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Intracortical microstimulation of human somatosensory cortex induces natural perceptual biases

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Abstract

Time-order error, a psychophysical phenomenon in which the duration in between successive stimuli alters perception, has been studied for decades by neuroscientists and psychologists. To date, however, the locus of these effects is unknown. We use intracortical microstimulation of somatosensory cortex in three humans with spinal cord injury as a tool to bypass initial stages of processing and restrict the possible locations that signals could be modified. Using a 2-interval forced choice amplitude discrimination paradigm, we first assessed the extent to which order effects are observed. Comparing trials where the standard stimulus was in the first or second interval, we found that systematic biases are exhibited, typically causing the intensity of the second stimulus to be overestimated The degree of this overestimation for individual electrodes was dependent on the perceptual sensitivity to changes in stimulus amplitude. To investigate the role of memory on this phenomenon, we implemented a 2-interval magnitude estimation task in which participants were instructed to ignore the first stimulus and again found that the perceptual intensity of the second stimulus tended to be enhanced by the first in a manner that depended on the amplitude and duration of the first stimulus. Finally, we repeated both paradigms while varying the inter-stimulus interval to examine the timescale over which these effects occur and found that longer inter-stimulus intervals reduced the effect size. These results show that direct activation of primary somatosensory cortex is sufficient to induce time-order errors.

1. Introduction

Psychophysical measures of the limits of human perception were some of the earliest forays into understanding how the brain processes sensory information. One of the earliest acknowledged and most studied psychophysical phenomena is that of the time-order errors (TOEs): where an interaction occurs between two sequentially presented stimuli leading to a perceptual bias of either stimulus [1–4]. Indeed, these findings have shaped experimental design for the last century as scientists endeavor to minimize confounds when presenting many successive stimuli. The most common observation with pairs of stimuli is that the second stimulus tends to be perceived more intensely than expected, typically referred to as an enhancement effect [5–10]. Research has attributed these sequential order effects to memory [6,11], attention [5,12], and gain modulation [10,13,14]. Consistent with these hypotheses, the magnitude of the error has been shown to be in part dependent upon the inter-stimulus interval (ISI) [15]. While these hypotheses indicate top-down modulation, the locus through which this is affected is unclear. Alternatively, modulation of tactile sensations has been shown to occur in both the brainstem [16,17] and in the thalamus [18,19], suggesting that time-order errors could also occur as a result of sub-cortical regulation.

Intracortical microstimulation (ICMS) of sensory structures evokes percepts associated with the somatotopically appropriate body part. In the case of ICMS in the visual cortex, this usually results in phosphenes [20] – bright spots in the visual field – while in the somatosensory cortex a variety of sensations such as pressure, buzzing or tapping can be evoked depending on the electrode [21,22]. Typically, ICMS is modulated through varying either the stimulus amplitude [22–24] or frequency [23,25], resulting in varying levels of intensity and thus allowing for different force levels to be perceived [22,24]. Much like natural touch, ICMS-evoked tactile percepts seem to follow Weber's scaling law, where the ability to discriminate a stimulus is determined by the stimulus range [3], although this is not universally observed [22,23].

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Additionally, ICMS has been shown to influence perceptual judgements when delivered to visual cortex [26] or reaches when delivered to Area 2 [27].

As ICMS allows for bypassing lower-order structures and can directly activate intermediary or higher-order structures, it provides a novel avenue for studying psychophysical phenomena (including time-order errors). Consequently, ICMS allows us to probe higher-level structures in the absence of bottom-up effects such as adaptation of the peripheral afferents [28,29]. Additionally, examining these phenomena with ICMS allows us to question the extent to which ICMS mimics natural tactile stimulation: if ICMS evokes similar phenomena, then we can deduce that similar structures might be recruited by ICMS and natural touch. Alternatively, if ICMS is not susceptible to these psychophysical effects, experimental design will need to be adjusted accordingly. The implications for experimental design are of particular importance as brain computer interfaces that include ICMS become more common [22,30–32], and researchers seek to fully understand their findings and optimize their devices appropriately.

In this study, we provide ICMS to three participants with cervical spinal cord injuries with microelectrode arrays implanted into Brodmann's Area 1 (A1) of somatosensory cortex. This robustly evokes tactile sensations on their contralateral hand while manipulation of the stimulus amplitude modulates the perceived intensity of the sensation [22,24,33]. We implemented both amplitude discrimination and magnitude estimation paradigms [3] to probe the perceptual consequences of sequential stimulation with a view of understanding whether time-order effects can be entirely attributed to higher-order cortical regions or if, instead, preceding neural structures (mechanoreceptors, dorsal root ganglia, cuneate, or thalamus) play a significant role in these perceptual biases. Our investigation revealed that time-order errors arose when using ICMS with both paradigms and that the magnitude of the error was influenced by the inter-stimulus interval.

2. Methods

2.1. Participants

This study was conducted under an Investigational Device Exemption from the U.S. Food and Drug Administration and approved by the Institutional Review Boards at the Universities of Pittsburgh and Chicago. The clinical trial is registered at ClinicalTrials.gov (NCT01894802). Informed consent was obtained from all participants before any study procedures were conducted. Participant C1 (m), 55–60 years old at the time of implant, presented with a C4-level ASIA D spinal cord injury (SCI) that occurred 35 years prior to implant. Participant P2 (m), 25–30 years old at the time of implant, presented with a C5 motor/C6 sensory ASIA B SCI that occurred 10 years prior to implant. Participant P3 (m), 25–30 years old at the time of implant, presented with a C6 ASIA B SCI that occurred 12 years prior to implant.

2.2. Cortical implants and stimulation

Four microelectrode arrays (Blackrock Neurotech, Salt Lake City, UT, USA) were implanted in each participant. Two arrays were implanted in the hand representation of Brodmann's area 1 of somatosensory cortex and two arrays were implanted in the hand and arm region of motor cortex. The two arrays in BA1 were 2.4 mm × 4 mm, composed of 60 electrodes 1.5 mm in length, and wired in a checkerboard pattern such that 32 electrodes could be stimulated [22,34]. Two percutaneous connectors (Blackrock Neurotech) were fixed to the skull, each attached to one motor and one sensory array. ICMS was delivered through each electrode with a CereStim 96 (Blackrock Neurotech) stimulator. The stimulus pulses consisted of a 200 μs cathodic phase followed by a half-amplitude 400 μs anodic phase (to maintain charge balance), with a 100 μs interphase duration.

To choose electrodes for the tasks described below, we only used electrodes whose detection thresholds were significantly below 40 μA such that there was a >90 % chance of detection for any of the stimuli given. Briefly, we used a 3-down 1-up 2-interval forced choice paradigm [35] in which the participant had to report in which interval the stimulus was present. We continued the paradigm for 7 reversals to ensure we had converged on the correct threshold. After the protocol was complete, the mean of the last 5 reversal amplitudes was computed as the detection threshold.

2.3. Amplitude discrimination

For each trial, a 60 μA standard was used and 6 comparison stimuli ranged between 40 and 80 μA (excluding 60 μA). Participants were cued to the stimuli with a fixation cross presented on a computer monitor. One second before trial start a white fixation cross would appear to indicate that the trial was about to begin, it would turn green when the first stimulus was presented, revert to white for the inter-stimulus interval, and then turn green again during the second stimulus interval. For each electrode the trials were counterbalanced, randomized, and presented in a block format (minimum of 8 blocks), totaling at least 192 trials (6 amplitudes, 2 orders, 2 ISI, 8 blocks). Participants were encouraged to discard trials that they were either unsure of or had not paid attention to for whatever reason to minimize uncertainty biases. Any discarded trials were repeated at the end of the block.

During all amplitude discrimination experiments, a minimum inter-trial interval of 5 s was used for all experiments, although this does not include the time taken by participants to respond. The inter-stimulus interval varied between 0.1 and 5 s depending on the exact experiment. Most experiments used pulses delivered at 50 Hz, though a subset used 100 or 200 Hz stimulation and are described as such in the main text. Data were collected from 25 electrodes in participant C1, and from 5 electrodes in both participants P2 and P3.

For the mechanical version of the task, a linear actuator (V308, Physik Instrumente, Germany) was used to control a 5 mm diameter aluminum probe with a beveled tip. Stimuli were trapezoidal in shape (composed of a linear indentation, hold, and then linear retraction phase), with the standard stimulus depth being 1 mm and the comparison stimuli being between 0.85 and 1.15 mm in depth. To conserve the profile of the trapezoid, speeds varied (4.25–5.75 mm/s) such that the transient components of the trapezoid were 0.1 s and the stationary phase was 0.8 s (totaling 1 s duration).

To produce psychometric functions, the proportion of trials in which each comparison stimulus was reported as being more intense was computed. Then, least-squares optimization was used to fit a 2-term logistic function to these points. Both the x-offset (midpoint) and growth parameter of the function were left unconstrained (*EQ (1)*). The just-noticeable-difference (JND) was computed as half of the difference of the inverse of the sigmoid where p equaled 0.75 (*EQ (2)*). To determine the change in the point of subjective equality (ΔPSE) between orders, the above fits were repeated after the trials were split according to the interval in which the comparison stimulus was presented. The ΔPSE was thus computed as the difference in the x-offset between the two functions. As the ΔPSE is equivalent to the interval bias (Supplementary Fig. 1B), individual electrode effects were tested for significance with a binomial test.

$$p = \frac{1}{1 + e^{-k*x}} \quad \text{EQ1}$$

Where p is the proportion of times each comparison stimulus was selected as being more intense than the reference, k is the growth term of the exponential function, and x is the value (charge or amplitude) of comparison stimulus.

$$jnd = \frac{\log\left(\frac{1}{.75} - 1\right)}{-k} \quad \text{EQ2}$$

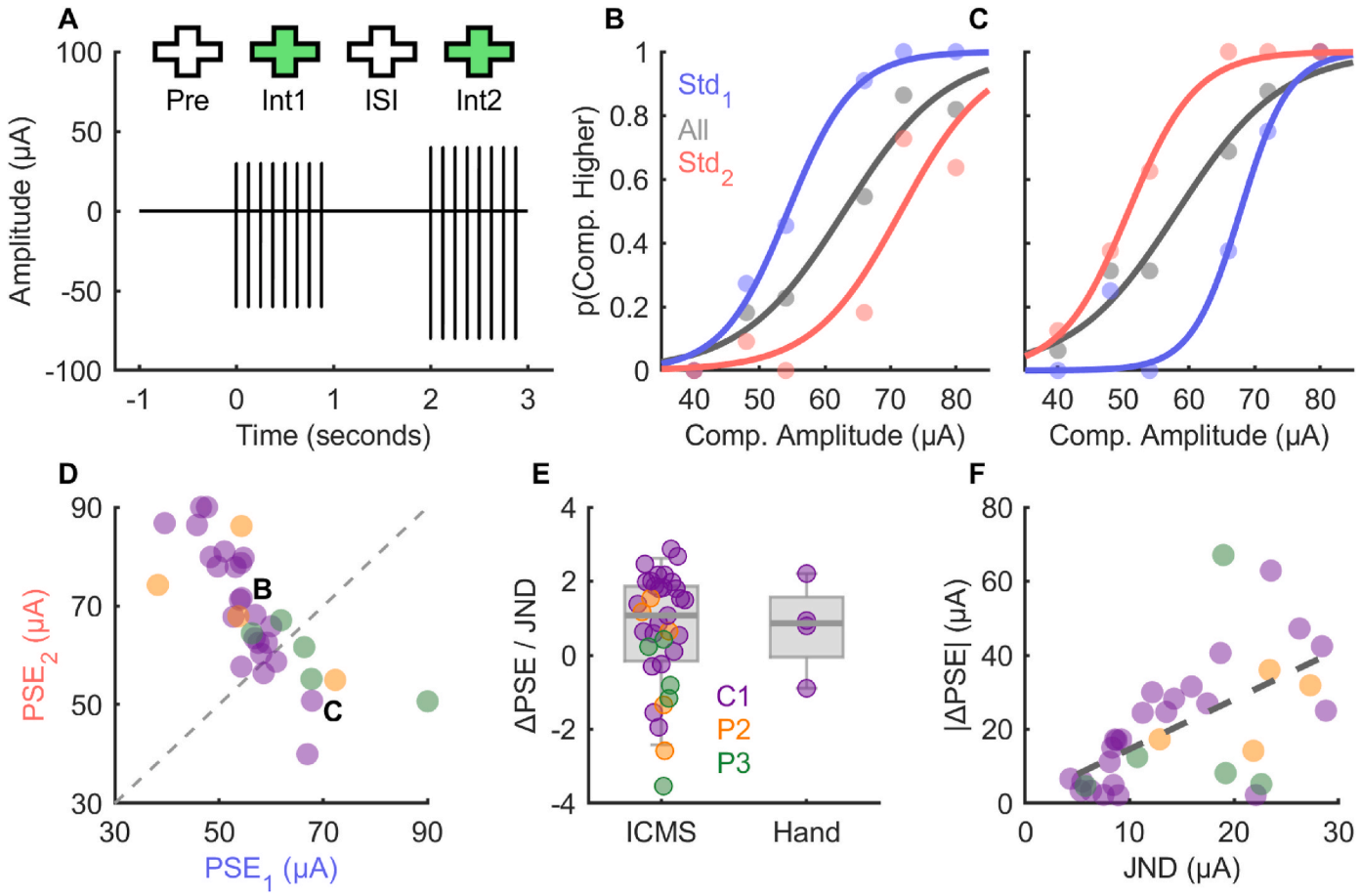


Fig. 1. Amplitude discrimination reveals order dependent psychometric functions. A) Task schematic for an amplitude discrimination trial. Two ICMS trains are delivered, the participant is cued with a fixation cross, and the participant is asked to report which of the two stimuli was more intense. Note that the cathodic (negative) peak indicates train amplitude. **B,C)** Example psychometric functions for two electrodes when trials are split into those in which the standard stimulus (60 μA) was presented in the 1st (Std_1, blue) or 2nd (Std_2, red) interval, or when they are combined (All, gray). Separation of these curves indicates order-dependent biases. **D)** PSEs with respect to standard interval across all electrodes. Labels indicate example electrodes shown in panels **B** & **C**. PSE outliers are capped at 30 or 90 μA for illustrative purposes. **E)** The normalized order effect for both ICMS and tactile amplitude discrimination tasks. **F)** Amplitude sensitivity (JND) of each electrode and the absolute difference in the PSE. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Where k is growth term computed in *EQ (1)*.

2.4. Magnitude estimation

The magnitude estimation experiment was only performed in participant C1. Each trial followed a similar format to the amplitude discrimination experiments regarding fixation crosses, randomization, block design, inter-trial intervals, and discard strategy but did not require counterbalancing. Participant C1 was explicitly told to ignore the first stimulus and only consider the intensity of the stimulus presented in the second interval for all reports. After both stimuli were delivered, the participant verbally gave a free magnitude rating of the intensity of the second stimulus and was instructed to keep the relative value of their reports consistent across trials such that, for example, a stimulus of double the intensity was ascribed double the value [3]. On a subset of trials, no stimulus was given during the first interval, but the participant was still cued to the interval – these are termed catch trials. On the small percentage of trials where the participant did not detect any stimulus in the second interval the trial was discarded.

The magnitude estimation experiment used 50 Hz stimulation with a 5 s inter-trial interval and either a 1 or 5 s inter-stimulus interval. As in the amplitude discrimination experiments, test amplitudes varied between 40 and 80 μA. The conditioning stimulus varied in either duration (0.1–1 s) or amplitude (10–80 μA) and in some cases was delivered to a secondary electrode selected based on whether its projected field was near or distant to that of the test electrode.

2.5. Statistics

Due to the difficulties associated with collecting large datasets with multiple participants, the majority of the data was collected from a single participant at the University of Chicago (C1) and some supportive replication experiments were conducted with two participants at the University of Pittsburgh (P2 and P3). Consequently, some analyses are only performed on C1's data as analysis of data from P2 or P3 would be underpowered.

2.5.1. Amplitude discrimination binomial tests

To compute the significance of the ΔPSE for each electrode, we used a binomial test to compare the number of trials for which the second interval was selected by the participant and computed the Binomial statistic. For an electrode in which no bias was present, the participants would select the second interval with a probability of 0.5 due to the counterbalanced nature of the task while an electrode with a bias towards the second interval would be greater and vice versa for those with a bias towards the first interval.

2.5.2. Magnitude estimation normalization

The normalized intensity was computed for each electrode on a per-block basis by first dividing the reported intensity on each trial to the mean intensity across the entire block. Then, to compute the relative effect of the conditioning stimulus, magnitudes were again normalized within each test amplitude by dividing the normalized intensity value by the mean intensity during catch trials at the same test amplitude. The relative intensity was then combined across test amplitudes when comparing the effect of the conditioning stimulus. Full model ANOVAs were used to perform analyses and the test statistics for each factor are reported throughout.

3. Data & code availability

All data is stored at the Data Archive BRAIN Initiative (https://dabi.loni.usc.edu/dsi/IB30CTQCJ6OP) and code for analysis can be found on GitHub (https://github.com/CorticalBionics/ICMSOrderEffects).

4. Results

4.1. Interval biases are revealed by amplitude discrimination

Time-order errors often present as recency bias: when observed, stimuli that occur closer to the time at which the participant makes a judgement are reported as feeling more intense than those that occurred earlier [6]. In amplitude discrimination experiments, where a participant is asked to compare the intensity of two stimuli presented in succession, this results in a bias towards reporting the second stimulus as more intense. To test whether this occurs with ICMS, we implemented a 2-interval forced choice (2AFC) amplitude discrimination task (Fig. 1A). Briefly, the participant was cued using a fixation cross presented on a computer monitor and two ICMS trains were delivered during which the color of the fixation cross was changed to green. The participant was asked to report which of the two stimuli was more intense. On each trial, a standard stimulus train of 60 μA and a comparison stimulus train between 40 and 80 μA were given (all stimulus trains were 1 s long, 50 Hz, and separated by a 1 s ISI). Importantly, trials were counterbalanced such that there was an equal proportion of trials in which the standard stimulus train was delivered in the first or second interval and all unique stimulus pairs were delivered in a block format where stimulus order was randomized for each block. The participants were asked to report which interval contained the stronger stimulus train and the proportion of trials in which the interval containing the comparison stimulus train was reported as being stronger was computed (Fig. 1B and C).

To measure participant performance for each electrode, a sigmoid function (*EQ (1)*) was fit to each of these points. From this fit, the point of subjective equality (PSE: the point at which the sigmoid equals 0.5) and the just noticeable difference (JND: the difference in amplitude required for the participant discriminate the comparison stimulus from the standard stimulus on 75 % of trials) were derived (*EQ (2)*). Participants were able to perform this task across the vast majority of electrodes tested (Supplementary Fig. 1A), however the results were discarded for the two electrodes that they could not use for the task ($n = 2$).

After splitting the trials into those where the standard stimulus was presented in the first or second interval (Fig. 1B and C) we compared their psychometric fits. As indicated from the example psychometric plots shown, we found a systematic effect of stimulus order upon the PSE (Fig. 1D; binomial test: $p < 0.05$: 14/25 for C1, 3/5 for P2, and 1/5 for P3) where participants would consistently rank one interval as being more intense than the other, resulting in differences in the PSEs (Supplementary Fig. 1B, adjusted coefficient of determination, $R^2 = 0.65$, $F_{[33,31]} = 17$, $p = 0.9e^{-5}$). This effect occurred for each participant on a subset of electrodes, though C1 and P2 tended to overestimate the 2nd interval (Fig. 1D, points above and to the left of the unity line; example in Fig. 1B; sign-rank test for participant C1: $Z_{[32]} = 3.37$, $p < 0.001$) while P3 overestimated the first (Fig. 1D, points below and to the right of the unity line; example in Fig. 1C). Those points above the line are consistent with tactile literature on enhancement [10]; while those below the line were perhaps susceptible to masking [36]. Crucially, while our description focuses on enhancement of the comparison stimulus in the second interval, the standard stimulus was also susceptible to enhancement when in the second interval, resulting in symmetrical shifts in the psychometric function.

Next, we investigated if stimulus order had an effect on the discrimination performance (JND) across electrodes and found a similar effect where JNDs tended to be higher when the standard was in the second interval (Supplementary Fig. 1C; sign-rank test for participant C1: $Z_{[24]} = 3.45$, $p < 0.001$), though this effect did not appear consistent with the other participants. Thus, the observed effects appear to be predominantly caused by a systematic overestimate (especially in C1) or underestimate of one stimulus resulting in symmetrical shifts from the mean.

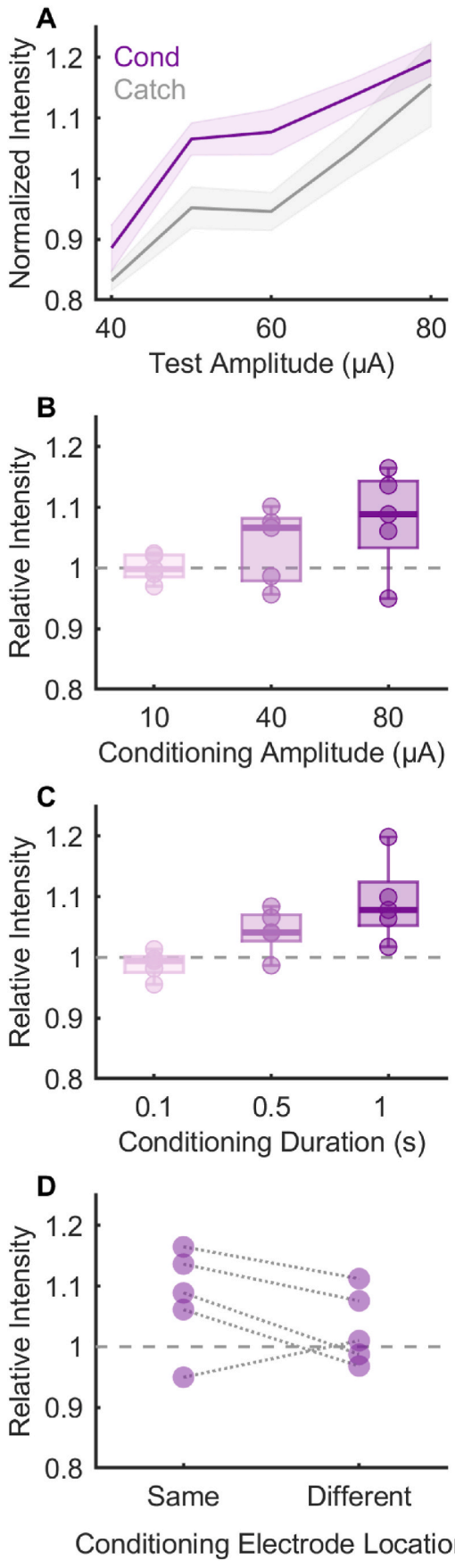
Finally, to contextualize the effect, we implemented a similar paradigm with mechanical stimulation of one participant's ipsilateral hand (C1 has normal sensation in the ipsilateral hand). After normalizing the effect size by the sensitivity to changes in amplitude to standardize the units (Fig. 1E), we observed that there was no difference in the total magnitude of the effect across stimulus methods (Wilcoxon rank sum test, $Z_{[24,4]} = 0.025$, $p = 0.67$) and further, that there was no difference in variation (2-sample F-test, $F_{[23,3]} = 0.89$, $p = 0.728$).

We then sought to find an explanation for the diversity in the effect across electrodes. We observed that there was a moderate relationship between the absolute ΔPSE and the JND (Fig. 1F, Pearson's correlation, $r = 0.72$, $p < 0.001$, C1 only) suggesting that the effect was magnified for less sensitive electrodes, consistent with the idea that there is an underlying bias that can be overpowered with sufficient information (i.e., amplitude-sensitive electrodes). The inverse of this – underlying bias overpowering amplitude-insensitive electrodes – could explain the small subset of electrodes with negative ΔPSEs, or it could be due to natural variation within each participant.

We also examined if the detection threshold of the electrode might influence the JND or ΔPSE in participant C1 and found a weakly negative effect for both (Pearson's correlation; JND: $r = -0.51$, $p = 0.0099$; ΔPSE: $r = -0.48$, $p = 0.017$) perhaps suggesting that stimuli nearer the detection threshold had less of an enhancement effect. Finally, we repeated the experiment with multiple frequencies interleaved (50, 100, and 200 Hz) on a subset of electrodes ($n = 5$) and examined if the ΔPSE or ΔJND systematically varied with frequency. We found substantial but not systematic variation on the ΔPSE (Supplementary Figs. 1D and 1-way ANOVA, $F_{[2,17]} = 0.91$, $p = 0.42$) whereas there was a weak but significant decrease in the ΔJND as frequency increased (Supplementary Figs. 1E and 1-way ANOVA, $F_{[2,17]} = 4.69$, $p = 0.026$). This is likely a result of the general tendency for JNDs to decrease with frequency (Supplementary Figs. 1F and 1-way ANOVA, $F_{[2,17]} = 5.4$, $p = 0.0171$).

4.2. Sequential magnitude estimation reveals an enhancement effect

Amplitude discrimination paradigms require that the participants hold both sensations in memory and are therefore susceptible to memory effects and recency biases [6]. To determine if the observed effect might be attributed to a memory effect or an enhancement effect, where the preceding stimulus causes the subsequent stimulus to feel more intense [10], we implemented a sequential magnitude estimation paradigm in one participant (C1). Much like the amplitude discrimination task (Fig. 1A), two stimuli (1 s duration, 50 Hz) were delivered with a 1 s ISI and were cued with fixation crosses. However, in this experiment the participant was instructed to only report the intensity of the second stimulus (cued by the second green fixation cross). This paradigm removes any memory effects and allows probing of the subjective intensity of the most recent stimulus without any attentional effect as the participant always knew when and where to expect the second



(caption on next column)

Fig. 2. Sequential magnitude estimation shows enhancement effects. A) Example normalized intensity reports in the presence (cond) or absence (catch) of an 80 μA conditioning stimulus. Mean and SEM shown. **B)** Distribution of test intensities relative to the catch intensities for different conditioning amplitudes (all 1 s in duration) or **C)** durations (all at 80 μA). Each point represents the mean relative value for each electrode across test amplitudes. **D)** Relative intensity for each test electrode when the conditioning stimulus was on the same or an adjacent electrode. All data from C1.

stimulus.

Consequently, we compared the reported intensity of the second stimulus when there was a conditioning stimulus (on the same electrode between 10 and 80 μA) or not (catch) and found enhancement of the second stimulus when a conditioning stimulus was present (example shown in Fig. 2A). Furthermore, the magnitude of this effect was partly determined by the strength of the conditioning stimulus and was consistent across electrodes (Fig. 2B) where more intense conditioning stimuli resulted in more enhancement (3-way ANOVA; electrode: $F_{[3, 1193]} = 1.89$, $p = 0.11$; conditioning amplitude: $F_{[3, 1193]} = 24.9$, $p < 0.01$; test amplitude: $F_{[4, 1193]} = 102.34$, $p < 0.001$). Next, we repeated the paradigm but kept the intensity of the conditioning stimulus equal and instead varied its duration. We found, in keeping with the prior result, that longer conditioning stimuli tended to induce more enhancement (Figs. 2C and 3-way ANOVA; electrode: $F_{[3, 972]} = 0.42$, $p = 0.79$; conditioning duration: $F_{[3, 972]} = 16.66$, $p < 0.01$; test amplitude: $F_{[4, 972]} = 73.63$, $p < 0.001$).

Finally, we compared whether the location of the conditioning electrode played a role in the enhancement effect by measuring magnitude estimates after providing a 80 μA conditioning stimulus to either the same electrode or an adjacent electrode with a nearby projected field (interleaved with catch trials). We found that the effect was reduced for all tested electrodes but was not completely abolished for two of the five (Figs. 2D and 3-way ANOVA; electrode: $F_{[4, 598]} = 2.95$, $p = 0.0198$; conditioning location: $F_{[1, 598]} = 12.95$, $p < 0.001$; test amplitude: $F_{[3, 598]} = 34.97$, $p < 0.01$).

4.3. Enhancement effects decay with inter-stimulus interval

Interactions between successive stimuli leading towards increases in percept intensity depends on the ISI [14,37]. A potential explanation for this phenomenon is that the brain continuously integrates information within a finite window, and at greater ISIs the initial stimulus falls outside that integration window. To test whether ICMS is consistent with a cortical integration mechanism, we performed both amplitude discrimination and magnitude estimation experiments with either 1 or 5 s ISIs (and 6 s inter-trial intervals). When comparing psychometric functions across the two conditions (Fig. 3A inset), order effects were significantly reduced when the ISI was 5 s (Fig. 3A, signed rank test, $Z_{[25]} = 2.71$, $p < 0.0066$). Crucially, this was true for both positive and negative ΔPSEs, with the distribution of the ΔPSE at 5 s being much smaller than those at 1 s (2-sample F-test: $F_{[23,23]} = 5.07$, $p < 0.01$). Furthermore, the sequential magnitude estimation paradigm revealed a similar result (Fig. 3B and C) where ISI had a significant effect on the perceived intensity of the test stimulus (4-way ANOVA; electrode: $F_{[4, 1745]} = 3.35$, $p < 0.001$; conditioning amplitude: $F_{[2, 1745]} = 13.37$, $p < 0.001$; ISI: $F_{[1, 1745]} = 99.32$, $p < 0.01$; test amplitude: $F_{[4, 1745]} = 164.49$, $p < 0.001$). Finally, we repeated the amplitude discrimination experiments on a subset of electrodes with 4 inter-stimulus intervals (0.5–5 s, Fig. 3D) and found a similar trend, though more variation was observed at the shortest ISI than might be expected (Fig. 3E). Consequently, both the order effect observed in the amplitude discrimination task and the enhancement effect observed in the magnitude estimation are both sensitive to the inter-stimulus interval and may be caused by a shared mechanism.

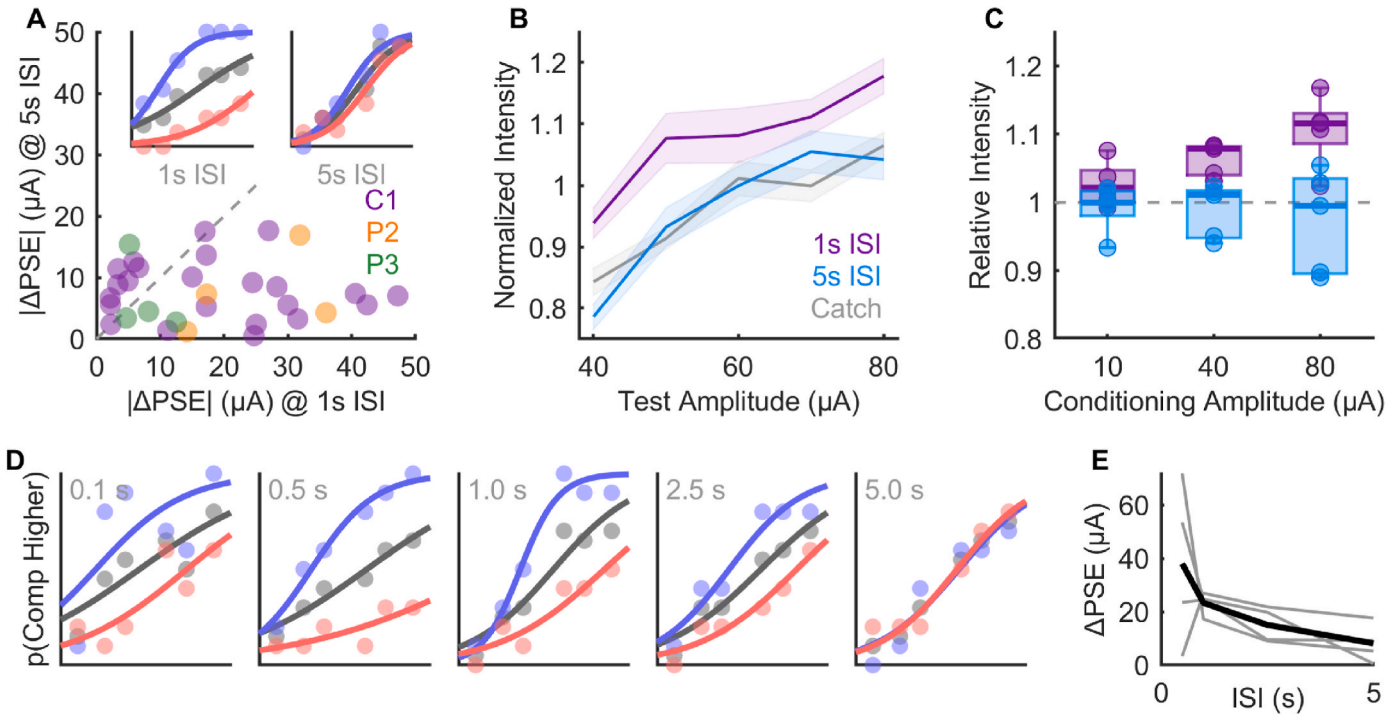


Fig. 3. Sequential effects are ISI dependent. A) The absolute ΔPSE when amplitude discrimination is performed with a 1 or 5 s ISI. **Inset)** Example psychometric functions for an example electrode at each ISI. **B)** Example normalized intensity reports for an example electrode when sequential stimuli are delivered with either a 1 or 5 s ISI. Catch stimuli indicate when the first interval contained no stimulus. **C)** Test intensities at both ISIs relative to the catch stimulus for different conditioning amplitudes (all 1 s in duration). **D)** Psychometric functions from a single electrode at 5-different ISIs. **E)** Absolute ΔPSE from 4 electrodes at multiple ISIs. Data in panels B–E from C1.

5. Discussion

5.1. Enhancement dependent order effects are mediated by higher order structures

Intracortical microstimulation allows for precise stimulation of cortical structures; this bypasses any modulation or gating that may occur at earlier structures (mechanoreceptors, dorsal root ganglia, brainstem nuclei, or thalamus). It does not, however, prevent higher order structures such as secondary somatosensory cortex or prefrontal cortex from exerting top-down control upon S1. The fact that time-order errors were observed in all 3 participants tested (Fig. 1D) reveals that lower order structures are not necessary for these phenomena. These results do not, however, preclude the possibility that these effects are mediated by bottom-up effects that start in Area 1, potentially including thalamocortical synchronization [38], local rebound excitation [39], or spatial attention [40]. Similar psychophysical phenomena such as adaptation [28,41–43] are also likely mediated by higher order structures, though further testing is necessary to confirm this. However, the results presented here only pertain to ICMS of Area 1 and similar experiments would be required to test other sensory structures as well as non-sensory structures such as motor cortex or frontal eye field.

5.2. Adaptation and enhancement occur over different timescales

The results shown here imply that over certain timescales, stimuli should get more and more intense (Figs. 1 and 2). However, existing vibrotactile [28,42,44], peripheral nerve stimulation [43], and even other ICMS [45] literature implies that repeated stimulation should desensitize participants. Though these results may seem in conflict, they in fact occur together. Indeed, in magnitude estimation experiments we typically normalize all ratings within blocks to offset a global reduction in reported intensities caused by desensitization, though the degree to which this occurs is electrode dependent. Short term enhancement effects thus occur on a smaller timescale relative to the level of global sensitivity on each trial.

5.3. ICMS-evoked and natural sensations exhibit similar psychophysical phenomena

The fact that the magnitude of the observed TOE effects evoked by ICMS were similar to those driven by natural touch (Fig. 1E) suggests that the activity of higher-order cortical areas in response to ICMS is sufficiently similar to what occurs naturally. The fact that the degree of TOE observed was determined in part by the intensity or duration (Fig. 2B and C) of the first stimulus [7–9] and the inter-stimulus interval (Fig. 3) [15], in keeping with existing literature, implies that the neural mechanisms are similar between ICMS and touch. The one caveat we observed, however, is that at very short ISIs, the relationship became much less consistent (Fig. 3E). We posit that this is due to the kind of idiosyncratic rebound excitation or inhibition observed and simulated with ICMS immediately following a stimulation train [39,46].

This demonstrates that ICMS may be used to study other psychophysical phenomena, such as the duration of neural integration windows [47], and also shows that stimuli influence one-another over several seconds in the supra-threshold regime. However, at this point, is it unclear whether these observations will extend to the peri-threshold regime. Indeed, studies of vibrotactile thresholds show that a smaller time constant (on the order of 200 ms) is likely applicable [48]. That said, it should also be cautioned that temporal summation observed when stimuli were delivered at the afferent level could be filtered or tuned at intermediary structures and that the use of ICMS would prevent an analysis of this effect across regions. Consequently, ICMS should be used as a tool in conjunction with physical stimuli to understand these processes.

5.4. Implications for BCI experiments

These findings further cement the notion that ICMS can act upon the brain in a similar manner to natural stimuli and thus is susceptible to the same effects observed with natural stimuli (specifically touch but likely other natural stimuli). Furthermore, these results imply that there are likely to be well established phenomena in the psychophysical literature that risk confounding ICMS experiments and researchers should take this into consideration when designing experiments [49]. In particular, amplitude discrimination experiments, a pillar of ICMS experiments for determining electrode sensitivity, must either include long ISIs, or be explicitly counterbalanced to ensure equal stimulus presentation weighting. Furthermore, magnitude estimates should be performed using long inter-trial intervals (>3 s) to minimize the interactions between successive stimuli.

CRediT authorship contribution statement

Charles M. Greenspon: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Natalya D. Shelchkova:** Writing – review & editing, Writing – original draft, Investigation. **Taylor G. Hobbs:** Writing – review & editing, Investigation, Data curation. **Sliman J. Bensmaia:** Supervision, Funding acquisition, Conceptualization. **Robert A. Gaunt:** Writing – review & editing, Supervision, Funding acquisition.

Declaration of competing interest

RG served as consultants for Blackrock Neurotech, Inc, at the time of the study. RG is also on the scientific advisory board of Neurowired LLC. RG received research funding from Blackrock Neurotech, Inc. Though that funding did not support the work presented here.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2024.10.005.

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