimulus was not significant. Interestingly, based on the mean values, the minimum absolute amplitude for N1 and P2 components for every condition was reached for either the 250 or the 450 ms SOA range (see Figure 5, middle and bottom). Concerning the latency of N1 and P2 components, post-hoc comparisons showed a trend of gradual latency increase with a decrease of the SOA range. Significant post-hoc comparisons ($p < .05$) are reported in Figure 6 (middle and bottom).

Post-hoc comparisons for the two modes of presentation revealed significant increases of N1 and P2 absolute amplitudes in the alternating mode compared to the fixed mode in 6 of the 12 conditions within the three shortest SOA ranges (Figure 5, middle and bottom). Post-hoc comparisons also showed three conditions with a significant reduction of N1 and P2 latencies in the alternating presentation mode compared to the fixed presentation mode. These results suggest less adaptation of N1 and P2 generators in the alternating presentation mode for short SOA ranges. The significant planned comparisons are again shown in Figure 6 (middle and bottom).

Finally, post-hoc comparisons revealed significant larger P2 amplitudes for the tone-burst with a frequency of 500 Hz in comparison to the 2000 Hz tone-burst in the fixed presentation mode for SOA ranges 850 and 1650 ms (Figure 5, bottom).

CAEP RMS Value

The RMS value of the CAEP is convenient to investigate the global cortical response amplitude variation. Repeated measures ANOVA showed a significant main effect of the stimulus, the mode of presentation, and SOA on the CAEP RMS calculated over the 0 to 300 ms window (Table 2). Post-hoc comparisons revealed significantly larger amplitudes in the alternating presentation mode for the tone-burst with a frequency of 500 Hz for the 250 and 450 ms SOA ranges, as well as for the 2000 Hz tone-burst for the 150 and 450 ms SOA range (Figure 7).

Post-hoc comparison of the different SOAs showed a significant decrease of the CAEP RMS amplitude for the 2000 Hz tone-burst stimulus between the SOA ranges 150 and 450 ms (Figure 7). This trend was not significant for the tone-burst stimulus with a frequency of 500 Hz. Conversely, a significant increase of the RMS amplitude was found between the SOA ranges 450 and 1650 ms for the 500 Hz tone-burst stimulus (Figure 7).

The ANOVAs revealed significant interactions between the factors of SOA and stimulus for the RMS amplitude ($F(4,40) = 6.76$; $p = 0.0006$; $\epsilon = 1$).

Simulation using the “transient reduction of excitability (TREX) model”

The average RMS amplitude of the two tone-burst stimuli was calculated for the fixed and alternating presentation and is represented in Figure 8. The RMS amplitude in the 0-300 ms window, which contains activity from the P1-N1-P2 complex, reaches a minimum value when the SOA range is jittered around 450 ms.

Zacharias et al. (2012a) developed the TREX model which reflected the importance of history of stimulation on the amplitude of the N1m response. The model succeeds in reliably predicting responses in both random and fixed presentation rates in their study, utilizing SOAs between 250 ms and 10 s. Their study quantifies the size of the cortical response in regard to the timing characteristics of the stimulation sequence. The TREX model has 7 parameters, including two time constants for the reduction in excitability and for the recovery, in addition to two delay parameters. Another primary parameter of the model is the initial number of excitable neurons which gives rise to the amplitude of the neural response.

Previous studies reporting findings for the amplitude of the N1 component were partly interpreted using the physiological model of latent inhibition stating that there is a temporal lag after stimulus onset for the inhibition to be effective (Loveless et al., 1996, McEvoy et al., 1997, Sable et al., 2004). The analogy to the latent inhibition model in the TREX model stands on the lag $\Delta\tau_a$ after stimulus onset, before decay of the population of excitable neurons. This interval can be taken as the timing needed before inhibition becomes fully effective.

At greater delay after onset, the temporal evolution of the population of excitable neurons is described by the sum of two exponentials. The first is a fast exponential component corresponding to the decrease in excitability (alteration of the percentage of neurons capable of firing), while the second slow component represents the recovery. The amplitude of the

cortical response is thus related to the number of excitable cortical neurons available at a certain point in time, which is dependent on the history of stimulation. The last parameter of the model accounts for the effect of stimulus alternation on response amplitude. It is expressed as the degree of overlap of cortical neuronal population when stimuli of different frequencies are used (Zacharias et al., 2012b).

As represented in Figure 8, there is good agreement between the amplitude measured in our experiment and the amplitude predicted by the TREX model. We used the model parameters deduced by Zacharias et al. (2012a) for both the fixed and the alternating presentation mode (Fixed Conditions: $R^2=0.90$; Alternating condition: $R^2=0.99$). The good fit between the experimental data and the model suggests that the lag of inhibition with respect to excitation in the TREX model is sufficient to describe the relationship between SOA-history and cortical response amplitude. The initial number (pool) of excitable neurons was adjusted to fit our data to the fixed condition and set to 7.8 in order to generate a response amplitude measured in μV . The parameter accounting for overlap was then adjusted to fit the alternating condition. In this paradigm, where the frequencies of the two stimuli (500 Hz and 2000 Hz) were systematically alternated, the best fit was obtained when the overlap parameter was set to 80%. Such a model is not only useful for predicting future experimental results, but also for understanding how the auditory cortex transforms its input into neuronal activity. It indicates the applicability of the model of latent inhibition when short SOAs are separating pairs of stimuli. However, further investigation is needed to explore whether the model can successfully predict response amplitude when more than two stimuli are separated by short time intervals.

Discussion

The main purpose of this study was to present experimental data using the theoretical framework of LS deconvolution described in an accompanying paper on overlapping cortical responses obtained by stimuli presented at short SOAs. This new analysis technique allows the extraction of overlapping AEPs in response to sequences composed of multiple stimuli, and optimizes the solution by minimizing the sum of squares of the errors. This study allows the validation of the technique for CAEPs generated by two tone-burst stimuli using five SOAs and two modes of presentation.

Experimental application of the deconvolution on CAEPs

This study demonstrates that it is possible to separate temporally superimposed components of CAEPs generated by the first and the second tone-burst of a pair. Moreover, it allows for the investigation of changes in CAEP morphology for different timings between the two stimuli of the pair. Firstly, we found that the CAEP elicited by the first stimulus of the pair, which was systematically preceded by an SOA range of 1650 ms, was not affected by the succeeding SOA, despite varying across four ranges from that centred around 150 ms to that of 850 ms. Over the four SOA ranges, the similarity in the morphology of the cortical waveform was noticeable both by visual inspection and by computing the ICC on the grand average waveform (≥ 0.95) (see Figures 3 and 4). These results show that the second stimulus of the pair does not appreciably affect the morphology of the CAEP generated by the first, even where response overlap occurs. Thus, any interaction is confirmed to be an effect of stimulus 1 on the response elicited by stimulus 2.

Effect of Stimulus Onset-Asynchrony

After correction for response overlap, one of the interesting findings in this study is that the overall CAEP amplitude, characterised by the RMS amplitude, reaches a minimum for the 450 ms SOA range before rising again for shorter or longer SOA ranges. In contrast, the

latencies of the N1 and P2 components of the cortical response steadily increase with a decrease of the SOA from 1650 to 150 ms.

A decrease of the cortical amplitude associated with an increase of the presentation rate is well described in the literature for responses recorded with fixed SOA larger than 500 ms (Davis et al., 1966, Picton et al., 1978, Sussman et al., 2008). The amplitude decays of the response have been fitted previously by the exponential equation $P(1 - e^{-(t-t_0)/\tau})$, where P , τ and t_0 are respectively representing amplitude, time constant and time of decay onset (Näätänen et al., 1981). Within the field, the effects of the SOA on the CAEP have been reported with different defining terms including habituation, refractoriness, lateral inhibition and sensory gating. To date there is no consensus about which physiological mechanisms explain these results. However, this study shows that SOA affects response amplitude when randomised across a wide range (70 to 2240 ms). As demonstrated by Zacharias et al. (2012a) and by the good fit of the TREX model to our data, the variation of the amplitude of the cortical response is both affected by the immediately preceding stimuli, as well by the long-term history of stimulation which induces habituation. In this study, using a paired tone-burst paradigm, we have used the term “inhibition” to characterise the change of CAEP amplitude for varying SOAs because we have used a latent inhibition model to model our data.

Much less is known about the morphology of the cortical waveform for cases where SOAs are less than 500ms and responses are overlapping. Available studies have reported results on only the N1 component (Budd et al., 1994, Fox et al., 2010, Sable et al., 2004, Wang et al., 2008). Each of these studies have used a single repeated sound and have analyzed their data using the “ADJAR” level 1 method (Woldorff, 1993) to separate the responses. Three different paradigms were used in these studies, all of which showed an increase in N1 amplitude with reducing SOAs (shorter than 400ms). In the first stimulus paradigm, the SOA

jitter was large (900 ms) and positioned randomly in the sequence. Budd et al. (1994) and Wang et al. (2008) used tone-burst stimuli (30 ms duration) presented with SOAs randomly distributed between 70 and 970 ms with tone-burst frequencies of 1000 Hz and 800 Hz respectively. The ADJAR technique was used to disentangle the overlapping responses.

In the second stimulus paradigm, stimuli were presented in pairs, leading to a temporal overlap of the cortical auditory responses (Fox et al., 2010, Loveless et al., 1989). Fox et al. (2010) used stimuli of the same frequency (1000 Hz tone-bursts, 20 ms duration) presented with different unjittered SOAs (45 ms, 70 ms, 170 ms, 270 ms, 470 ms, 870 ms). The inter-pair interval was fixed at 2 s and the SOA between the pairs was randomly assigned. In the third stimulus paradigm, Sable et al. (2004) used short sequences of five tones harmonically enriched (50 ms duration) presented at fixed presentation rates (SOA: 100 ms, 200 ms, 300 ms, 400 ms) with 4 second intervals between each sequence and evaluated changes in N1 peak amplitude for the second stimulus of the sequence. All three paradigms demonstrate that N1 peak amplitude increases as SOAs decrease (< 400ms) when the stimulus sequence contains a large amount of SOA variation.

The present data suggest that active inhibition is maximal for SOA ranges jittered around 250 or 450 ms. However, statistical analysis shows different behaviours for the three components of the cortical response. First, the absolute amplitude of the P1 component steadily increased when the SOA was reduced from 1650 to 150 ms. The enhanced amplitude of the P1 component for the short SOA range might possibly reflect a neural facilitation process for acoustic stimuli occurring shortly after another stimulus which itself is preceded by a relatively long silence. The P1 component can, however, be difficult to identify due to its low signal amplitude and further studies using a larger number of presentations to increase the SNR of this component are needed to confirm this trend. Second, the magnitude of the N1 component reached a minimum value for the SOA condition of 250 ms in 3 out of the 4

stimulus conditions before increasing for the 150 ms SOA range (Figure 5, middle). Finally, the magnitude of the P2 component was minimal in the 450 ms SOA condition (Figure 5, bottom). These results suggest that, for closely spaced stimuli, each component of the cortical response is separately modulated by the underlying excitatory and inhibitory processes.

The physiological mechanisms underlying the response increments with fast presentation rates of the stimuli are not yet completely understood. Enhanced neural responses for pairs of stimuli have previously been observed in single- and multi-unit recordings in the auditory cortex of lightly anaesthetised macaque monkeys (Brosch et al., 1999). Budd et al. (1994) proposed a “special facilitatory activity” for very short SOA ranges occurring in the primary auditory cortex, to explain the N1 amplitude enhancement. In contrast, Fox et al. (2010) and Sable et al. (2004) refer to an alternative model to explain their data, based on the concept of latent inhibition which was originally proposed by McEvoy et al. (1997). According to the latent inhibition model, the enhancement of the N1 amplitude occurs in the short period of time after stimulus onset; as inhibitory interneurons become optimally active after 450 ms. Of note is the similar trend in our results for the P2 component originating from Heschl’s gyrus (Eggermont et al., 2002), which has not been reported previously.

Modeling of the SOA results

The TREX model presented by Zacharias et al. (2012a) was used to simulate the main effect of the SOA on the CAEP amplitude using the timing sequence of stimulation as input. This is the first study evaluating the fit of this model using short SOAs in a paired paradigm. A direct comparison of the predicted amplitude with the experimental data shows a good degree of agreement when using the simulation parameters derived by Zacharias et al. (2012a). This was demonstrated in Figure 8 where the RMS response amplitude (dashed line) is plotted with the model fitted responses (diamonds and circles) for both the fixed and alternating

presentation mode. The temporal lag of inhibition with respect to excitation is modelled here by delay $\Delta\tau_a$ and accounts for the latent inhibition model. The results of the simulation show a similar minimum RMS amplitude for the SOA jittered around 450 ms for both presentation modes. These findings suggest that an event-based model, such as “TREX” where the potential pool of neurons available to fire is the sum of two exponentials, can be an efficient way to simulate the amplitude of the cortical response as a function of temporal history of the auditory stimulation. More generally, the results of the model are likely to reflect the balance of excitation to inhibition in the auditory cortex. An obvious advantage of this model concerns its simplicity using a limited number of parameters and its ability to predict CAEP amplitude under these conditions. Modelling the adaptation of each component of the CAEP was outside the scope of this study.

Effect of stimulus frequency

Another main observation was that a significantly larger CAEP measured for the lower frequency tone-burst stimulus (500 Hz) in comparison to the higher frequency tone-burst stimulus (2000 Hz). This amplitude difference is consistent with findings of previous studies (Jacobson et al., 1992, Näätänen et al., 1987, Picton et al., 1978) and has been explained on the basis of the tonotopic organisation of the human auditory cortex (Liégeois Chauvel et al., 2001, Pratt et al., 2009).

Effect of mode of presentation

Previous conclusions about CAEP morphology for short SOA ranges have, in general, been drawn from experiments using stimulus sequences composed of one stimulus. On the other hand, in this study, the stimulus frequency was systematically alternated, showing significantly larger response amplitudes. Using the physiological model of lateral inhibition proposed by McEvoy et al. (1997), the inhibition of the CAEP was greatest when the two

tone-burst stimuli were the same frequency, resulting in smaller amplitudes. The aptitude of the auditory cortex to inhibit sensory responses is considered to represent our ability to habituate to repeated irrelevant sensory information such as repeated stimuli (Elden et al., 2002, Grunwald et al., 2003). Conversely, varying the frequency of the stimuli can lead to the activation of different neural generators and a “dishabituation” pattern characterised by larger CAEP amplitudes. These results are in agreement with previous studies (Butler, 1968, 1972, Friesen et al., 2010, Herrmann et al., 2013, Näätänen et al., 1988, Picton et al., 1978), suggesting that the cortical response of the second stimulus of the pair received the greatest release from inhibition in the alternating mode. The RMS amplitudes of the cortical response for fixed and alternating presentation modes were generated by combining the results of the two stimuli with frequencies 500 Hz and 2000 Hz. Interestingly, a minimum absolute mean value can be observed for the 450 ms SOA condition for both presentation modes (see Figure 8). The effect of the mode of presentation was also modelled in the “TRES model” for the RMS amplitude using an overlapping parameter, which defines the proportion of common neurons firing depending on the frequency separation of the two stimuli (see Figure 8). The best fit to our data was obtained with an overlapping factor of 80% of the total neurons responding to the two stimuli, suggesting that only a small proportion of the neurones activated were frequency-specific.

Moreover, an interesting pattern may be seen in a qualitative comparison of the grand average waveforms generated by the two presentation modes for the shortest SOA ranges 150 and 250 ms. Firstly, the N1 component is narrower and larger in the alternating presentation mode. Secondly, the P2 component which was almost abolished in the fixed presentation mode seems to recover in the alternating presentation mode.

Previous studies investigating CAEPs for short SOA ranges have not reported latency variations. A striking point in this study is the significant decrease of the N1 and P2 latencies

in the alternating compared to fixed presentation mode for the SOA condition of 150 ms for the 500 Hz tone-burst. This finding is concordant with the statistical analysis showing an interaction between mode of presentation and SOA for both N1 and P2 latency. It may reflect increased fatigue of neural generators when stimulated repeatedly in the fixed presentation mode for SOA ranging between 120 and 190 ms.

Methodological consideration

The LS deconvolution used for the data analysis of CAEPs in response to stimuli presented with short SOAs is an extension of the time-domain deconvolution technique introduced by Delgado et al. (2004). The deconvolution process is only possible through the introduction of SOA jitter and the application of the LS optimization method by minimizing residual errors. The novelty in the method lies in the ability to recover individual responses for multiple stimuli and in the ability to use a small jitter range. It is important to note that the presence of interactions between responses, the non-linearity of the responses for different SOAs, and the presence of noise in the data can be limiting factors in achieving an accurate estimation of the CAEP by deconvolution.

Further investigations

This study has identified the feasibility of LS deconvolution in disentangling overlapping CAEPs measured using EEG. This method could be applied to the physiological problem of interpreting intra-cortical recordings of AEPs (Liégois Chauvel et al., 2001, Rosburg et al., 2004, Schönwiesner et al., 2008), and to clinical problems where rapid stimulus presentation has neuropsychological validity, such as in children with delays in developing spoken language (Choudhury et al., 2011).

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Figures

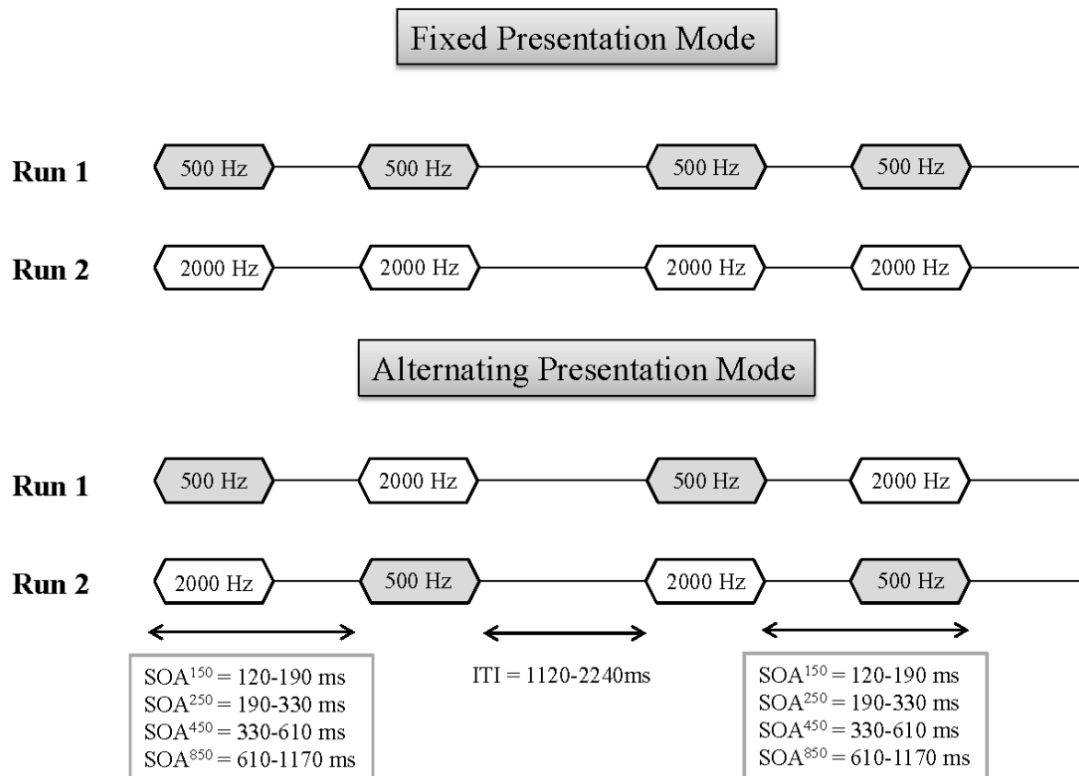


Figure 1. Schematic illustration of paired stimulus trains. All stimuli are tone-bursts, 50 ms in duration, and presented binaurally at 50 dB SL through insert earphones. In fixed presentation mode, the tone-burst has a frequency of 500 Hz in Run 1 and of 2000 Hz in Run 2. In alternating presentation mode, Run 3 uses a 500 Hz stimulus in the first position of the pair, whereas Run 4 has a 2000 Hz stimulus in the first position. The SOA within a pair was randomly assigned to one of four SOA ranges ($SOA^{150} = 120-190$ ms; $SOA^{250} = 190-330$ ms; $SOA^{450} = 330-610$ ms; $SOA^{850} = 610-1170$ ms). The inter-pair interval was randomly chosen from $SOA^{1650} = 1120$ to 2240 ms.

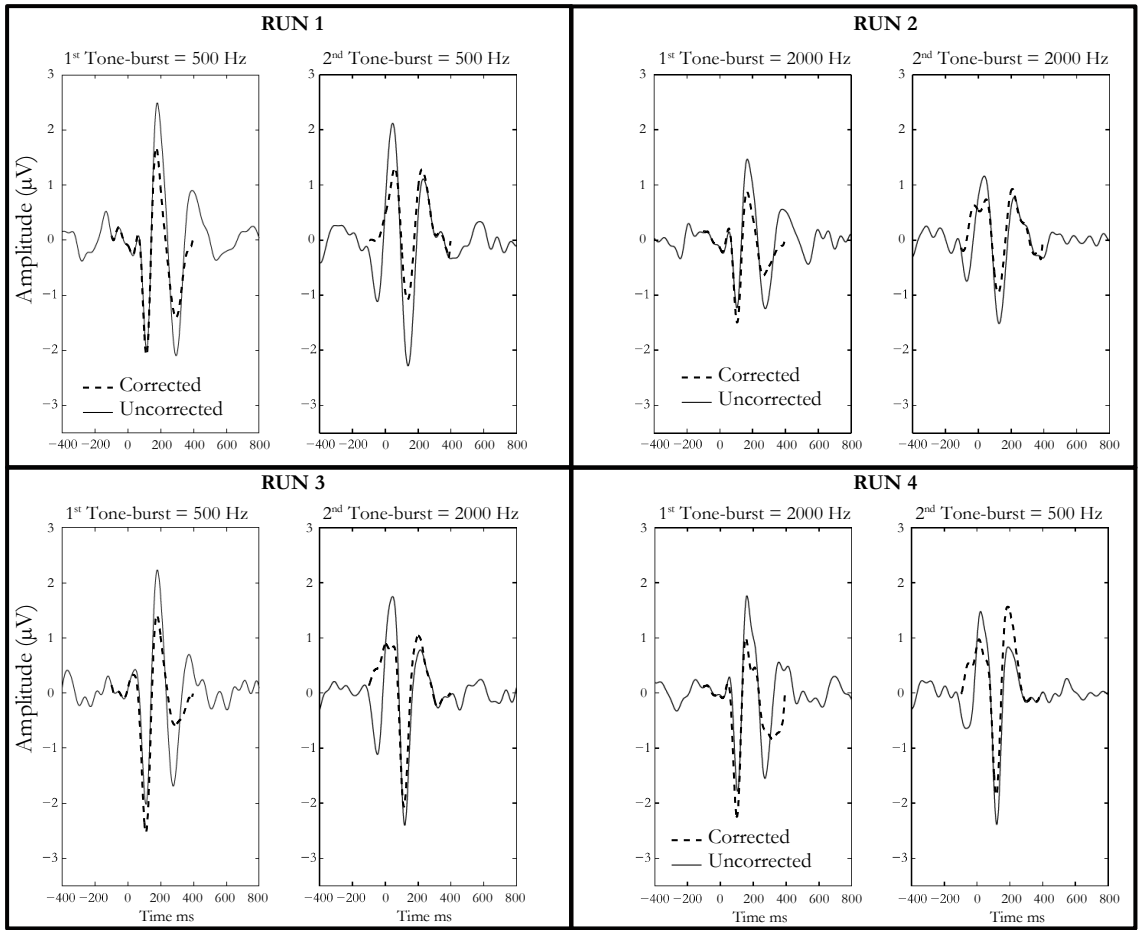


Figure 2. Corrected (dashed line) and uncorrected (solid line) grand average CAEP waveforms (n=11) in response to the tone-burst 500 and 2000 Hz in fixed or alternating presentation mode (represented in Figure 1) for a SOA within the pair jittered around 150 ms. The CAEPs were recorded at electrode positions Cz and M2.

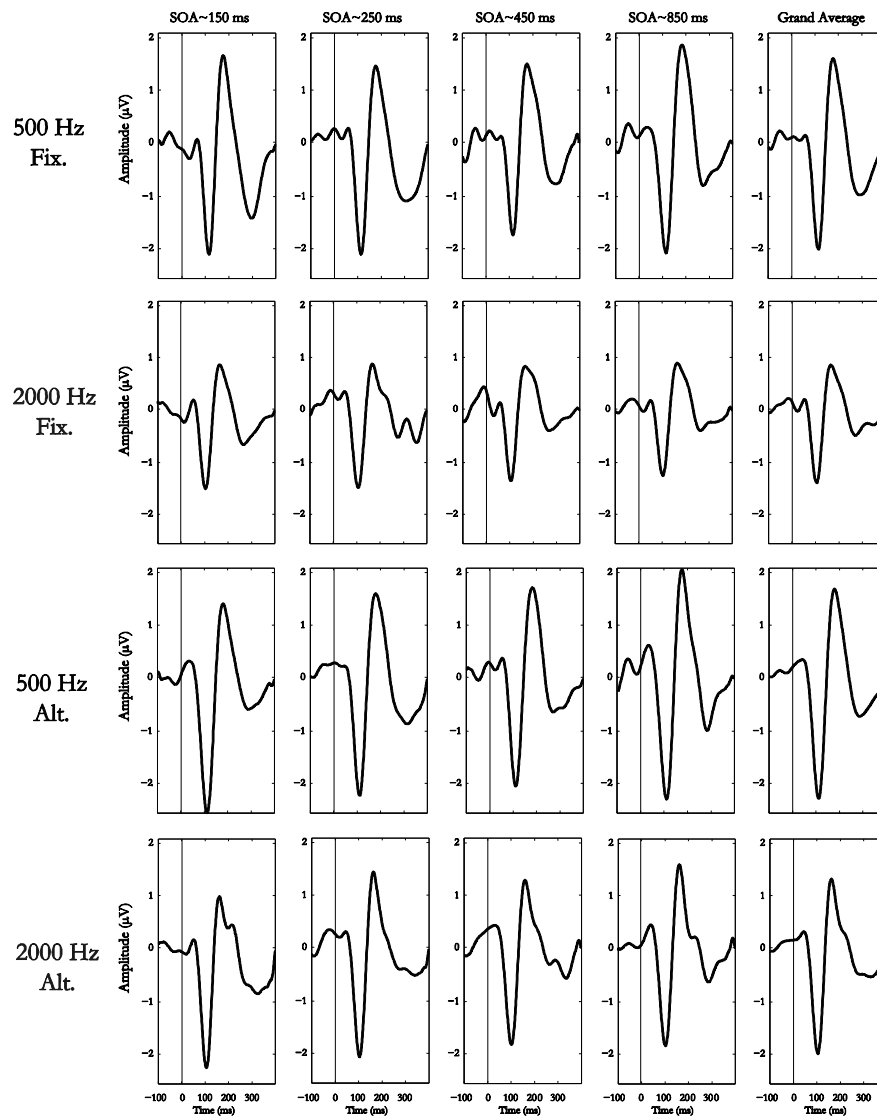


Figure 3. CAEP waveforms (n=11) generated by the first stimulus of the pair (always preceded by an SOA from the range 1120 to 2240 ms), recorded at electrode positions Cz and M2 for 500 Hz and 2000 Hz using fixed and alternating presentation modes for the four different succeeding SOAs, jittered around 150, 250, 450 and 850 ms. The grand average CAEP across SOA is displayed in the right column and labelled SOA~1650 ms.

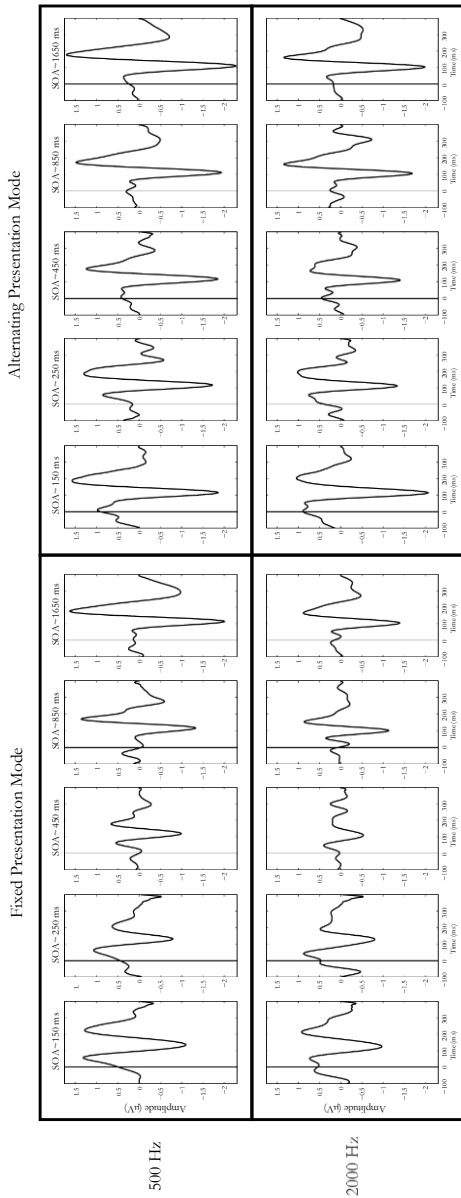


Figure 3.4 Grand average CAEP waveforms (n=11) recorded at electrode positions Cz and M2 for 500 Hz (upper graphs) and 2000 Hz (lower graphs) using fixed (left) and alternating (right) presentation modes for five different SOAs jittered around 150, 250, 450, 850 and 1650 ms. The three shortest SOA ranges were corrected for response overlap using LS deconvolution.

Figure 4. Grand average CAEP waveforms (n=11) recorded at electrode positions Cz and M2 for 500 Hz (upper graphs) and 2000 Hz (lower graphs) using fixed (left) and alternating (right) presentation modes for five different SOAs jittered around 150, 250, 450, 850 and 1650 ms. The three shortest SOA ranges were corrected for response overlap using LS deconvolution.

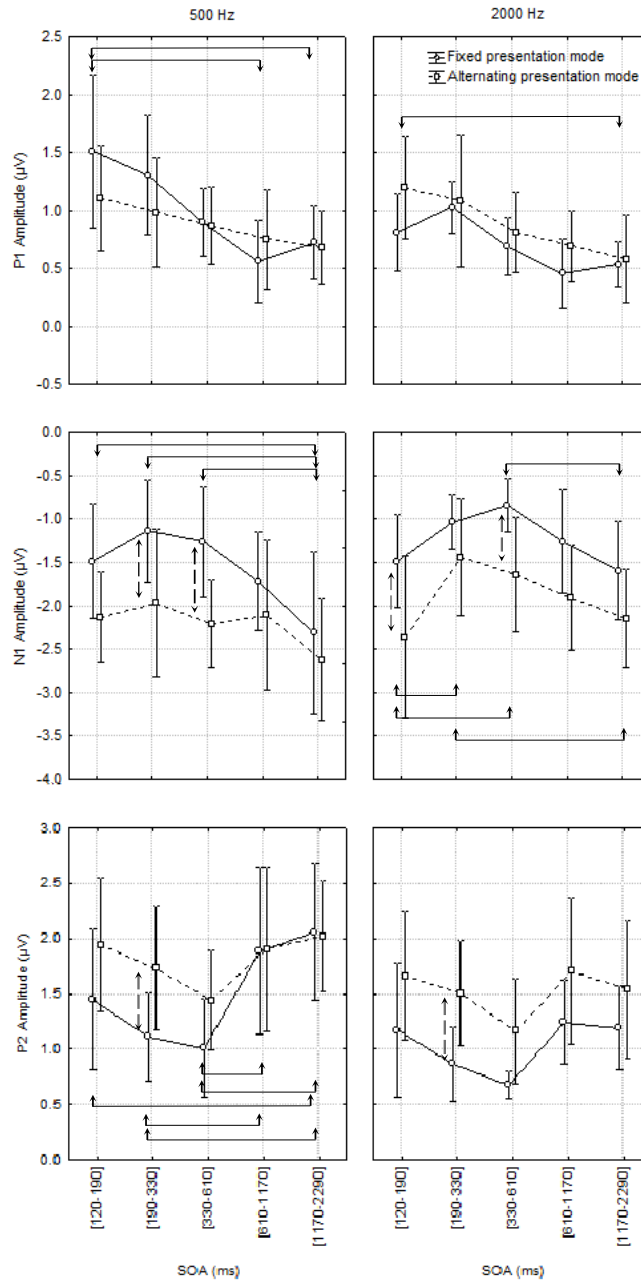


Figure 5. P1, N1 and P2 amplitudes of the CAEP recorded at electrode positions Cz and M2 using fixed (solid line) and alternating (dashed line) tone-burst stimuli with frequencies of 500 Hz and 2000 Hz for 5 SOA ranges: 120-190 ms, 190-330 ms, 330-610 ms, 610-1170 ms and 1170-2290 ms. Significant Tukey pair-wise comparisons are indicated ($p < 0.05$) by a double arrow. Error bars indicate 95% confidence intervals. (NB: vertical scales are different for each figure).

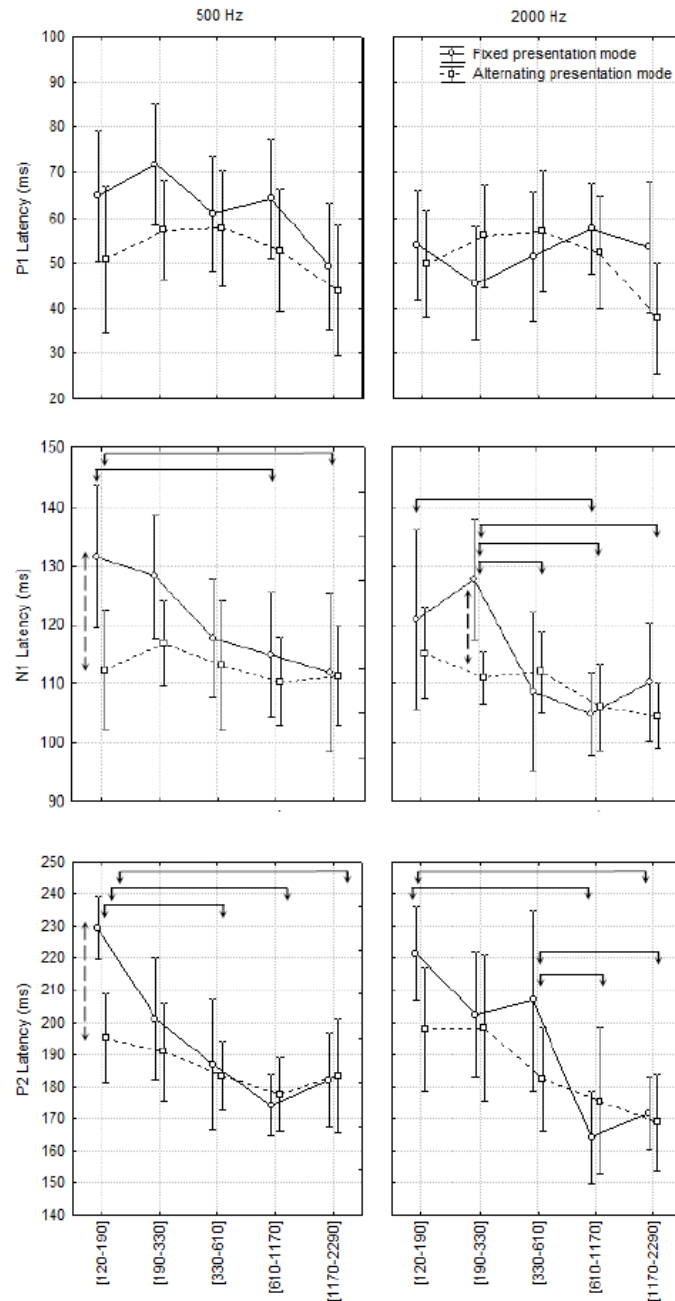


Figure 6. P1, N1 and P2 latencies of the CAEP recorded at electrode positions Cz and M2 using fixed (solid line) and alternating (dashed line) tone-burst stimuli with frequencies of 500 Hz and 2000 Hz for 5 SOA ranges: 120-190 ms, 190-330 ms, 330-610 ms, 610-1170 ms and 1170-2290 ms. Significant Tukey pair-wise comparison are indicated by a double arrow = $p < .05$. Error bars indicate 95% confidence intervals. Error bars indicate 95% confidence intervals. (NB: vertical scales are different for each figure).

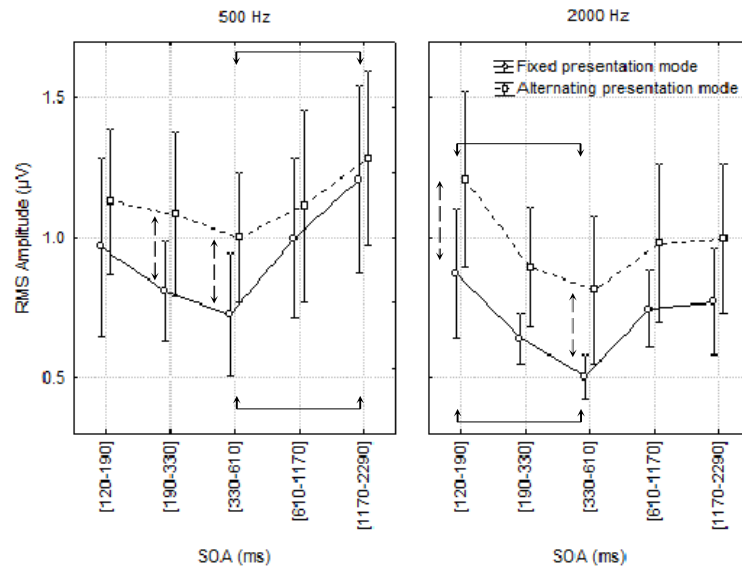


Figure 7. Amplitude RMS of the CAEP recorded from 0 to 300 ms after onset at electrode positions Cz and M2 using fixed (solid line) and alternating (dashed line) tone-burst stimuli with frequencies of 500 Hz and 2000 Hz for 5 SOA ranges: 120-190 ms, 190-330 ms, 330-610 ms, 610-1170 ms and 1170-2290 ms. Significant Tukey pair-wise comparison are indicated by a double arrow = $p < 0.05$. Error bars indicate 95% confidence intervals. (NB: vertical scales are different for each figure).

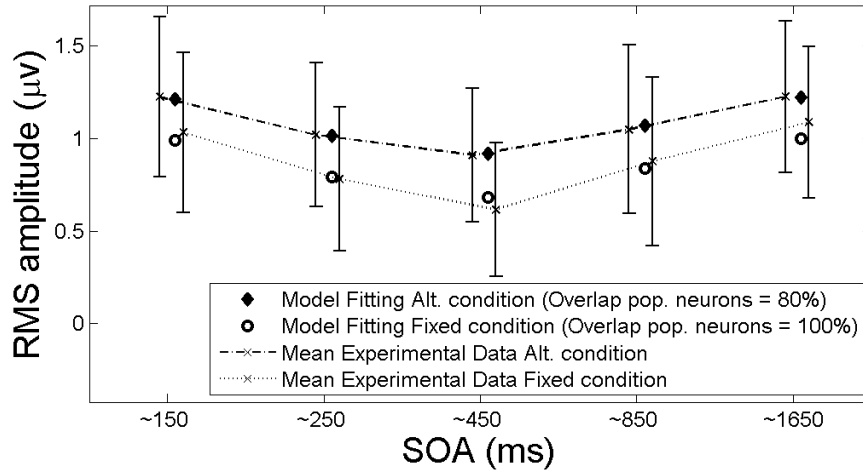


Figure 8. Fit of experimental data using the transient reduction of excitability (TRES) model. The dashed line marks the average RMS amplitude for the four conditions of the experiments plotted in figure 5 (2000 Hz – 500 Hz for the fixed and alternating presentation mode) for 5 SOA ranges. Error bars indicate standard deviation. The simulated data marked with diamonds and circles are obtained using the timing characteristic of the stimulus sequence. The parameters used for the simulation are those derived by Zacharias et al. (2012) with an original pool size $P1=8.4 \mu\text{V}$; $f=0.37$; $\tau_a=0.02 \text{ s}$; $\tau_b=2.77 \text{ s}$; $\Delta\tau_a=0.24 \text{ s}$; $\Delta\tau_b=0.38 \text{ s}$ and $o=80\%$.

Tables

	Fixed 500 Hz	Alt 500 Hz	Fixed 2000 Hz	Alt 2000 Hz
	Run 1	Run 2	Run 3	Run 4
ICC on Grand Average	0.95	0.96	0.95	0.95
Mean ICC per Subject	0.78	0.81	0.62	0.72
Stdev ICC per Subject	0.14	0.14	0.19	0.14

Table 1 Intra-class correlation coefficients (ICCs) between the four different SOA ranges, calculated on the cortical waveform generated by the first stimulus of the pair for the 500Hz and 2000Hz using fixed and alternating presentation modes.

		SOA			Mode of Presentation			Stimulus		
		F(4,40)	p	ϵ	F(1,10)	p	ϵ	F(1,10)	p	ϵ
P1	Amplitude	10.77	0.001	0.46	0.10	0.75	1	1.70	0.22	1
	Latency	3.50	0.031	0.69	4.21	0.067	1	15.76	0.003	1
N1	Amplitude	5.18	0.016	0.45	21.56	0.0009	1	6.66	0.027	1
	Latency	8.64	0.0039	0.41	6.51	0.029	1	6.75	0.026	1
P2	Amplitude	11.85	0.0002	0.45	16.62	0.002	1	11.29	0.007	1
	Latency	10.77	0.000002	0.60	0.12	0.73	1	21.28	0.0009	1
RMS	Amplitude	10.07	0.0006	0.87	18.15	0.001	1	19.55	0.0012	1

Table 2 Statistical p-values for the SOA, the mode of presentation, and the stimulus effect for P1, N1, P2, P1-N1 and N1-P2 amplitudes and latencies. Greenhouse-Geisser corrections of the degrees of freedom were used where an assumption of sphericity was not appropriate.

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