Temporal integration of short-duration pulse trains in cochlear implant listeners: Psychophysical and electrophysiological measurements

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TEMPORAL INTEGRATION OF SHORT-DURATION PULSE TRAINS IN COCHLEAR IMPLANT LISTENERS: PSYCHOPHYSICAL AND ELECTROPHYSIOLOGICAL MEASUREMENTS

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ABSTRACT

While electrically-evoked auditory brainstem response (eABR) thresholds for low-rate pulse trains correlate well with behavioral thresholds measured at the same rate, the correlation is much weaker with behavioral thresholds measured at high rates, such as used clinically. This implies that eABRs to low-rate stimuli cannot be reliably used for objective programming of threshold levels in cochlear implant (CI) users. Here, we investigate whether the use of bunched-up pulses (BUPS), consisting of groups of closely-spaced pulses may be used as an alternative stimulus.

Experiment 1 measured psychophysical detection thresholds for several stimuli having a period of 32 ms in nine CI subjects implanted with a Med-EL device. The stimuli differed in the number of pulses present in each period (from 1 to 32), the pulse rate within period (1000 pps and as high as possible for BUPS) and the electrode location (apical or basal). The correlation between psychophysical thresholds obtained for a high-rate (1000 pps) clinical stimulus and for the BUPS stimuli increased as the number of pulses per period of BUPS increased from 1 to 32. This first psychophysical experiment suggests that the temporal processes affecting the threshold of clinical stimuli are also present for BUPS.

Experiment 2 measured eABRs on the apical electrode of eight CI subjects for BUPS having 1, 2, 4, 8, 16 or 32 pulses per period. For all subjects, wave V was visible for BUPS having up to 16 pulses per period. The latency of wave V at threshold increased as a function of the number of pulses per period, suggesting that the eABR reflects the integration of multiple pulses at such low levels or that the neural response to each individual pulse increases along the sequence due to facilitation processes. There was also a strong within-subject correlation between electrophysiological and behavioral thresholds for the different BUPS stimuli. This demonstrates that the drop in behavioral threshold obtained when increasing the number of pulses per period of the BUPS can be measured electrophysiologically using eABRs. In contrast, the across-subject correlation between eABR thresholds for BUPS and clinical thresholds remained relatively weak and did not increase with the number of pulses per period. Implications of the use of BUPS for objective programming of CIs are discussed.

1. INTRODUCTION

In cochlear implants (CIs), the current level needed to produce an auditory sensation in a given subject may depend on many factors such as the position of the electrode(s) relative to the auditory nerve fibers and the amount of neural survival (Bierer, 2010; Long et al., 2014; Mesnildrey et al., 2020). Usually, fitting a CI requires clinicians to measure thresholds and comfortable listening levels for each individual electrode. As these levels may change over time, particularly during the first months after activation, this fitting process needs to be repeated on multiple sessions. The time devoted to cochlear programming in clinics has, therefore, increased tremendously over the past decades, especially since the number of CI implantation is constantly increasing. In addition, fitting young children remains a complicated process because there is currently no reliable method that allows the clinician to determine thresholds and most comfortable levels objectively.

A lot of effort has been devoted into finding electrophysiological measures able to predict the current levels needed for each electrode to produce a given sensation. Electrically-evoked compound action potentials (eCAPs) and auditory brainstem responses (eABRs) are two examples of such *objective* measures which are usually recorded using a relatively low stimulation pulse rate (a few tens of Hz). At these low rates, eCAP and eABR thresholds correlate well with psychophysical thresholds measured at the same rate (see Miller et al., 2008 for a review). However, contemporary CIs use much higher pulse rates than that, usually higher than 900 pps. Psychophysical thresholds measured at such high rates do not correlate well with eCAP or eABR thresholds measured at low rates (Brown et al., 1999). The reason for this is the across-electrode and across-subject variability in temporal integration. When pulse rate increases, the psychophysical threshold drops but the magnitude of this drop is variable both across subjects and across electrodes within a given subject (McKay et al., 2013a).

At the level of the auditory nerve, there may be several temporal processes affecting the neural response to individual pulses, as reviewed by Boulet et al. (2016). These processes

may partly or fully be responsible for the observed variability in temporal integration. When pulse rate is increased, the relative effects of neural refractoriness, accommodation, facilitation and spike-rate adaptation may change and consequently modify the neural response to each pulse. Although the relative contributions of these processes have not been unravelled in CI users, it is expected that refractoriness, adaptation and accommodation reduce the response to subsequent pulses in a pulse train whereas facilitation should have the opposite effect. In addition, at a more central level, neural activity is believed to be temporally integrated across different time scales. Even though the exact site(s) at which this temporal integration occurs remain unclear, phenomenological threshold and loudness models usually implement this process using a sliding temporal integration window with a short duration ranging from about 7 to 20 ms (McKay and McDermott, 1998; Carlyon et al., 2005; Macherey et al., 2007; McKay et al., 2013b). These models predict that an increase in pulse rate will increase the number of spikes falling into the window which will consequently lower the threshold or increase the loudness.

The aim of the present study is to modify the signal used to measure eABRs (i.e. low-rate pulse train) to make it perceptually closer to the stimuli used clinically (i.e., high-rate pulse trains). Our modification is based on a study by McKay et al. (2013a) who measured behavioral threshold as a function of pulse rate for several electrodes and subjects. They reported highly variable slopes of temporal integration functions between 40 and 500 pps. Above 500 pps, however, the slopes were more consistent both across electrodes and across subjects. This suggests that if we were able to predict the threshold for an arbitrarily high rate of stimulation, we could potentially infer the approximate threshold for any stimulus with a rate above 500 pps which would be relevant clinically. Here, therefore, we choose to focus on very high rates of stimulation and to insert gaps within the stimulus to be able to record the eABR response in the absence of stimulus artefacts. In the following, we refer to this class of stimuli as “bunched-up pulses stimuli” (BUPS, c.f. Figure 1) which consist of sequences of closely-spaced pulses repeated at a relatively low sequence rate. As the amount of temporal integration at the level

of the brainstem remains poorly known, the following experiments are performed for sequences containing different numbers of pulses ranging from 1 to 32.

In Experiment 1, we measure psychophysical thresholds for different BUPS stimuli. In particular, we investigate whether the correlation between psychophysical thresholds for a clinical stimulus and for BUPS increases when increasing the number of pulses within the stimulus sequence. In Experiment 2, we test the feasibility of measuring eABRs in response to different BUPS stimuli.

2. EXPERIMENT 1: PSYCHOPHYSICAL THRESHOLDS

2.1. METHODS

2.1.1. Subjects and Experimental Platform

Nine Med-EL CI users took part (c.f. Table 1 for biographical details). The psychophysical procedures were programmed in Matlab and used the Research Interface Box (RIB2, University of Innsbruck) and a National Instruments card (PCI-6533, National Instruments, Austin, TX) connected to a PC to stimulate the implant. Subjects provided informed consent and were paid for their participation. All experiments were approved by the Local Ethics committee (Eudract 2012-A00438-35).

2.1.2. Stimuli

All stimuli were electrical pulse trains having a period of 32 ms (31 Hz) as shown in Figure 1. Within each period, the stimuli consisted of sequences of 1, 2, 4, 8, 16 or 32 electrical anodic-first symmetric biphasic pulses with a 2.1- µs inter-phase gap presented either at a rate of 1000 pps or at the maximum rate possible (corresponding to a gap between the offset of one pulse and the onset of the next pulse of 2.1 µs). The stimuli presented at a “clinical” rate of 1000 pps are referred to as CLIN (clinical stimulus) while those presented at the maximum rate are referred to as BUPS (bunched-up pulses stimulus). The number *n* following each of these

acronyms refers to the number of pulses present within a period. Note that when only 1 pulse per period is present, BUPS1 and CLIN1 are identical. Therefore, in total, 11 stimulus conditions were tested.

The experiment was repeated on two electrodes which were the most apical and the most basal active electrode in each subject's processor map. In case the most basal electrode produced uncomfortable percepts, the next most basal electrode was chosen instead. These electrodes are indicated in Table 2 for each subject. The phase duration differed across subjects and was chosen to match the longer phase duration of the two electrodes tested as specified in the clinical maps of the subjects. Consequently, both the within-period pulse rate and the duration of the BUPS sequences also varied across subjects (c.f. Table 2). The total stimulus duration (difference between the onset of the first pulse of the first sequence and the offset of the last pulse of the last sequence) was fixed at a value as close as possible to 420 ms. Because some of our stimuli had large gaps between periods, this duration could slightly vary across conditions (between 419.3 and 451.3 ms). An inspection of Donaldson et al.'s (1997) data suggest that such small differences in stimulus duration should not affect detection thresholds.

2.1.3. Procedure

Thresholds and Most Comfortable Loudness (MCL) levels were first approximately determined using a loudness chart labeled from '0' (no sound) to '10' (too loud), label '1' corresponding to detection threshold and label '6' to MCL. Detection thresholds were then measured adaptively in a two-interval, two-alternative, three-down, 1-up forced choice task (Levitt, 1971). In each trial, two intervals were presented separated by a 500-ms gap. The intervals were cued visually on a computer screen. One interval contained the stimulus while the other contained no sound. Subjects had to identify in which interval (1 or 2) a sound was present by clicking on one of two virtual buttons displayed on the screen. The starting level was set to 25% of the dynamic range (expressed in μA) as initially measured using the loudness chart. This ensured that the stimulus was clearly audible at the beginning of the procedure. After three consecutive correct

responses, the stimulus level was decreased while it was increased after each incorrect response. The amount of increase and decrease varied during the procedure: it was equal to 0.6 dB before the first reversal, 0.3 dB before the third reversal and 0.15 dB subsequently. Each procedure was resumed after 10 reversals and the threshold was defined as the mean of the last 6 reversals. Feedback was provided after each trial.

2.1.4. Sessions

For each electrode, data were collected in blocks of 11 adaptive runs corresponding to each stimulus condition presented in random order. Six data blocks (2 electrodes x 3 repeats) were collected across three sessions lasting 2 to 3 hours each.

2.1.5. Modeling

The loudness model of McKay et al. (2013b), incorporating refractoriness and temporal integration, was implemented and fitted to the threshold data averaged across electrodes and subjects. For each stimulus, the model first determines the magnitude of the neural response to each pulse relative to the very first pulse. Then, this activity is integrated by a sliding temporal integration window whose shape derives from normal-hearing psychoacoustic data (Oxenham, 2001). Such temporal integration window models have previously been shown to account for normal hearing behavior on a variety of tasks such as level increment detection or forward masking (Oxenham & Moore, 1994; Moore et al., 1996; Oxenham, 2001). The shape of the temporal window is given by:

$$W(t) = (1-w)\exp\left(\frac{t}{T_{b1}}\right) + w\exp\left(\frac{t}{T_{b2}}\right), t < 0, \quad \text{(eq. 1)}$$

$$W(t) = \exp(-t/T_a), t \geq 0$$

where t is the time relative to the peak of the window, T_{b1} and T_{b2} are two time constants modeling the decay of forward masking, w weights the relative importance of these two time constants and T_a is the time constant modeling the decay of backward masking. Similar to

McKay et al. (2013b), we used the parameter values obtained by Oxenham (2001): T_{b1}=4.6 ms, T_{b2}=16.6 ms, w=0.17, and T_a =3.5 ms.

Finally, the overall excitation is assumed to correspond to the maximum output of the integrator across the stimulus. The model makes the assumption that the threshold difference between two stimuli corresponds to the difference in current level needed to obtain the same maximum output of the integrator.

In the present case, the model predicts a threshold difference between each stimulus and our reference pulse train CLIN1/BUPS1. For CLIN1/BUPS1, there is only one pulse presented every 32 ms and complete recovery from refractoriness is assumed between periods, meaning that the neural responses produced by all pulses are identical. For a higher number of pulses per period, the neural response produced by the first pulse is assumed to be the same as for CLIN1/BUPS1. The response produced by subsequent pulses *within* each period, however, is assumed to be reduced by a factor α for CLIN and β for BUPS compared to that to the first pulse. Refractory effects are assumed to fully recover between periods for all stimuli except for CLIN32. For CLIN32, which is a continuous 1000-pps pulse train, the responses to all pulses (except the very first one) of the whole stimulus are reduced by the same factor α. This can be viewed as a constant effect of refractoriness across the period. Finally, the threshold difference between a given stimulus and the reference is assumed to be equal to the difference in dB between the excitation produced by this stimulus and that produced by the reference, divided by a parameter S representing the slope of the current versus neural excitation function in log/log units (c.f. McKay et al., 2013b for details). The three model parameters α, β, and S were fitted by minimizing the sum of the squared differences between model predictions and threshold data averaged across electrodes and subjects.

2.2. RESULTS

Figure 2A shows for each subject, the mean threshold as a function of number of pulses per period for both CLIN and BUPS stimuli for the two electrodes tested. Before computing the

correlations between BUPS and CLIN thresholds which was the main aim of this experiment, all data except the CLIN1/BUPS1 thresholds were analyzed in a 3-way repeated measures ANOVA with factors STIMULUS TYPE (CLIN and BUPS), ELECTRODE (apical and basal) and NUMBER OF PULSES per period (2, 4, 8, 16 and 32). In case Mauchly's test of sphericity was significant, the Greenhouse-Geissler correction was applied and corrected degrees of freedom are indicated below. The analysis revealed no effect of ELECTRODE ($F(1,8)=0.28$, $p=0.6$) but significant effects of the main factors STIMULUS TYPE ($F(1,8)=41.08$, $p<0.001$) and NUMBER OF PULSES ($F(1.11,8.92)=86.05$, $p<0.001$). Not surprisingly, thresholds decreased when the number of pulses within each period increased. This decrease, averaged across electrodes, amounted to 1.2 dB and 1.9 dB per doubling of the number of pulses for CLIN and BUPS, respectively (c.f. Figure 2B). The mean threshold difference between CLIN and BUPS increased from 0.48 dB for 2 pulses to 3.43 dB for 32 pulses (significant NUMBER OF PULSES by STIMULUS TYPE interaction: $F(1.62,12.95)=27.87$, $p<0.001$; c.f. Figure 2C). Post-hoc t-tests with Bonferroni correction showed that the difference between CLIN and BUPS was significantly larger for 32 pulses than for all other numbers of pulses and also larger for 16 pulses than for 2 and 4 pulses. This specific result will be discussed in section 4.1. The other interaction terms of the ANOVA were not significant.

The model predictions for BUPS and CLIN are shown by the dotted lines in Figure 2B together with the mean thresholds across subjects. The model provides a good fit, showing lower thresholds for BUPS than for CLIN for all conditions except for CLIN2/BUPS2. Furthermore, the values of the fitted parameters α (0.3) and S (1.9) were in the same range as the parameters fitted on the threshold vs. pulse rate functions of McKay et al. (2013b) for whom α was roughly equal to 0.55 and the optimal S was 1.7. Similar to the subjects' data, the predicted threshold difference between BUPS and CLIN (dotted line in Figure 2C) increases as a function of the number of pulses per period. This is specifically due to the shape of the temporal integration window which attenuates the response to additional pulses more when they are separated by large inter-pulse intervals. This makes the added pulses of CLIN contribute less and less to the response relatively compared to the added BUPS pulses.

As our final aim was to investigate whether BUPS may be used to predict the threshold of clinical stimuli, we calculated the correlation coefficients between the threshold for CLIN32 (which is a regular 1000-pps stimulus, similar to pulse trains used clinically) and the threshold for the different BUPS stimuli, i.e. for the different numbers of pulses per period. Figures 3A and 3B show these correlations for the apical and basal electrodes, respectively. The correlation coefficients ranged from 0.65 for BUPS1 to 0.80 for BUPS32 for the apical electrode and from 0.88 to 0.97 for the basal electrode (c.f. Table 3). After applying Bonferroni-Holm correction for multiple comparisons, none of the coefficients obtained for the apical electrode remained significant ($p>0.05$) unlike the coefficients for the basal electrode which were all significant ($p<0.05$). Importantly, Mann-Kendall tests showed for both electrodes a trend for increased correlation with increases in the number of pulses ($S=13$, $p=0.008$ for both electrodes).

We also investigated whether the across-electrode CLIN32 threshold difference could be accounted for by BUPS thresholds by correlating the differences in threshold between the apical and basal electrodes for the CLIN32 and the different BUPS stimuli, again as a function of the number of pulses per period of the BUPS (c.f. Table 3). The correlation coefficients ranged from 0.78 to 0.84 and were all significant after Bonferroni-Holm correction ($p<0.05$). Here again, Mann-Kendall test revealed a significant trend for increased correlation with increases in the number of pulses ($S=11$, $p=0.028$).

To summarize, these results demonstrate that an increasing part of the across-subject threshold variance in clinical stimuli is captured by BUPS when increasing the number of pulses per period. Therefore, BUPS appear to be a promising tool to use for eABR recordings. More specifically, if we were able to predict the psychophysical threshold of BUPS stimuli using eABR, we may be able to further infer the psychophysical threshold of a regular clinical high-rate pulse train (called CLIN32 here) from this measure.

3. EXPERIMENT 2: ELECTROPHYSIOLOGICAL THRESHOLDS

The aim of Experiment 2 was to investigate the possibility of recording eABRs to BUPS with a large number of pulses and to test if the behavioral and electrophysiological thresholds for BUPS correlate.

3.1. METHODS

3.1.1. Subjects

Ten subjects took part in this experiment, including eight who already participated in Experiment 1 (i.e., all subjects except M005) and two who did not (M016 and M017) . The stimuli were delivered to the implant using the same hardware and a similar Matlab interface as in Experiment 1. All measures were performed within a single session lasting 3 to 4 hours.

3.1.2. Stimuli

eABRs were recorded in response to six BUPS stimuli (N=1, 2, 4, 8, 16 and 32) presented on the most apical electrode only (electrode 1). In order to reduce the influence of the stimulus artefacts in the recordings, the BUPS were presented in alternating polarity. This means the electrical pulses were all anodic-first in the odd-numbered periods of the stimulus and cathodic-first in the even-numbered periods. The phase duration was the same as in Experiment 1 for subjects who participated in both experiments or was equal to the phase duration used in the clinical map for the other participants (c.f. Table 1).

3.1.3. Threshold and MCL determination

At the beginning of the session, comfortably-loud levels (labelled as ‘7’ on the loudness chart) were first measured for the six BUPS stimuli using the same loudness chart as in Experiment 1. Because eABR measures require long stimulus presentations (several thousands of repetitions), we checked that the comfortably loud levels obtained with 420-ms stimuli were

still comfortable when increasing the duration to 5 seconds. The subjects were informed that they would later have to listen to this sound for several minutes. In case a stimulus was perceived as too loud or uncomfortable, the level was decreased in steps of 0.1 dB until the subject judged it to be acceptable. Due to time limitations, detection thresholds were measured using a 1-up, 1-down procedure which aimed to be faster than the forced-choice procedure of Experiment 1. For each stimulus, the subjects were asked to raise their hands any time they heard a sound. The presentation level started at comfort and was manually decreased in steps of 0.5 dB until the subject could not hear it. Then it was increased in steps of 0.1 dB until it was detected again. Five reversals were obtained and the threshold was assumed to correspond to the average of the last 4 reversals. In addition to the threshold measures of the six BUPS stimuli to be used in the eABR measurements, we also measured detection thresholds for 420-ms anodic-first and cathodic-first 1000-pps pulse trains presented on electrode 1 (i.e. stimuli corresponding to CLIN32 of Expt. 1). All thresholds were measured twice in pseudo-random order and the average of the two values was kept for further analysis.

3.1.4. Electrically-evoked Auditory Brainstem Responses (eABR)

For the eABR measurements, the participants seated in a comfortable reclining chair in an electrically-shielded, sound-attenuated room and were asked to rest or sleep with their eyes closed. The PC-based system controlled the timing of the stimulus presentations and delivered an external trigger to the evoked potential recording system (Microvitae, µV-ABR). Auditory brainstem responses were collected at a 30-kHz sampling rate with three Ag-AgCl scalp electrodes placed on the forehead (Fz - active), the nape of the neck (reference) and the earlobe contralateral to the implanted ear (ground). Electrode impedances were kept below 5 kΩ.

To ensure that the neural responses were not contaminated by CI and muscular artifacts, online averaging was enabled using artefact rejection for visualizing purposes. All recording traces exceeding ± 30 µV between 2-ms and 10-ms post-stimulus time were rejected from online averaging but were saved on the PC. Recording lasted until approximately three

thousand non-artefacted sweeps were reached for each stimulus and participant even though, due to time restrictions or especially noisy recordings, this number was not always reached. On average, 3417 sweeps (s.d. = 436) were obtained for each stimulus.

eABR functions were collected for BUPS stimuli in the following order N=1, 4, 16, 2, 8, and 32. For each stimulus, the recording usually started at a subthreshold level of 9 µA to be able to compare the suprathreshold recordings to it and then at levels corresponding to 100, 75 and 50% of the perceptual dynamic range. If there still was a detectable response at 50%, the level was further decreased to 25%, otherwise, it was increased to 62.5% (i.e., the level between 50 and 75%). The dynamic range was subsequently bisected depending on whether or not a visually-detectable response was present in the recording. Except for a few exceptions detailed below where eABRs were difficult or impossible to observe, between 4 and 7 recordings (4.8 on average) containing a detectable response were obtained for each stimulus and subject.

3.1.5. Data analysis

All analyses were performed using custom MATLAB scripts (MathWorks). First, electrophysiological recordings were bandpass filtered between 70 and 2500 Hz using a 2nd order Butterworth filter. Then, sweeps with activity exceeding ± 30 µV between 2-ms and 10-ms post-stimulus time were rejected as artefact. eABR traces were further averaged over a 0 to 15-ms window. Wave V peaks and troughs were identified visually based on the latency and decrease in amplitude with decreasing stimulus level. Amplitudes were calculated as the difference (in µV) between the positive peak and the following trough for wave V. Similar to Bierer et al. (2011), the eABR threshold was arbitrarily defined as the current level for which the amplitude of Wave V was 0.1 µV. This threshold level was either interpolated from the input-output growth function or, in case the smallest response obtained had an amplitude larger than 0.1 µV, it was *extrapolated* assuming a linear decrease of the amplitude growth function from the two lower-level responses collected. The latency of wave V was defined as the time difference between the positive peak and the stimulus onset.

3.2. RESULTS

Two out of the ten subjects either showed no measurable eABR responses (M001) or only a response at the highest level for BUPS1 (M014). The following analyses are therefore restricted to the remaining eight subjects. An example of eABR responses for the different BUPS stimuli is shown in Figure 4 for subject M002. It was possible to record eABRs in all eight subjects up to 16 pulses. For 32 pulses, the artefact prevented us from observing wave V in 4 subjects. Long-lasting artefacts were also sometimes present for high numbers of pulses, as shown for BUPS16 in Figure 4. Because we were only able to measure responses to BUPS32 in 4 subjects, the analyses below encompass, except otherwise stated, the data obtained with all stimuli except BUPS32.

3.2.1. Analysis of wave V amplitudes at the minimum and maximum stimulation levels

Figures 5A and 5B show the amplitude of wave V at the maximum stimulation level (corresponding to a comfortably loud percept) and at the minimum level at which a response could be detected, respectively. The minimum and maximum amplitude values were analyzed in a two-way repeated measures ANOVA with within-subject factors NUMBER OF PULSES (five levels: 1, 2, 4, 8 and 16 pulses) and STIMULATION LEVEL (two levels: min and max amplitudes). Not surprisingly, the analysis showed significantly larger amplitudes at high stimulation level (main effect of STIMULATION LEVEL: $F(1,7)=74.7$, $p<0.001$). The NUMBER OF PULSES did not significantly affect wave V amplitudes ($F(4,28)=2.11$, $p=0.11$). Moreover, the sensitivity of eABRs to changes in stimulation level did not significantly change when increasing the number of pulses (STIMULATION LEVEL by NUMBER OF PULSES interaction: $F(4,28)=1.83$, $p=0.15$). Note that the above analysis on wave V amplitudes was performed for stimuli eliciting the same loudness percept (either near-threshold or at MCL). However, given both threshold and MCL decrease when increasing the number of pulses, this implies that for a fixed current level, the amplitude of wave V tended to be larger when the number of pulses in the stimulus increased.

3.2.2. Analysis of wave V latencies at the minimum and maximum stimulation levels

Figures 5C and 5D show the latency of wave V also at the maximum and minimum levels, respectively. The latency values were analyzed in a two-way repeated measures ANOVA which showed highly significant effects of STIMULATION LEVEL ($F(1,7)=243.09$, $p<0.001$), NUMBER OF PULSES ($F(4,28)=11.27$, $p<0.001$) and of their interaction ($F(4,28)=11.99$, $p<0.001$). This interaction was further examined in two additional one-way repeated measures ANOVA performed separately at the two levels. These analyses showed a significant effect of NUMBER OF PULSES at the minimum ($F(4,28)=14.49$, $p<0.001$) but not at the maximum level ($F(4,28)=1.70$, $p=0.18$). At the minimum level (Fig. 5D), the latency increased on average from 4.12 ms for BUPS1 to 4.60 ms for BUPS16. Post-Hoc Pairwise comparisons with Bonferroni correction showed significantly longer latencies for BUPS16 than for BUPS1 ($p=0.011$), BUPS2 ($p=0.008$) and BUPS4 ($p=0.011$). This increased latency for a large number of pulses per period cannot be explained by differences in amplitude because, as previously shown, the amplitudes were similar across BUPS conditions at this minimum level (Fig. 5B). This result, therefore, suggests that at low levels, wave V of the eABR reflects some sort of short-term integration of neural activity or, alternatively, that the response to pulses presented later in the pulse sequence is larger than the response to the early pulses. This aspect of the data will be discussed in section 4.3.

3.2.3. Analysis of eABR thresholds

As the main aim of this experiment was to evaluate if eABR and behavioral thresholds for BUPS correlate, we arbitrarily defined the eABR threshold as the stimulation current level producing a wave V amplitude of 0.1 µV (c.f. Bierer et al., 2011). These eABR thresholds were inferred from wave-V amplitude growth functions for the different BUPS conditions as shown in Figure 6 for subjects M016 and M017.

Similar to the psychophysical thresholds measured in Experiment 1 (c.f. Fig. 2), eABR thresholds decreased when increasing the number of pulses as shown in Figure 7A. This observation was confirmed by a one-way repeated measures ANOVA showing a highly

significant effect of the factor NUMBER OF PULSES ($F(4,28)=21.16$, $p<0.001$). Post-hoc pairwise comparisons using the Bonferroni correction showed the threshold to be significantly lower for BUPS16 than for BUPS1 ($p=0.002$) and BUPS2 ($p=0.003$), lower for BUPS8 than for BUPS1 ($p=0.006$) and lower for BUPS4 than for BUPS1 ($p=0.001$). The decrease in eABR threshold when doubling the number of pulses within the stimulus amounted to 1.1 dB (averaged across conditions and subjects). This value is smaller than the value found psychophysically in Experiment 1 (1.9 dB).

To test whether the *within-subject differences* in eABR thresholds obtained for different BUPS were related to the change in behavioral thresholds, we normalized the threshold of each subject relative to its mean threshold across conditions separately for behavioral thresholds and for eABR thresholds. The data points from all subjects were then pooled together, as shown in Figure 7B and further subjected to a correlation analysis. This normalization caused an additional loss of 1 degree of freedom per subject. The result showed a strong correlation between the normalized behavioral and eABR thresholds ($r=0.89$, $d.f.=34$, $p<0.001$). This means that about 80% of the within-subject variance in behavioral thresholds for the different BUPS conditions is captured by the eABR measurements.

Across-subject correlations between eABR thresholds for different number of pulses and clinical (behavioral) thresholds were also analyzed and are shown in Figure 8. The correlation coefficients ranged from 0.49 to 0.72 but none were significant after Bonferroni-Holm correction. In addition, contrary to the correlations reported in Experiment 1, there was no trend for increased correlation with increases in the number of pulses per period.

4. DISCUSSION

In sections 4.1 to 4.3, we discuss the main observations of Experiments 1 and 2, compare the results with data available in the literature and propose possible underlying mechanisms that may account for them. Section 4.4 focuses on the use of BUPS for objective fitting of CIs, which was the main aim of this study.

4.1. FACTORS AFFECTING PSYCHOPHYSICAL THRESHOLD DIFFERENCES BETWEEN CLIN AND BUPS

Experiment 1 showed that psychophysical thresholds for both BUPS and CLIN decreased when increasing the number of pulses per period from 1 to 32. This result is consistent with previous studies showing that increasing the number of pulses within a stimulus (via an increase in stimulus duration and/or pulse rate) yields lower threshold (Donaldson et al., 1997; Kreft et al., 2004; McKay et al., 2013a; Zhou et al., 2015). Below we discuss two outcomes of Experiment 1: the fact that thresholds for BUPS were consistently lower than for CLIN for all numbers of pulses per period (c.f. Figure 2A, B) and that this threshold difference increased when increasing the number of pulses (c.f. Figure 2C).

We showed that both outcomes could be accounted for by the temporal integration model of McKay et al. (2013b) which incorporates refractoriness and temporal integration. On the one hand, the smaller inter-pulse intervals of BUPS increase the effect of refractoriness within each stimulus period compared to CLIN. This tends to *decrease* the overall amount of activity for BUPS pulses. On the other hand, the smaller inter-pulse intervals of BUPS imply that the overall neural activity produced within a period is more compressed in time than for CLIN and, therefore, more efficiently integrated by the temporal window. With the set of model parameters derived from the data, this more efficient integration overcomes the effect of refractoriness and predicts lower thresholds for BUPS than for CLIN. Furthermore, as the number of pulses increases, more and more CLIN pulses start to fall outside the integration window, making the threshold difference between BUPS and CLIN even larger.

In addition to the effects of refractoriness and central integration, several additional processes that were not modeled may also influence the response of auditory nerve fibers differently for CLIN and BUPS. Boulet et al. (2016) classified these processes depending on their timescale range of operation. Let us first consider the processes occurring shortly after each pulse (facilitation and accomodation). First, there is evidence from computational modeling (Boulet et al., 2016), single-unit recordings in cats (Zhang et al., 2007; Heffer et al.,

2010) and eCAP measurements in humans (Hey et al., 2017) that the neural response to a pulse can be enhanced when it is shortly preceded by a subthreshold pulse. The time constant of this *facilitation* phenomenon as measured in humans using eCAPs was found to be in the 100-150 µs range (Tabibi et al., 2019). It should, therefore, be especially strong for BUPS but less for CLIN, and should consequently produce the opposite effect as refractoriness, i.e., lowering BUPS thresholds compared to CLIN. The potential effects of accommodation (also sometimes referred to as *subthreshold adaptation*) are more difficult to predict. Accomodation corresponds to the decreased response probability of a nerve fiber following a subthreshold stimulus and should therefore have an opposite effect to facilitation. However, modeling work suggests that the operating timescale of accomodation ranges from 0.5 to 5 ms, which is slightly longer than the operating timescale of facilitation (Boulet et al., 2016). Given the interpulse intervals within each BUPS sequence are much shorter than that (c.f. Table 2), it is possible that the responses to each pulse were not affected much by this process for BUPS. In contrast, the interpulse interval within each CLIN stimulus sequence is 1 ms suggesting accommodation may have played a larger role in this case. This mechanism could therefore be a contributor to the increased threshold difference between CLIN and BUPS observed when increasing the number of pulses per period.

Finally, we have so far mostly reasoned on what may occur *within* each period of a stimulus. It is worth noting that all stimuli except CLIN32 show large gaps (> 16 ms) between the offset of a pulse sequence and the onset of the next pulse sequence (i.e. the next period). These large gaps may have the effect of partially resetting spike-rate adaptation between periods. This could, therefore, provide the opportunity to detect the stimulus across multiple periods (via “multiple looks”, Viemeister and Wakefield, 1991; Donaldson et al., 1997). This ability should be reduced for CLIN compared to BUPS because the gaps between periods are longer for BUPS. For example, CLIN32 is a constant-rate pulse train and has been shown in single-unit recordings to produce spike-rate adaptation across the whole stimulus duration (Zhang et al., 2007). It is, therefore, possible that a stronger across-period adaptation for CLIN

than for BUPS also contributed to the increased threshold difference between BUPS and CLIN when increasing the number of pulses per period.

In conclusion, although our threshold data can simply be accounted for by only considering refractoriness and central integration, it is possible that they result from a more complex interplay between these different processes, especially since the effects of facilitation, accomodation and spike-rate adaptation may be partially counteracting each other and are expected to depend on the interpulse interval.

4.2. CAVEAT OF USING DIFFERENT PHASE DURATIONS ACROSS SUBJECTS

As one aim of the present study was to use the same stimuli in the psychophysical and electrophysiological experiments, we anticipated that it would be easier to measure eABRs for pulse sequences having a short duration. This is why we chose to use the shortest phase duration possible for each subject in both experiments. One caveat arising from this experimental design is that the phase duration varied across subjects and may have provided an additional source of across-subject variance in the threshold data. During the analysis, we noticed that the subjects with relatively long phase durations were those showing the largest threshold drop when increasing the number of pulses per period. Phase duration was shown to correlate with the threshold difference between BUPS1 and BUPS32 ($r=0.71$, $d.f.=7$, $p=0.03$) and also with the threshold difference between CLIN1 and CLIN32 ($r=0.69$, $d.f.=7$, $p=0.04$). This means that the longer the phase duration the larger the threshold drop when increasing the number of pulses per period. Thus it cannot be excluded that the stronger correlation between BUPS thresholds and CLIN32 found when increasing the number of pulses per period was also partly driven by this difference in phase duration.

4.3. MEASURING eABR TO PULSE TRAINS

Below, we list three main results of Experiment 2 and discuss them in relation with previously published data.

(i) The wave-V amplitude vs. current level growth functions collected in Experiment 2 shifted towards lower level when increasing the number of pulses per period (c.f. Figure 6). This suggests that for a fixed current level, increasing the number of pulses per period tends to yield larger wave-V amplitudes.

Davids et al. (2008a) measured eABRs following 500-pps pulse trains with durations ranging from 2 ms (containing 2 pulses) to 10 ms. Their experiment was performed at a single "comfortably loud" current level held constant for all stimulus durations. Contrary to our results, they did not find larger wave-V amplitudes when keeping the current level fixed and increasing the duration. One possible explanation for this discrepancy could be the large rate difference between their stimuli and ours. In our case, the within-period pulse rate of BUPS varied from 14.3 to 29.4 kpps whereas their pulse rate was only 500 pps. It is possible that increasing the number of pulses per period has a larger effect on the neural response amplitude at high rate, i.e. that it produces larger perceptual and electrophysiological changes. This explanation would be consistent with behavioral data showing that the slope of the threshold vs. stimulus duration functions are steeper at high (1000 pps) than at low pulse rate (100 pps; Pfingst et al., 1991). Moreover, our observation that wave-V amplitude increases when increasing the number of pulses per period is consistent with the results of Kodera et al. (1983) showing that the ABR of *normal-hearing* cats increases with stimulus duration up to 2-4 ms at 2000 Hz and up to 4-8 ms at 500 Hz.

(ii) The wave-V latency (relative to stimulus onset) of the eABR responses of Experiment 2 was similar across the different stimuli at most comfortable loudness levels but increased as a function of the number of pulses per period at low level.

In another study, Davids et al. (2008b) fixed the stimulus duration of their stimuli at 2 ms and measured eABR responses for pulse trains having different rates (varying from 500 to 3600 pps) and also for a single pulse. They found no effect of stimulus condition on the mean wave-V latency measured relative to the *offset* of the stimulus. Expressing their latencies in a similar way as we did (i.e., relative to the onset), this may imply that the response latencies of their 2-ms pulse trains were actually longer than that of their single pulse. This would be consistent with our observation that at low level, latency increases with the number of pulses per period. Similarly, Kodera et al. (1983) found that the ABR latency of their acoustically-stimulated cats increased as a function of duration and that this increase was larger at low levels.

This leads us to discuss the cause of these eABR amplitude *(i)* and latency *(ii)* increases as a function of the number of pulses per period. We think it may be the result of two mechanisms. First, it is possible that wave V reflects the output of an *integration* of neural activity across a few milliseconds, which would be consistent with the normal hearing cats' data previously mentioned (Kodera et al., 1983) and would explain why the eABR response amplitude tends to grow when increasing the number of pulses (keeping the current level fixed). Concerning the response latencies, at low levels, the probability of auditory nerve fiber discharge may be similar for the different pulses within the BUPS sequence, thereby inducing an increase in latency when increasing the number of pulses. At high levels, however, most fibers may discharge in response to the first pulse and be refractory to the subsequent pulses, yielding similar response latencies for the different BUPS stimuli. This *integration* explanation seems, however, difficult to reconcile with the observation by Davids et al. (2008b) that the eABR response amplitude was not larger for a 2-ms, 3600-pps pulse train than for a single pulse presented at the same current level. Or it would mean that the very first pulse of their 2-

ms stimulus contributed almost exclusively to the neural response, e.g. due to nerve fibers being in their refractory state or strongly adapted for the subsequent pulses. Another explanation could be that the increased amplitude and latency do not arise from the integration of neural activity but are the result of neural facilitation processes and that wave V represents the aggregate (compound) of the responses to several individual pulses. Facilitation is expected to be stronger at our very high rates (BUPS) than at 3600 pps and is also more effective at low than at high levels (Tabibi et al., 2019). It is therefore possible that at low current levels, the response to individual pulses becomes larger and larger across the BUPS period. Such a response build-up could in principle yield an increased amplitude of the compound response (larger wave-V amplitude) and may also shift the *peak* of the compound response in time, thereby producing an increase in wave-V latency. At high levels, however, as previously mentioned, the response may be dominated by the first pulse(s) in the train with the later pulses contributing less because of refractoriness.

(iii) eABR thresholds (defined as the current level needed to reach a wave-V amplitude of 0.1 µV) decreased when increasing the number of pulses per period.

In contrast, Davids et al. (2008b) did not find an effect of pulse rate on eABR thresholds. More specifically, threshold was not different between their single-pulse stimulus and their 2-ms pulse trains (which contained 8 pulses at most). The cause of this discrepancy with our data also remains unclear but may be due to different definitions of thresholds between studies (lowest current at which wave V could be identified for Davids et al. vs. arbitrary fixed-amplitude response here) or, once more, to differences in pulse rate. As discussed previously, the higher rate used in the present study is expected to yield a stronger effect of neural facilitation and a more efficient integration within the hypothetical temporal integration window.

4.4. IMPLICATIONS FOR CI FITTING

Independently of the mechanisms underlying our observations, Experiment 2 showed a strong within-subject correlation between behavioral and eABR thresholds for the different BUPS stimuli. This suggests that part of the temporal integration observed behaviorally can be captured by the eABR measurements. Note, however, that the final aim would be to use these stimuli to predict clinical thresholds in patients. For it to be possible, it would be necessary that the eABR thresholds for BUPS also correlate with clinical thresholds *across-subjects*. In Experiment 2, there was no increased correlation between BUPS eABR thresholds and behavioral clinical thresholds when increasing the number of pulses within the BUPS sequence. This contrasts with the increased correlation observed in Experiment 1 when comparing clinical and *behavioral* BUPS thresholds. While this result does not appear encouraging, we think it is premature to draw conclusions on the potential usefulness of BUPS for clinical threshold predictions for two reasons. First, as already stated in section 4.2, the across-subject correlations reported in the present study may all be affected by across-subject differences in phase duration and should, therefore, be taken with caution. Second, the size of our subject sample remains small and Experiment 2 should only be considered as a first attempt to evaluate the possibility to record eABRs to BUPS. Experiments involving a larger number of subjects tested with the same phase duration are currently running in our labs to identify if BUPS can provide a method to reliably predict clinical thresholds using eABR measurements.

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TABLES

Subject	Age (y)	CI use (y)	Etiology	Duration of deafness (y)	Electrode array
M001	52	4	post-chemotherapy	14	flex soft 31
M002	68	3	unknown	3	standard long
M004	74	6	unknown	10	standard long
M005	36	2	congenital hereditary	20	standard long
M010	36	6	congenital	16	standard long
M012	66	5	unknown	2	standard long
M013	72	1	unknown	1	standard long
M014	58	1	autoimmune disease	1	flex 28
M015	48	2	unknown	15	flex 28
M016	43	2	congenital hereditary	20	flex 28
M017	68	1	unknown	3	flex 28

Table 1 : Subject details showing age (years), duration of cochlear implant use (years), etiology, duration of profound deafness (years), type of electrode array, electrodes tested (M016 abd M017 only took part in Expt. 2 and were therefore only tested on their most apical electrode) and phase duration in µs.

Subject	Electrodes tested	Phase dur. (µs)	Within-period rate (kpps)	BUPS1 dur. (µs)	BUPS2 dur. (µs)	BUPS4 dur. (µs)	BUPS8 dur. (µs)	BUPS16 dur. (µs)	BUPS32 dur. (µs)
M001	1 & 10	38	12.47	78	158	319	640	1281	2564
M002	1 & 11	25	18.45	52	106	215	432	865	1732
M004	1 & 12	25	18.45	52	106	215	432	865	1732
M005	1 & 10	25	18.45	52	106	215	432	865	1732
M010	1 & 8	15	29.24	32	66	135	272	545	1092
M012	1 & 10	33	14.25	68	138	279	560	1121	2244
M013	1 & 8	20	22.62	42	86	175	352	705	1412
M014	1 & 11	41	11.60	84	170	343	688	1377	2756
M015	1 & 11	21	21.65	44	90	183	368	737	1476
M016	1	24	19.16	50	102	207	416	833	1668
M017	1	21	21.65	44	90	183	368	737	1476

Table 2: Electrodes tested and stimulus parameters used in the two experiments including phase duration, pulse rate within a BUPS sequence and durations of the BUPS sequences.

#pulses	Apex	Base	Difference Apex-Base
1	0.651	**0.884**	**0.779**
2	0.619	**0.907**	**0.781**
4	0.666	**0.918**	**0.799**
8	0.745	**0.941**	**0.829**
16	0.789	**0.924**	**0.796**
32	0.805	**0.967**	**0.842**

Table 3: Results of the correlation analyses between behavioral thresholds for BUPS and behavioral thresholds for CLIN32. The first two columns show the correlation coefficients for analyses performed on the apical and basal electrode data. The third column shows the correlation coefficients for the between-electrode threshold differences. Bolded values indicate statistically significant correlations after Bonferroni-Holm correction ($p<0.05$).

FIGURE CAPTIONS

Figure 1: Schematic representation of the CLIN and BUPS stimuli used in Experiments 1 and 2. The pulse rate within period was 1000 pps for CLIN and was as fast as possible for BUPS.

Figure 2: (A) Results of Experiment 1 showing, for each subject, the psychophysical thresholds as a function of the number of pulses per period for CLIN and BUPS and for the two electrodes. (B) Symbols: Mean threshold drop (averaged across electrodes and subjects) as a function of number of pulses expressed relative to the threshold for the CLIN1/BUPS1, Dotted line: model fit using McKay et al.'s temporal integration model. (C) Mean threshold difference between CLIN and BUPS (averaged across electrodes and subjects) as a function of number of pulses and model predictions (dotted line).

Figure 3: Evolution of the correlation coefficient between CLIN32 threshold and BUPS threshold as a function of the number of pulses within a BUPS period. Panels (A) and (B) show the across-subject correlations for the apical and basal electrodes, respectively. The values of the correlation coefficients are given in Table 3.

Figure 4: Example of eABR waveforms collected in subject M002 for the different BUPS conditions. The waveforms were shifted vertically for better visualization and ordered based on the current level. The tick spacing on the y-axis corresponds to an amplitude difference of 2 µV. The red crosses show the peak of wave V; this time point was taken to compute the latencies. The amplitudes were assumed to be equal to the difference in amplitude between this peak and the next trough. The traces do not all start at time 0 because the trigger was sent to the recording system when the last pulse of each period was presented.

Figure 5: (A) and (B) Wave V amplitudes measured at the maximum and minimum levels, respectively, for the different subjects and across-subject mean. (C) and (D) Wave-V latencies

measured at the maximum and minimum levels, respectively, for the different subjects and across-subject mean. For all panels, the thin lines represent individual subjects while the thick line shows the mean and standard error across subjects.

Figure 6: Examples of input-output growth functions of wave V amplitudes obtained in two subjects M016 and M017. The open symbols represent real data points of the functions while the filled symbols are the thresholds (either interpolated or extrapolated from the actual measurements). Threshold was assumed to correspond to the current level for which the amplitude is equal to 0.1 µV. These values were obtained by interpolation or extrapolation of the growth functions.

Figure 7: (A) eABR thresholds as a function of number of pulses per period for individual subjects and mean across subjects; (B) within-subject correlation between eABR and behavioral thresholds for BUPS stimuli. Each color represent one BUPS condition, using the same color code as in Figure 6.

Figure 8: Across-subject correlations between BUPS eABR thresholds and clinical thresholds measured behaviorally for different number of pulses per BUPS period.

Figure 1

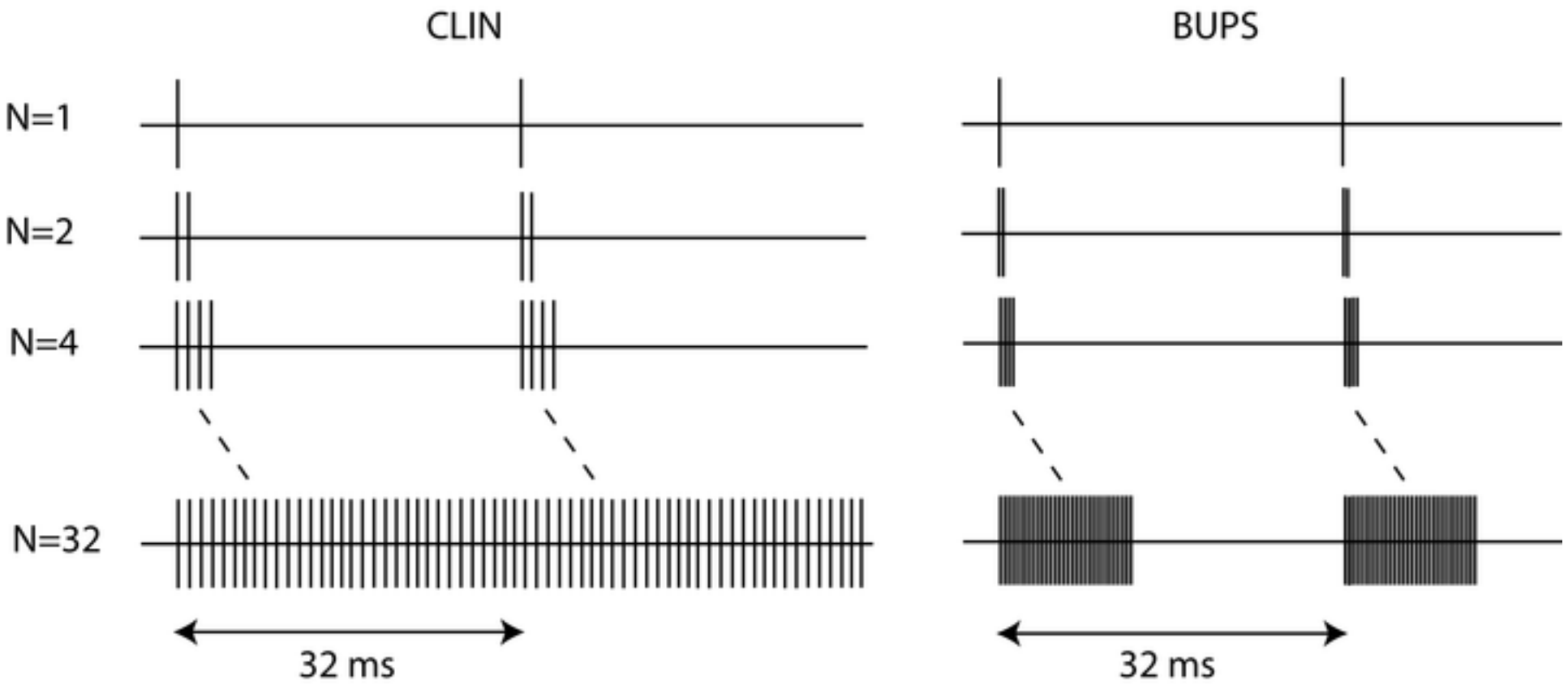

Figure 2

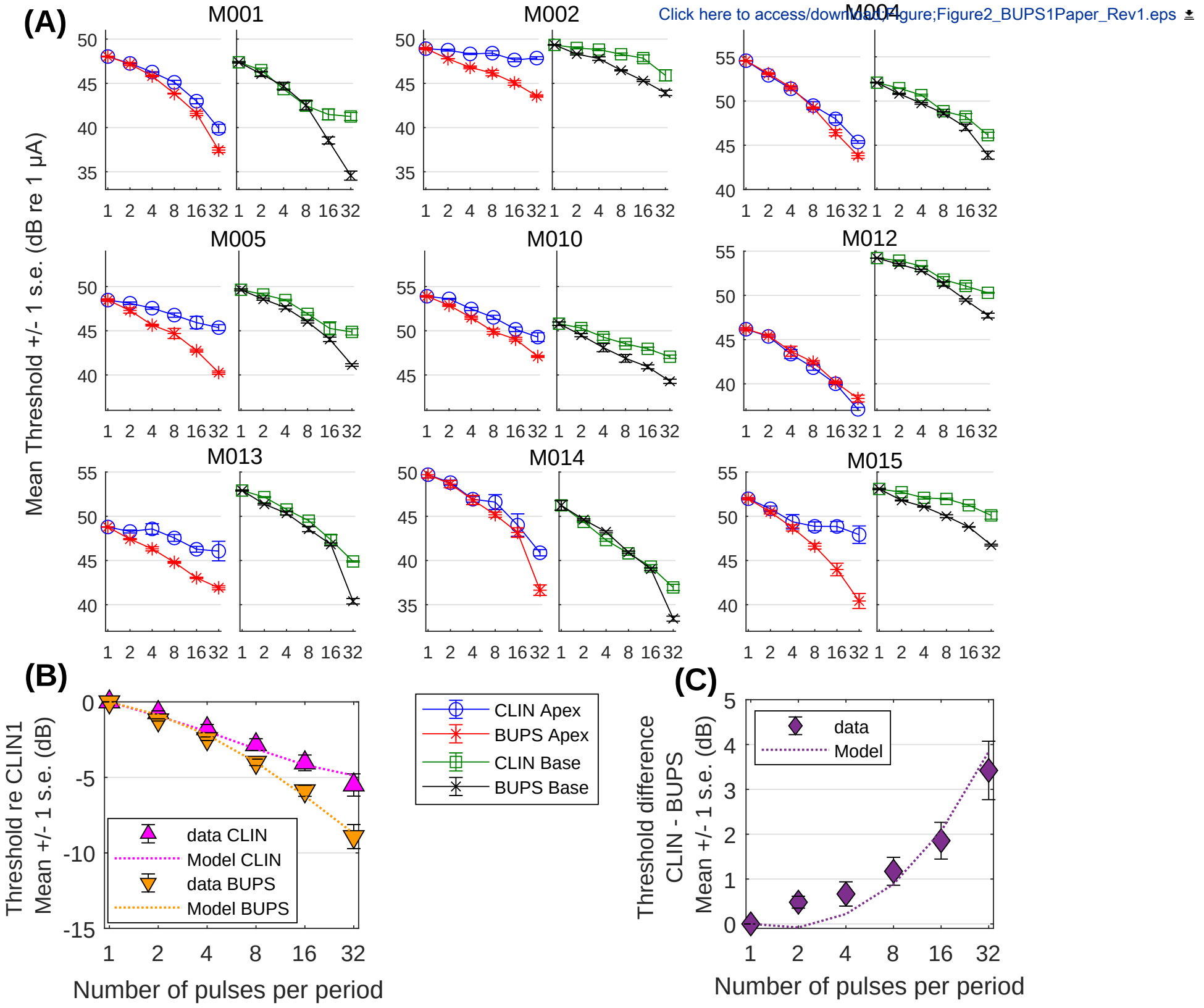

Figure 3

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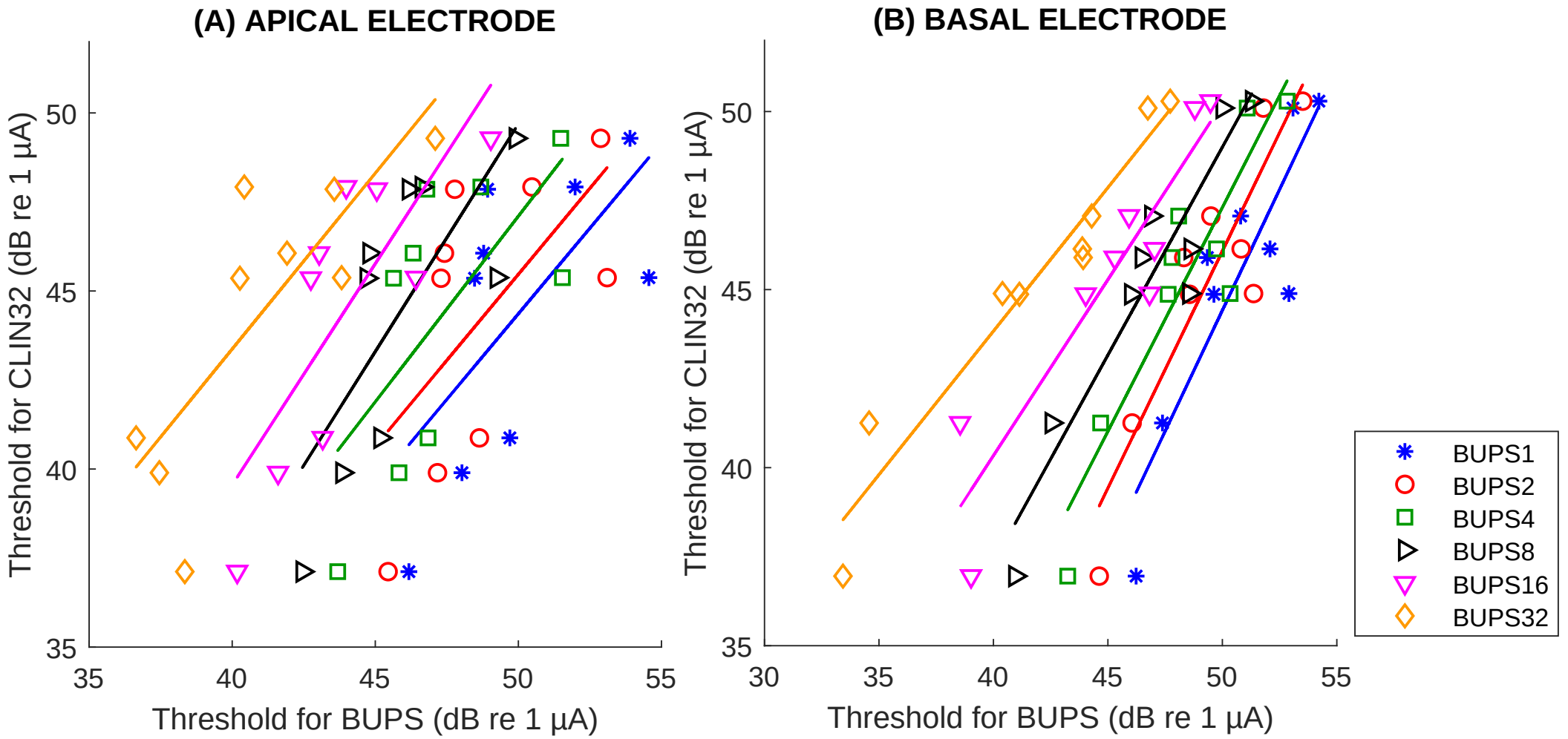

Figure 4

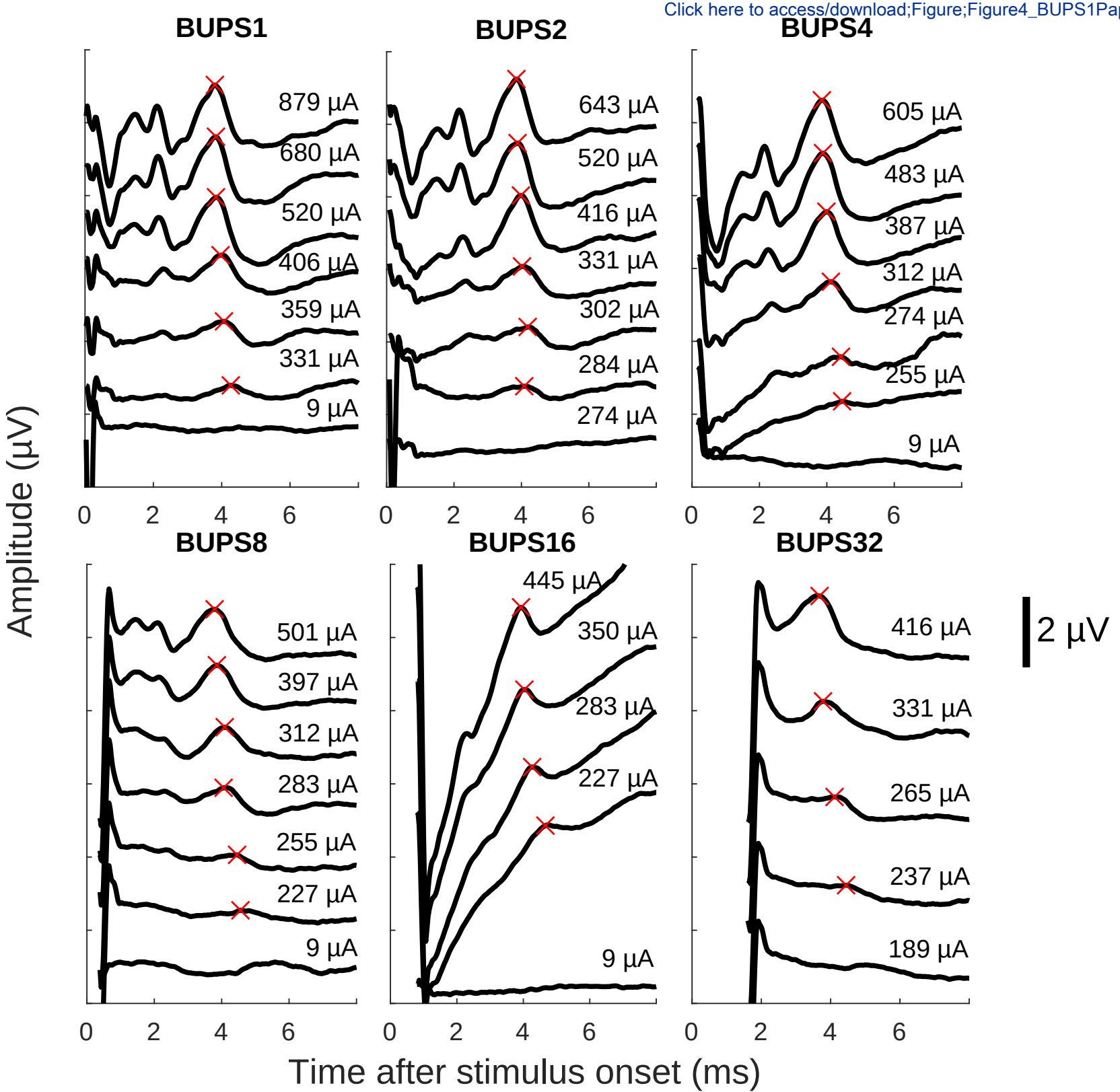

Figure 5

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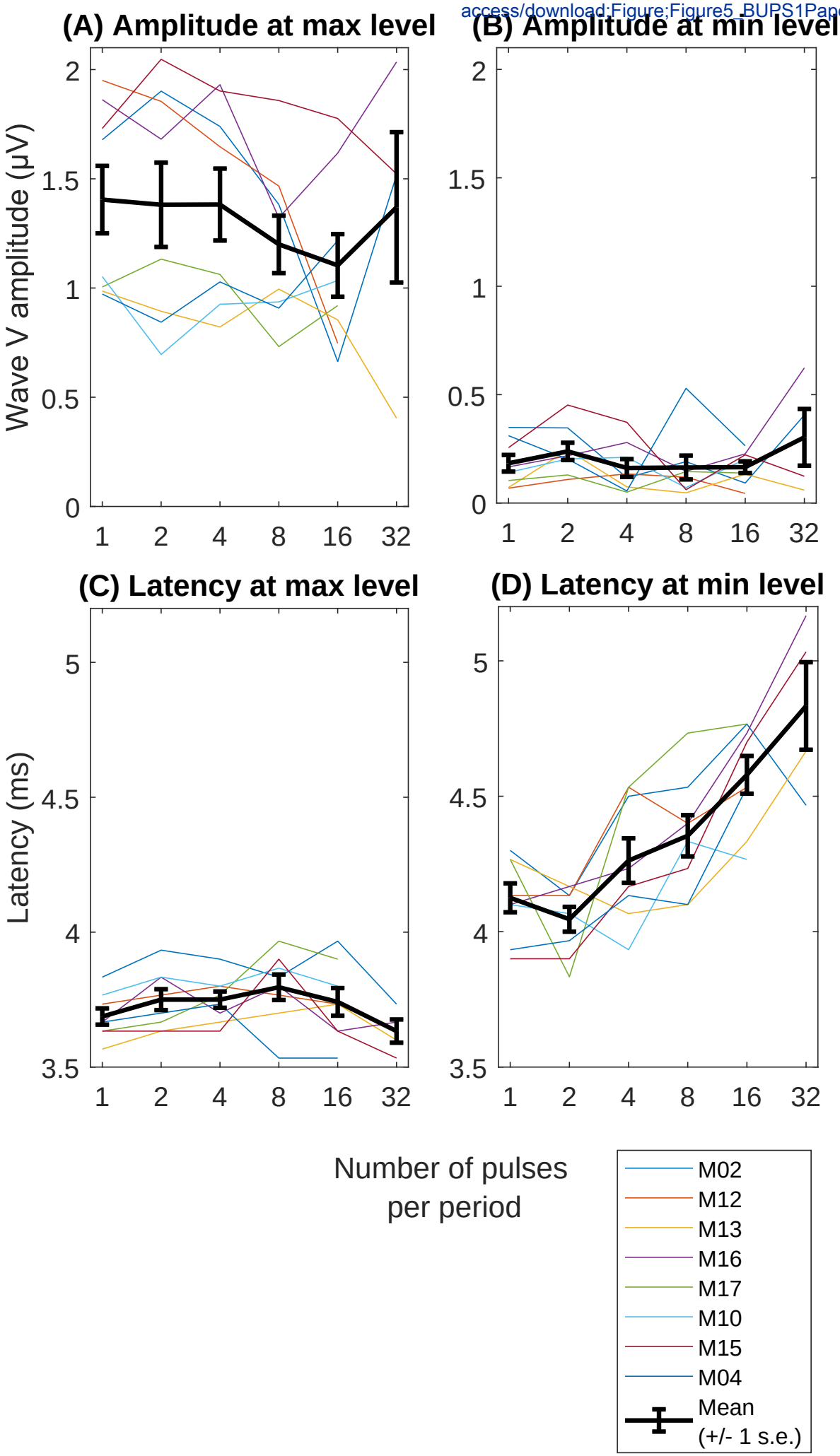

Figure 6

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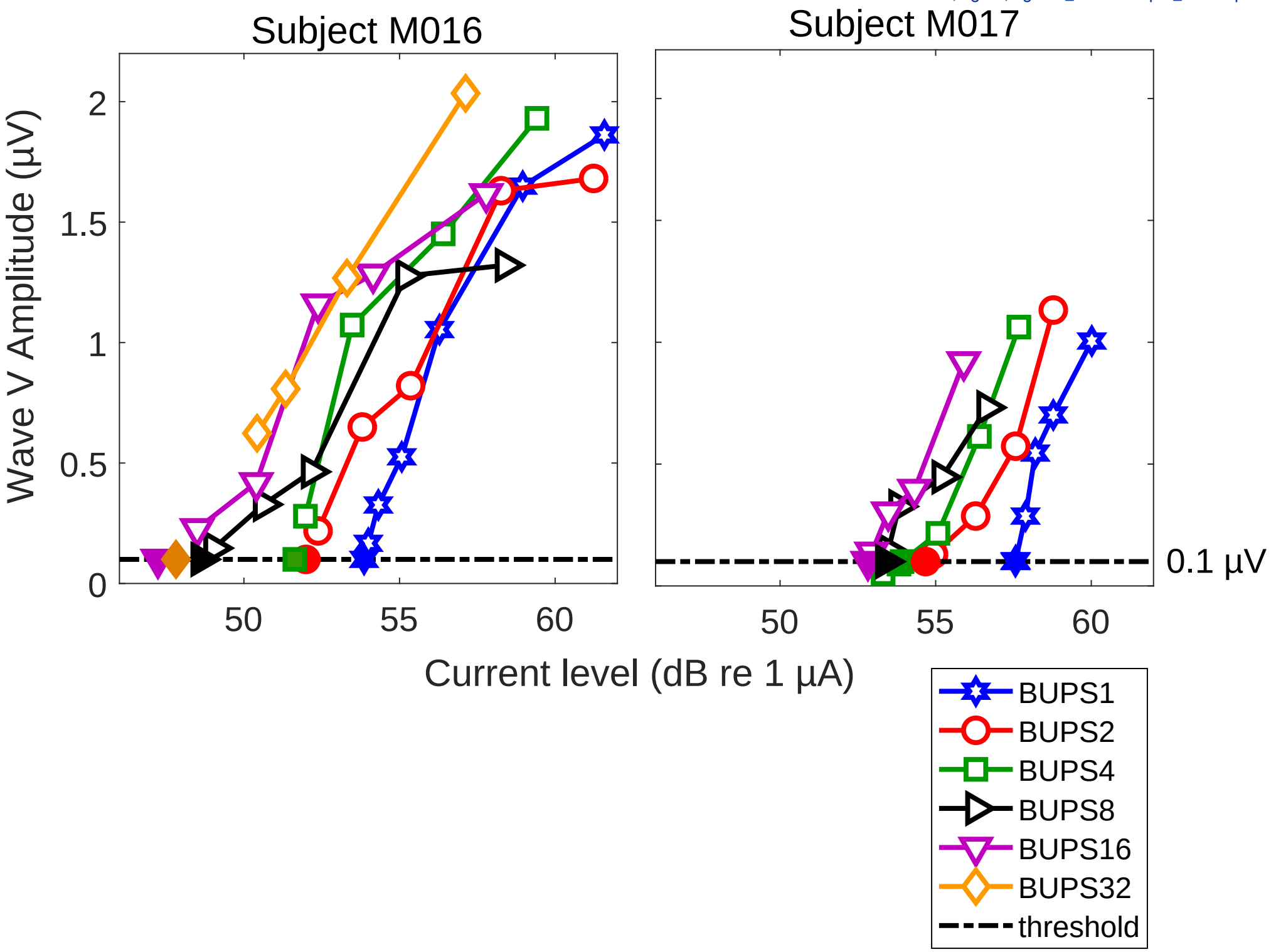

Figure 7

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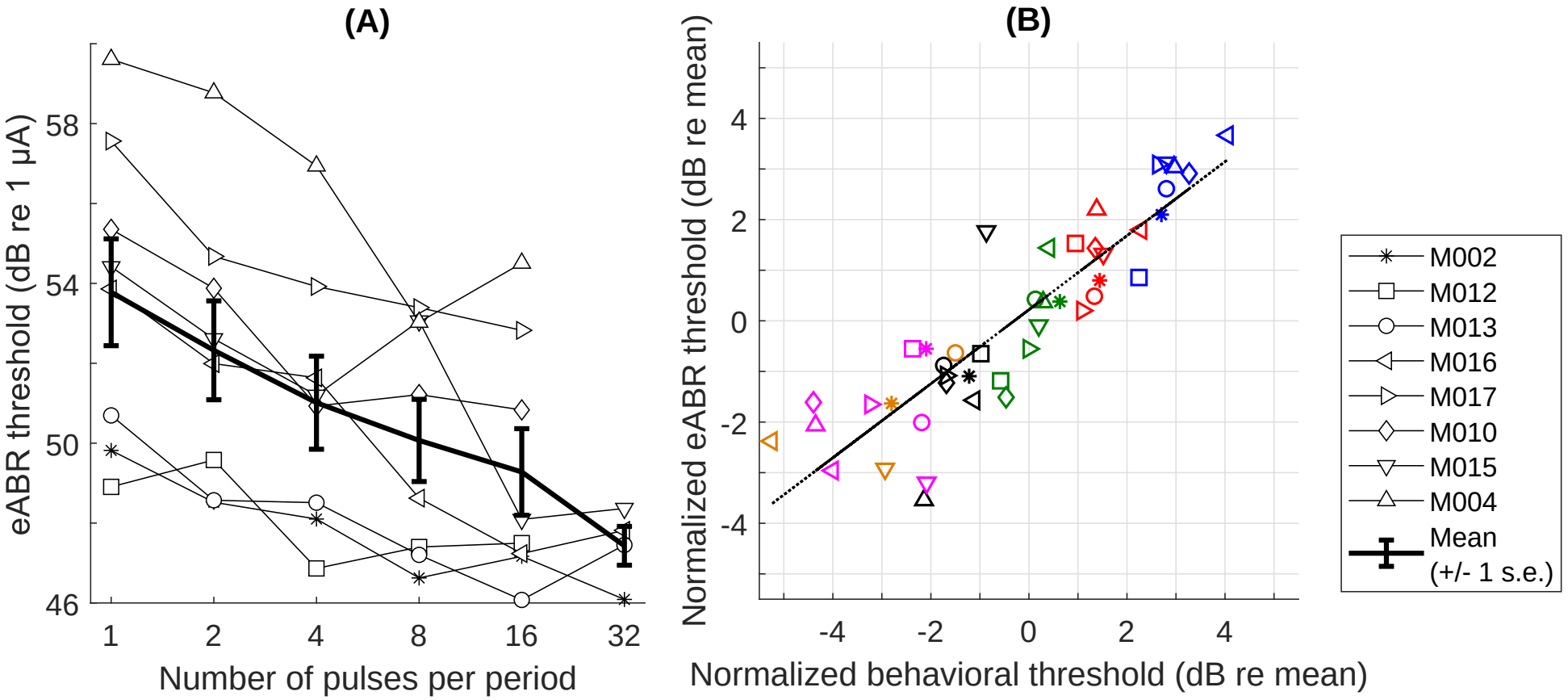

Figure 8

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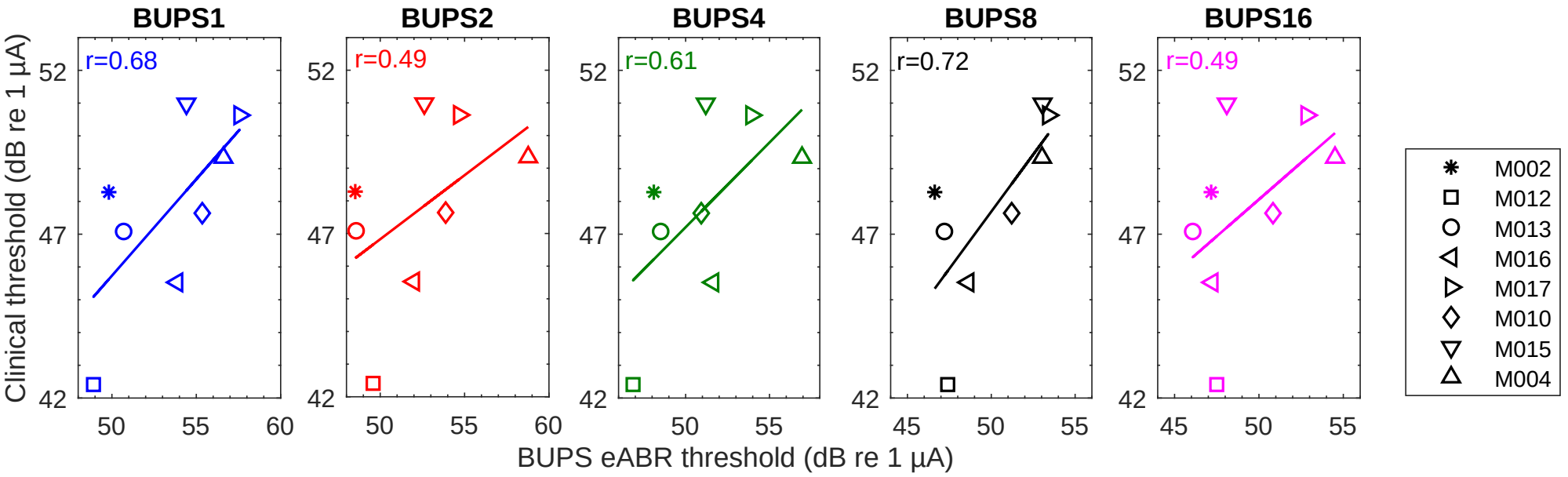

COVER LETTER

Dear Editor,

Please find our manuscript entitled “TEMPORAL INTEGRATION OF SHORT-DURATION PULSE TRAINS IN COCHLEAR IMPLANT LISTENERS: PSYCHOPHYSICAL AND ELECTROPHYSIOLOGICAL MEASUREMENTS” for submission to Hearing research. This is an original work that has not been published nor submitted to another journal.

Sincerely,

Olivier Macherey