

1 Effects of stimulus pulse rate on somatosensory adaptation in the 2 human cortex

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12 Abstract

13 *Background:* Intracortical microstimulation (ICMS) of the somatosensory cortex can restore
14 sensation to people with neurological diseases. However, many aspects of ICMS are poorly
15 understood, including the effect of continuous stimulation on percept intensity over time.

16 *Objective:* Here, we evaluate how tactile percepts, evoked by ICMS in the somatosensory cortex
17 of a human participant adapt over time.

18 *Methods:* We delivered continuous and intermittent ICMS to the somatosensory cortex and
19 assessed the reported intensity of tactile percepts over time in a human participant. Experiments
20 were conducted across approximately one year and linear mixed effects models were used to
21 assess significance.

22 *Results:* Continuous stimulation at high frequencies led to rapid decreases in intensity, while low
23 frequency stimulation maintained percept intensity for longer periods. Burst-modulated
24 stimulation extended the time before the intensity began to decrease, but all protocols ultimately
25 resulted in complete sensation loss within one minute. Intermittent stimulation paradigms with
26 several seconds between stimulus trains also led to decreases in intensity on many electrodes,
27 but never resulted in extinction of sensation after over three minutes of stimulation. Additionally,
28 longer breaks between each pulse train resulted in some recovery of the stimulus-evoked
29 percepts. For several electrodes, intermittent stimulation had almost no effect on the perceived
30 intensity.

31 *Conclusions:* Intermittent ICMS paradigms were more effective at maintaining percepts, and given
32 that transient activity in the somatosensory cortex dominates the response to object contact, this
33 stimulation method may mimic natural cortical activity and improve the perception of stimulation
34 over time.

35 Keywords

36 Intracortical microstimulation; sensory restoration; somatosensory cortex; adaptation; brain-
37 computer interfaces; microelectrode arrays

38 Introduction

39 Intracortical microstimulation (ICMS) of the somatosensory cortex can elicit tactile percepts, even
40 many years after spinal cord injury [1–3]. This can be useful for restoring sensation to people with

41 neurological disease, particularly in the context of a bidirectional brain-computer interface (BCI)
42 [4,5]. The sensations evoked by ICMS can improve robotic arm control by decreasing the time it
43 takes for a person to successfully grasp objects [6]. Apart from functional improvements, ICMS
44 can evoke detectable percepts over many years and stimulation itself does not appear to cause
45 damage that affects neural recordings or detection thresholds [7]. While these factors address
46 the long-term stability and functionality of ICMS, other phenomena may be relevant over short
47 time scales.

48 One potential issue for sensory feedback via ICMS is percept adaptation. We use the term
49 adaptation to mean a reduction in percept intensity that occurs over time. This effect has been
50 documented for ICMS in the visual cortex [8], stimulation of peripheral nerves [9–11], as well as
51 cutaneous stimulation for sensory substitution [12–14]. Continuous stimulation of peripheral
52 nerves increased the amount of charge required to evoke detectable sensations over time [9–11]
53 and this effect occurred more rapidly at higher stimulation frequencies [10]. However, intermittent
54 stimulation paradigms reduced the effects of adaptation for cutaneous stimulation [13] and in the
55 visual cortex, longer breaks between successive stimulation trains improved the recovery rate of
56 ICMS-evoked percepts [8].

57 In order for ICMS in the somatosensory cortex to provide a meaningful benefit for people,
58 stimulation will need to provide reliable feedback. Here, we studied the ICMS-evoked perceptual
59 adaptation in the somatosensory cortex to understand the effects of stimulation parameter
60 choices on perceived intensity with the goal of designing better encoding algorithms for
61 bidirectional BCIs.

62 **Materials and Methods**

63 *Regulatory and participant information*

64 This study was conducted under an Investigational Device Exemption from the U.S. Food and
65 Drug administration, approved by the Institutional Review Boards at the University of Pittsburgh
66 (Pittsburgh, PA) and the Space and Naval Warfare Systems Center Pacific (San Diego, CA), and
67 registered at ClinicalTrials.gov (NCT0189-4802). Informed consent was obtained before any
68 study procedures were conducted. The purpose of this trial is to collect preliminary safety
69 information and demonstrate that intracortical electrode arrays can be used by people with
70 tetraplegia to both control external devices and generate tactile percepts from the paralyzed limbs.
71 This manuscript presents the analysis of data that were collected during the participant's
72 involvement in the trial, but does not report clinical trial outcomes.

73 A single 28-year-old male subject with a C5 motor/C6 sensory ASIA B spinal cord injury was
74 implanted with two microelectrode arrays (Blackrock Microsystems, Salt Lake City, UT) in the
75 somatosensory cortex. Data from this participant have been reported previously, including
76 implantation details and initial perceptual effects of ICMS [1], the long-term stability of these
77 devices [7], the effect of ICMS parameters on perception [15,16], and how including ICMS can
78 improve robotic arm control [6]. Each electrode array consisted of 32 wired electrodes arranged
79 on a 6 x 10 grid with a 400 μm interelectrode spacing, resulting in a device with an overall footprint
80 of 2.4 x 4 mm. The remaining 28 electrodes were not wired due to technical constraints related to
81 the total number of electrical contacts on the percutaneous connector. Electrode tips were coated
82 with a sputtered iridium oxide film (SIROF). Additional details on these implants have been
83 published elsewhere [1].

84 *Stimulation protocol*

85 Stimulation was delivered using a CereStim C96 multichannel microstimulation system (Blackrock
86 Microsystems, Salt Lake City, UT). Pulse trains consisted of cathodal phase first, current-
87 controlled, charge-balanced pulses which were delivered at frequencies from 20-300 Hz and at
88 amplitudes from 2-100 μ A. The cathodal phase was 200 μ s long, the anodal phase was 400 μ s
89 long, and the anodal phase was set to half the amplitude of the cathodal phase. The phases were
90 separated by a 100 μ s interphase period. The maximum stimulus train duration for continuous
91 stimulation was 15 s at 100 Hz or 5 s at 300 Hz based on previously defined safety studies [17].
92 Following any stimulation lasting 15 s, an equal amount of time was spent with no stimulation (50
93 % duty cycle, 15 s on followed by 15 s off).

94 *Stimulation adaptation protocols*

95 In the first experiment, the participant used an analog slider to indicate changes in intensity over
96 time while they received continuous stimulation. Analog slide values were scaled from 0-1,
97 representing the minimum and maximum positions of the slider. We considered the intensity to
98 have changed from baseline when the participant moved the slider below 0.95 and the sensation
99 to be completely extinguished when the slider value was less than 0.05. We used these values to
100 account for noise in the analog slider signal. Recordings were taken up to 15 s after stimulation
101 ceased to measure changes in intensity following cessation of stimulation.

102 We first tested continuous stimulation and delivered pulse trains of 20, 100, and 300 Hz at 60 μ A
103 to single electrodes (Fig. 1A). We delivered 15 s of stimulation at 20 and 100 Hz and 5 s of
104 stimulation at 300 Hz on 5 electrodes for one trial each.

105 For burst-modulated stimulation, we delivered pulse trains at 100 Hz and 60 μ A to single
106 electrodes. To maintain stimulation over longer periods of time, we used a burst modulation
107 scheme with three different burst modulation paradigms: 100 ms, 200 ms, and 500 ms (Fig. 2A).
108 Each of these burst modulation protocols consisted of a burst of stimulation followed by a period
109 of no stimulation of equal length. We delivered 60 s of stimulation for each of these burst
110 modulations on 10 different electrodes for one trial each.

111 For intermittent stimulation trials, there was an initial adaptation period followed by a recovery
112 period. In the adaptation period, the participant received 1 s of stimulation at 60 μ A followed by 5
113 s of no stimulation for 50 repetitions to measure changes in intensity over time (Fig. 3A). After
114 each 1 s pulse train, the participant verbally reported the perceived intensity on a self-selected
115 scale. The participant had performed similar magnitude estimation tasks in previous studies, and
116 used consistent ratings for the same parameters and electrodes across sessions [15]. We had
117 the participant use a self-selected scale rather than normalizing to the first value because we
118 were interested in whether the magnitude of the initial perceived intensity on different electrodes
119 related to the change in intensity over time. After the adaptation period, the participant received
120 1 s of stimulation followed by 61 s without stimulation for another 5 repetitions. We used this
121 period to assess any recovery in the perceived intensity over time.

122 Seven electrodes were tested twice with the intermittent paradigm at 100 Hz to measure
123 differences in adaptation over time between electrodes. Four electrodes were also tested four
124 times with the intermittent paradigm at 20, 100, and 250 Hz to measure differences in adaptation
125 as a function of stimulation frequency.

126 *Detection threshold adaptation protocol*

127 We measured detection thresholds using a two-alternative forced choice task. Two intervals were
128 presented with one containing stimulation. The participant was asked to report which interval

129 contained the stimulus. Amplitude was modulated using a one-up three-down staircase method
130 [18,19]. The initial current amplitude was 10 μ A and was increased or decreased by a factor of 2
131 dB with a constant frequency of 100 Hz. After five changes in the direction of the current amplitude
132 (increasing to decreasing, or decreasing to increasing), the trial was stopped. The detection
133 threshold was calculated as the average of the last 10 values tested before the fifth direction
134 change. Following the first detection task, the participant received stimulation using a 15 s on 15
135 s off protocol – the maximum time we can stimulate continuously – at 60 μ A and 100 Hz for 240
136 s. The detection task was then repeated. We conducted this task on 12 different electrodes each
137 with one trial.

138 *Statistics*

139 All statistical analysis was conducted in MATLAB (Mathworks, Natick, MA). We used linear mixed
140 effects models to test for relationships among the variables of interest (fixed effects) while
141 excluding the impact of variables not of interest (random effects).

142 For the continuous and burst stimulation paradigms, we defined the time at which the intensity fell
143 below 0.95 to be the initial adaptation time. To understand how intensity decreased as a function
144 of frequency for the intermittent stimulation paradigm, we compared the intensity after the first
145 stimulus train of the adaptation period to the intensity after the last stimulus train of the adaptation
146 period. We repeated this analysis for the recovery period by comparing the intensity of the last
147 repetition of the adaptation period to the last repetition of the recovery period.

148 To determine if the ability to detect stimulation changed with long periods of stimulation, we
149 compared the detection thresholds measured before and after a long period of continuous
150 stimulation. Reported p-values are for the coefficient of the fixed effect and were considered to
151 be significant at $\alpha = 0.05$.

152 The analog slider values are plotted as the median and the interquartile ranges (IQR). Data from
153 other experiments were also found to be non-normal using the Anderson-Darling test. For all other
154 analysis we used bootstrapping to calculate the median from a random sampling of each data set
155 with replacement and repeated this 10000 times, resulting in 10000 estimated medians. The
156 mean and standard deviation of these bootstrapped samples were used to estimate the
157 population median and standard error [20].

158 **Results**

159 *Continuous stimulation at higher frequencies results in faster adaptation*

160 We delivered continuous stimulation for 15 seconds at 20 and 100 Hz and for 5 seconds at 300
161 Hz on 5 electrodes (Fig. 1A). The time at which the intensity began to decrease was significantly
162 different between different stimulus frequencies ($p = 8.1e-5$, Fig. 1B,C). 300 Hz stimulation
163 resulted in the fastest change from baseline, with the median intensity falling to 69% of the
164 baseline intensity after 5 s of stimulation. The median intensity remained unchanged from
165 baseline after 5 s of stimulation at both 20 Hz and 100 Hz. However, starting 7 s after stimulation
166 onset, 100 Hz stimulation caused changes in percept intensity that fell to 64% after 15 s of
167 stimulation. Stimulation at 20 Hz had no effect on intensity during the 15 s stimulation window.
168 Ultimately, higher stimulation frequencies caused faster adaptation (Fig. 1C).

169 *Burst stimulation extinguishes sensation over short periods*

170 To potentially extend the time ICMS could be provided, we tested burst-modulated ICMS using
171 100 Hz pulse trains for 60 seconds. Burst modulation stimulus trains with a 50% duty cycle and
172 burst durations of 100 ms, 200 ms, and 500 ms were tested (Fig. 2A). All burst modulation

173 schemes delivered the same number of pulses in 60 s. Stimulation for 60 s caused a complete
174 extinction of the evoked sensation on 26 of the 30 trials (Fig. 2B) and there was no difference in
175 the time at which the perceived intensity began to decrease between burst paradigms ($p = 0.76$,
176 Fig. 2C). However, there was a difference in the time required for the sensations to become
177 undetectable between the three burst stimulation paradigms, with the 500 ms paradigm causing
178 the fastest extinction ($p = 0.012$, Fig. 2D).

179 Compared to continuous stimulation at 100 Hz, the initial adaptation during burst stimulation
180 happened more slowly, but this difference was not significant ($p = 0.13$). Ultimately, decreasing
181 the burst duration extended the useful perceptual window, but the intensity always decreased
182 over time, and regardless of the burst duration, sensations were completely extinguished over
183 relatively short periods of time (Fig. 2B,D).

184 *Increasing time between stimulus trains preserves evoked percepts*

185 Next, we tested an intermittent stimulation protocol with larger gaps between stimulation trains.
186 This protocol was divided into an adaptation period and a recovery period. In both periods the
187 stimulus trains were 1 s long, but the gap between trains was increased from 5 s in the adaptation
188 period to 61 s in the recovery period (Fig. 3A) to allow us to measure whether percept intensity
189 recovered. With this protocol, the median percept intensity still decreased during the adaptation
190 period, however the percepts were not completely extinguished and also increased in intensity
191 during the recovery period (Fig. 3B). Additionally, while the percepts became very weak on some
192 electrodes during the adaptation period, the participant still reported feeling them and no
193 electrodes ever became imperceptible (Fig. 3C). Considering all of the electrodes together, the
194 median intensity decreased to 40% of the initial intensity during the adaptation period and
195 recovered back to 75% of the initial intensity by the end of the recovery period (Fig. 3B).

196 There was considerable variability between the electrodes in how much the percept intensity
197 adapted and recovered (Fig. 3C). In both sessions, the sensations on two electrodes were nearly
198 extinguished – the perceived intensity decreased to less than 6% of the initial intensity – during
199 the adaptation period (Fig. 3C,D, Elec 36 and Elec 64) with varying amounts of recovery. On the
200 other hand, the intensity on two electrodes decreased to 48-79% (Fig. 3C,D, Elec 4 and 54), while
201 one electrode showed no change in intensity (Fig. 3C,D, Elec 22).

202 *Decreases in intensity of intermittent stimulation are consistent across frequencies*

203 We repeated the intermittent stimulation paradigm on four electrodes at 20 Hz, 100 Hz, and 250
204 Hz (Fig. 4). These three frequencies represent low, intermediate, and high frequencies within our
205 stimulus range. Consistent with previous findings [15], we found that frequency had electrode
206 specific effects on the evoked intensity; stimulation on one electrode elicited the highest intensity
207 at the lowest frequency (Fig. 4A, Elec 54) while stimulation on the other three electrodes elicited
208 the highest intensity at the highest frequency (Fig. 4A, Elec 4, 22 and 36), resulting in different
209 initial intensities at different frequencies. The effect of frequency on intensity changes during the
210 adaptation period were minimal in this latter group of electrodes. However, on electrode 54,
211 stimulation at higher frequencies led to more adaptation (Fig. 4B), although the intensity
212 decreases during the adaptation period and increases during the recovery period were not
213 significantly different across frequencies for any electrode ($p \geq 0.05$, Fig. 4B). This indicates that
214 the magnitude of the change in intensity was constant, despite the different initial intensities.

215 *Detection thresholds did not change after continuous stimulation*

216 We also measured the detection threshold before and after long periods of stimulation. We
217 measured the detection threshold and then delivered 4 minutes of stimulation using 15 s of

218 stimulation followed by a 15 s break, which was the maximal length of time we could continuously
219 deliver stimulation. We then remeasured the detection thresholds. Using this protocol, we found
220 no significant difference in the thresholds measured before and immediately after stimulation
221 across 12 electrodes ($p = 0.10$, Fig. 5) with a median threshold increase of $1.3 \mu\text{A}$ following
222 continuous stimulation.

223 **Discussion**

224 *Effect of stimulation frequency on adaptation*

225 Continuous stimulation at high frequencies as well as burst-modulated stimulation protocols
226 caused adaptation of the perceived intensity, and eventually extinction of the sensations for burst-
227 modulated paradigms. However, at the lowest stimulation frequency there was no change in the
228 perceived intensity over 15 s of stimulation. This is analogous to observations in the peripheral
229 nervous system in which lower frequencies increased the time before intensity decreases
230 occurred [10], although this has not been true for all studies [9]. More rapid adaptation with higher
231 frequencies has also been noted for electrocutaneous stimulation [12,14] as well as for vibrotactile
232 stimulation [21–25] where higher frequencies resulted in larger and faster changes in detection
233 thresholds as well as decreases in the ability to discriminate stimuli. For electrocutaneous
234 stimulation, stimulus rates over 1000 Hz led to sensation extinction within seconds [14], while
235 lower frequencies and burst paradigms allowed sensations to be evoked for many minutes [12].

236 Here, the only stimulus paradigm that that did not cause adaptation was continuous stimulation
237 at 20 Hz for 15 s. Due to protocol limitations, driven by concerns about stimulation-driven tissue
238 damage [26,27], we do not stimulate continuously for periods longer than this, so we cannot know
239 if these low frequencies would have caused adaptation over longer periods of time. While this is
240 encouraging, there are limitations using low frequency stimulation. Low frequency stimulation
241 typically evokes qualities of “tapping” or “sparkle” that could be undesirable for object grasping,
242 and on some electrodes low frequencies are unable to drive sensation at all [15]. Therefore, low
243 frequency stimulation itself will not provide a practical means to provide reliable sensations for all
244 electrodes and qualities.

245 *Intermittent stimulation reduced adaptation*

246 Intermittent stimulation allowed sensations to be evoked over much longer periods of time than
247 continuous stimulation, similar to electrocutaneous stimulation [13]. While adaptation still
248 occurred with intermittent stimulation, the magnitude and duration were electrode dependent,
249 similar to the effects of ICMS in the visual cortex [8]. Interestingly, these electrode-dependent
250 effects ranged from stimulation nearly eliminating the percepts, to having no effect at all (Fig. 3C).
251 Importantly, intermittent stimulation never completely extinguished the sensations over 200 s
252 using 100 Hz stimulus trains. Intermittent stimulation conceptually mimics the transient neural
253 activity of many cortical neurons during touch [28] and could provide stimulation during important
254 task-dependent intervals, evoking more reliable sensations over longer periods of time.

255 *Detection thresholds did not change after long periods of stimulation*

256 Although both continuous and intermittent stimulation affected the perceived intensity, we did not
257 find any significant effect on the detection thresholds. This stands in contrast to results for
258 peripheral nerve and electrocutaneous stimulation, where detection thresholds increased
259 significantly after continuous stimulation [9,12]. Furthermore, this result appears to be inconsistent
260 with the decreases in intensity that occurred. However, there are two relevant factors to consider.

261 First, detection thresholds and intensity perception are not necessarily measures of the same
262 phenomenon [15]. We found that in the human somatosensory cortex higher stimulation
263 frequencies always decreased detection thresholds, but had variable effects on perceived
264 intensity at suprathreshold amplitudes. Second, measuring detection thresholds took 2-5 minutes
265 and consisted of 1 s stimulus trains followed by a delay of 5-10 seconds for the null stimulus
266 interval and participant response. This made the detection threshold protocol similar to the
267 intermittent stimulation protocol, which itself caused adaptation. In fact, we found that changes in
268 percept intensity driven by intermittent stimulation stabilized after approximately 100 s (Fig. 4).
269 This would mean that the detection task alone could drive adaptation. Unfortunately, any task
270 used to calculate detection thresholds necessarily requires stimulation, making the direct effect
271 of stimulation on thresholds difficult to determine.

272 *Physiological mechanisms of adaptation*

273 Adaptation of the perceived intensity and changes in the ability to both discriminate and detect
274 tactile stimuli occur in normal touch [21–25,29–33] and are most likely driven by central
275 mechanisms [33]. This adaptation occurs in multiple sensory cortices, where a constant stimulus
276 typically results in rapidly decreasing neural responses [34,35]. Additionally, adaptation of neural
277 responses has been observed for ICMS in mouse cortex, where high-frequency stimulation led to
278 rapid adaptation of neurons away from the electrode [36]. One possible mechanism, short-term
279 depression, has previously been implicated in adaptation, specifically for thalamocortical
280 projections [37]. Short-term depression at thalamocortical synapses was purported to play a
281 strong role in rapid adaptation to brief stimuli provided to the whisker or electrical stimulation
282 (adaptation and recovery within seconds), but separate mechanisms were suggested for slow
283 adaptation (adaptation for minutes or longer). Another possible mechanism is inhibitory neuron
284 drive [38–43]. Two specific types of inhibitory interneurons, parvalbumin and somatostatin
285 neurons, play important roles in adaptation in the auditory cortex [42,43], with parvalbumin
286 neurons providing continuous inhibition throughout the stimulus and somatostatin neurons
287 providing dynamic inhibitory drive based on the number of repetitions.

288 Taken together, the literature suggests that adaptation occurs as a normal part of cortical
289 processing of sensory information. Slow adaptation may depend more on the activity of different
290 neuronal subtypes while rapid adaptation depends more on short-term depression at synapses.
291 This could explain why continuous ICMS led to consistent decreases in intensity while intermittent
292 ICMS had more electrode specific effects. Electrode specific effects may be related to the density
293 of different neuronal subtypes recruited by ICMS. Because ICMS bypasses subcortical inputs,
294 adaptation that occurs from ICMS may look different than normal sensory adaptation and may
295 depend on the targeted area and stimulated electrode. Normal tactile input leads to changes in
296 intensity, but not extinction of perception. Continuous ICMS leads to extinction, implying that
297 adaptation driven by ICMS is not identical to adaptation driven in normal sensory processing.

298 *Limitations*

299 This study represents the first study of adaptation to ICMS in human somatosensory cortex.
300 However, there are several limitations that should be considered. First, these experiments were
301 only conducted in one participant. Additional data in other participants will be needed to
302 understand if there are participant or implant location specific effects. Additionally, there is a very
303 large parameter space (electrode, amplitude, frequency, burst intervals, etc.) and only a few
304 specific parameter combinations were considered here. One reason for this is that there is
305 typically limited experimental time available with human participants, making it difficult to explore
306 comprehensive parameter sets. Further, we were not able to change pulse width because of
307 limitations in our protocols. Data collected in more participants with additional parameter

308 variations will provide further insights into the nature of adaptation. Working in humans also limits
309 our ability to directly measure neural activity during stimulation, limiting our ability to comment on
310 neural mechanisms.

311 *Implications for bidirectional brain-computer interfaces*

312 There are at least two approaches to encoding sensory information in stimulus trains: biomimetic
313 [44–46] and engineered [6,47,48] encoding. Biomimetic approaches aim to create patterns of
314 stimulation that mimic the neural activity that occurs during natural touch, while engineered
315 approaches aim to provide informative stimulation that can be learned to represent specific inputs.
316 Both approaches have met with success in applications in the peripheral nervous system for
317 improving robotic arm control [44,45,48,49]. Biomimetic feedback in the peripheral nervous
318 system evoked more natural sensations and improved performance on some motor tasks [45].
319 Biomimetic stimulation has not been tested for ICMS, however, a simple encoding in which force
320 was linearly transformed to amplitude improved neuroprosthetic control [6]. However, if contact is
321 maintained for long periods of time with this paradigm, the percepts will become undetectable
322 after just a few seconds (Fig 2). Burst stimulation and lower frequencies could help extend the
323 percept time, but with limitations.

324 Biomimetic encoding may drive more natural adaptation processes. Biomimetic pulse trains can
325 be built from computational models that predict neural activity based on tactile input [50–52].
326 These models predict that during object contact, large populations of neurons become active with
327 high firing rates. During maintained contact, the number of active neurons and their firing rates
328 are significantly reduced, which aligns with recorded neural activity in the cortex during touch [28].
329 Biomimetic stimulus trains would naturally resemble the intermittent stimulation protocols tested
330 here (Fig. 3), allowing sensations to persist over longer periods of time without extinction. We
331 suggest that biomimetic approaches may provide a reliable way to provide sensory feedback for
332 bidirectional BCI applications and may align more directly with normal cortical activation and
333 adaptation.

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344 **Data Statement**

345 Data and code are available upon reasonable request.

346 **CRedit authorship contribution statement**

347 **Christopher L. Hughes:** Conceptualization, Methodology, Software, Formal Analysis,
348 Investigation, Writing-Original Draft, Writing-Review & Editing, Visualization. **Sharlene N.**
349 **Fletcher:** Conceptualization, Methodology, Software, Investigation, Writing-Review & Editing.

350 **Robert A. Gaunt:** Conceptualization, Methodology, Writing-Review & Editing, Visualization,
351 Supervision.

352 **Declaration of competing interest**

353 None.

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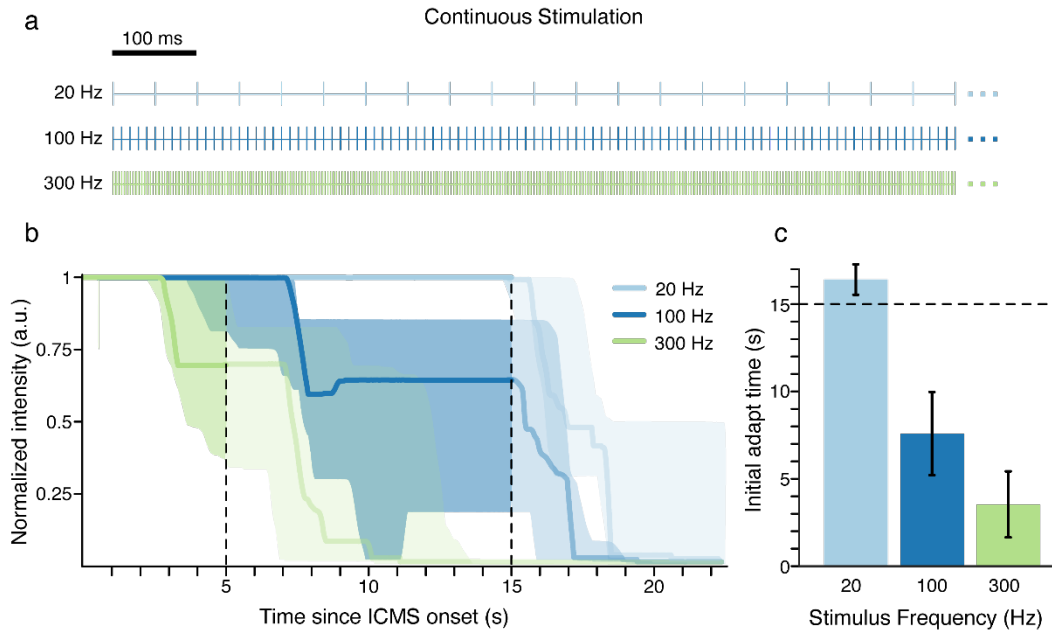
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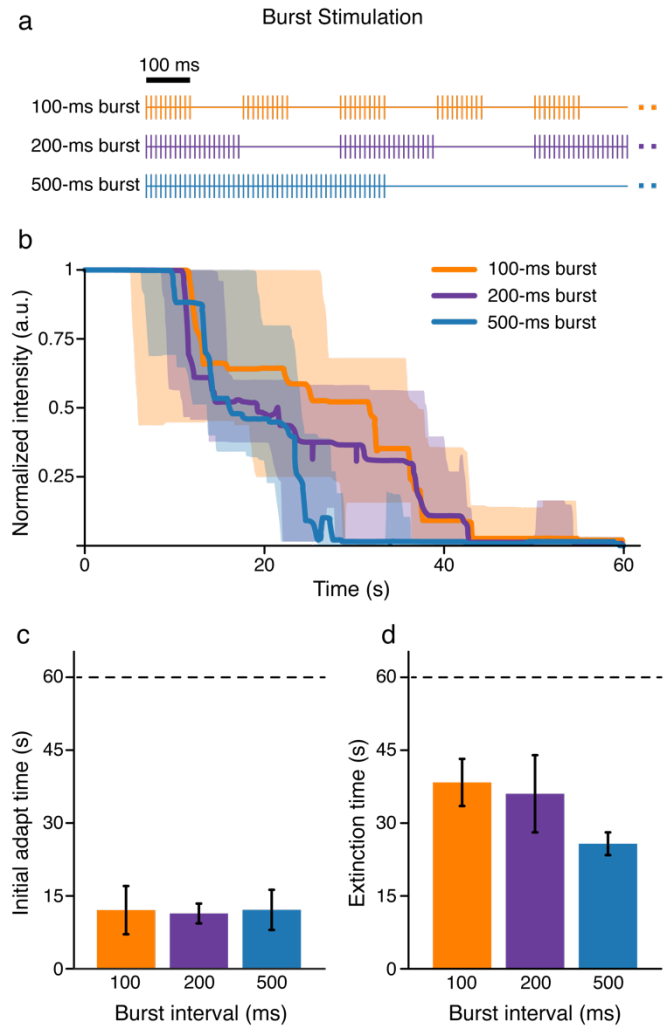
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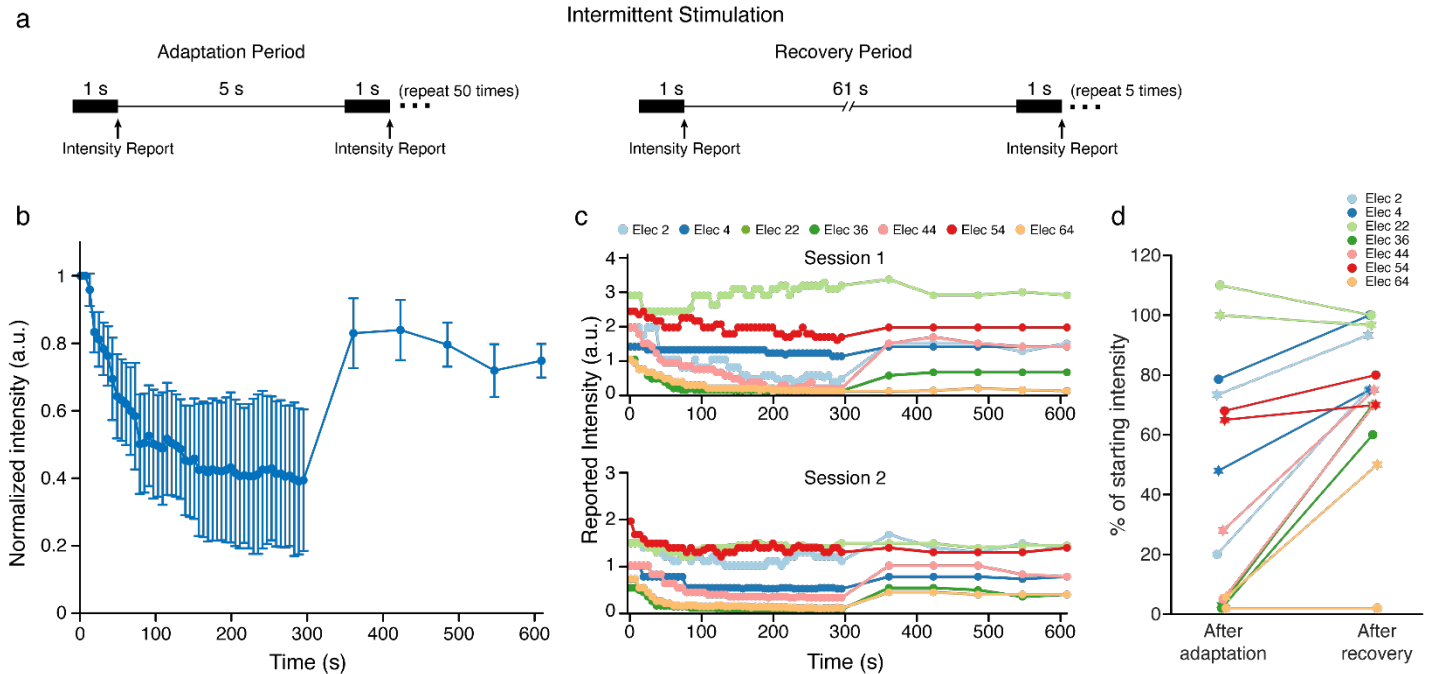
502

503 **Figure 1. Continuous stimulation at higher frequencies resulted in faster adaptation.** A) Continuous
504 frequency trains. Each line represents an individual pulse. B) The participant reported the perceived
505 intensity of the ICMS-evoked sensations using an analog slider. The slider always started at a value of 1
506 and the participant moved the slider to indicate changes in perceived intensity. Each colored line represents
507 the median intensity for 5 electrodes at a given frequency. The shaded regions represent the interquartile
508 range. The vertical dotted lines indicate the end of stimulation for the 300 Hz train at 5 s and the end of
509 stimulation for the 20 and 100 Hz trains at 15 s. Slider values after stimulation stopped are shown in a
510 lighter shade to emphasize the effects during stimulation. C) Time at which the perceived intensity began
511 to decrease for the median response at each stimulus frequency. Error bars show the estimated standard
512 error and the dotted line indicates the maximum stimulation time of 15 s.

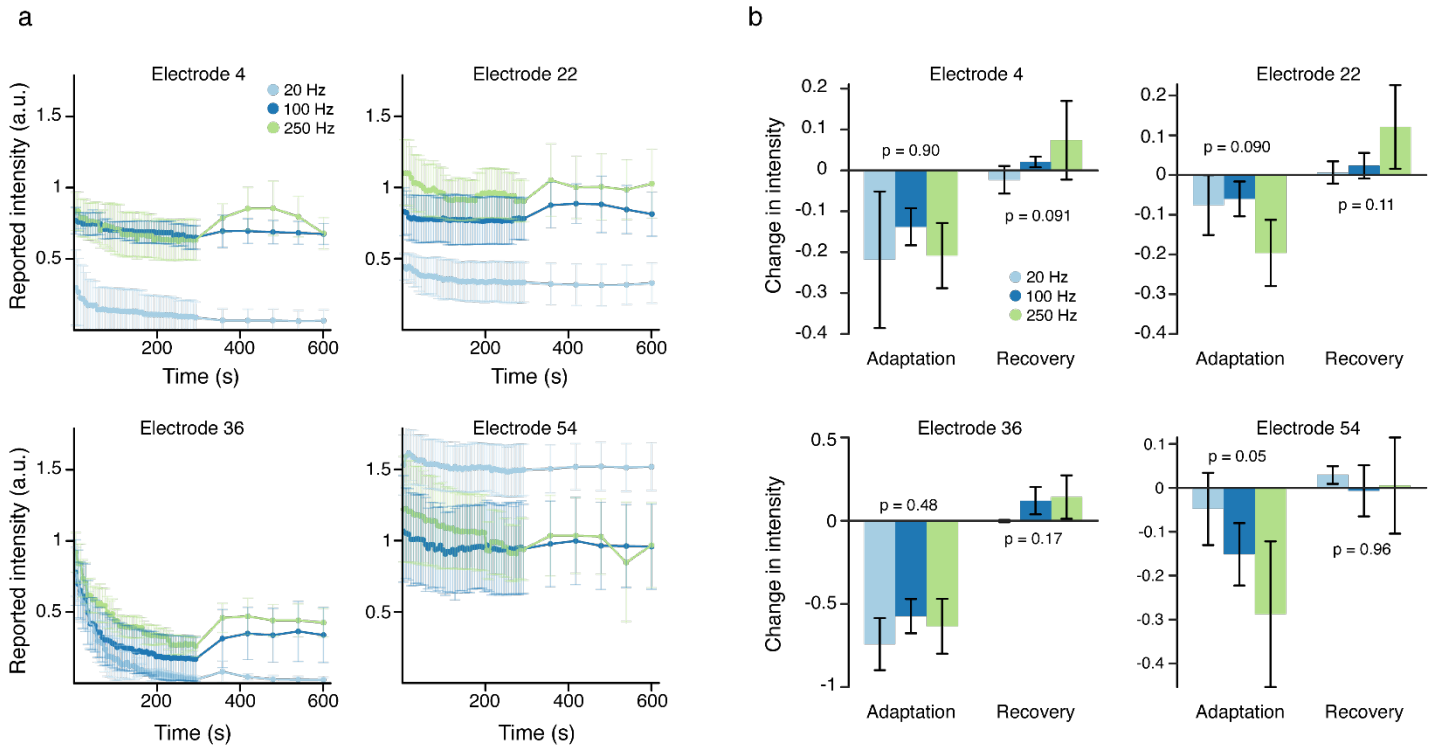


513

514 **Figure 2** Burst-modulated stimulation extinguished all percepts within 60 s. A) Burst modulated trains. Each
515 line represents an individual pulse. B) The participant indicated the perceived intensity of ICMS with an
516 analog slider. The slider always started at a value of 1 and the participant moved the slider to indicate
517 changes in perceived intensity. Each line represents the median intensity value across 10 tested electrodes
518 for a given burst length. The shaded regions represent the IQR. C-D) Bar plots showing C) the time at which
519 the percept intensity began to decrease and D) the time at which the percept became was extinguished.
520 Error bars show the estimated standard error. The dotted line indicates the maximum stimulation time of
521 60 s.

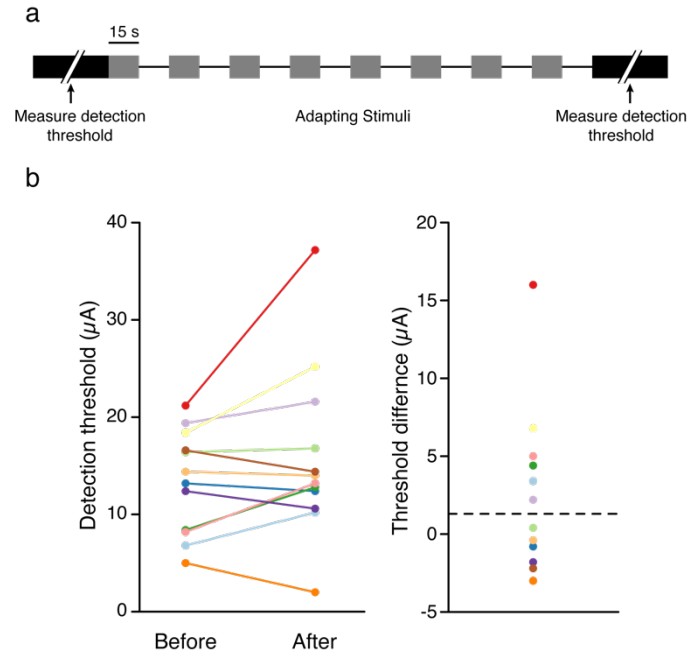


522 **Figure 3. Intermittent stimulation caused less adaptation, which partially recovered over time.** A)
523 Intermittent adaptation and recovery paradigms. The participant indicated the perceived intensity for each
524 stimulus train directly following each stimulation train. B) Blue dots represent the median intensity value
525 measured at each time point across all electrodes. Error bars show the estimated standard error. (C) The
526 response of each electrode in two sessions during the adaptation and recovery periods. (D) The percent
527 change in intensity for each electrode after the adaptation and recovery periods. The change in intensity is
528 calculated from each electrode's initial intensity. Circular markers indicate the first session while star
529 markers indicate the second session.



530 **Figure 4. Stimulation frequency did not affect adaptation and recovery on individual electrodes.** A) Using
531 the intermittent stimulation protocol, four different electrodes were stimulated at 20, 100, and 250 Hz.
532 Colored dots represent the median intensity value measured at each time point across 4 test sessions.
533 Error bars show the estimated standard error. Different colors indicate the different stimulation frequencies.
534 B) Intensity changes during adaptation and recovery at the three different frequencies. The change in
535 intensity for the adaptation period was the measured between the beginning and end of the adaption
536 period while the change for the recovery period was measured between the between the end of the adaptation
537 period and end of the recovery period. Each bar shows the median difference across four test sessions.
538 Error bars show the estimated standard error.

539



540

541 **Figure 5. Long periods of stimulation did not have a significant effect on detection thresholds.** A) We
542 measured the detection threshold and then applied stimulation for 15 s at 100 Hz followed by 15 s of no
543 stimulation for four minutes and then measured the detection threshold. B) Detection thresholds before and
544 after adaptation protocol. Each color represents a different electrode. C) The difference in detection
545 thresholds before and after the adaptation paradigm. Colors are the same as in panel b. The dotted line
546 represents the median threshold difference.