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

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17 **Keywords** : temporal integration, electrically-evoked auditory brainstem response, objective
18 measures, cochlear implant fitting, neural facilitation

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34 **ABSTRACT**

1
2 35 While electrically-evoked auditory brainstem response (eABR) thresholds for low-rate pulse
3
4 36 trains correlate well with behavioral thresholds measured at the same rate, the correlation is
5
6 37 much weaker with behavioral thresholds measured at high rates, such as used clinically. This
7
8 38 implies that eABRs to low-rate stimuli cannot be reliably used for objective programming of
9
10 39 threshold levels in cochlear implant (CI) users. Here, we investigate whether the use of
11
12 40 bunched-up pulses (BUPS), consisting of groups of closely-spaced pulses may be used as an
13
14 41 alternative stimulus.

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16
17 42 Experiment 1 measured psychophysical detection thresholds for several stimuli having
18
19 43 a period of 32 ms in nine CI subjects implanted with a Med-EL device. The stimuli differed in
20
21 44 the number of pulses present in each period (from 1 to 32), the pulse rate within period (1000
22
23 45 pps and as high as possible for BUPS) and the electrode location (apical or basal). The
24
25 46 correlation between psychophysical thresholds obtained for a high-rate (1000 pps) clinical
26
27 47 stimulus and for the BUPS stimuli increased as the number of pulses per period of BUPS
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29 48 increased from 1 to 32. This first psychophysical experiment suggests that the temporal
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31 49 processes affecting the threshold of clinical stimuli are also present for BUPS.

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33
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35 50 Experiment 2 measured eABRs on the apical electrode of eight CI subjects for BUPS
36
37 51 having 1, 2, 4, 8, 16 or 32 pulses per period. For all subjects, wave V was visible for BUPS
38
39 52 having up to 16 pulses per period. The latency of wave V at threshold increased as a function
40
41 53 of the number of pulses per period, suggesting that the eABR reflects the integration of multiple
42
43 54 pulses at such low levels or that the neural response to each individual pulse increases along
44
45 55 the sequence due to facilitation processes. There was also a strong within-subject correlation
46
47 56 between electrophysiological and behavioral thresholds for the different BUPS stimuli. This
48
49 57 demonstrates that the drop in behavioral threshold obtained when increasing the number of
50
51 58 pulses per period of the BUPS can be measured electrophysiologically using eABRs. In
52
53 59 contrast, the across-subject correlation between eABR thresholds for BUPS and clinical
54
55 60 thresholds remained relatively weak and did not increase with the number of pulses per period.
56
57
58
59 61 Implications of the use of BUPS for objective programming of CIs are discussed.

62 1. INTRODUCTION

63
64 In cochlear implants (CIs), the current level needed to produce an auditory sensation in a given
65 subject may depend on many factors such as the position of the electrode(s) relative to the
66 auditory nerve fibers and the amount of neural survival (Bierer, 2010; Long et al., 2014;
67 Mesnildrey et al., 2020). Usually, fitting a CI requires clinicians to measure thresholds and
68 comfortable listening levels for each individual electrode. As these levels may change over
69 time, particularly during the first months after activation, this fitting process needs to be
70 repeated on multiple sessions. The time devoted to cochlear programming in clinics has,
71 therefore, increased tremendously over the past decades, especially since the number of CI
72 implantation is constantly increasing. In addition, fitting young children remains a complicated
73 process because there is currently no reliable method that allows the clinician to determine
74 thresholds and most comfortable levels objectively.

75 A lot of effort has been devoted into finding electrophysiological measures able to
76 predict the current levels needed for each electrode to produce a given sensation. Electrically-
77 evoked compound action potentials (eCAPs) and auditory brainstem responses (eABRs) are
78 two examples of such *objective* measures which are usually recorded using a relatively low
79 stimulation pulse rate (a few tens of Hz). At these low rates, eCAP and eABR thresholds
80 correlate well with psychophysical thresholds measured at the same rate (see Miller et al.,
81 2008 for a review). However, contemporary CIs use much higher pulse rates than that, usually
82 higher than 900 pps. Psychophysical thresholds measured at such high rates do not correlate
83 well with eCAP or eABR thresholds measured at low rates (Brown et al., 1999). The reason
84 for this is the across-electrode and across-subject variability in temporal integration. When
85 pulse rate increases, the psychophysical threshold drops but the magnitude of this drop is
86 variable both across subjects and across electrodes within a given subject (McKay et al.,
87 2013a).

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

90 may partly or fully be responsible for the observed variability in temporal integration. When
91 pulse rate is increased, the relative effects of neural refractoriness, accommodation, facilitation
92 and spike-rate adaptation may change and consequently modify the neural response to each
93 pulse. Although the relative contributions of these processes have not been unravelled in CI
94 users, it is expected that refractoriness, adaptation and accommodation reduce the response
95 to subsequent pulses in a pulse train whereas facilitation should have the opposite effect. In
96 addition, at a more central level, neural activity is believed to be temporally integrated across
97 different time scales. Even though the exact site(s) at which this temporal integration occurs
98 remain unclear, phenomenological threshold and loudness models usually implement this
99 process using a sliding temporal integration window with a short duration ranging from about
100 7 to 20 ms (McKay and McDermott, 1998; Carlyon et al., 2005; Macherey et al., 2007; McKay
101 et al., 2013b). These models predict that an increase in pulse rate will increase the number of
102 spikes falling into the window which will consequently lower the threshold or increase the
103 loudness.

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

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

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

124 2. EXPERIMENT 1: PSYCHOPHYSICAL THRESHOLDS

125 2.1. METHODS

126 2.1.1. *Subjects and Experimental Platform*

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

133 2.1.2. *Stimuli*

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

145 acronyms refers to the number of pulses present within a period. Note that when only 1 pulse
1 per period is present, BUPS1 and CLIN1 are identical. Therefore, in total, 11 stimulus
2 146
3
4 147 conditions were tested.

5
6 148 The experiment was repeated on two electrodes which were the most apical and the
7
8
9 149 most basal active electrode in each subject's processor map. In case the most basal electrode
10
11 150 produced uncomfortable percepts, the next most basal electrode was chosen instead. These
12
13 151 electrodes are indicated in Table 2 for each subject. The phase duration differed across
14
15 152 subjects and was chosen to match the longer phase duration of the two electrodes tested as
16
17 153 specified in the clinical maps of the subjects. Consequently, both the within-period pulse rate
18
19 154 and the duration of the BUPS sequences also varied across subjects (c.f. Table 2). The total
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21 155 stimulus duration (difference between the onset of the first pulse of the first sequence and the
22
23 156 offset of the last pulse of the last sequence) was fixed at a value as close as possible to 420
24
25 157 ms. Because some of our stimuli had large gaps between periods, this duration could slightly
26
27 158 vary across conditions (between 419.3 and 451.3 ms). An inspection of Donaldson et al.'s
28
29 159 (1997) data suggest that such small differences in stimulus duration should not affect detection
30
31 160 thresholds.

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36 162 *2.1.3. Procedure*

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38 163 Thresholds and Most Comfortable Loudness (MCL) levels were first approximately determined
39
40 164 using a loudness chart labeled from '0' (no sound) to '10' (too loud), label '1' corresponding to
41
42 165 detection threshold and label '6' to MCL. Detection thresholds were then measured adaptively
43
44 166 in a two-interval, two-alternative, three-down, 1-up forced choice task (Levitt, 1971). In each
45
46 167 trial, two intervals were presented separated by a 500-ms gap. The intervals were cued visually
47
48 168 on a computer screen. One interval contained the stimulus while the other contained no sound.
49
50 169 Subjects had to identify in which interval (1 or 2) a sound was present by clicking on one of
51
52 170 two virtual buttons displayed on the screen. The starting level was set to 25% of the dynamic
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54 171 range (expressed in μA) as initially measured using the loudness chart. This ensured that the
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56 172 stimulus was clearly audible at the beginning of the procedure. After three consecutive correct
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173 responses, the stimulus level was decreased while it was increased after each incorrect
174 response. The amount of increase and decrease varied during the procedure: it was equal to
175 0.6 dB before the first reversal, 0.3 dB before the third reversal and 0.15 dB subsequently.
176 Each procedure was resumed after 10 reversals and the threshold was defined as the mean
177 of the last 6 reversals. Feedback was provided after each trial.

2.1.4. Sessions

178
179 For each electrode, data were collected in blocks of 11 adaptive runs corresponding to each
180 stimulus condition presented in random order. Six data blocks (2 electrodes x 3 repeats) were
181 collected across three sessions lasting 2 to 3 hours each.

2.1.5. Modeling

182 The loudness model of McKay et al. (2013b), incorporating refractoriness and temporal
183 integration, was implemented and fitted to the threshold data averaged across electrodes and
184 subjects. For each stimulus, the model first determines the magnitude of the neural response
185 to each pulse relative to the very first pulse. Then, this activity is integrated by a sliding temporal
186 integration window whose shape derives from normal-hearing psychoacoustic data (Oxenham,
187 2001). Such temporal integration window models have previously been shown to account for
188 normal hearing behavior on a variety of tasks such as level increment detection or forward
189 masking (Oxenham & Moore, 1994; Moore et al., 1996; Oxenham, 2001). The shape of the
190 temporal window is given by:

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

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

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

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

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

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

222

223 2.2. RESULTS

224

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

227 correlations between BUPS and CLIN thresholds which was the main aim of this experiment,
1
2 228 all data except the CLIN1/BUPS1 thresholds were analyzed in a 3-way repeated measures
3
4 229 ANOVA with factors STIMULUS TYPE (CLIN and BUPS), ELECTRODE (apical and basal)
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6 230 and NUMBER OF PULSES per period (2, 4, 8, 16 and 32). In case Mauchly's test of sphericity
7
8 231 was significant, the Greenhouse-Geissler correction was applied and corrected degrees of
9
10 232 freedom are indicated below. The analysis revealed no effect of ELECTRODE ($F(1,8)=0.28$,
11
12 233 $p=0.6$) but significant effects of the main factors STIMULUS TYPE ($F(1,8)=41.08$, $p<0.001$)
13
14 234 and NUMBER OF PULSES ($F(1.11,8.92)=86.05$, $p<0.001$). Not surprisingly, thresholds
15
16 235 decreased when the number of pulses within each period increased. This decrease, averaged
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18 236 across electrodes, amounted to 1.2 dB and 1.9 dB per doubling of the number of pulses for
19
20 237 CLIN and BUPS, respectively (c.f. Figure 2B). The mean threshold difference between CLIN
21
22 238 and BUPS increased from 0.48 dB for 2 pulses to 3.43 dB for 32 pulses (significant NUMBER
23
24 239 OF PULSES by STIMULUS TYPE interaction: $F(1.62,12.95)=27.87$, $p<0.001$; c.f. Figure 2C).
25
26 240 Post-hoc t-tests with Bonferroni correction showed that the difference between CLIN and
27
28 241 BUPS was significantly larger for 32 pulses than for all other numbers of pulses and also larger
29
30 242 for 16 pulses than for 2 and 4 pulses. This specific result will be discussed in section 4.1. The
31
32 243 other interaction terms of the ANOVA were not significant.
33
34
35
36
37

38 244 The model predictions for BUPS and CLIN are shown by the dotted lines in Figure 2B
39
40 245 together with the mean thresholds across subjects. The model provides a good fit, showing
41
42 246 lower thresholds for BUPS than for CLIN for all conditions except for CLIN2/BUPS2.
43
44 247 Furthermore, the values of the fitted parameters α (0.3) and S (1.9) were in the same range as
45
46 248 the parameters fitted on the threshold vs. pulse rate functions of McKay et al. (2013b) for whom
47
48 249 α was roughly equal to 0.55 and the optimal S was 1.7. Similar to the subjects' data, the
49
50 250 predicted threshold difference between BUPS and CLIN (dotted line in Figure 2C) increases
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52 251 as a function of the number of pulses per period. This is specifically due to the shape of the
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54 252 temporal integration window which attenuates the response to additional pulses more when
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56 253 they are separated by large inter-pulse intervals. This makes the added pulses of CLIN
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58 254 contribute less and less to the response relatively compared to the added BUPS pulses.
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255 As our final aim was to investigate whether BUPS may be used to predict the threshold
1 of clinical stimuli, we calculated the correlation coefficients between the threshold for CLIN32
2 256 of clinical stimuli, we calculated the correlation coefficients between the threshold for CLIN32
3
4 257 (which is a regular 1000-pps stimulus, similar to pulse trains used clinically) and the threshold
5
6 258 for the different BUPS stimuli, i.e. for the different numbers of pulses per period. Figures 3A
7
8 259 and 3B show these correlations for the apical and basal electrodes, respectively. The
9
10 correlation coefficients ranged from 0.65 for BUPS1 to 0.80 for BUPS32 for the apical electrode
11 260
12 and from 0.88 to 0.97 for the basal electrode (c.f. Table 3). After applying Bonferroni-Holm
13 261
14 correction for multiple comparisons, none of the coefficients obtained for the apical electrode
15 262
16 remained significant ($p>0.05$) unlike the coefficients for the basal electrode which were all
17 263
18 significant ($p<0.05$). Importantly, Mann-Kendall tests showed for both electrodes a trend for
19 264
20 increased correlation with increases in the number of pulses ($S=13$, $p=0.008$ for both
21 265
22 electrodes).
23 266

267 We also investigated whether the across-electrode CLIN32 threshold difference could
28
29 268 be accounted for by BUPS thresholds by correlating the differences in threshold between the
30
31 apical and basal electrodes for the CLIN32 and the different BUPS stimuli, again as a function
32 269
33 of the number of pulses per period of the BUPS (c.f. Table 3). The correlation coefficients
34 270
35 ranged from 0.78 to 0.84 and were all significant after Bonferroni-Holm correction ($p<0.05$).
36 271
37 Here again, Mann-Kendall test revealed a significant trend for increased correlation with
38 272
39 increases in the number of pulses ($S=11$, $p=0.028$).
40 273

42 274 To summarize, these results demonstrate that an increasing part of the across-subject
43
44 275 threshold variance in clinical stimuli is captured by BUPS when increasing the number of
45
46 276 pulses per period. Therefore, BUPS appear to be a promising tool to use for eABR recordings.
47
48 More specifically, if we were able to predict the psychophysical threshold of BUPS stimuli using
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50 eABR, we may be able to further infer the psychophysical threshold of a regular clinical high-
51 278
52 rate pulse train (called CLIN32 here) from this measure.
53 279

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283 3. EXPERIMENT 2: ELECTROPHYSIOLOGICAL THRESHOLDS

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2 284
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4 285 The aim of Experiment 2 was to investigate the possibility of recording eABRs to BUPS with a
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6 286 large number of pulses and to test if the behavioral and electrophysiological thresholds for
7
8 287 BUPS correlate.

10 288 11 12 13 289 3.1. METHODS

14 290 15 16 17 291 *3.1.1. Subjects*

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19
20 292 Ten subjects took part in this experiment, including eight who already participated in
21
22 293 Experiment 1 (i.e., all subjects except M005) and two who did not (M016 and M017) . The
23
24 294 stimuli were delivered to the implant using the same hardware and a similar Matlab interface
25
26 295 as in Experiment 1. All measures were performed within a single session lasting 3 to 4 hours.

27 296 28 29 30 31 297 *3.1.2. Stimuli*

32
33 298 eABRs were recorded in response to six BUPS stimuli (N=1, 2, 4, 8, 16 and 32) presented on
34
35 299 the most apical electrode only (electrode 1). In order to reduce the influence of the stimulus
36
37 300 artefacts in the recordings, the BUPS were presented in alternating polarity. This means the
38
39 301 electrical pulses were all anodic-first in the odd-numbered periods of the stimulus and cathodic-
40
41 302 first in the even-numbered periods. The phase duration was the same as in Experiment 1 for
42
43 303 subjects who participated in both experiments or was equal to the phase duration used in the
44
45 304 clinical map for the other participants (c.f. Table 1).

46 305 47 48 49 50 51 306 *3.1.3. Threshold and MCL determination*

52
53 307 At the beginning of the session, comfortably-loud levels (labelled as '7' on the loudness chart)
54
55 308 were first measured for the six BUPS stimuli using the same loudness chart as in Experiment
56
57 309 1. Because eABR measures require long stimulus presentations (several thousands of
58
59 310 repetitions), we checked that the comfortably loud levels obtained with 420-ms stimuli were

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

325

326 *3.1.4. Electrically-evoked Auditory Brainstem Responses (eABR)*

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

335 To ensure that the neural responses were not contaminated by CI and muscular
336 artifacts, online averaging was enabled using artefact rejection for visualizing purposes. All
337 recording traces exceeding $\pm 30 \mu\text{V}$ between 2-ms and 10-ms post-stimulus time were rejected
338 from online averaging but were saved on the PC. Recording lasted until approximately three

339 thousand non-artefacted sweeps were reached for each stimulus and participant even though,
1
2 340 due to time restrictions or especially noisy recordings, this number was not always reached.
3
4 341 On average, 3417 sweeps (s.d. = 436) were obtained for each stimulus.
5

6 342 eABR functions were collected for BUPS stimuli in the following order N=1, 4, 16, 2, 8,
7
8 343 and 32. For each stimulus, the recording usually started at a subthreshold level of 9 μ A to be
9
10 344 able to compare the suprathreshold recordings to it and then at levels corresponding to 100,
11
12 345 75 and 50% of the perceptual dynamic range. If there still was a detectable response at 50%,
13
14 346 the level was further decreased to 25%, otherwise, it was increased to 62.5% (i.e., the level
15
16 347 between 50 and 75%). The dynamic range was subsequently bisected depending on whether
17
18 348 or not a visually-detectable response was present in the recording. Except for a few exceptions
19
20 349 detailed below where eABRs were difficult or impossible to observe, between 4 and 7
21
22 350 recordings (4.8 on average) containing a detectable response were obtained for each stimulus
23
24 351 and subject.
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31 353 3.1.5. Data analysis

32
33 354 All analyses were performed using custom MATLAB scripts (MathWorks). First,
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35 355 electrophysiological recordings were bandpass filtered between 70 and 2500 Hz using a 2nd
36
37 356 order Butterworth filter. Then, sweeps with activity exceeding $\pm 30 \mu$ V between 2-ms and 10-
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39 357 ms post-stimulus time were rejected as artefact. eABR traces were further averaged over a 0
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41
42 358 to 15-ms window. Wave V peaks and troughs were identified visually based on the latency and
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44 359 decrease in amplitude with decreasing stimulus level. Amplitudes were calculated as the
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46 360 difference (in μ V) between the positive peak and the following trough for wave V. Similar to
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48
49 361 Bierer et al. (2011), the eABR threshold was arbitrarily defined as the current level for which
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51 362 the amplitude of Wave V was 0.1 μ V. This threshold level was either interpolated from the
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53 363 input-output growth function or, in case the smallest response obtained had an amplitude larger
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55 364 than 0.1 μ V, it was *extrapolated* assuming a linear decrease of the amplitude growth function
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58 365 from the two lower-level responses collected. The latency of wave V was defined as the time
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60 366 difference between the positive peak and the stimulus onset.
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367 3.2. RESULTS

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2 368
3
4 369 Two out of the ten subjects either showed no measurable eABR responses (M001) or only a
5
6 370 response at the highest level for BUPS1 (M014). The following analyses are therefore
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8 371 restricted to the remaining eight subjects. An example of eABR responses for the different
9
10 372 BUPS stimuli is shown in Figure 4 for subject M002. It was possible to record eABRs in all
11
12 373 eight subjects up to 16 pulses. For 32 pulses, the artefact prevented us from observing wave
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14 374 V in 4 subjects. Long-lasting artefacts were also sometimes present for high numbers of
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16 375 pulses, as shown for BUPS16 in Figure 4. Because we were only able to measure responses
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18 376 to BUPS32 in 4 subjects, the analyses below encompass, except otherwise stated, the data
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20 377 obtained with all stimuli except BUPS32.
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26 379 *3.2.1. Analysis of wave V amplitudes at the minimum and maximum stimulation levels*
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28 380 Figures 5A and 5B show the amplitude of wave V at the maximum stimulation level
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30 381 (corresponding to a comfortably loud percept) and at the minimum level at which a response
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32 382 could be detected, respectively. The minimum and maximum amplitude values were analyzed
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34 383 in a two-way repeated measures ANOVA with within-subject factors NUMBER OF PULSES
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36 384 (five levels: 1, 2, 4, 8 and 16 pulses) and STIMULATION LEVEL (two levels: min and max
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38 385 amplitudes). Not surprisingly, the analysis showed significantly larger amplitudes at high
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40 386 stimulation level (main effect of STIMULATION LEVEL: $F(1,7)=74.7$, $p<0.001$). The NUMBER
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42 387 OF PULSES did not significantly affect wave V amplitudes ($F(4,28)=2.11$, $p=0.11$). Moreover,
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44 388 the sensitivity of eABRs to changes in stimulation level did not significantly change when
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46 389 increasing the number of pulses (STIMULATION LEVEL by NUMBER OF PULSES interaction:
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48 390 $F(4,28)=1.83$, $p=0.15$). Note that the above analysis on wave V amplitudes was performed for
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50 391 stimuli eliciting the same loudness percept (either near-threshold or at MCL). However, given
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52 392 both threshold and MCL decrease when increasing the number of pulses, this implies that for
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54 393 a fixed current level, the amplitude of wave V tended to be larger when the number of pulses
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56 394 in the stimulus increased.
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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

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

430 To test whether the *within-subject differences* in eABR thresholds obtained for different
431 BUPS were related to the change in behavioral thresholds, we normalized the threshold of
432 each subject relative to its mean threshold across conditions separately for behavioral
433 thresholds and for eABR thresholds. The data points from all subjects were then pooled
434 together, as shown in Figure 7B and further subjected to a correlation analysis. This
435 normalization caused an additional loss of 1 degree of freedom per subject. The result showed
436 a strong correlation between the normalized behavioral and eABR thresholds ($r=0.89$, $d.f.=34$,
437 $p<0.001$). This means that about 80% of the within-subject variance in behavioral thresholds
438 for the different BUPS conditions is captured by the eABR measurements.

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

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49 445 **4. DISCUSSION**

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51 447 In sections 4.1 to 4.3, we discuss the main observations of Experiments 1 and 2, compare the
52 448 results with data available in the literature and propose possible underlying mechanisms that
53 449 may account for them. Section 4.4 focuses on the use of BUPS for objective fitting of CIs,
54 450 which was the main aim of this study.

451 4.1. FACTORS AFFECTING PSYCHOPHYSICAL THRESHOLD DIFFERENCES
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2 452 BETWEEN CLIN AND BUPS
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6 454 Experiment 1 showed that psychophysical thresholds for both BUPS and CLIN
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9 455 decreased when increasing the number of pulses per period from 1 to 32. This result is
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11 456 consistent with previous studies showing that increasing the number of pulses within a stimulus
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13 457 (via an increase in stimulus duration and/or pulse rate) yields lower threshold (Donaldson et
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15 458 al., 1997; Kreft et al., 2004; McKay et al., 2013a; Zhou et al., 2015). Below we discuss two
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17 459 outcomes of Experiment 1: the fact that thresholds for BUPS were consistently lower than for
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20 460 CLIN for all numbers of pulses per period (c.f. Figure 2A, B) and that this threshold difference
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22 461 increased when increasing the number of pulses (c.f. Figure 2C).
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24 462 We showed that both outcomes could be accounted for by the temporal integration
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26 463 model of McKay et al. (2013b) which incorporates refractoriness and temporal integration. On
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28 464 the one hand, the smaller inter-pulse intervals of BUPS increase the effect of refractoriness
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31 465 within each stimulus period compared to CLIN. This tends to *decrease* the overall amount of
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33 466 activity for BUPS pulses. On the other hand, the smaller inter-pulse intervals of BUPS imply
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35 467 that the overall neural activity produced within a period is more compressed in time than for
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38 468 CLIN and, therefore, more efficiently integrated by the temporal window. With the set of model
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40 469 parameters derived from the data, this more efficient integration overcomes the effect of
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42 470 refractoriness and predicts lower thresholds for BUPS than for CLIN. Furthermore, as the
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44 471 number of pulses increases, more and more CLIN pulses start to fall outside the integration
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46 472 window, making the threshold difference between BUPS and CLIN even larger.
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49 473 In addition to the effects of refractoriness and central integration, several additional
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51 474 processes that were not modeled may also influence the response of auditory nerve fibers
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53 475 differently for CLIN and BUPS. Boulet et al. (2016) classified these processes depending on
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55 476 their timescale range of operation. Let us first consider the processes occurring shortly after
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58 477 each pulse (facilitation and accommodation). First, there is evidence from computational
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60 478 modeling (Boulet et al., 2016), single-unit recordings in cats (Zhang et al., 2007; Heffer et al.,
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1 479 2010) and eCAP measurements in humans (Hey et al., 2017) that the neural response to a
2 480 pulse can be enhanced when it is shortly preceded by a subthreshold pulse. The time constant
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4 481 of this *facilitation* phenomenon as measured in humans using eCAPs was found to be in the
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6 482 100-150 μ s range (Tabibi et al., 2019). It should, therefore, be especially strong for BUPS but
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8 483 less for CLIN, and should consequently produce the opposite effect as refractoriness, i.e.,
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11 484 lowering BUPS thresholds compared to CLIN. The potential effects of accommodation (also
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13 485 sometimes referred to as *subthreshold adaptation*) are more difficult to predict. Accomodation
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15 486 corresponds to the decreased response probability of a nerve fiber following a subthreshold
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17 487 stimulus and should therefore have an opposite effect to facilitation. However, modeling work
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19 488 suggests that the operating timescale of accomodation ranges from 0.5 to 5 ms, which is
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21 489 slightly longer than the operating timescale of facilitation (Boulet et al., 2016). Given the
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23 490 interpulse intervals within each BUPS sequence are much shorter than that (c.f. Table 2), it is
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25 491 possible that the responses to each pulse were not affected much by this process for BUPS.
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27 492 In contrast, the interpulse interval within each CLIN stimulus sequence is 1 ms suggesting
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29 493 accommodation may have played a larger role in this case. This mechanism could therefore
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31 494 be a contributor to the increased threshold difference between CLIN and BUPS observed when
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33 495 increasing the number of pulses per period.
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38 496 Finally, we have so far mostly reasoned on what may occur *within* each period of a
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40 497 stimulus. It is worth noting that all stimuli except CLIN32 show large gaps (> 16 ms) between
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42 498 the offset of a pulse sequence and the onset of the next pulse sequence (i.e. the next period).
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44 499 These large gaps may have the effect of partially resetting spike-rate adaptation between
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46 500 periods. This could, therefore, provide the opportunity to detect the stimulus across multiple
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48 501 periods (via “multiple looks”, Viemeister and Wakefield, 1991; Donaldson et al., 1997). This
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50 502 ability should be reduced for CLIN compared to BUPS because the gaps between periods are
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52 503 longer for BUPS. For example, CLIN32 is a constant-rate pulse train and has been shown in
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54 504 single-unit recordings to produce spike-rate adaptation across the whole stimulus duration
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56 505 (Zhang et al., 2007). It is, therefore, possible that a stronger across-period adaptation for CLIN
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2 506 than for BUPS also contributed to the increased threshold difference between BUPS and CLIN
3 507 when increasing the number of pulses per period.

4 508 In conclusion, although our threshold data can simply be accounted for by only considering
5 509 refractoriness and central integration, it is possible that they result from a more complex
6 510 interplay between these different processes, especially since the effects of facilitation,
7 511 accomodation and spike-rate adaptation may be partially counteracting each other and are
8 512 expected to depend on the interpulse interval.

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10 514 4.2. CAVEAT OF USING DIFFERENT PHASE DURATIONS ACROSS SUBJECTS

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12 516 As one aim of the present study was to use the same stimuli in the psychophysical and
13 517 electrophysiological experiments, we anticipated that it would be easier to measure eABRs for
14 518 pulse sequences having a short duration. This is why we chose to use the shortest phase
15 519 duration possible for each subject in both experiments. One caveat arising from this
16 520 experimental design is that the phase duration varied across subjects and may have provided
17 521 an additional source of across-subject variance in the threshold data. During the analysis, we
18 522 noticed that the subjects with relatively long phase durations were those showing the largest
19 523 threshold drop when increasing the number of pulses per period. Phase duration was shown
20 524 to correlate with the threshold difference between BUPS1 and BUPS32 ($r=0.71$, $d.f.=7$, $p=0.03$)
21 525 and also with the threshold difference between CLIN1 and CLIN32 ($r=0.69$, $d.f.=7$, $p=0.04$).
22 526 This means that the longer the phase duration the larger the threshold drop when increasing
23 527 the number of pulses per period. Thus it cannot be excluded that the stronger correlation
24 528 between BUPS thresholds and CLIN32 found when increasing the number of pulses per period
25 529 was also partly driven by this difference in phase duration.

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534 4.3. MEASURING eABR TO PULSE TRAINS

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4 536 Below, we list three main results of Experiment 2 and discuss them in relation with previously
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6 537 published data.

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11 539 (i) *The wave-V amplitude vs. current level growth functions collected in Experiment 2*
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13 540 *shifted towards lower level when increasing the number of pulses per period (c.f. Figure 6).*
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15 541 *This suggests that for a fixed current level, increasing the number of pulses per period tends*
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17 542 *to yield larger wave-V amplitudes.*

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22 544 Davids et al. (2008a) measured eABRs following 500-pps pulse trains with durations
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24 545 ranging from 2 ms (containing 2 pulses) to 10 ms. Their experiment was performed at a single
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26 546 “comfortably loud” current level held constant for all stimulus durations. Contrary to our results,
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28 547 they did not find larger wave-V amplitudes when keeping the current level fixed and increasing
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30 548 the duration. One possible explanation for this discrepancy could be the large rate difference
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32 549 between their stimuli and ours. In our case, the within-period pulse rate of BUPS varied from
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34 550 14.3 to 29.4 kpps whereas their pulse rate was only 500 pps. It is possible that increasing the
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36 551 number of pulses per period has a larger effect on the neural response amplitude at high rate,
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38 552 i.e. that it produces larger perceptual and electrophysiological changes. This explanation would
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40 553 be consistent with behavioral data showing that the slope of the threshold vs. stimulus duration
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42 554 functions are steeper at high (1000 pps) than at low pulse rate (100 pps; Pfingst et al., 1991).
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44 555 Moreover, our observation that wave-V amplitude increases when increasing the number of
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46 556 pulses per period is consistent with the results of Kodera et al. (1983) showing that the ABR
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48 557 of *normal-hearing* cats increases with stimulus duration up to 2-4 ms at 2000 Hz and up to 4-
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50 558 8 ms at 500 Hz.

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560 (ii) The wave-V latency (relative to stimulus onset) of the eABR responses of Experiment
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2 561 2 was similar across the different stimuli at most comfortable loudness levels but increased as
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4 562 a function of the number of pulses per period at low level.
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9 564 In another study, Davids et al. (2008b) fixed the stimulus duration of their stimuli at 2
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11 565 ms and measured eABR responses for pulse trains having different rates (varying from 500 to
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13 566 3600 pps) and also for a single pulse. They found no effect of stimulus condition on the mean
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15 567 wave-V latency measured relative to the *offset* of the stimulus. Expressing their latencies in a
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17 568 similar way as we did (i.e., relative to the onset), this may imply that the response latencies of
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19 569 their 2-ms pulse trains were actually longer than that of their single pulse. This would be
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22 570 consistent with our observation that at low level, latency increases with the number of pulses
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24 571 per period. Similarly, Kodera et al. (1983) found that the ABR latency of their acoustically-
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26 572 stimulated cats increased as a function of duration and that this increase was larger at low
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29 573 levels.

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31 574 This leads us to discuss the cause of these eABR amplitude (i) and latency (ii)
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33 575 increases as a function of the number of pulses per period. We think it may be the result of two
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35 576 mechanisms. First, it is possible that wave V reflects the output of an *integration* of neural
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37 577 activity across a few milliseconds, which would be consistent with the normal hearing cats'
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39 578 data previously mentioned (Kodera et al., 1983) and would explain why the eABR response
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42 579 amplitude tends to grow when increasing the number of pulses (keeping the current level
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44 580 fixed). Concerning the response latencies, at low levels, the probability of auditory nerve fiber
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46 581 discharge may be similar for the different pulses within the BUPS sequence, thereby inducing
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49 582 an increase in latency when increasing the number of pulses. At high levels, however, most
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51 583 fibers may discharge in response to the first pulse and be refractory to the subsequent pulses,
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53 584 yielding similar response latencies for the different BUPS stimuli. This *integration* explanation
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55 585 seems, however, difficult to reconcile with the observation by Davids et al. (2008b) that the
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58 586 eABR response amplitude was not larger for a 2-ms, 3600-pps pulse train than for a single
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60 587 pulse presented at the same current level. Or it would mean that the very first pulse of their 2-

588 ms stimulus contributed almost exclusively to the neural response, e.g. due to nerve fibers
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2 589 being in their refractory state or strongly adapted for the subsequent pulses. Another
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4 590 explanation could be that the increased amplitude and latency do not arise from the integration
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6 591 of neural activity but are the result of neural facilitation processes and that wave V represents
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8 592 the aggregate (compound) of the responses to several individual pulses. Facilitation is
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11 593 expected to be stronger at our very high rates (BUPS) than at 3600 pps and is also more
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13 594 effective at low than at high levels (Tabibi et al., 2019). It is therefore possible that at low
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15 595 current levels, the response to individual pulses becomes larger and larger across the BUPS
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17 596 period. Such a response build-up could in principle yield an increased amplitude of the
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19 597 compound response (larger wave-V amplitude) and may also shift the *peak* of the compound
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21 598 response in time, thereby producing an increase in wave-V latency. At high levels, however,
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24 599 as previously mentioned, the response may be dominated by the first pulse(s) in the train with
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26 600 the later pulses contributing less because of refractoriness.

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31 602 *(iii) eABR thresholds (defined as the current level needed to reach a wave-V amplitude*
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33 603 *of 0.1 μ V) decreased when increasing the number of pulses per period.*

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38 605 In contrast, Davids et al. (2008b) did not find an effect of pulse rate on eABR thresholds.
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40 606 More specifically, threshold was not different between their single-pulse stimulus and their 2-
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42 607 ms pulse trains (which contained 8 pulses at most). The cause of this discrepancy with our
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44 608 data also remains unclear but may be due to different definitions of thresholds between studies
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46 609 (lowest current at which wave V could be identified for Davids et al. vs. arbitrary fixed-amplitude
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48 610 response here) or, once more, to differences in pulse rate. As discussed previously, the higher
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51 611 rate used in the present study is expected to yield a stronger effect of neural facilitation and a
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53 612 more efficient integration within the hypothetical temporal integration window.

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616 4.4. IMPLICATIONS FOR CI FITTING

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4 618 Independently of the mechanisms underlying our observations, Experiment 2 showed a strong
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6 619 within-subject correlation between behavioral and eABR thresholds for the different BUPS
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8 620 stimuli. This suggests that part of the temporal integration observed behaviorally can be
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10 621 captured by the eABR measurements. Note, however, that the final aim would be to use these
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12 622 stimuli to predict clinical thresholds in patients. For it to be possible, it would be necessary that
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14 623 the eABR thresholds for BUPS also correlate with clinical thresholds *across-subjects*. In
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16 624 Experiment 2, there was no increased correlation between BUPS eABR thresholds and
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18 625 behavioral clinical thresholds when increasing the number of pulses within the BUPS
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20 626 sequence. This contrasts with the increased correlation observed in Experiment 1 when
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22 627 comparing clinical and *behavioral* BUPS thresholds. While this result does not appear
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24 628 encouraging, we think it is premature to draw conclusions on the potential usefulness of BUPS
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26 629 for clinical threshold predictions for two reasons. First, as already stated in section 4.2, the
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28 630 across-subject correlations reported in the present study may all be affected by across-subject
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30 631 differences in phase duration and should, therefore, be taken with caution. Second, the size of
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32 632 our subject sample remains small and Experiment 2 should only be considered as a first
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34 633 attempt to evaluate the possibility to record eABRs to BUPS. Experiments involving a larger
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36 634 number of subjects tested with the same phase duration are currently running in our labs to
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38 635 identify if BUPS can provide a method to reliably predict clinical thresholds using eABR
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40 636 measurements.
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55 642 PDOC-0022).
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752 **TABLES**

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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

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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 μ s.

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Subject	Electrodes tested	Phase dur. (μ s)	Within-period rate (kpps)	BUPS1 dur. (μ s)	BUPS2 dur. (μ s)	BUPS4 dur. (μ s)	BUPS8 dur. (μ s)	BUPS16 dur. (μ s)	BUPS32 dur. (μ s)
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

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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.

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#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 ($p < 0.05$).

777 **FIGURE CAPTIONS**

1 778
2 779
3 780 **Figure 1:** Schematic representation of the CLIN and BUPS stimuli used in Experiments 1 and
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5 781 2. The pulse rate within period was 1000 pps for CLIN and was as fast as possible for BUPS.
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10 783 **Figure 2:** (A) Results of Experiment 1 showing, for each subject, the psychophysical thresholds
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12 784 as a function of the number of pulses per period for CLIN and BUPS and for the two electrodes.
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14 785 (B) Symbols: Mean threshold drop (averaged across electrodes and subjects) as a function of
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16 786 number of pulses expressed relative to the threshold for the CLIN1/BUPS1, Dotted line: model
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18 787 fit using McKay et al.'s temporal integration model. (C) Mean threshold difference between
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20 788 CLIN and BUPS (averaged across electrodes and subjects) as a function of number of pulses
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22 789 and model predictions (dotted line).
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28 791 **Figure 3:** Evolution of the correlation coefficient between CLIN32 threshold and BUPS
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30 792 threshold as a function of the number of pulses within a BUPS period. Panels (A) and (B) show
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32 793 the across-subject correlations for the apical and basal electrodes, respectively. The values of
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34 794 the correlation coefficients are given in Table 3.
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39 796 **Figure 4:** Example of eABR waveforms collected in subject M002 for the different BUPS
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41 797 conditions. The waveforms were shifted vertically for better visualization and ordered based
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43 798 on the current level. The tick spacing on the y-axis corresponds to an amplitude difference of
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45 799 2 μ V. The red crosses show the peak of wave V; this time point was taken to compute the
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47 800 latencies. The amplitudes were assumed to be equal to the difference in amplitude between
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49 801 this peak and the next trough. The traces do not all start at time 0 because the trigger was sent
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51 802 to the recording system when the last pulse of each period was presented.
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56 804 **Figure 5:** (A) and (B) Wave V amplitudes measured at the maximum and minimum levels,
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58 805 respectively, for the different subjects and across-subject mean. (C) and (D) Wave-V latencies
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806 measured at the maximum and minimum levels, respectively, for the different subjects and
807 across-subject mean. For all panels, the thin lines represent individual subjects while the thick
808 line shows the mean and standard error across subjects.

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

816
817 **Figure 7:** (A) eABR thresholds as a function of number of pulses per period for individual
818 subjects and mean across subjects; (B) within-subject correlation between eABR and
819 behavioral thresholds for BUPS stimuli. Each color represent one BUPS condition, using the
820 same color code as in Figure 6.

821
822 **Figure 8:** Across-subject correlations between BUPS eABR thresholds and clinical thresholds
823 measured behaviorally for different number of pulses per BUPS period.

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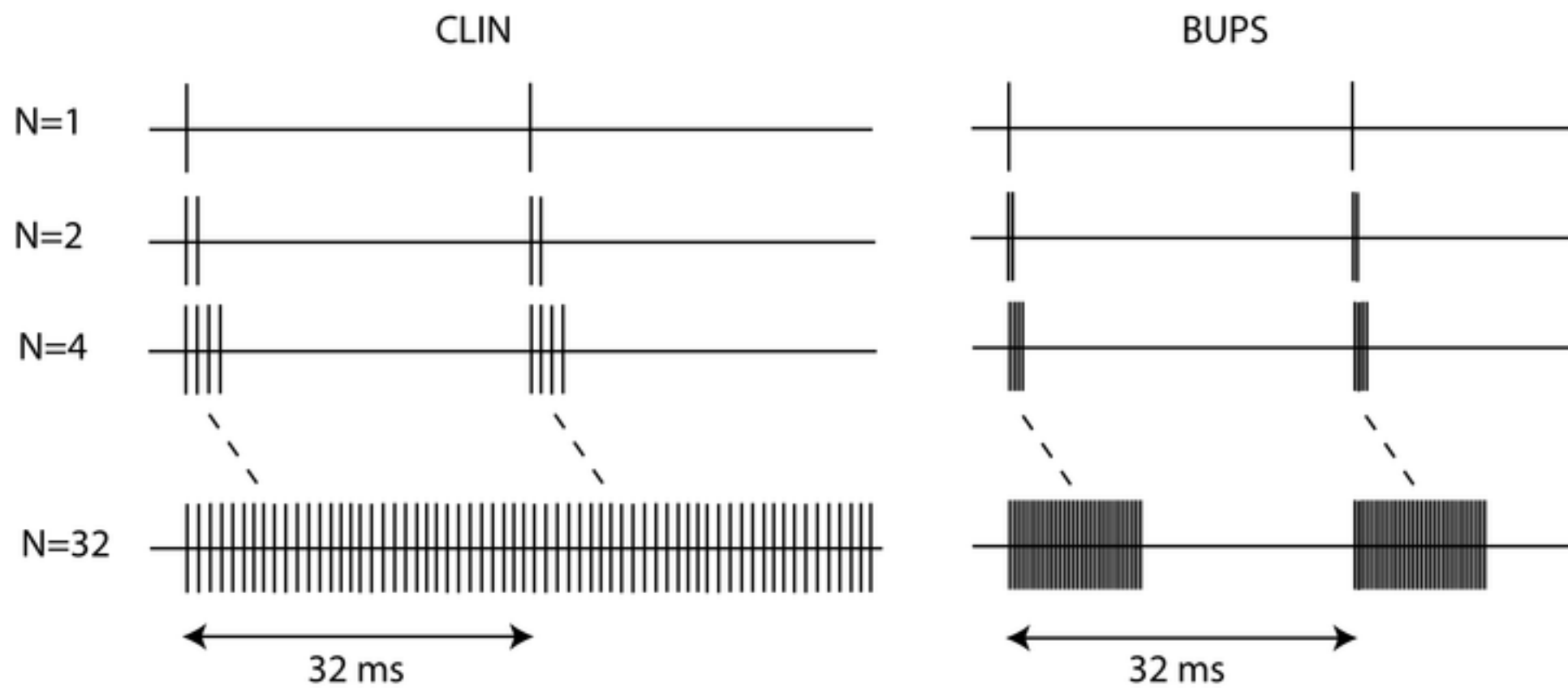
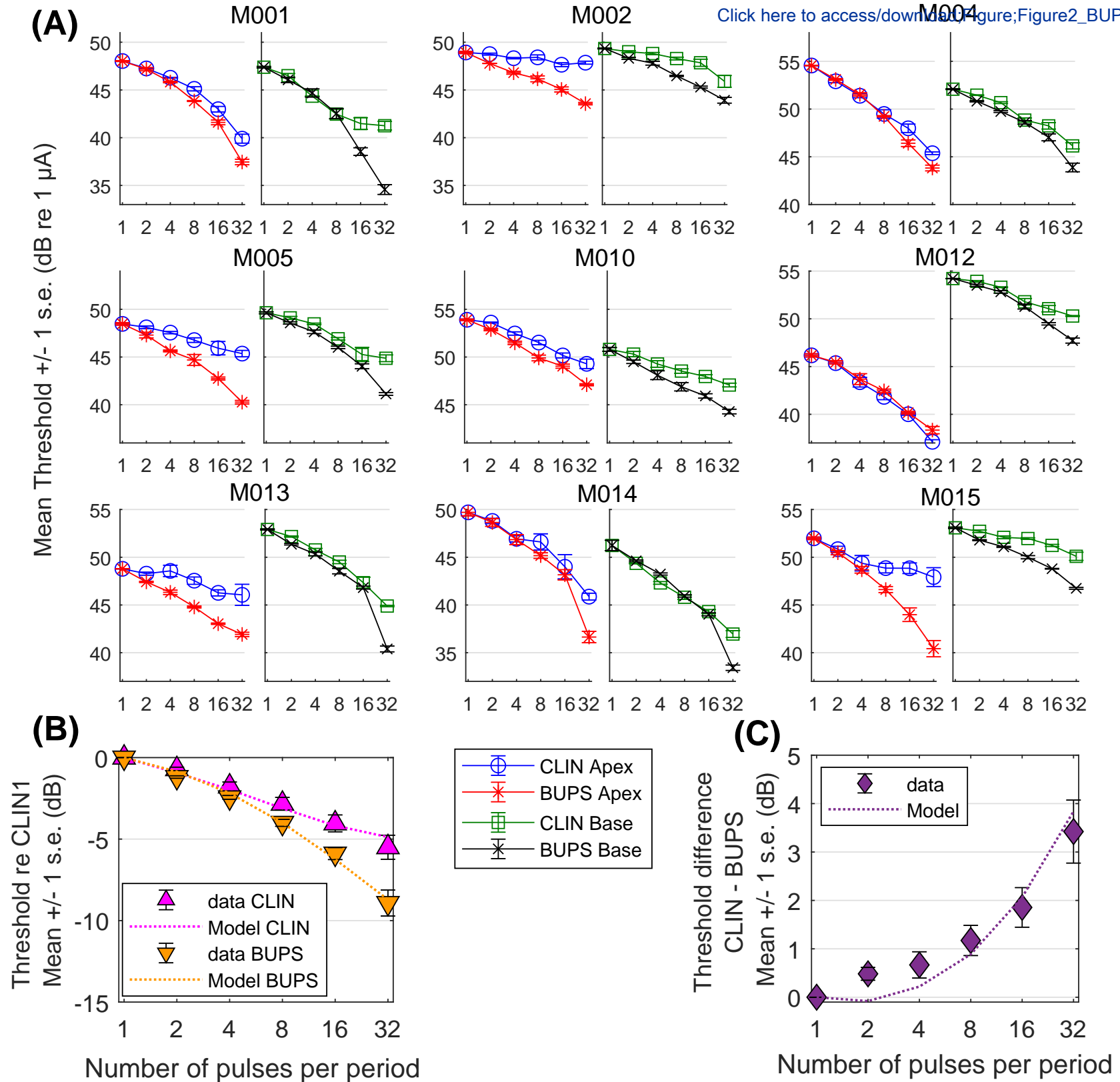


Figure 2

[Click here to access/download/Modeling/Modeling_Figure2_BUPS1Paper_Rev1.eps](#)



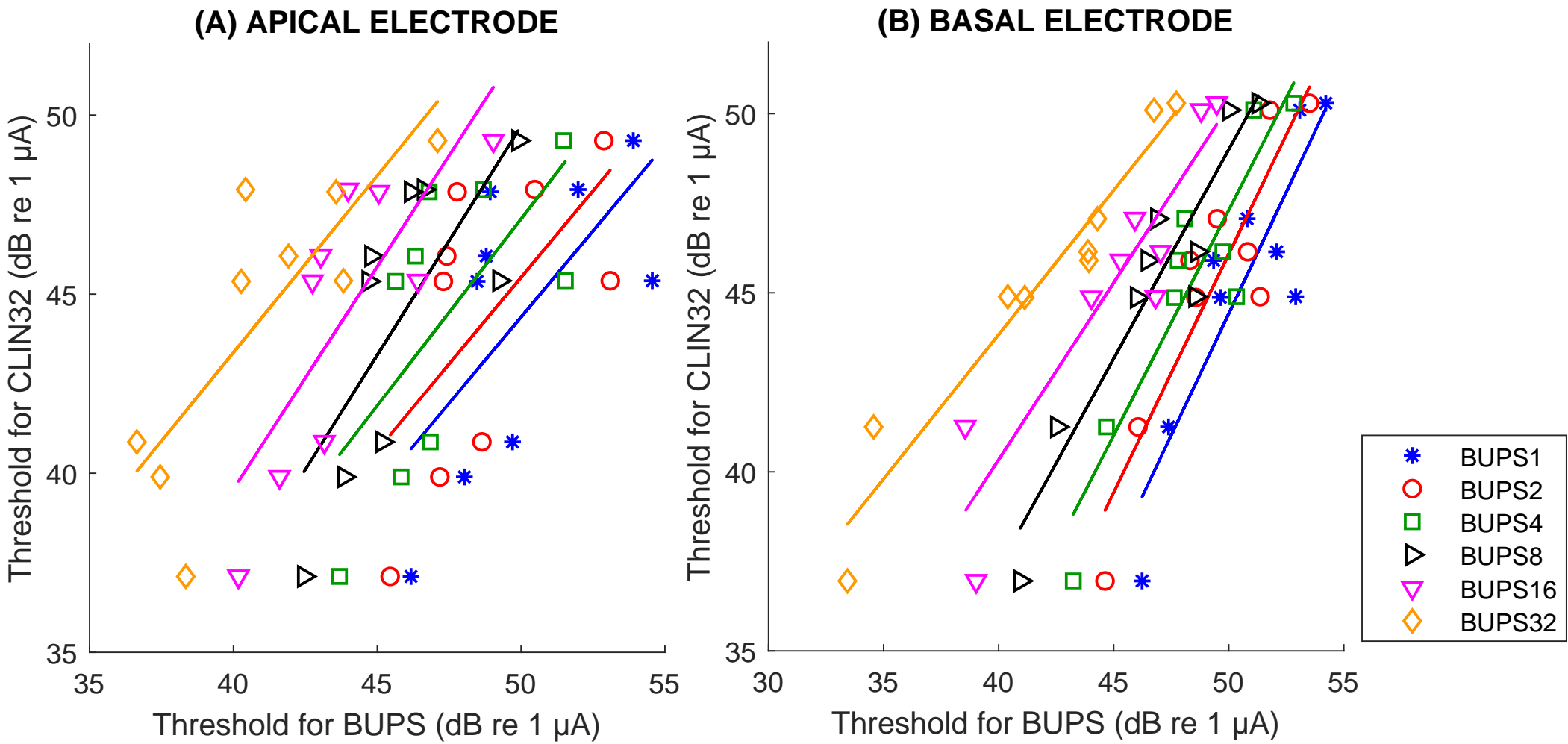
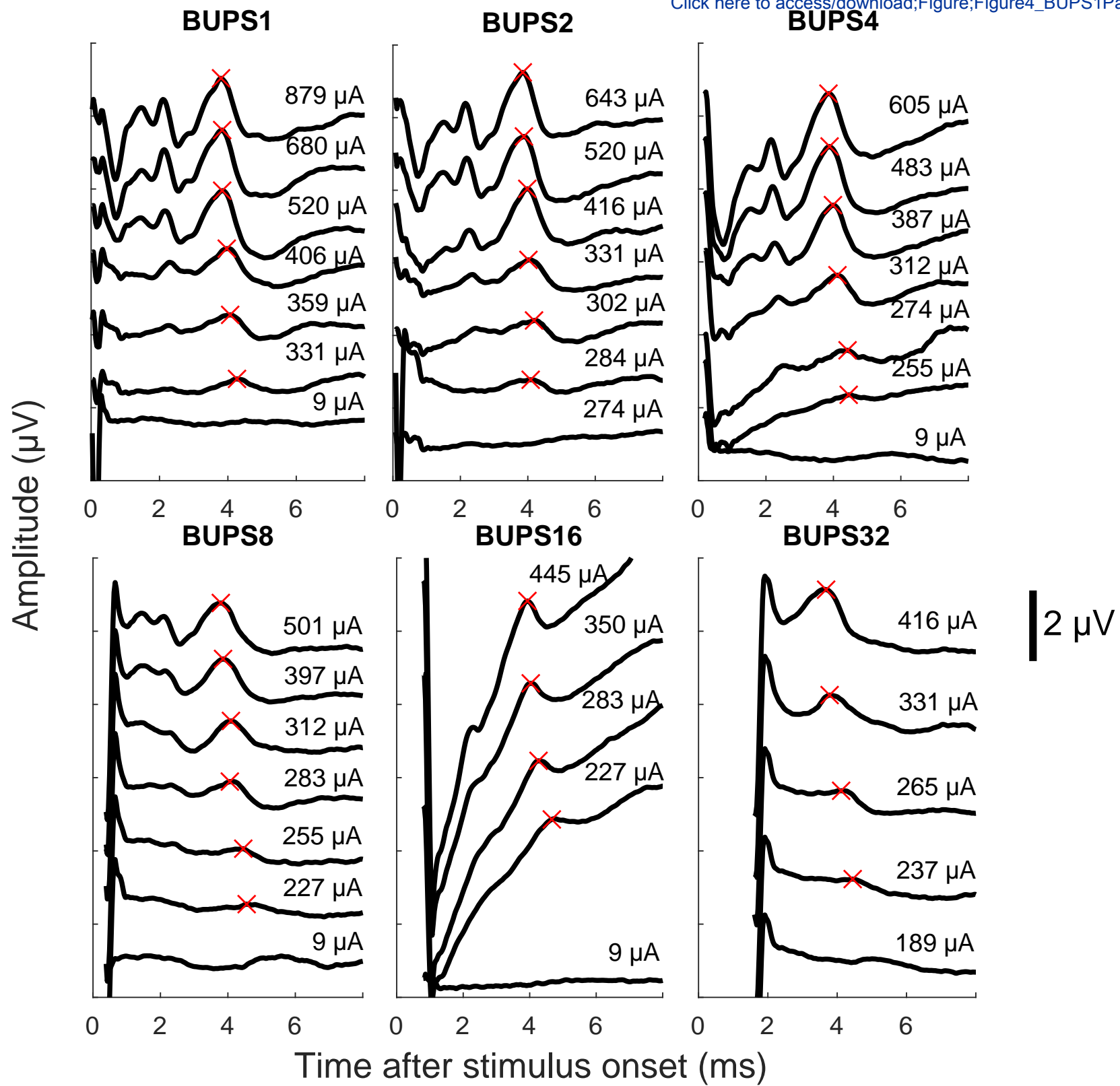


Figure 4



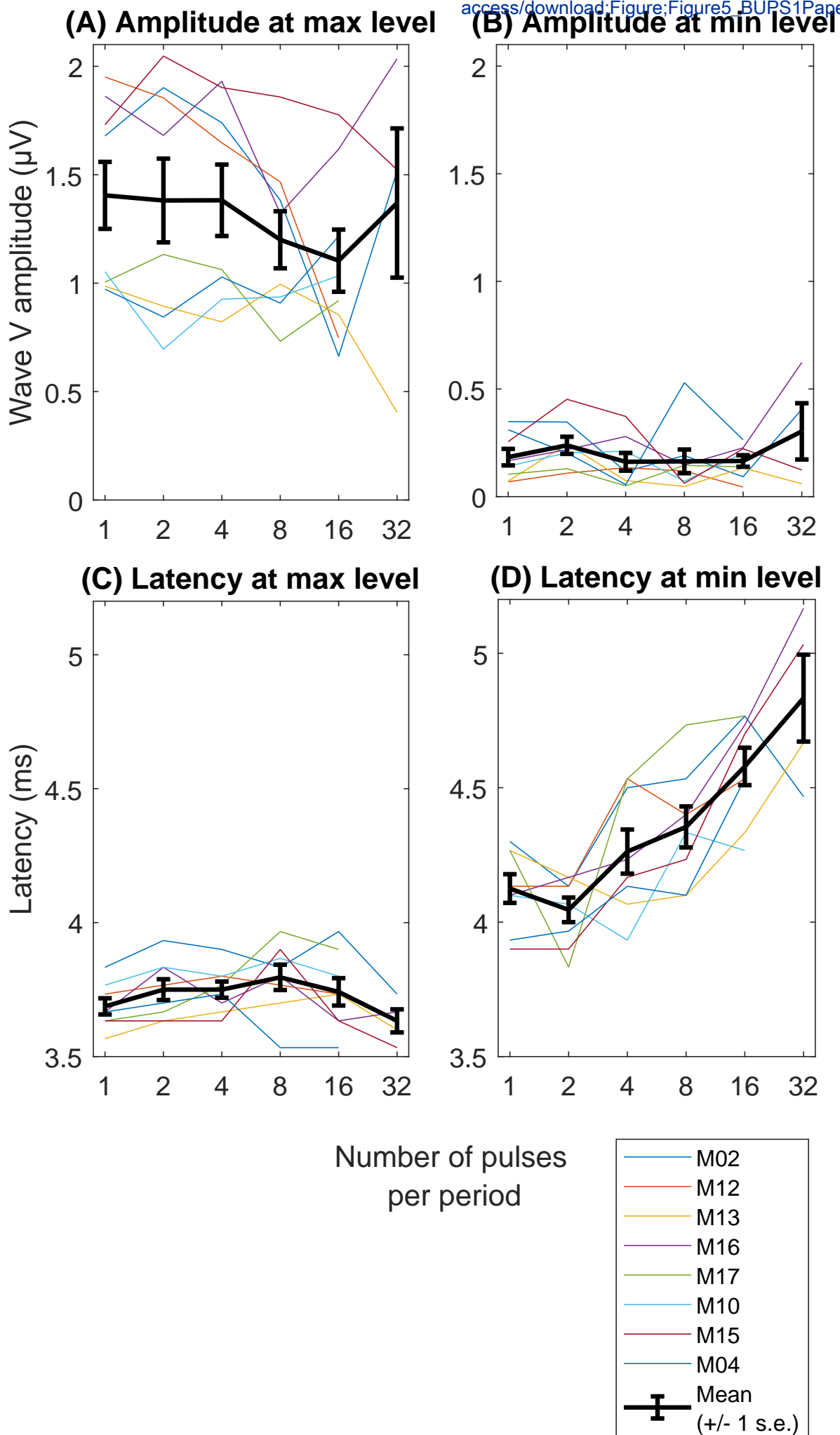
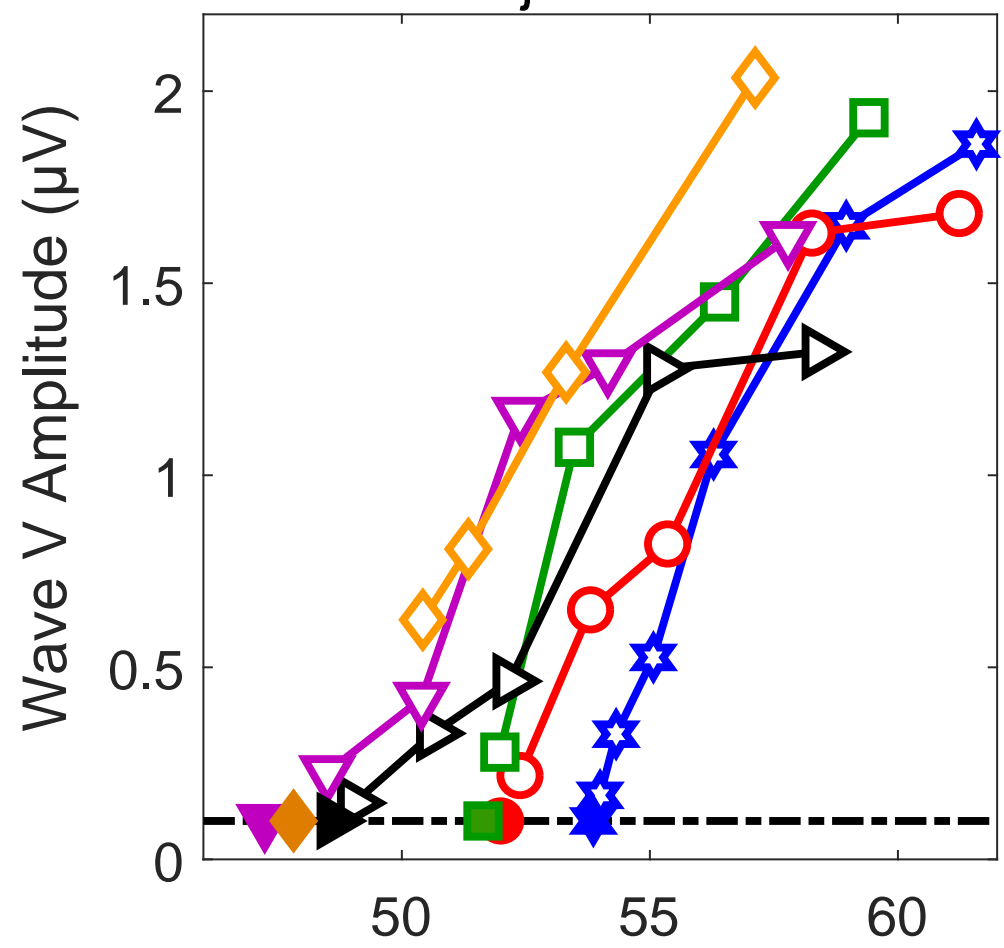
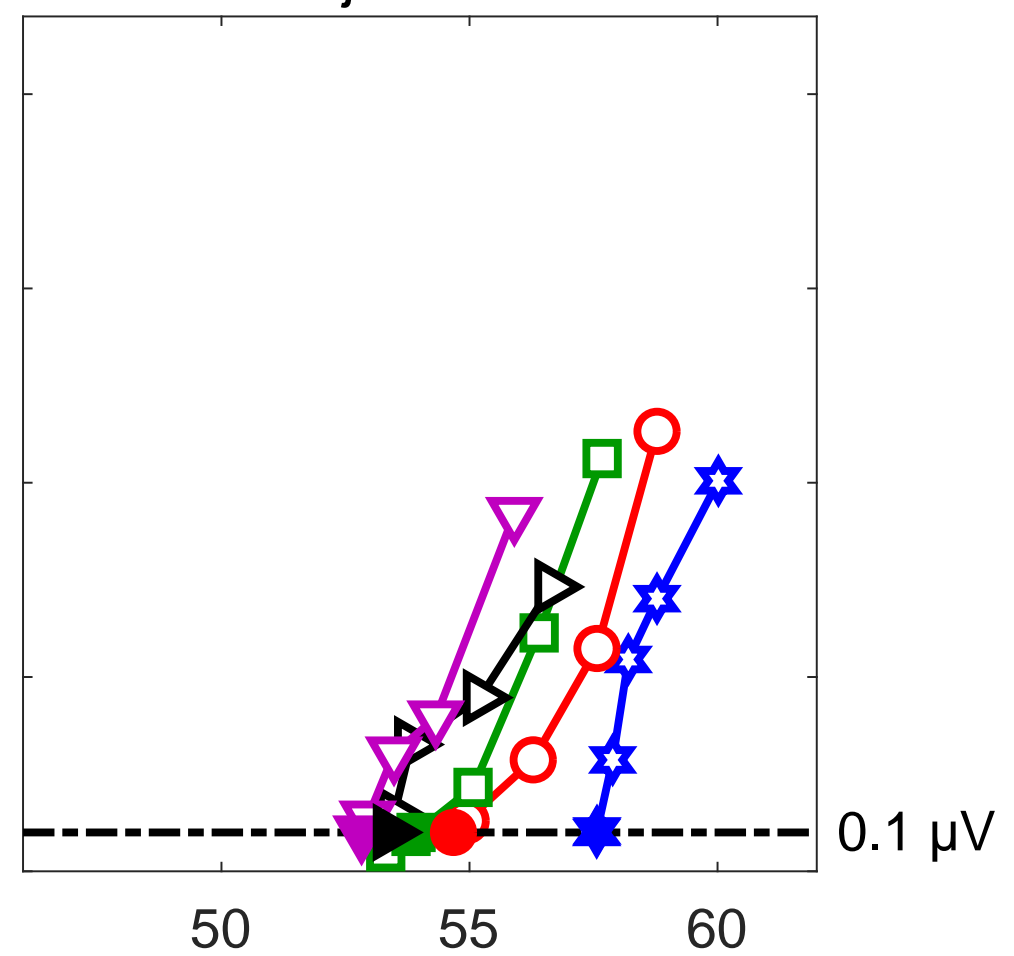


Figure 6

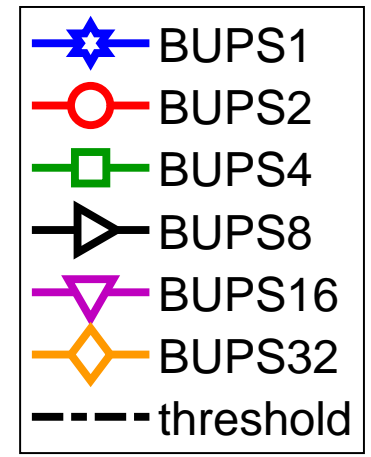
Subject M016

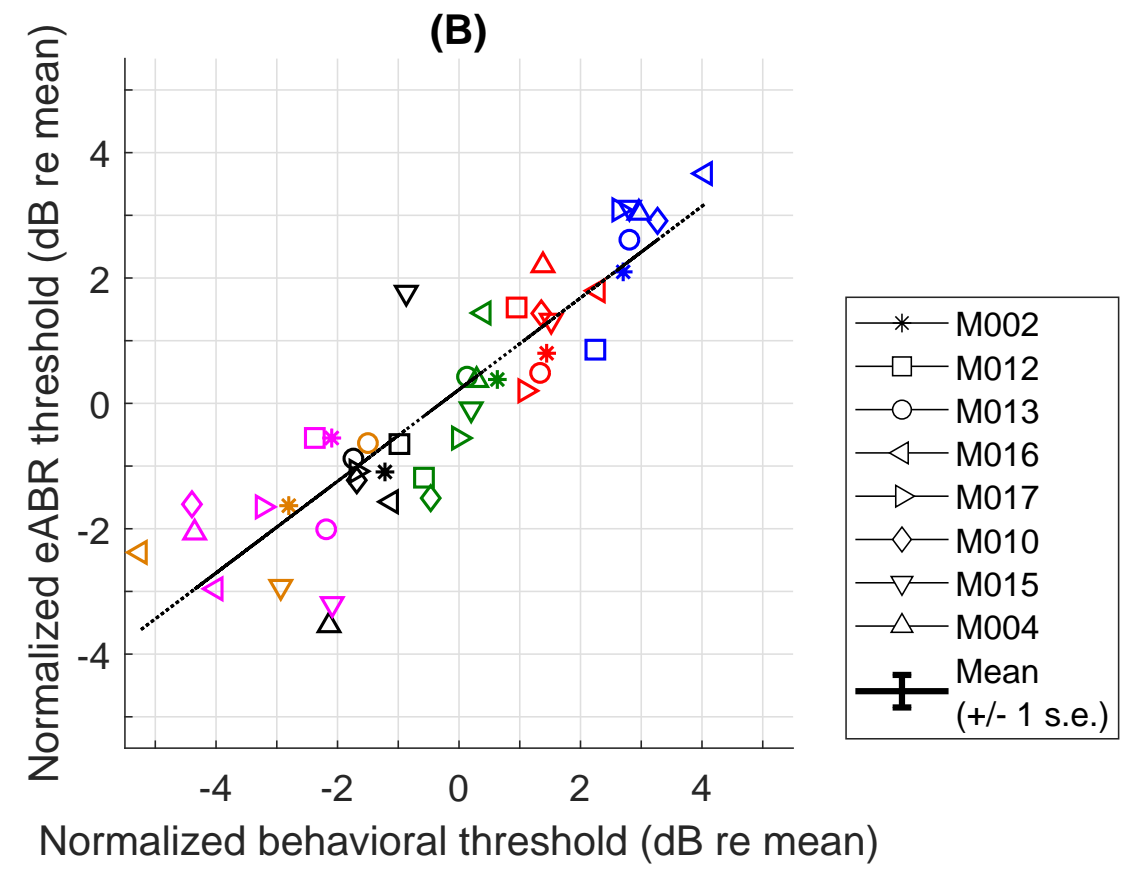
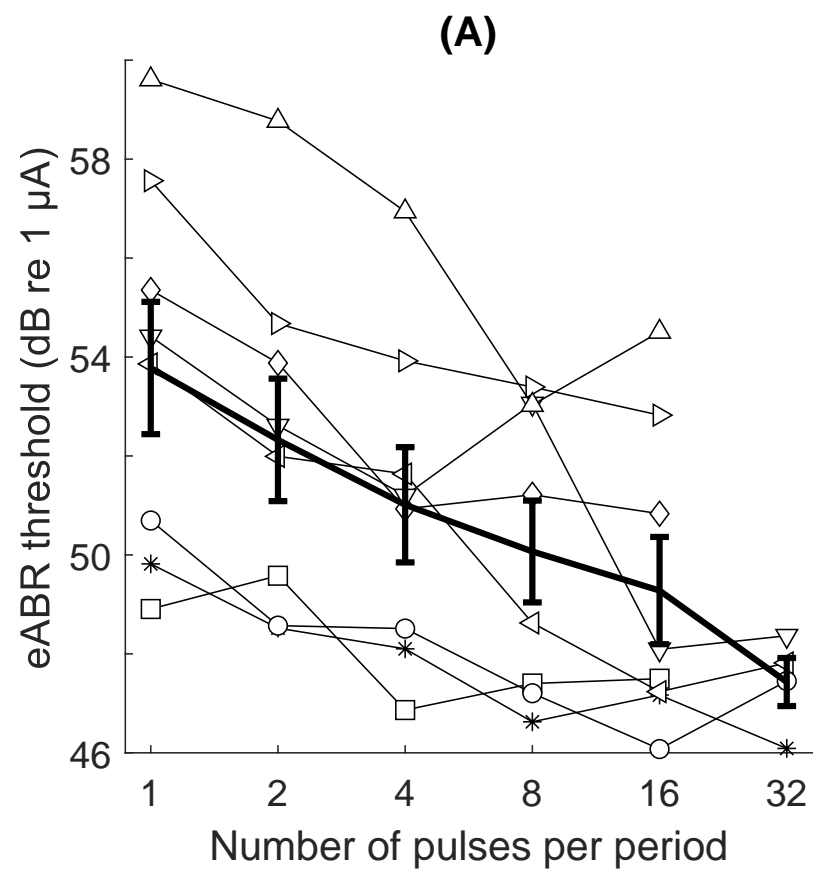


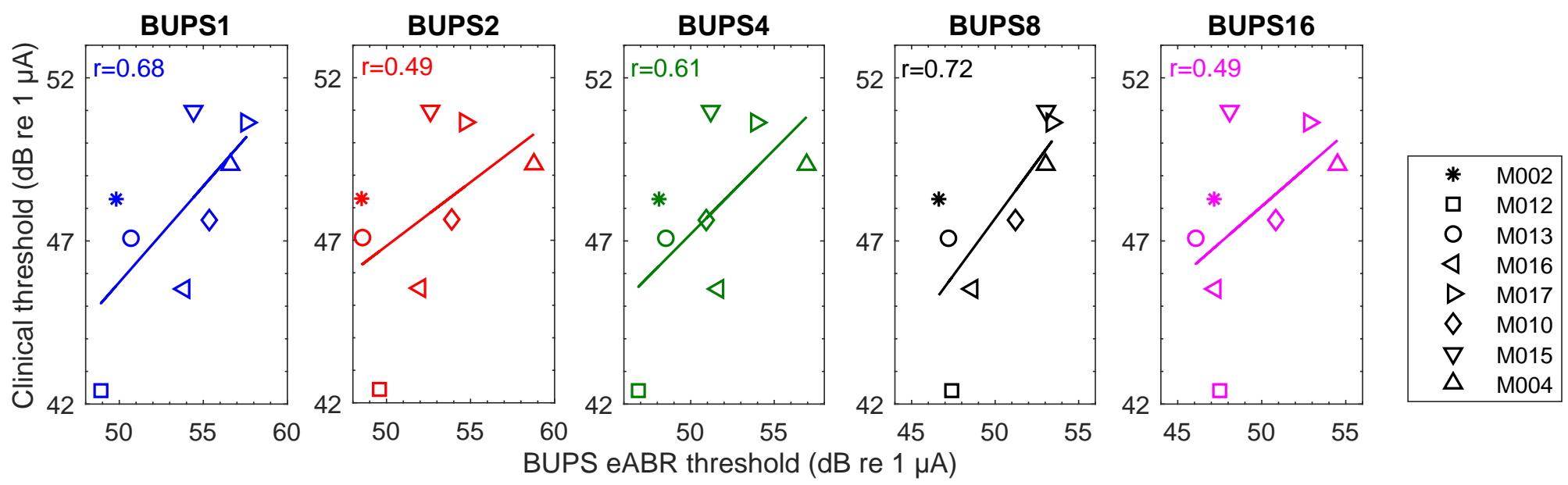
Subject M017



Current level (dB re 1 μ A)







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