Temporal patterns in electrical nerve stimulation: burst gap code shapes tactile frequency perception

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Abstract

We have described a novel temporal encoding mechanism in the somatosensory system, where tactile pulses grouped into periodic bursts create a perceived frequency based on the duration of the silent gap between bursts, rather than the mean rate or the periodicity. This coding strategy may offer new opportunities for transmitting information to the brain using various sensory neural prostheses and brain-machine interfaces. However, it was not known whether the same coding mechanisms apply when electrical, rather than mechanical, stimulation is used. Here, we demonstrate that the predictions of the burst gap coding model for frequency perception apply to burst stimuli delivered with electrical pulses, re-emphasising the importance of the temporal structure of spike patterns in neural processing and perception of tactile stimuli. Reciprocally, the electrical stimulation data confirm that the results observed with mechanical stimulation do indeed depend on neural processing mechanisms in the central nervous system and are not due to mechanical effects in the skin or afferent population activation patterns. Our results suggest that spike intervals contribute to perceived frequency with perceptual weights that depend on their duration, and that a generalised frequency processing system would explain the constancy of vibrotactile frequency perception across different receptor types.

Introduction

Temporal features of neural spike activity play a major role in encoding tactile information [1-4]. In a previous study, we used pulsatile mechanical stimulation to investigate the neural basis of frequency perception in the flutter range. When we grouped pulsatile stimulation patterns into periodic bursts, we found that perceived frequency was determined by the duration of the silent gap between bursts of spikes in peripheral afferents, irrespective of the number of spikes within a burst or the burst rate [5]. This stands in contrast to the mean spike rate or periodicity code that are often proposed to be

neural codes for frequency perception in higher neural centres [6-9]. Effective deployment of this burst coding may be useful in restoring the sense of touch in amputees using a prosthesis through electrical stimulation [10-12] or in the treatment of movement disorders through deep brain stimulation as several studies have established [13-16].

The discovery of the burst gap code for perceived frequency depended on brief mechanical pulses that only evoke a single spike in responding afferents, as had been verified using microneurography, allowing us to precisely control the spiking pattern of responding tactile afferents [5, 17, 18]. On the other hand, electrical stimulation activates peripheral axons in a manner different than that of mechanical stimulation [19], by bypassing the specialised mechanoreceptors in the skin and directly stimulating the tactile afferent axons [20, 21]. Electrocutaneous stimulation non-selectively activates the different types of tactile afferents (associated with different skin receptors) [22, 23], which contrasts with mechanical stimulation where the type of afferent recruited varies depending on the sensitivity of the fibre type to stimulus characteristics such as the vibration frequency of a mechanical sinusoid [24, 25].

A single tap on a finger generates a complex propagating wave on the fingertip skin [26, 27] that will evoke complex and potentially variable population spike patterns due to sporadically responding afferents [28]. In particular, such a stimulus would reliably activate afferents whose receptive fields are directly under the probe, but this activation would become stochastic at some distance from the locus of stimulation [25, 29]. This raises the possibility that the burst gap code that we observed with mechanical stimulation is in some way dependent on these spatial activation patterns and/or predominant activation of certain afferent types. As an alternative, electrical stimulation is a robust method to reliably activate axons, and a simple technique to implement in brain-computer interfaces or haptic displays [30]. Thus, in this study we used electrical stimuli to directly evoke spike trains in tactile afferent fibres while avoiding complex mechanical skin phenomena. We aimed to establish that the burst gap encoding for frequency perception is genuinely caused by neural

processing mechanisms in the central nervous system and not the result of a complex population effect, and to demonstrate the efficacy of this technique for use in interfaces with the nervous system.

Materials and methods

Subjects

Two separate experiments were conducted. Twelve subjects (aged 21-26, 5 females) participated in Experiment 1. Eight subjects (aged 21-25, 5 females) participated in Experiment 2. Three of the subjects participated in both experiments. All subjects were healthy and without any known history of altered tactile function. The experimental protocols were approved by the Human Research Ethics Committee (HC16245) of UNSW Sydney and written consent was obtained from subjects before experimentation began.

Apparatus

Stimulus patterns were generated via a CED Power1401 mk II data acquisition system using Spike2 (Cambridge Electronic Design, Cambridge, UK) and MATLAB (Mathworks, Natick, USA) software. These patterns triggered constant current electrical pulses from a DS7AH stimulator (Digitimer, Welwyn Garden City, UK). The electrical stimuli were delivered to the right index finger of subjects using Kendall 200 Series foam electrodes (Covidien, Mansfield, MA, USA), with one electrode placed on the distal interphalangeal joint and another on the proximal phalanx, to stimulate the digital nerve. A button box was used by subjects to indicate their responses to the psychophysical task. Compound action potentials were recorded using a PowerLab data acquisition system and LabChart software (ADInstruments, Sydney, Australia).

Stimulation patterns

Experiment 1

The stimulus timing patterns used were based on that of our previous study [5]. In our first experiment, the aim was to determine whether burst gap coding would best describe the perception of frequency in subjects. The test stimuli consisted of one of four trains with periodic bursts of 2-4 pulses (Fig 1A), such as would be generated in the afferent response to high-amplitude vibration [25, 31]. The individual pulses were spaced either 4.35 ms (stimuli a-c) or 8.7 ms (stimulus d) apart within the burst. The period between repeating bursts was fixed at 43.5 ms, resulting in a burst rate of 23 Hz. However, the mean pulse rate varied considerably between the four stimuli, ranging from 46 to 92 Hz.

Experiment 2

In our second experiment, we measured the critical value of the inter-pulse interval within a burst that determined how the pulses contribute to perceived frequency. The test stimuli were one of 13 trains of a 2-pulse burst (doublet) with a short interval (t_S) and a long interval (t_L) (Fig 1B). The short inter-pulse interval (t_S) ranged from 4.35 ms to 56.55 ms, increasing in steps of 4.35 ms. The long interval was fixed at 87 ms. The burst gap code predicts that when two pulses are close enough in time, they will be treated as a burst and accordingly the perceived frequency will be determined by the burst gap (approximately 11.5 Hz in this experiment).

Fig 1. Schematic of stimulus patterns and experimental protocol, each red vertical line represents an electrical pulse. (A) In Experiment 1, test stimuli have the same periodicity (burst rate), but different overall pulse rates. (B) In Experiment 2, test stimuli consisted of a short interval doublet (t_s), followed by an 87 ms long inter-pulse interval (t_L). The short inter-pulse interval was varied in

steps of 4.35 ms, from 4.35 ms up to 56.55 ms. (C) Two interval forced choice procedure used to determine perceived frequency of test stimuli.

Electrical stimulation parameters

Electrical stimuli were 0.1 ms wide square pulses. Prior to the start of each experiment, the electrical current level was optimised for the subject so that the electrical pulses were perceived clearly as a series of taps without discomfort. Current levels used ranged from 6.5 to 11.5 mA across subjects and were kept at a fixed level within a session.

Verifying the stable activation of a population of afferents

Sensory nerve action potentials (SNAPs) were obtained in two subjects by stimulating the sensory nerves distally and recording the compound action potential more proximally [32]. The stimulating electrodes were positioned on the finger as described above to stimulate the digital nerves which innervate the index finger. The recording electrodes were located on the wrist to record activity in the median nerve, while the ground electrode was placed on the thenar eminence. These recordings were used to verify that the afferent axons fired reliably to each electrical pulse within a burst in our closely spaced stimulation patterns.

Measuring point of subjective equality for frequency

To determine the perceived frequency of each test stimulus, a two-interval forced choice paradigm was used as in our previous study [5]. Test stimuli were compared against 6-8 different comparison stimuli, which were regular trains of pulses with repetition rates ranging from 14-54 Hz for Experiment 1 and 7-21 Hz for Experiment 2. For each trial, a test stimulus and a comparison stimulus were presented for 1 s each, in a random order and separated by 500 ms (Fig 1C). The subject indicated which of the two stimuli had the higher frequency. To obtain psychometric curves, each test condition was compared 20 times against each of the regular comparison frequencies, giving

rise to 120-160 trials per test stimulus. Following optimisation of the electrical current, a practice round was conducted which comprised a selection of test and comparison stimuli to familiarise subjects with the task, before the actual test procedure began.

At each comparison frequency, we determined the proportion of times the subject indicated that the comparison stimulus had a higher frequency than the test stimulus (P_H). To obtain a linear psychometric function, the logit transformation $\ln(P_H/(1-P_H))$ was applied to the data [33]. The value of the comparison frequency that is equally likely to be judged as higher or lower than the test stimulus was taken as the point of subjective equality (PSE). This value corresponds to the frequency where the zero crossing of the logit axis occurs for the regression line fitted to the logit transformed data (example in S1 Fig).

Statistical analysis

For Experiment 1, linear regression was performed to determine if the slope of the line fitted to the data would be better explained by the burst gap code or the periodicity, which was constant at 23 Hz. A two-way ANOVA (repeated measures within the same subject for the different stimulation methods) was used to determine if there were differences between the data collected here using electrical stimulation and the mechanical data collected in our previous study. For Experiment 2, a joinpoint regression model created using Joinpoint Trend Analysis Software (National Cancer Institute, Bethesda, MD, USA) was used to determine the trend that best fitted the psychophysical data. An alpha level of 0.05 was used for all statistical tests.

Results

Stable activation of the afferent population

Electrical stimulation with patterns used in Experiment 1 (Fig 1A) resulted in SNAPs that were of consistent amplitude during a burst irrespective of inter-pulse intervals used or number of pulses within a burst (Fig 2). Fig 3 illustrates the consistency of the slopes for each averaged SNAP waveform within a burst in both subjects, indicating that the afferent population recruited remained stable between pulses in a burst.

Fig 2. Sensory nerve action potential (SNAP) recordings. Average of 200 compound action potentials recorded from the median nerve in response to Experiment 1 stimulation patterns illustrated in Fig 1A. The red circles indicate SNAPs, while the clipped waveform occurring before each SNAP represents the electrical stimulation artefact.

Fig 3. Consistency of evoked SNAPs within a burst. Each panel represents the slopes measured from the downward phase of the averaged waveform (n = 200) for evoked SNAPs within a burst in a single subject (n = 2). Error bars denote standard deviation.

How is perceived frequency encoded?

In Experiment 1, the aim was to determine which coding mechanism could best describe the perception of frequency in subjects when the electrical pulses were grouped into bursts. The mean data from the 12 subjects are shown in Fig 4. The observed perceived frequencies were 2- to 4-fold lower than that predicted by the mean pulse rate (Fig 4A), indicating that a simple rate code could not explain perceived frequency in subjects. Linear regression was performed between the reciprocal of the burst gap (t_L) and the perceived frequency for each stimulus (Fig 4B). The regression line had a slope that was non-zero (1.2, 95% CI 1.0-1.4; $R^2 = 0.76$; $p < 0.0001$), which does not correspond to that of the periodicity (expected slope 0), but is a good match to the reciprocal of the

burst gap (t_L). The slope here closely resembles that of the mechanical data from our previous study (slope = 1.3, 95% CI 1.0-1.5; $R^2 = 0.68$; $p < 0.0001$), which also best matched $1/t_L$ [5].

Fig 4. Possible coding schemes for frequency perception of electrical burst stimuli. (A) Boxplots with whiskers represent the subjective perceived frequency of the electrical stimuli used in Experiment 1 (n = 12). Green and pink arrowheads indicate predicted PSE values if the frequency judgement had been based on the mean pulse rate and the burst rate (periodicity), respectively. (B) Fitted regression line (black line) indicating that the mean electrical PSE data (black circles; n = 12) from this study is a close match to the reciprocal of the burst gap t_L. The regression line fitted to mechanical data from our previous study [5] is shown for comparison (orange line). The dotted line is the line of identity, where the PSE would equal the reciprocal of the burst gap t_L. Error bars denote 95% confidence intervals.

A two-way ANOVA indicated that there was a statistically significant main effect by the stimulus pattern ($p < 0.0001$, $F_{2,44} = 143$, 71% of total variation) and the method of stimulation ($p = 0.0084$, $F_{1,22} = 8.4$, 4.7% of total variation). However, there was no interaction effect ($p = 0.36$, $F_{3,66} = 1.1$), suggesting that varying the stimulation pattern had the same effect on frequency perception regardless of whether mechanical or electrical stimulation was used.

What defines an inter-pulse interval as part of a burst?

For Experiment 2, we varied the duration of the short interval to determine which inter-pulse intervals (t_S) would be treated as a burst, so that the perceived frequency depended only on the longer interval (t_L). The results from the 8 subjects are shown in Fig 5 which plots the apparent frequency of each stimulus. A joinpoint regression model was fitted, which indicated that the data was best explained by three linear segments. The first segment extended from 4.35 to 13.05 ms,

with a slope that was not significantly different from zero ($p = 0.64$). The next two segments had slopes that were significantly non-zero. The second segment spanned 13.05 to 34.8 ms and had a slope of 0.2 ($p = 0.0002$). The last segment had a range between 34.8 and 56.55 ms, with a slope of -0.08 ($p = 0.0002$).

The slope for the segments here were similar to those reported in our previous study involving mechanical stimulation (Fig 5, Mechanical PSE), though the joinpoint between the second and third segments occurred at 30.45 ms in that study [5], thus at a slightly shorter inter-pulse interval than in the current study (34.8 ms). Nevertheless, the same basic findings were observed in both studies, as shown by the confidence intervals overlapping with the joinpoint model based on the mechanical data and an identical first jointpoint. This suggests that the same definition of a burst can be applied to both mechanical and electrical stimulation.

Fig 5. Relationship between the short inter-pulse interval and perceived frequency. PSE values obtained using Experiment 2 stimuli, indicated by black circles (Electrical PSE; n = 8). The black line signifies the three fitted linear segments as determined by the joinpoint regression model. The green and blue lines represent predicted PSE values if frequency judgement had been based on the mean pulse rate and the burst gap code, respectively. The orange line (Mechanical PSE) is the joinpoint model based on the mechanical data from our previous study [5]. Error bars denote 95% confidence intervals.

Discussion

The main objective of the present study was to verify whether the burst gap coding model for frequency perception could be observed with electrical stimulation. This is an important step which had to be demonstrated due to the potential value of this coding strategy for implementation in

230 bionic systems for providing somatosensory information. Our results show that the burst gap code
231 could reliably predict perceived frequency of complex bursting spike patterns when the spikes were
232 elicited by electrical pulse stimulation of axons. This means that the same overall spike rate in an
233 axon can produce a different frequency percept, depending on how those spikes are arranged in
234 time. This reinforces the importance of the temporal structure of spiking patterns in neural
235 processing and sensory perception.

236 Electrical stimulation bypasses the complex viscoelastic properties of the skin that may have affected
237 previous work using mechanical stimulation, and so provides strong independent confirmation of
238 the burst gap code. We verified that the efficiency of the electrical stimulus was not affected by the
239 repetition rate with SNAP recordings, which showed that even the shortest inter-pulse interval (4.35
240 ms) resulted in reliable and consistent activation of tactile afferents. As we used a reasonably strong
241 stimulation current at a supra-threshold level, it was expected that a majority, if not all, of the large
242 myelinated afferents of the digital nerve would be reliably activated regardless of the inter-pulse
243 interval that was chosen.

244 Although the results in our first experiment, where we used electrical pulses to create bursting trains
245 of the same periodicity but different number of spikes, were best explained by the burst gap code
246 rather than a periodicity or rate code, the mean PSEs were lower than that would be predicted
247 simply from the burst gap duration. One explanation for this bias towards lower frequencies may be
248 that electrical stimulation recruits all afferent types non-selectively, so that the slowly adapting (SA)
249 afferents would be recruited in addition to the fast adapting (FA) afferents, whereas the mechanical
250 stimulus predominantly activated FA afferents [5]. Although previous research has found that SA
251 afferents and their corresponding cortical sensory neurons do not contribute to vibrotactile
252 frequency perception [34-36], their activation and the corresponding sense of pressure they convey
253 [24] may bias subject judgements in psychophysics tests. However, although the difference in PSEs
254 between electrical and mechanical stimulation was statistically significant, it is unknown whether

this difference indicates any physiological importance, as the difference is well within the Weber fraction of ~0.2-0.3 that has been previously reported in the literature [11, 17, 37-40].

The data from the second experiment, where doublets of different inter-pulse durations were tested, clearly indicate that the frequency of periodic doublets is perceived in a similar manner for both mechanical and electrical stimuli, as the criterion defining a burst observed with mechanical stimuli [5] could also be applied to electrical stimulation. When the inter-pulse interval is sufficiently brief (<15 ms), the pulses are interpreted as belonging to a single burst event and the burst gap determines the perceived frequency. As the separation of the two pulses is increased beyond 15 ms, the propensity for two consecutive pulses to be regarded as a burst decreases and the short interval appears to have a partial weighted contribution to frequency perception [41]. Beyond 30-35 ms, each individual pulse becomes a discrete event and the perceived frequency resembles the mean pulse rate.

These findings lend weight to another recent study which revealed that spiking pattern determined the perceived frequency of mechanical stimuli, even when driven by different receptor types [17]. In that study, we found that low-frequency spike trains in Pacinian (FA2) afferents could induce a vibratory precept, even though Meissner (FA1) afferents had been traditionally thought to be solely responsible for perception of low frequency flutter vibrations (<60 Hz), whereas higher frequency activation of Pacinian (FA2) afferents would evoke a different percept of vibratory hum [25]. A generalised frequency processing system that operates across a variety of receptor type inputs would explain these findings, and the constancy of vibrotactile frequency perception across different skin regions innervated by different afferent types [37, 42], e.g. hairy skin lack Meissner corpuscles [43, 44]. The congruence of the present results using electrical stimulation whereby all types of afferents are recruited non-selectively, with the previous results using mechanical stimuli that activated predominantly FA afferents, supports the suggestion of a generalised frequency processing mechanism.

Natural stimuli encountered during object manipulation and surface exploration generally evoke complex discharge patterns in tactile afferents [2, 45-47]. Additionally, numerous studies have implicated the importance of frequency content in skin vibrations for encoding tactile information such as texture [45, 48, 49]. Accordingly, the frequency perception mechanism substantiated here may represent a more universal method of encoding complex naturalistic patterns of vibration, which may not necessarily have a simple fixed periodicity. For instance, we previously showed that this sensory coding strategy also applied to stimuli that are irregular or aperiodic in nature, as it relies on the processing of individual inter-pulse intervals by weighting their perceptual contribution to perceived frequency depending on their duration, rather than detection of periodicity or spike counting [41]. Hence, this neural coding strategy may provide a good way to manipulate frequency perception while providing sensory feedback in settings such as neural prostheses or haptic displays, through electrical stimulation of the tactile system.

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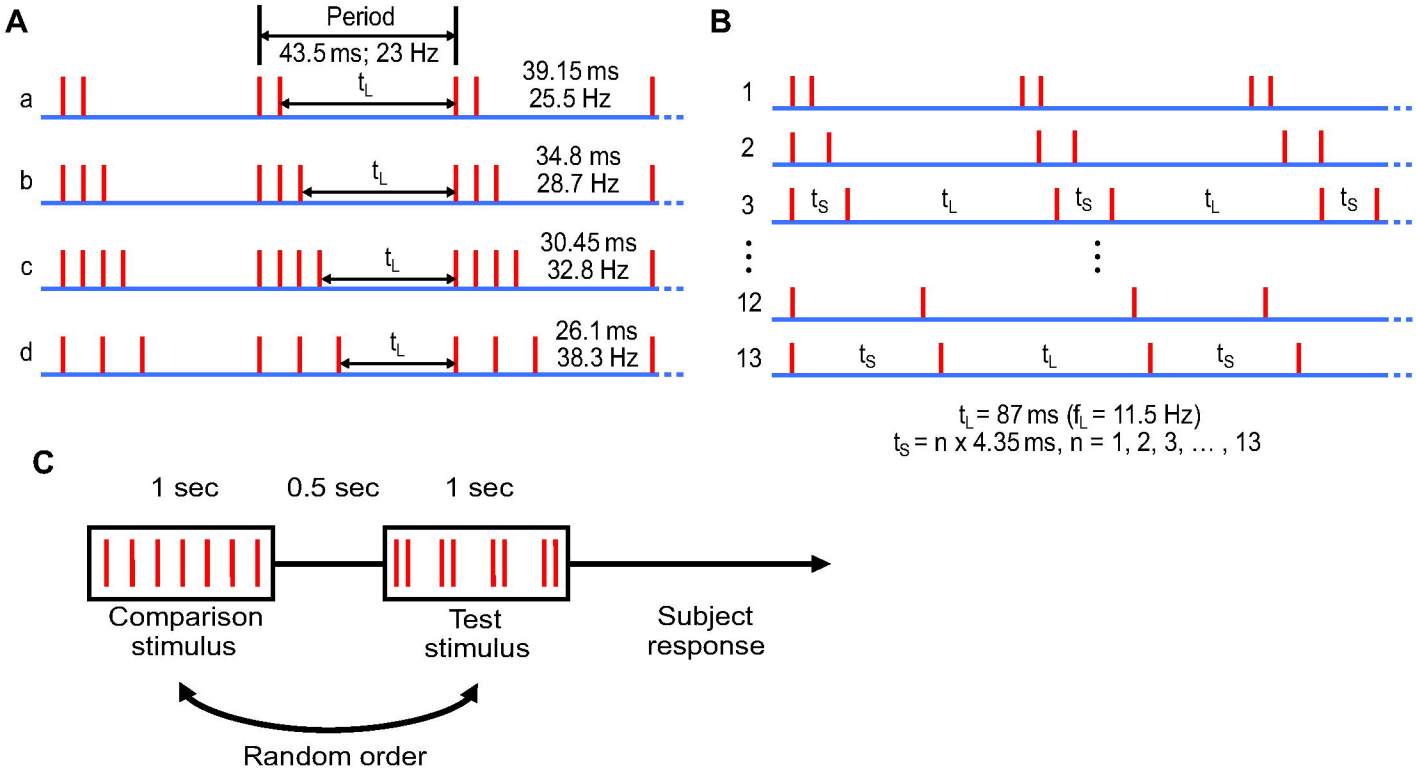
460

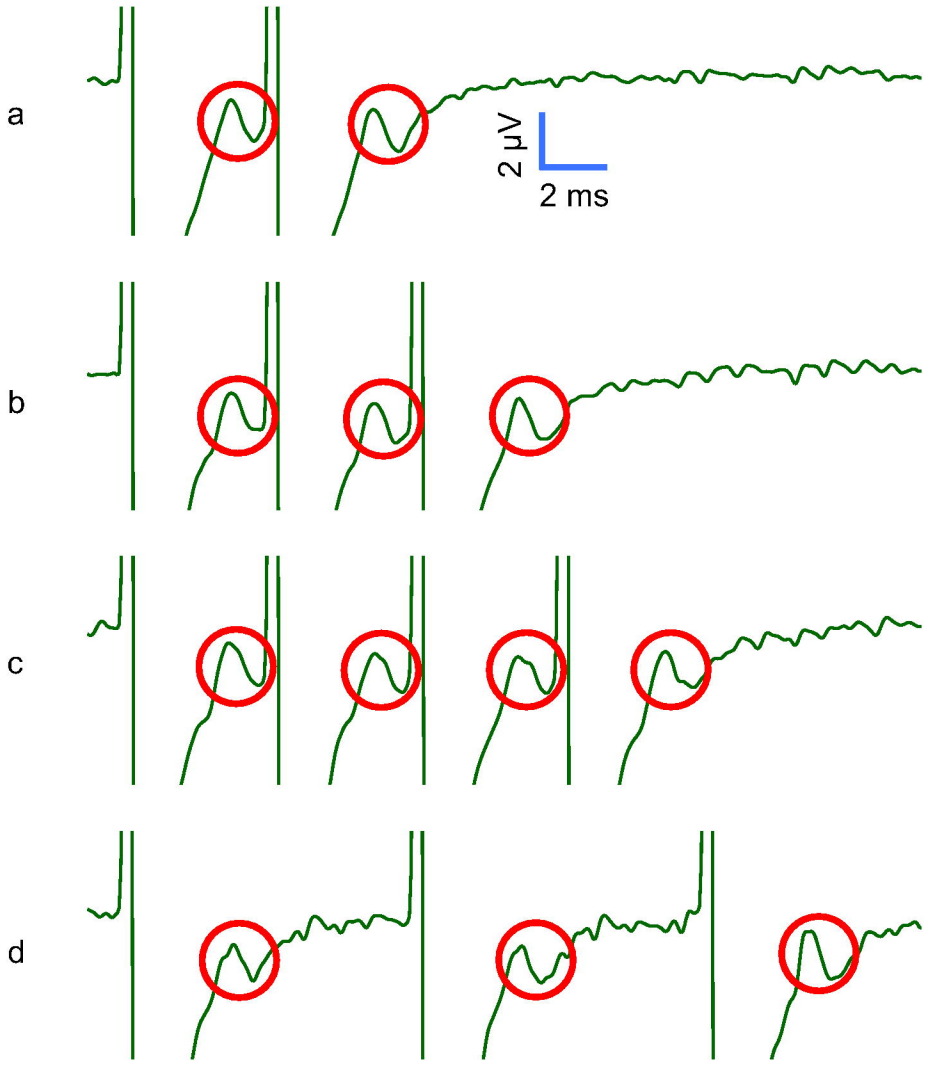
461

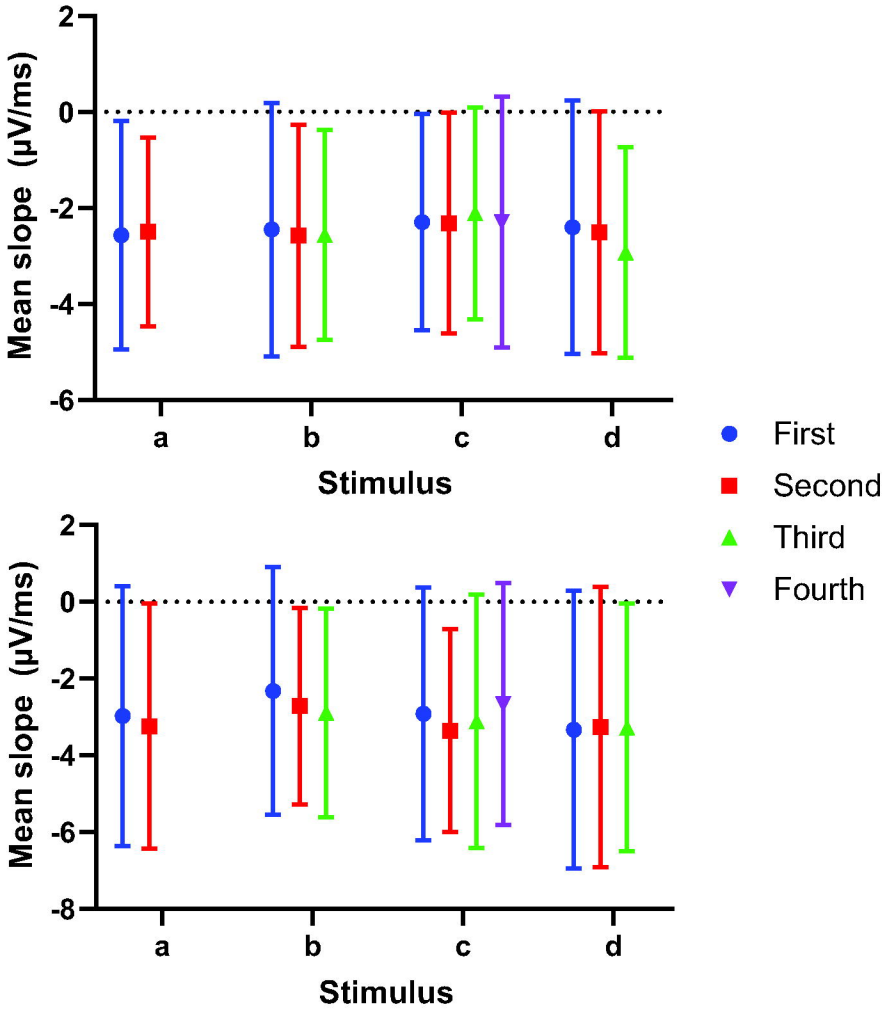
Supporting information

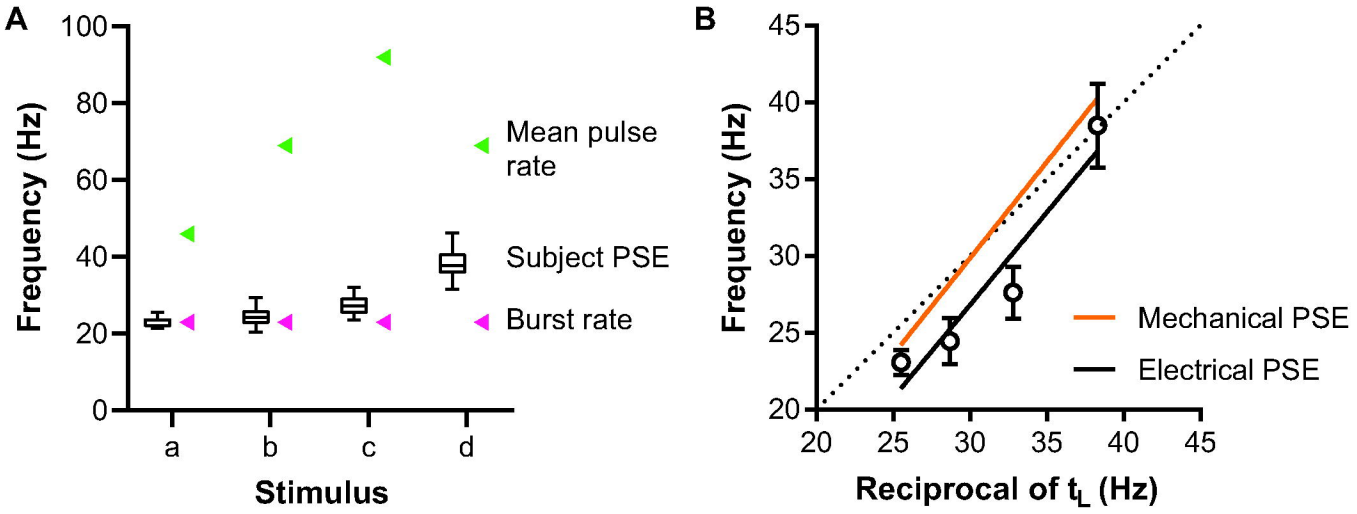
S1 Fig. Example psychometric function. An example of a logistic regression fit applied to psychometric data from a single subject in one test condition (Experiment 1, stimulus d). PSE (point of subjective equality) is determined as the frequency that gives logit = 0 from the fitted regression line. In this case, PSE was estimated to be 38.1 Hz.

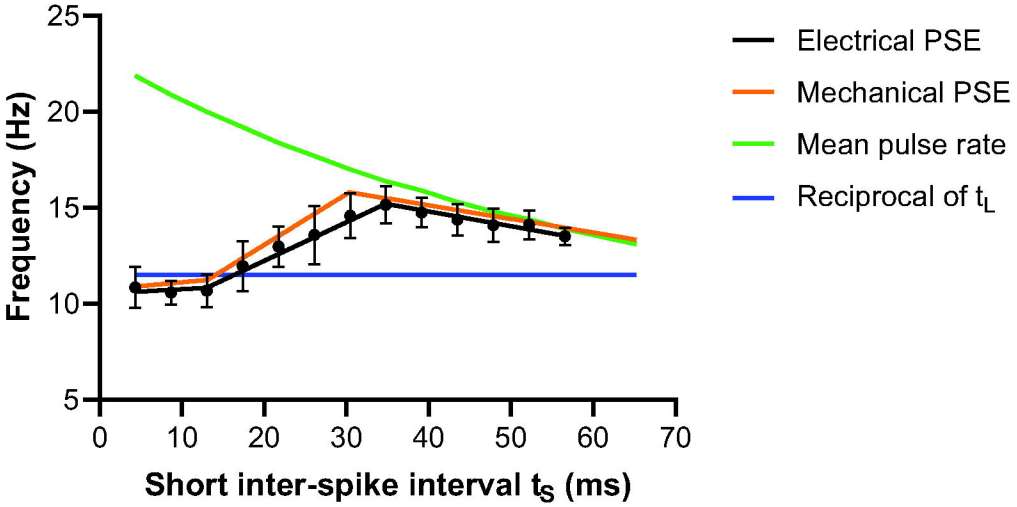
S2 Dataset. Individual subject PSE values for each experiment.


A
Period
43.5 ms; 23 Hz
a
t_L
39.15 ms
25.5 Hz
b
t_L
34.8 ms
28.7 Hz
c
t_L
30.45 ms
32.8 Hz
d
t_L
26.1 ms
38.3 Hz
B
1
2
3
t_S
t_L
t_S
t_L
t_S
12
13
t_S
t_L
t_S
t_L = 87 ms (f_L = 11.5 Hz)
t_S = n x 4.35 ms, n = 1, 2, 3, … , 13
C
1 sec
0.5 sec
1 sec
Comparison stimulus
Test stimulus
Subject response
Random order


a
2 µV
2 ms
b
c
d


2
0
-2
-4
-6
Mean slope (µV/ms)
a
b
c
d
Stimulus
2
0
-2
-4
-6
-8
Mean slope (µV/ms)
a
b
c
d
Stimulus
First
Second
Third
Fourth


A
100
80
60
40
20
0
Frequency (Hz)
a
b
c
d
Stimulus
Mean pulse rate
Subject PSE
Burst rate
B
45
40
35
30
25
20
Frequency (Hz)
20
25
30
35
40
45
Reciprocal of t_L (Hz)
Mechanical PSE
Electrical PSE


25
20
15
10
5
Frequency (Hz)
0
10
20
30
40
50
60
70
Short inter-spike interval t_S (ms)
Electrical PSE
Mechanical PSE
Mean pulse rate
Reciprocal of t_L