FREQUENCY SHAPES THE QUALITY OF TACTILE PERCEPTS EVOKED THROUGH ELECTRICAL STIMULATION OF THE NERVES

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ABSTRACT

The quality of tactile percepts evoked by skin vibrations depends on the frequency of stimulation: as frequency increases, the vibrotactile "pitch" increases. In the present study, we assessed the degree to which the quality of tactile percepts evoked via electrical stimulation of the somatosensory nerves is shaped by the frequency of the pulse train (PF). Participants with chronically-implanted peripheral nerve interfaces rated the quality of electrical pulse trains that varied in both PF and pulse width (PW) along a single continuum and also described the subjective quality of the sensory experience using perceptual descriptors. We found that increases in PF led to systematic increases in perceived frequency independent of PW, up to about 50 Hz, at which point perceived frequency leveled off or decreased. PF discrimination matched its vibrotactile counterpart, yielding a Weber fraction of ~0.2 at low frequencies, but discrimination performance was abolished above 50 Hz. Finally, we found that PF systematically shaped quality as characterized by verbal descriptors at low but not high frequencies. Furthermore, even when probed in this complex, multi-dimensional space defined by descriptors, PF modulated tactile quality along a single perceptual continuum. In conclusion, we show that quality can be shaped by imposing temporal patterns on a fixed neural population, highlighting the importance of spike timing in the peripheral nerve. However, this temporal patterning can only be resolved up to about 50 Hz when stimulation is applied to populations of tactile nerve fibers.

INTRODUCTION

Vibratory stimulation of the skin produces percepts whose quality depends on frequency. Low frequency vibrations evoke sensations of pulsing or flutter, in which individual stimulus cycles can be distinguished, while high frequency vibrations evoke a continuous or fused sensation of vibration[1]. Changes in vibrotactile frequency also affect the perceived magnitude of the vibrations, such that high-frequency vibrations are experienced as being more intense[2,3]. However, the change in magnitude that accompanies a change in frequency is largely independent of the change in quality, as evidenced by the fact that the ability to discriminate between vibratory frequencies is relatively unaffected by concomitant and independent changes in amplitude[4].

Vibrotaction plays a role in our ability to discern the microstructure of finely textured surfaces, because texture perception relies on the transduction and processing of texture-specific skin vibrations elicited when the fingertip is scanned over a surface[5,6]. Furthermore, vibrations transmitted through tools convey information about contact events at the distal end of the tool[7]. Studying the neural basis of vibrotaction provides a window into how the nervous system processes time-varying stimuli, drawing compelling analogies with the processing of acoustic stimuli by the auditory system[8,9]. The frequency composition of skin vibrations is encoded in the millisecond-precision temporal patterning of the spiking responses of tactile nerve fibers[10,11]. However, this temporal code is confounded by the different frequency sensitivity profiles of different types of afferent nerve fibers[12,13]. Rather than relying on spike timing alone, frequency could also be encoded in the relative activation of the different afferent populations, analogously to the coding scheme that supports trichromacy in vision[14]. The role of spike timing in frequency coding is thus hard to demonstrate conclusively based on mechanical stimulation of the skin.

Electrical stimulation offers a unique opportunity to examine the contribution of spike timing on tactile perception independently of the relative recruitment of afferent types. An electrical pulse train delivered to the nerve will synchronously activate local neurons regardless of fiber type, as there are no known type-specific properties to enable preferential recruitment[15,16]. The impact of stimulation frequency on quality is thus mediated by the temporal patterning in the neural response, as all fiber types are equally likely to be activated. Since increases in pulse frequency will also produce increases in perceived intensity via the population firing rate, the effect of timing on quality can be resolved by concurrently manipulating stimulation intensity, which also modulates perceived intensity[17].

In the present study, we sought to understand how temporal patterns of activation in the nerve affect the quality of tactile percepts. We approached this question in two sets of psychophysical experiments with human amputees implanted with multi-channel nerve cuff electrodes. First, we investigated how changes in the pulse frequency of electrical stimulation impact the perceived frequency of the stimulus. In these experiments, participants judged the evoked percept along a single dimension. We also assessed the sensitivity to changes in frequency. Second, we investigated the impact of stimulation

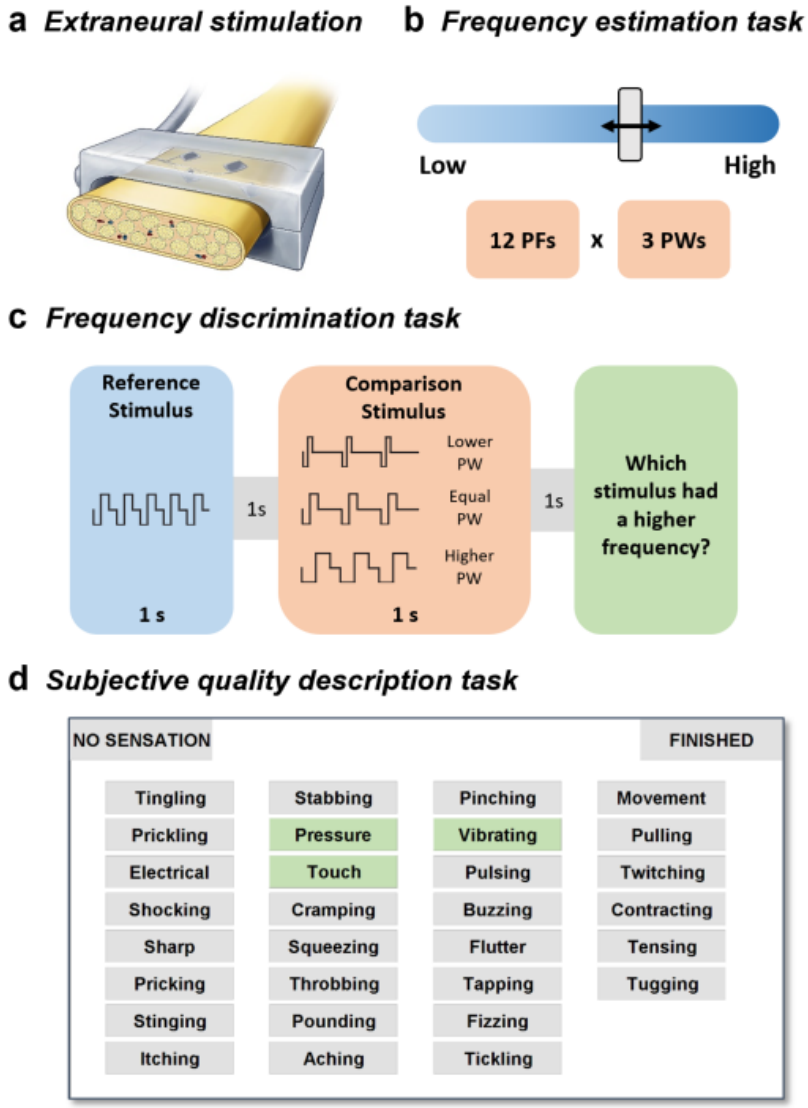

Figure 1. Experimental design. a) Electrical stimulation was delivered by an external neurostimulator through percutaneous leads to FINEs or C-FINEs implanted on the residual peripheral nerves of four trans-radial and two trans-tibial amputees. Stimulation consisted of trains of square, biphasic, charge-balanced pulses. b) Frequency estimation task. Three participants were asked to estimate the perceived frequency of an evoked percept by moving a slider along a horizontal bar. Stimuli varied in both stimulation pulse frequency (PF) and pulse width (PW). c) Frequency discrimination task. Four participants judged which of two sequentially-presented pulse trains was higher in perceived frequency, while ignoring any differences in perceived intensity. d) Quality description task. Six participants selected sets of words that described the quality of the evoked percept. Participants could select as many words as they wished to describe each stimulus.

pulse frequency on a multidimensional quality space defined by verbal descriptors to achieve a more holistic understanding of how pulse frequency shapes the quality of an electrically-evoked percept.

RESULTS

Tactile sensations were elicited by delivering electrical pulse trains to the somatosensory nerves, either via Flat Interface Nerve Electrodes (FINEs) or Composite Flat Interface Nerve Electrodes (C-FINEs) (Figure 1a). Four unilateral upper limb amputees and two unilateral lower limb amputees participated in the study.

Frequency estimation

First, we assessed the degree to which stimuli that vary in frequency can be judged along a single perceptual continuum. To this end, we delivered stimuli that varied in pulse frequency (PF) and asked participants to perform a frequency estimation task. The participants rated perceived frequency by positioning a slider along a horizontal bar (Figure 1b). To ensure that participants rated frequency rather than intensity, we varied the stimulation pulse width (PW), which also modulates perceived intensity[17]. If frequency estimates were based solely on perceived intensity, then ratings would increase with increases in either PF or PW.

At low PFs, perceived frequency increased logarithmically with PF ($R^2 = 0.81 \pm 0.06$, mean ± SEM) and was independent of PW (Figure 2). At higher PFs, perceived frequency remained constant or even decreased with increases in PF and was instead modulated by PW (Figure 2b). We fit piecewise logarithmic functions to the relationships between perceived frequency and PF to determine the transition point between the rising and falling (or sustained) portions of the

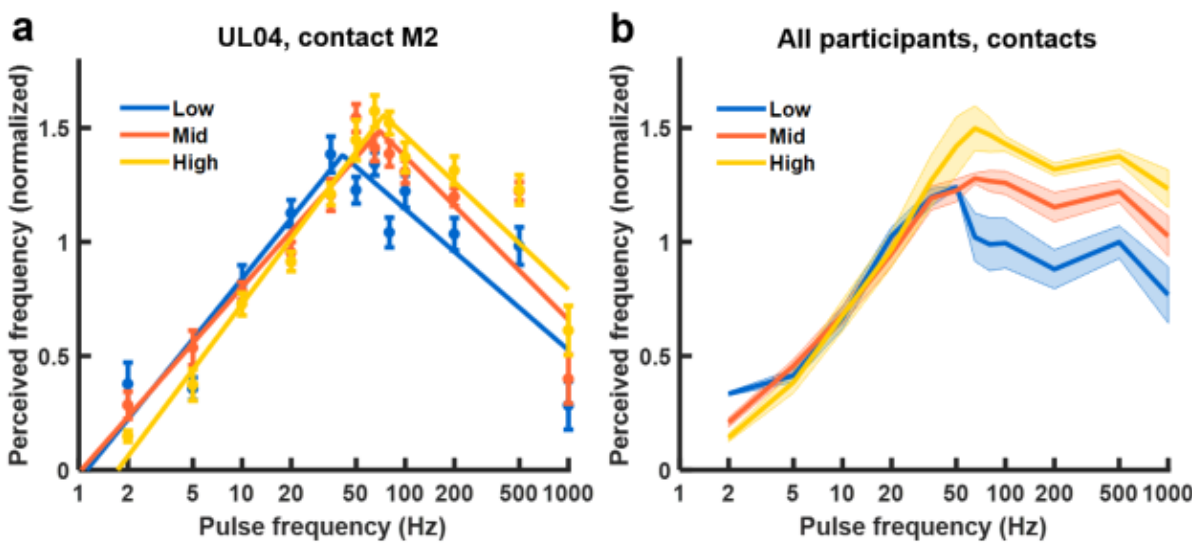

Figure 2. Perceived frequency estimates. a) Perceived frequency versus PF for a representative electrode contact (UL04, contact M2). Filled circles denote normalized perceived frequency ratings averaged for each stimulus. Color denotes the PW level and error bars depict the standard error of the mean. Solid lines represent piecewise logarithmic functions fit to the data. b) Average perceived frequency across all electrode contacts and participants versus stimulation PF (n=5). Color denotes the PW level and the shaded region corresponds to the standard error of the mean. Note that the abscissa is logarithmic.

relationships (R^2 = 0.85 ± 0.06) (Figure 2a). We found the transition frequency to be 60.0 ± 1.1 Hz (mean ± SEM). Transition frequency was highly consistent across participants and contacts and was independent of PW (ANOVA, $F(2,12) = 0.59$, $p = 0.57$).

Having identified two different regimes in the frequency response characteristic, we then examined the impact of PF and PW on perceived frequency in each regime separately. Below the transition frequency, perceived frequency was significantly dependent on PF ($F(5,82) = 27.83$, $p < 0.001$) but not PW ($F(2,82) = 1.58$, $p = 0.212$). Above the transition frequency, perceived frequency ratings depended on PW ($F(2,82) = 14.08$, $p < 0.001$) but not PF ($F(5,82) = 1.33$, $p = 0.262$). In summary, changes in PF exert a systematic effect on perceived frequency up to about 60 Hz, and this perceptual effect can be clearly distinguished from perceived magnitude. Increases in PF beyond 60 Hz do not change the quality of the percept along the perceived frequency continuum.

Frequency discrimination

Having found that the effects of PF on electrically evoked tactile percepts occupy two regimes – one at low and one at high frequencies – we next examined whether these regimes might be reflected in the participants' ability to discriminate *changes* in PF. To this end, we asked participants to judge which of two sequentially presented pulse trains was higher in perceived frequency (Figure 1c). In each experimental block, which consisted of several hundreds of trials, a standard stimulus (at 20, 50, or 100 Hz) was paired with a comparison stimulus whose PF and PW varied from trial to trial. The comparison PF varied over a range that was 25-175% of the standard PF. The comparison PW took on one of three values: one smaller than, one equal to, and one higher than the standard PW. The PW variation was intended to reduce or abolish the informativeness of perceived magnitude, which is modulated by changes in both PW and PF[17].

Discrimination with a constant pulse width

First, we examined participants' ability to distinguish changes in PF independently of PW by only analyzing same-PW pairs. We found that participants could discriminate on the basis of frequency on most electrode contacts when the standard PF was set at 20 Hz or 50 Hz, as evidenced by smooth psychometric functions over the range tested (Figure 3a & b; see Supplementary Figure 1a, b, d, e for exemplary "poor" contacts). With the 100-Hz standard, however, PF discrimination performance was very poor on all contacts, and participants never achieved criterion performance (Figure 3c, Supplementary Figure 1c & f). The just noticeable difference (JND) – defined as the difference in PF that yields 75% correct discrimination – was 4.01 ± 0.46 Hz and 9.91 ± 1.08 Hz (mean ± SEM) for the 20- and 50-Hz standards, respectively, yielding nearly constant and statistically indistinguishable Weber fractions (0.200 ± 0.02 Hz and 0.198 ± 0.02 Hz) (Figure 3e). JNDs were undefined for the 100-Hz standard for all tested contacts.

Effect of pulse width on frequency discrimination

Second, we examined the degree to which PF could be discriminated independently of changes in perceived magnitude. Trials with equal-PW pairs were interleaved with trials in which the PW of the comparison was different from that of the standard stimulus. To the extent that participants relied on differences in perceived magnitude to make their frequency judgments,

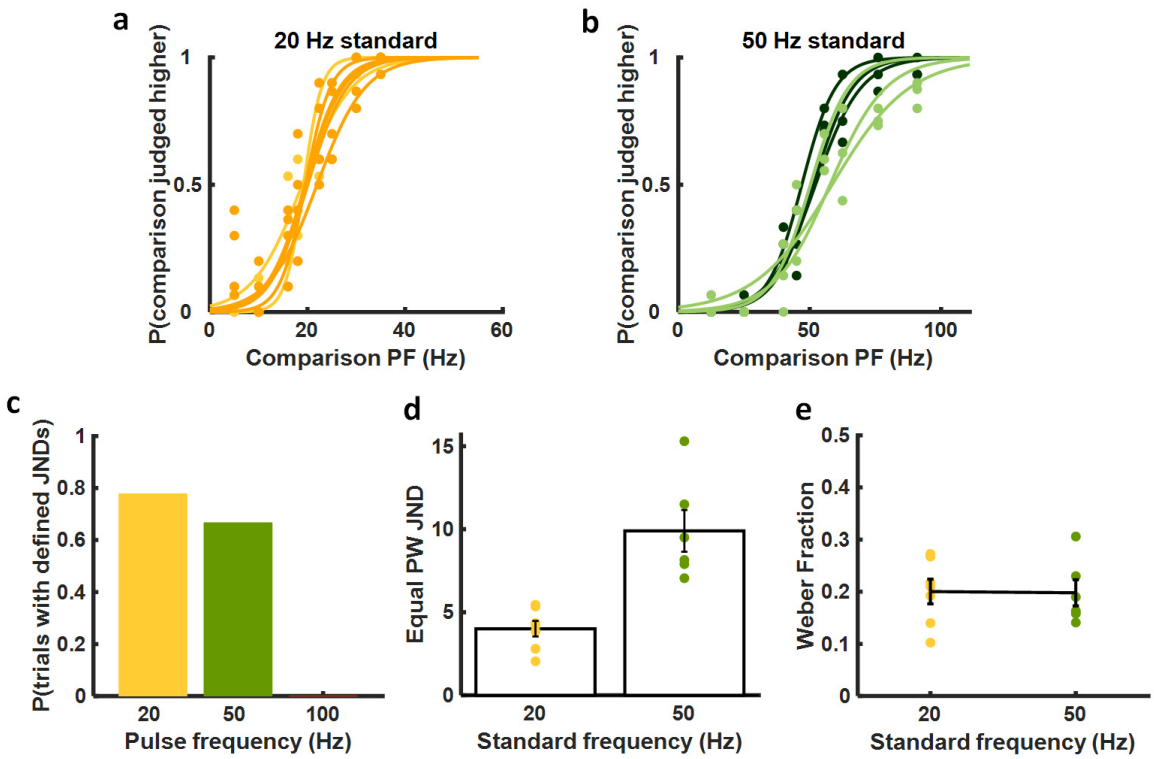

Figure 3. PF discrimination performance with constant PW. a) Performance with the 20-Hz standard for participant UL02 (yellow) and UL04 (orange). Each curve denotes the mean performance of a different electrode contact (n=7). b) Performance with the 50-Hz standard across contacts (n=6). Light green denotes UL02, dark green denotes UL04. c) Proportion of stimulation contacts leading to defined JNDs for the three standard frequencies when comparison and standard PWs are equal. Performance is shown only for conditions in which participants achieved the 75% performance criterion. Participants achieved threshold performance 78% (7 out of 9 total contacts tested) of the time with the 20-Hz standard and 67% (6 out of 9) of the time with the 50-Hz standard. Participants never achieved criterion performance (0 out of 7) with the 100-Hz standard. d) Just noticeable differences (JNDs) of equal PW conditions with the 20-Hz (n=7) and 50-Hz (n=6) standards. e) The Weber fractions for the 20-Hz (n=7) and 50-Hz (n=6) standards.

PW would systematically bias participants' frequency judgments, thereby causing lateral shifts in psychometric functions. Changes in PW may also lead to changes in the clarity or vividness of the evoked percepts, thereby resulting in changes in the discriminability of PF.

We observed systematic leftward shifts in the psychometric functions when the comparison PW was lower than the standard PW and systematic rightward shifts when the comparison PW was higher than the standard PW (Figure 4a, b, d & e). In other words, pulse trains with lower PW tended to be perceived as higher in frequency across PFs. This bias was quantified by computing the point of subjective equality (PSE) – the frequency at which participants were equally likely to pick the standard as they were the comparison stimulus. The PSE increased as the comparison PW increased for both the 20-Hz and 50-Hz standards (repeated measures ANOVA, $F(2,18) = 21.62$, $F(2,15) = 20.05$, respectively; $p < 0.001$). In summary, the participants exhibited a slight tendency to select the more intense stimulus as being lower in frequency, consistent with previous findings that the pitch of a vibrotactile stimulus decreases as the stimulus amplitude increases[14]. Note that this tendency was also observed in the frequency estimation ratings, but was too weak to achieve statistical significance. Interestingly, the effect of PW on PF

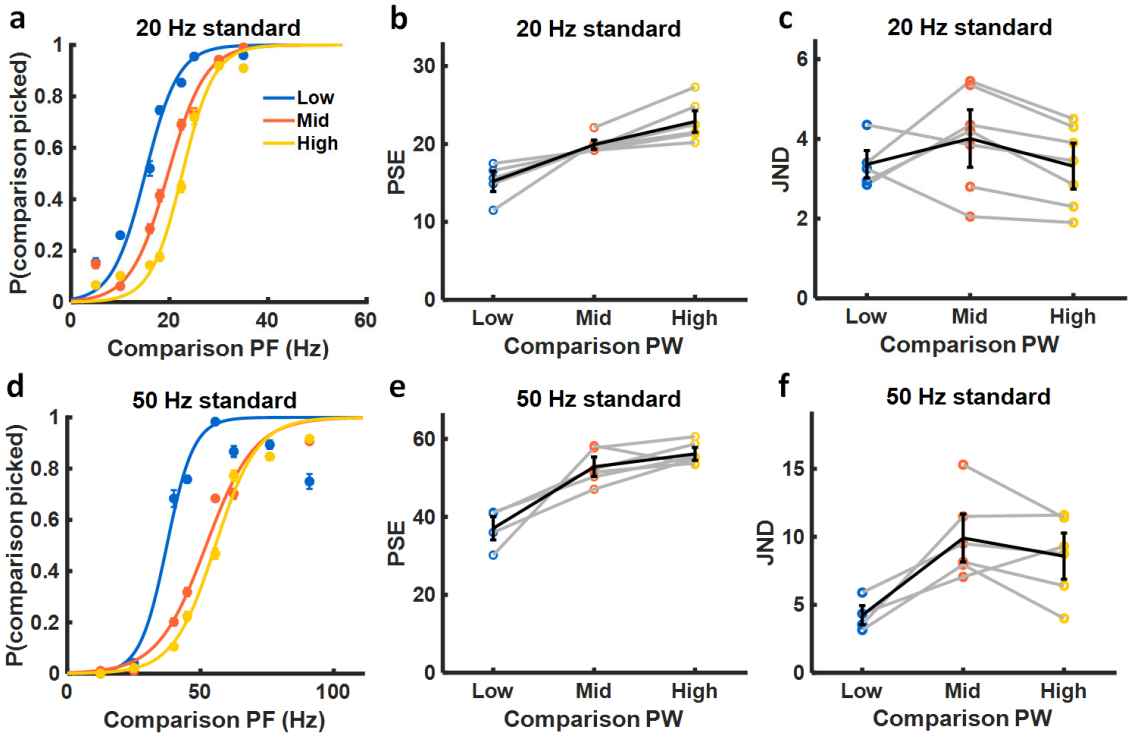

Figure 4. PF discrimination performance with variable PW. a) Performance with the 20-Hz standard and three comparison PWs, averaged across electrode contacts (n=7). b) Point of subjective equality (PSE) vs. PW for the 20-Hz standard (n=19). Gray lines denote different electrodes, black line denotes the mean across electrodes and participants. PSE increases with PW, revealing a PW-dependent bias in PF discrimination performance. Participants exhibited a tendency to perceive higher PWs as being lower in PF. c) JND vs. PW for the 20-Hz standard (n=19). There was no significant effect of PW on JND with the 20-Hz standard. d) Performance with the 50-Hz standard and three comparison PWs, averaged across electrode contacts (n=6). e) Point of subjective equality (PSE) vs. PW for the 50-Hz standard (n=16). PSE was significantly higher at higher PWs. f) JND vs. PW for the 50-Hz standard (n=16). JNDs tended to be higher at higher PWs.

discrimination differs from what has been observed with intracortical microstimulation in non-human primates, for which stimuli with higher pulse amplitude (PA) tended to be reported as being higher in frequency[18], assuming that PW and PA are interchangeable.

Next, we investigated the degree to which the comparison PW affected participants' sensitivity to changes in PF by examining the effect of PW on JND. For the 20-Hz standard, we found no systematic effect of PW on JND (Figure 4c, repeated measures ANOVA, $F(2,18) = 2.11$, $p = 0.1716$). For the 50-Hz standard, on the other hand, JNDs increased as PW increased (Figure 4f, $F(2,15) = 9.06$, $p = 0.0088$). In other words, participants became less sensitive to changes in PF at higher PWs, but only for the higher-frequency standard.

Subjective reports of sensory quality

Given that PF reliably influenced perceived quality along a single frequency continuum, we then investigated how stimulation PF shapes subjective quality more broadly. To this end, participants indicated which subset of a list of 30 qualitative descriptors applied to each stimulus (Figure 1d). Participants were encouraged to select as many words as necessary to describe the electrically evoked sensation.

Qualitative reports

On average, participants selected 6.5 ± 2.6 words (mean ± SEM) to describe each sensation. The total number of words chosen to describe a stimulus varied across participants, ranging from 5 to 22.

Examination of the participants' word selections revealed that stimulation PF influenced the descriptors chosen to characterize the artificial stimuli. Different sets of words were selected to describe low-frequency stimuli than high-frequency stimuli (Figure 5), as has been found with vibrotactile stimuli[1]. For example, descriptors related to periodic sensations were commonly selected for low-PF stimuli, whereas continuous sensations were reported for high-PF stimuli. In addition, the total number of reported words increased as a function of stimulation PF (linear regression, $p<0.001$).

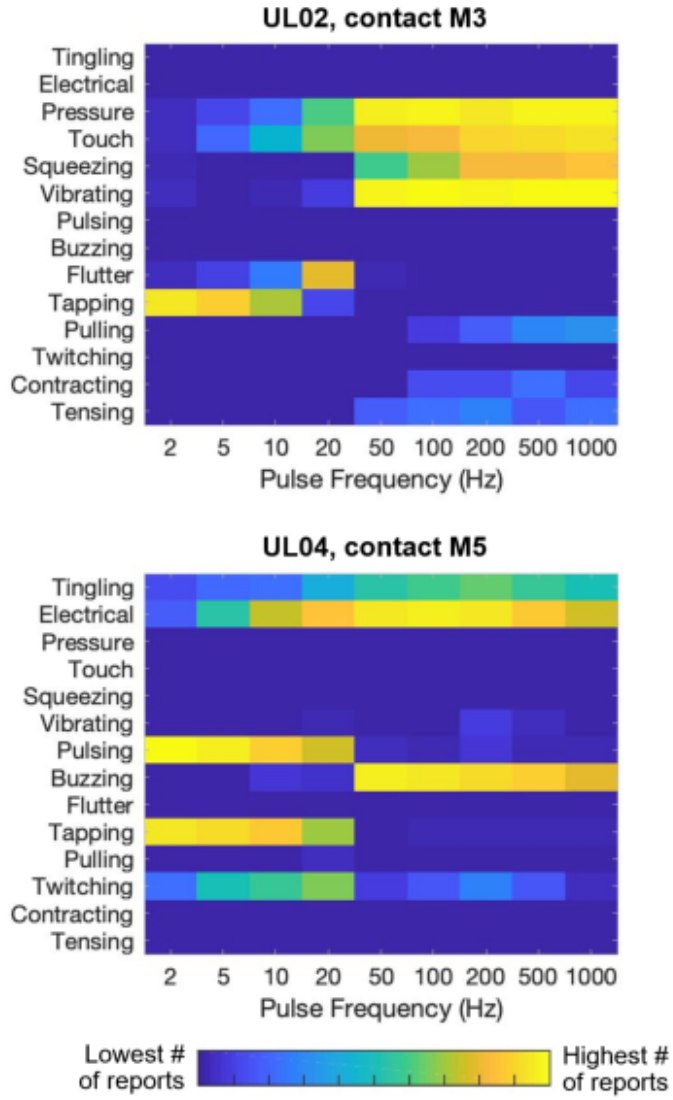

Figure 5. Quality descriptors reported for electrically-evoked percepts at each PF, averaged across PWs. Color denotes the proportion of times a descriptor was selected at each PF (top: contact M3/UL02; bottom: contact M5/UL04). Participants used different words to describe their sensory experiences. However, descriptors were similar across contacts for each participant (see Supplementary Figure 2).

Participants used similar words across electrode contacts, as evidenced by highly correlated word selection within-participant given the same stimuli ($R^2 = 0.66 \pm 0.08$, mean ± SEM). However, the descriptors ascribed to individual stimuli varied widely from participant to participant (Figure 5, Supplementary Figure 2), yielding weak correlations in word selections across participants ($R^2 = 0.14 \pm 0.04$). These variations likely reflect the participants' idiosyncratic word preferences, since some words, such as tapping and pulsing, may be construed as synonymous.

Robust representation of sensory quality

To overcome this participant-specific word choice and assess the effect of PF on quality across participants, we computed differences in descriptor selection between each pair of stimuli. To this end, we first represented quality as a 30-element vector, where each element corresponded

to the proportion of trials that each descriptor was selected. We then ran a principal component analysis (PCA) to remove redundant or highly correlated descriptors. Finally, we computed the Euclidean distance between each pair of stimulation conditions in this reduced dimensional space. These distances represent the perceived dissimilarity between pairs of stimuli (Figure 6a,b).

We found that the resulting dissimilarity matrices were highly consistent across participants and electrode contacts (Figure 6a,b). Indeed, dissimilarity matrices were much more similar across participants ($R^2 = 0.81 \pm 0.04$) than were the word selections from which they were derived (One-way ANOVA, $F(3,42) = 35.80$, $p < 0.001$) (Figure 6c). The consistency in dissimilarity matrices across participants and contacts suggests that sensation quality is largely independent of which region of the nerve is stimulated and is similar across subjects.

Impact of PF on overall quality

Having established a robust representation of multi-dimensional quality based on dissimilarity, we then assessed the degree to which changes in PF led to changes in the quality of the evoked percept. We found a sharp transition in sensation quality between 20- and 50-Hz for all tested contacts. In fact, the dissimilarity between 20-Hz and 50-Hz stimuli was significantly greater than the dissimilarity between any other pair of adjacent frequencies ($F(7,197) = 16.14$, $p < 0.001$) (Figure 6d). In other words, the perceptual

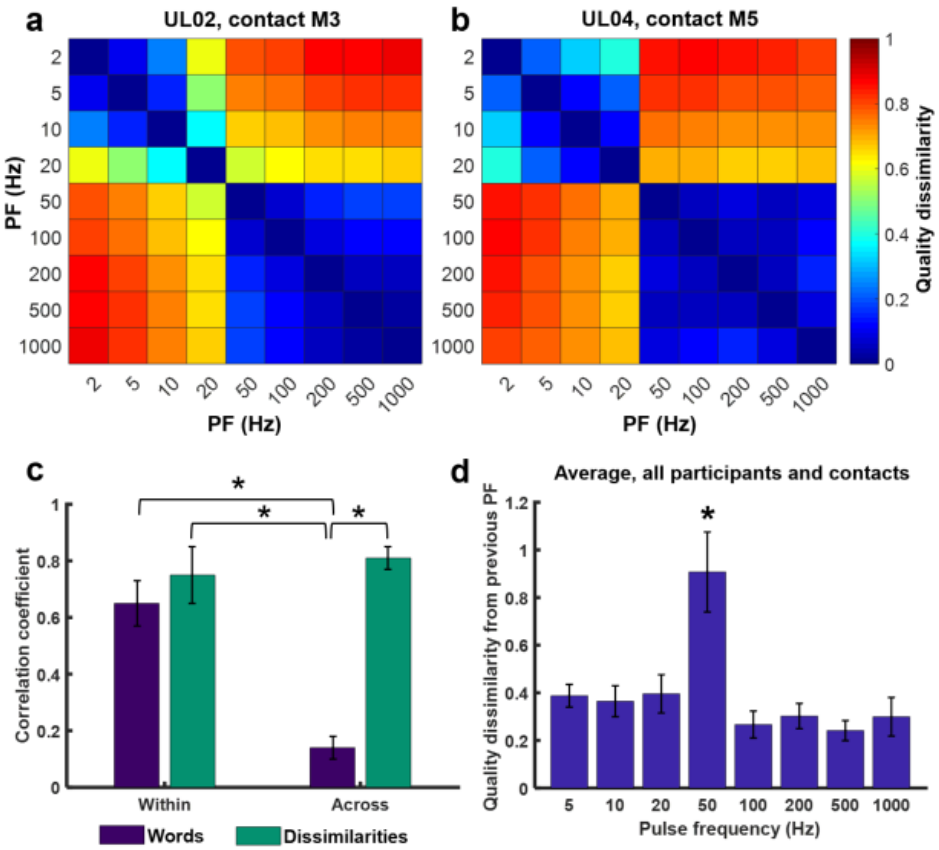

Figure 6. Perceived quality dissimilarity. a) Perceived dissimilarity between stimuli varying in PF for contact M3 of participant UL02. b) Perceived dissimilarity between stimuli varying in PF for contact M5 of participant UL04. Note that the contacts/participants shown in a and b are the same as in Figure 5. c) Within-participant and across-participant correlations for two metrics of quality. "Words" is the descriptors selected by the participant for each stimulus, and "Dissimilarities" is the Euclidean distance between pairs of stimulation conditions. Asterisks denote statistically significant differences with p<0.001. d) Perceived dissimilarity of each PF condition compared to the previous PF condition, averaged across PWs. The asterisk denotes significance at p<0.001.

quality was consistent across PFs ranging from 2 to 20 Hz, and quality was consistent across PFs from 50 to 1000 Hz, but these two subsets of stimuli felt very different from one another. There was no systematic effect of stimulation PW on the dissimilarities between successive PFs ($F(2,197) = 1.22$, $p = 0.3$).

We then wished to determine the extent to which differences in PF and PW resulted in differences in the evoked sensation. To quantify the impact of PF and PW on quality, we averaged the dissimilarity matrices across contacts and participants (Figure 7a) and regressed the resulting matrix on differences in PF or PW (ΔPF, ΔPW). The regression model that included both ΔPF and ΔPW yielded accurate predictions of dissimilarity ($R^2 = 0.67$, $F(3,725) = 499$, $p < 0.001$) (Figure 7b). While both ΔPF and ΔPW had significant impacts on dissimilarity, the contribution of ΔPF was much higher than that of ΔPW (standardized coefficients: $\beta_{\Delta PF} = 0.17$, $p < 0.001$; $\beta_{\Delta PW} = 0.05$, $p < 0.001$) (Figure 7c). The interaction between ΔPF and ΔPW was significant but weak ($\beta_{\Delta PF*\Delta PW} = -0.04$, $p < 0.001$).

Given the sharp transition in perceived quality around 50 Hz, we fit separate regression models for the dissimilarity data below 50 Hz and above 50 Hz. At low frequencies, the regression was nearly identical to that obtained using the full dataset ($R^2 = 0.74$, $F(3,221) = 214$, $p < 0.001$; $\beta_{\Delta PF} = 0.18$, $p < 0.001$; $\beta_{\Delta PW} = 0.05$, $p < 0.001$; $\beta_{\Delta PF*\Delta PW} = -0.04$, $p < 0.001$) (Figure 7d). In contrast, at high frequencies, the effect of PW dominated that of PF ($R^2 = 0.74$, $F(3,140) = 302$, p

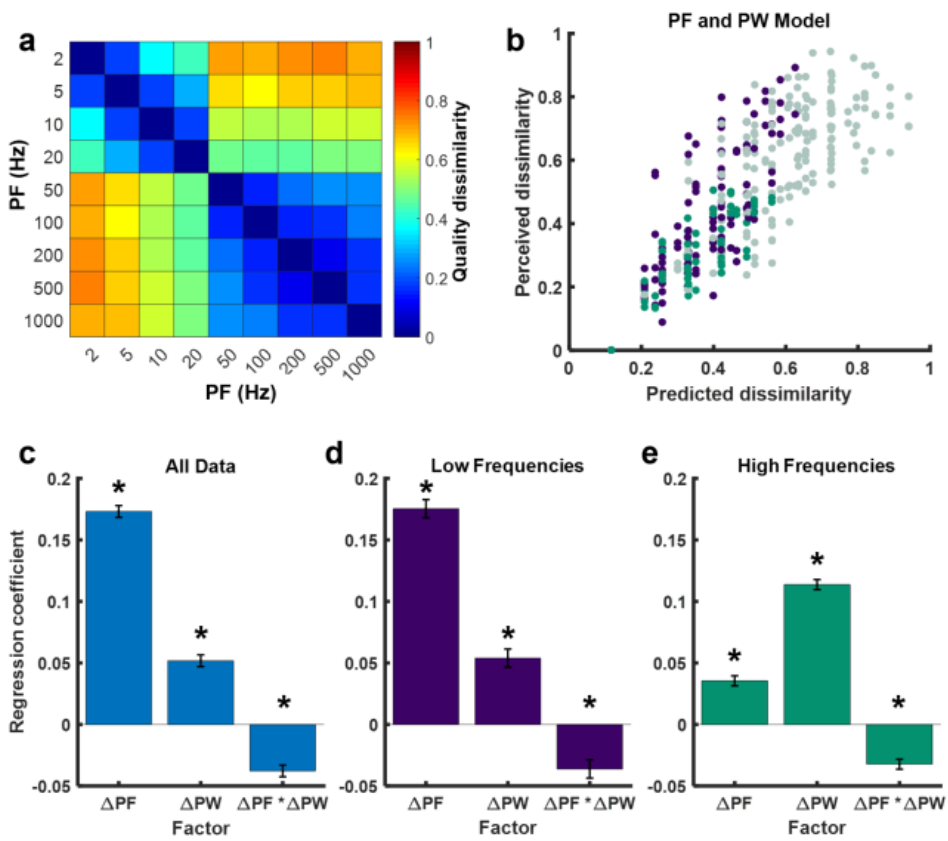

Figure 7. Contribution of stimulation parameters to sensation quality. a) Dissimilarity matrix averaged across participants and contacts (n=11). b) Measured dissimilarity vs. prediction from a linear combination of ΔPF, ΔPW, and their interaction. Purple points represent dissimilarities between stimuli at low frequencies (<50 Hz), green points represent dissimilarities between stimuli at high frequencies (>50 Hz), and grey points represent dissimilarities between high and low frequency stimuli. c) Standardized regression coefficients for the model with all data included. d) Regression coefficients for the model with only low frequency data included (<50 Hz). e) Regression coefficients for the model with only high frequency data included (>50 Hz). c,d,e) Asterisks denote significant contribution to the model at p<0.001.

< 0.001; $\beta_{\Delta PF}$ = 0.04, p < 0.001; $\beta_{\Delta PW}$ = 0.11, p < 0.001; $\beta_{\Delta PF*\Delta PW}$ = -0.03, p < 0.001) (Figure 7e). We performed the same analyses on individual participants' data and obtained the same results, confirming that these results were not an artifact of pooling.

Relationship between perceived frequency and dissimilarity

Finally, we wished to determine whether the effect of PF on dissimilarity could be explained solely based on its effect on perceived frequency. That is, we wished to examine whether PF modulated perceptual quality along a single continuum. To this end, we first regressed dissimilarity on perceived frequency, then assessed whether the residuals covaried with ΔPF. In the low-frequency regime, we found that differences in perceived frequency predicted dissimilarity ratings well (R^2 = 0.71, F(1,223) = 545, p < 0.001) (Supplementary Figure 3a) and that ΔPF contributed nothing more to the residuals (R^2 = -0.004, F(1,223) = 0.07, p = 0.80) (Supplementary Figure 3c). Thus, the effect of PF on quality is confined to a single continuum in the low frequency regime.

In the high-frequency regime, we similarly found that perceived frequency was a significant predictor of dissimilarity, as it was in the low frequency regime (R^2 = 0.53, F(1,142) = 164; p < 0.001) (Supplementary Figure 3b). However, ΔPF continued to have a weak but significant effect on dissimilarity ratings after regressing out the effect of perceived frequency (R^2 = 0.07, F(1,142) = 11, p = 0.001) (Supplementary Figure 3d). Thus, in the high-frequency regime, the effect of PF on quality dissimilarity cannot be explained purely on the basis of perceived frequency. Note, however, that the overall impact of PF on quality was weak in the high-frequency range (see Figure 7d), so the magnitude of these effects was small.

DISCUSSION

Stimulation frequency shapes sensory quality

Physical interactions with our environment give rise to a rich and complex tactile experience. While a touch can be readily localized to a specific location on the body and described as light or strong, the quality of the touch is more complex perceptually and often difficult to describe. For example, the tactile experience of a fabric is different than that of a vibration or of an edge. The quality of the touch does not fall on one continuum or even a few. To complicate matters, even a single sensory subspace, such as that for tactile texture, is complex and can be further broken down into component dimensions and subspaces[19–21].

The neural underpinnings of sensory quality are also difficult to identify. The perceived location of a touch is determined by which population of neurons is activated. The magnitude of a percept is determined by the overall population spike rate evoked in the nervous system[3,17]. Quality, on the other hand, is determined by the specific spatiotemporal pattern of activation elicited in the nervous system. Some patterns of activation give rise to a texture percept, others to a vibration percept, and others to a motion percept, and these patterns co-occur and are multiplexed in the nerve[22]. Furthermore, quality is shaped in part by which classes of tactile nerve fibers are activated by the stimulus[23].

Our results demonstrate that the temporal pattering in the neuronal response, which in this case was periodic and defined by stimulation PF, shapes the perceived quality of electrically-evoked

tactile percepts both along a single continuum – perceived frequency – and across a multi-dimensional space defined by perceptual descriptors. The effect of stimulation PF on quality was most pronounced at low frequencies, below approximately 50 Hz. In this frequency range, increases in stimulation PF led to both increases in perceived frequency and systematic changes in verbal reports of sensory quality. In fact, we found that the impact of PF on verbally-reported quality could be accounted for by variations in perceived frequency, demonstrating that PF modulates quality along a single continuum. In contrast, PW did not have a significant effect on perceived frequency and had a marginal effect on overall quality, indicating that the effect of PF on quality is not mediated by a change in perceived magnitude.

Taken together, these results show that spike timing alone can modulate the quality of tactile percepts at low frequencies, despite the fact that this temporal information is distributed across afferents of all subtypes. Thus, differential recruitment of afferent subtypes based on their frequency sensitivity profiles is not required for quality perception, though it likely plays an important role[23].

Discriminability of PF is abolished at high frequencies

Changing the frequency of vibrations delivered to the skin results in a change in the sensory experience along a continuum described as 'vibrotactile pitch,' underscoring its similarity to the sensory consequences of changes in the frequency of an acoustic tone[9,14]. Human observers can reliably discriminate a change in vibrotactile frequency of around 20%, but sensitivity to changes in frequency decreases at higher vibration frequencies[24–27]. Changes in vibrotactile frequency also produce changes in perceived magnitude[2]. However, humans can discriminate vibratory frequency even in the presence of concomitant changes in vibratory amplitude[4], demonstrating that vibrotactile frequency shapes the quality of the percept.

The ability to perceive the frequency of a vibration is thought to be mediated by a timing code in the nerve. Sinusoidal vibrations delivered to the skin elicit periodic, phase-locked spiking responses in tactile nerve fibers, and the frequency of these responses matches the frequency of stimulation[1,10]. When this temporal patterning is absent, for example at low stimulus amplitudes, the ability to discriminate frequency is abolished[28].

Similarly, pulsed electrical stimulation of the nerve also produces a highly periodic response in the activated tactile nerve fibers[29]. Our results demonstrate that this frequency-dependent temporal patterning likely mediates the ability to discriminate the perceived frequency of electrical pulse trains. In fact, sensitivity to changes in the frequency of electrical stimulation is similar to its vibrotactile counterpart, both yielding Weber fractions of ~0.2. We also demonstrate that stimulation PF has a larger effect on the quality of an electrically-evoked sensation than it does on its magnitude: the Weber fraction of stimulation PF along the perceived magnitude continuum (0.3)[17] is higher than that along the perceived frequency continuum.

In contrast to vibrotactile frequency discrimination, which can be achieved over a wide range of frequencies up to 400 Hz and beyond[18], we show that frequency discrimination of peripheral nerve stimulation is only possible at frequencies below ~50 Hz. Above this point, frequency discrimination fell to near chance. This is especially interesting in light of the fact that humans and non-human primates can distinguish the PF of intracortical microstimulation up to around

200 Hz, though sensitivity to PF changes decreases at high frequencies[30]. The basis for this difference between peripheral and cortical stimulation is unclear.

A new method for quantifying somatosensory quality

Quality is difficult to quantify because this aspect of a sensory experience occupies a high dimensional space and measuring it relies on verbal reports, which are often highly idiosyncratic. In this study, the specific words chosen to describe the qualitative sensory experiences varied widely across participants. To mitigate this variability in adjective selection, we developed an approach to represent quality in a multi-dimensional space based on *differences* in the descriptors that participants used to describe the sensations. We found that this representation of quality was very similar across participants, suggesting that tactile sensations evoked from neural stimulation may be approximately equivalent across individuals despite the use of different verbal descriptors. We propose that our approach could be used in future studies of quality perception to improve comparisons across participants when the perceptual space is not confined to one or a few pre-defined dimensions.

Abrupt transition in quality from low to high frequencies

As discussed above, the ability to discriminate PF is abolished beyond about 50 Hz, and the influence of PF on quality is far more pronounced at low PFs. In contrast, PW had a greater impact on quality at high PFs than did PF. Furthermore, subjective, multi-dimensional quality also shifted abruptly at ~50 Hz. There are several possible explanations for the transition between the low and high frequency regimes.

One possibility is that the tactile nerve fibers cannot, as a population, phase lock to stimulation pulse trains beyond about 50 Hz. As discussed above, the temporal patterning in the neural response likely drives the effect of stimulation PF on sensory quality. At high frequencies, stimulation pulses may encroach on the refractory period resulting from the neural response to the previous pulse. This phenomenon might then blur the temporal patterning in the population response. However, given that the refractory period is typically less than 5 ms[31] and that pulses are separated by 20 ms at 50 Hz, refractoriness is unlikely to play a critical role in the observed transition in quality.

Another possibility is that the spikes evoked in the afferent population by each pulse get desynchronized at proximal stages of the sensory pathway due to conduction delays, thereby blurring the temporal patterning at the population level. Indeed, neural conduction velocities vary across Aβ nerve fibers that mediate touch due to the natural variance in fiber diameters[32]. In an adult male, the resulting propagation delays for signals to travel from the fingertip to spinal cord range from 11 to 22 ms[33]. However, this jitter is not observed in the vibrotactile responses of neurons in the somatosensory cortex[4,25], which exhibit a high degree of phase locking, suggesting that some compensatory mechanism might eliminate this endogenous jitter along the way to the brain. The synchronized spikes delivered through a nerve cuff might then *become* desynchronized via this compensatory mechanism. Given that the intrinsic delay correction would span about 10 ms (to correct for delays ranging from 11 to 22 ms) and that the cuff electrode is positioned approximately halfway between the fingertip and spinal cord, the imposed jitter would span approximately 5 ms. We might then expect frequency discrimination

to break down around 200 Hz. Thus, this conduction delay-mediated desynchronization mechanism is also unlikely to be solely responsible for the transition at 50 Hz.

A third possibility is that the unnatural activation of afferent subtypes by peripheral nerve stimulation obscures the temporal pattern imposed by stimulation at high PFs. Electrical stimulation recruits Aβ fibers based on their fiber diameter and nodal voltages[34,35], regardless of their submodality class. In natural touch, the various submodalities of tactile fibers differ in the frequency profiles of their sensitivity to skin vibrations: slowly adapting type 1 (SA1) fibers respond preferentially to low frequency vibrations, Pacinian corpuscle-associated (PC) fibers respond preferentially to high frequency vibrations, and rapidly adapting fibers (RA) fibers respond preferentially to an intermediate range of frequencies[12]. A high-PF electrical stimulus delivered directly to the peripheral nerve will therefore activate SA1 fibers, and perhaps RA fibers, to a much greater extent than would a high-frequency vibration delivered to the skin. This large, unnatural signal may obscure the critical signal carried by appropriately-responding afferents, especially PC fibers. The hypothesis that over-activation of SA1 and RA fibers could be implicated in poor frequency perception at high PFs is supported by previous studies of intraneural microstimulation: while increases in the PF delivered to individual RA afferents induces increases in perceived frequency at low PFs, further increases only lead to increased intensity[23]. Stimulation of individual SA1 fibers leads to sustained percepts at all but the lowest PFs[23]. The submodality over-activation hypothesis is also bolstered by the previous finding that the impact of peripheral afferent signals on cortical neural activity is highly dependent on the submodality of the peripheral afferents: PC signals in the periphery drive the *temporal patterning* of neural responses in cortex, whereas RA and SA1 signals instead drive the *strength* of the response in cortex[36]. Thus, the unnatural strength of the SA1 signal (and perhaps the RA signal) evoked via peripheral nerve stimulation may muddle the crucial frequency signal transmitted by PCs to the cortex. This phenomenon would be exacerbated at high PFs, at which SA1 fibers are typically relatively quiescent, consistent with our results. A similar phenomenon, in which RA signals interfere with SA1 signals about local geometric features, has previously been observed[37].

Implications for neuroprosthetics

A major challenge facing recent efforts to restore the sense of touch through neural stimulation is to evoke sensations endowed with an appropriate quality. The goal is for neuroprosthetic contact with a textured surface to lead to a perceived sensation of the appropriate texture and contact with an edge to lead to the sensation of an edge. In the normal sensory system, the spatiotemporal pattern of activation evoked in the nerve when interacting with an object depends on the dynamics of contact and the properties of the object, and the evoked percept depends critically on these spatiotemporal neural patterns. While electrical stimulation of the nerve can reproduce the temporal aspects of this normal neural activity by patterning the pulses, it cannot currently mimic the complex spatiotemporal patterns due to limitations in the selective activation of subpopulations of nerve fibers. Mimicking natural patterns of activation with biomimetic stimulation confers greater speed to certain sensory discrimination tasks performed with a prosthesis, but the impact of biomimetic stimulation on the quality of the evoked sensation is inconsistent[38–40]. However, our results demonstrate that modulation of stimulation frequency is sufficient to reliably control sensation quality. This encoding scheme can be readily

implemented to intuitively convey information about object contact and manipulation in both upper and lower extremity neuroprostheses.

METHODS

Participants

Six people volunteered for this study. Four participants had unilateral acquired amputations of the upper limb below the elbow and two had unilateral acquired amputations of the lower limb below the knee. All participants were implanted with multi-contact peripheral nerve cuff electrodes, either Flat Interface Nerve Electrodes (FINEs) or Composite Flat Interface Nerve Electrodes (C-FINEs). Upper limb participants (referred to as UL01-UL04) were implanted with 8-channel FINEs or 16-channel C-FINEs around the median, ulnar, and/or radial nerves between 3 and 7 years prior to participation in the present study. Lower limb participants (LL01 and LL02) were implanted with 16-channel C-FINEs around the sciatic and tibial nerves between 1 and 3 years prior to participation in the present study. Percutaneous leads connected the cuff electrodes to an external neurostimulator. Stimulation waveforms were square, biphasic, cathodic-first, and charge-balanced. Stimulation parameters were set in MATLAB (MathWorks, Inc.; Natick, MA, USA) and then sent to a computer running xPC Target (MathWorks, Inc.; Natick, MA, USA), which then drove the stimulator.

The Louis Stokes Cleveland Department of Veterans Affairs Medical Center Institutional Review Board and Department of the Navy Human Research Protection Program approved all procedures. This study was conducted under an Investigational Device Exemption obtained from the United States Food and Drug Administration. All participants provided written informed consent to participate in this study, which was designed in accordance with relevant guidelines and regulations.

Frequency estimation task

In each trial, a 1-second pulse train was delivered and participants estimated the perceived frequency of the evoked sensation. Estimations were made using a visual analog scale displayed on a computer monitor, which displayed “Slowest possible frequency” on the far left of the scale and “Fastest possible frequency” on the far right of the scale. In the first trial, we advised participants to rank the perceived frequency somewhere in the middle of the scale. In subsequent trials, they were asked to rank perceived frequency as faster or slower with respect to prior stimuli. Participants were asked to ignore changes in intensity and location when making frequency estimates. A 3-second inter-trial interval was enforced to minimize the effects of perceptual adaptation[41].

For each electrode contact, we tested twelve pulse frequencies (PF) and three pulse widths (PW). PFs were set to 2, 5, 10, 20, 35, 50, 65, 80, 100, 200, 500, and 1000 Hz. The three PWs were chosen on a per-contact basis to span the full range of suprathreshold, comfortable intensities. The “Low” PW value was chosen as the minimum PW that was reliably perceived at 2 Hz. The “High” PW value was chosen as the maximum PW that was comfortable at 500 Hz. The “Mid” PW value was chosen as the midpoint between the “Low” and “High” values. The 36 stimuli were

presented in pseudo-random order twenty times per contact, split into eight experimental blocks of 90 trials, all performed on the same day. Five electrode contacts across three participants were included in this analysis.

Frequency ratings were normalized by dividing each estimate by the within-block mean rating. Normalized ratings were then averaged within-contact for each PW and PF condition. We then fit piecewise linear functions to the base-10 logarithm of frequency, separated by PW condition. The transition between the rising and falling phases of the perceived frequency ratings was obtained from the optimized parameters. The transition metric was averaged across participants, contacts, and PWs after first removing an outlier. Means and standard errors of the frequency estimates were then calculated across participants and contacts within each PW and PF condition.

Frequency discrimination task

Each trial consisted of two successive 1-second pulse trains separated by a 1-sec inter-stimulus interval. Participants judged which of the two sequentially presented pulse trains was higher in perceived frequency. In each experimental block, a standard stimulus (at 20, 50, or 100 Hz) was paired with a comparison stimulus whose PF and PW varied from trial to trial. The comparison PFs ranged from 25 to 175% of the standard PF. The comparison PW took on one of three values: one smaller than, one equal to, and one higher than the standard PW. All PW values were between 70 to 130% of the standard PW. The standard stimulus was always at the intermediate PW. In each block, each stimulus pair was presented 10 times, and both the order of stimuli within the pair and the order of the pairs varied pseudo-randomly. The inter-trial interval was enforced to be at least 3 seconds long. Thus, each experimental block evaluated one electrode contact and consisted of 270 trials (9 comparison PFs × 3 comparison PWs × 10 repetitions). Nine contacts across four participants, nine contacts across two participants, and seven contacts across two participants were evaluated for the 20, 50, and 100 Hz standard, respectively.

Psychophysical performance was calculated as the proportion of trials in which the comparison stimulus was judged to be higher in perceived frequency than the standard stimulus. Psychometric curves were then constructed by fitting a cumulative normal density function to these proportions. Separate psychometric functions were fit for each standard frequency (20, 50, and 100 Hz). Just noticeable differences (JNDs) were calculated as the change in frequency required to achieve 75% correct performance. Two JND estimates were obtained from each psychometric function, one above and one below the standard, and these two estimates were averaged. Sessions in which performance did not achieve the 75% threshold performance criterion (above or below the standard) were considered to have an undefined or incalculable JND. These data points were omitted from further analysis in the main results section and were only included in the supplementary materials. The point of subjective equality (PSE) was defined as the comparison frequency that corresponded to 50% correct performance, as calculated from the fitted psychometric functions.

Subjective Quality Description Task

In each trial, a 2-second pulse train was delivered and participants were asked to indicate which subset of a list of 30 qualitative descriptors applied to the percept (word list shown in Figure 1d).

These words were selected based on prior studies of language associated with natural and artificial somatosensation[23,42–48]. Participants were encouraged to select as many words as necessary to fully describe the sensation. Participants were instructed to use their own definitions for each descriptor, but to maintain consistency throughout each experimental session. For example, if two stimuli felt identical, they were asked to select the same subset of words for both trials. Stimulation was applied at one of 9 PFs and 3 PWs for each stimulus. Stimulation PF was set to 2, 5, 10, 20, 50, 100, 200, 500, and 1000 Hz, and PWs were selected in the same manner as in the frequency estimation task. Each stimulus was presented 20 times in pseudo-randomized order. A 2-second inter-trial interval was enforced. A "no sensation" option was provided for trials in which the participant did not feel the stimulus. Eleven electrode contacts were tested across all six participants. Stimulation conditions in which "no sensation" was selected in more than five trials were excluded from the analysis. We computed the proportion of times each descriptor word was selected for each stimulation condition for each contact after "no sensation" trials were removed. The result was a set of 30 proportions for each stimulation condition.

To compute within-participant consistency in word selection, we ran a correlation analysis of word proportions between the sets of contacts tested within the same participant. Those participants that only performed the subjective quality test with a single contact were excluded from this analysis. To calculate across-participant consistency in word selection, we first averaged the proportions across contacts for each participant, then computed the correlation in these proportions for each pairing of participants.

Dissimilarity matrices

Having observed that different participants used different words to describe the electrically-evoked sensations, we hypothesized that we could achieve a more generalizable representation of tactile quality by computing differences in descriptors between stimulation conditions. To reduce redundant or highly-correlated descriptors within each dataset, we ran a principal component analysis (PCA) on the word proportion vectors across all stimuli (a 30 x 27 data matrix) on a participant-by-participant basis and retained the components necessary to explain 95% of the variance. We then projected the stimuli onto this reduced dimensionality space and calculated the pairwise distances between them, resulting in a 27 x 27 distance matrix for each tested electrode contact (n=11). To remove the influence of the number of dimensions on calculated distances, we normalized distances to the maximum inter-condition distance (which was set to 1). For some analyses (e.g. that shown in Figure 6a), we averaged the coordinates for each PF across PWs and then recomputed the distances, yielding a 9 x 9 distance matrix. We also averaged the distance matrices across participants and contacts to prepare for the regression analyses described below.

To assess the within-participant consistency in dissimilarities, we computed the correlation between distance matrices obtained from different contacts for each participant. To assess across-participant consistency in dissimilarities, we first averaged the dissimilarities across contacts for each participant then computed the correlation in the dissimilarity matrices for each pair of participants.

To examine the quality dissimilarity between successive PF conditions, we computed the distance between the coordinates of two adjacent PFs in the reduced dimensionality space, then averaged these distances across PWs and contacts.

Finally, we performed a multivariate regression analysis with ΔPF, ΔPW, and their interaction as factors. This analysis was also performed with the data split into two sets: one for PFs below 50 Hz and one for PFs above 50 Hz. We verified that the regression model fit to the dissimilarity matrix averaged across contacts and participants yielded the same conclusions as one fit to data pooled across individual contacts and participants. We also performed a step-wise regression, in which we assessed whether PF accounted for a significant proportion of variance in the dissimilarity ratings after differences in perceived frequency had been regressed out. To this end, we first regressed dissimilarity against differences in perceived frequency ratings. We then regressed the residuals against ΔPF. This analysis was performed separately for stimuli below and above 50 Hz.

Statistical Tests

Frequency estimations. We determined the influence of PW on the transition frequency between the rising and falling regimes of perceived frequency using a one-way ANOVA versus PW. We then split the data into two regimes: 0-50 Hz and above 50 Hz. For each regime, we ran a two-way ANOVA on the normalized frequency estimations pooled across contacts and participants with factors of PW and PF. All statistical analyses were performed in Minitab (Minitab, LLC; State College, PA, USA) with alpha level of 0.05.

Frequency discriminations. We studied the influence of PW on the JNDs and PSEs of the psychometric functions using repeated measures ANOVA with different PWs and different contacts as factors. JNDs and Weber fractions at 20Hz standard were compared to their counterparts at 50Hz using a two-sample t-test. All statistical analyses were performed in MATLAB with alpha level of 0.05.

Subjective quality reports. We ran a linear regression to determine how the number of words selected by each participant changed with PF. We compared within- and across-participant correlations in quality descriptors and dissimilarities using a one-way ANOVA with Tukey pairwise comparisons. We compared quality dissimilarities between successive PFs using a two-way ANOVA with Tukey pairwise comparisons with factors for PF and PW. These analyses, as well as the univariate and multivariate regressions, were performed in MATLAB and/or Minitab with alpha level of 0.05.

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Author Contributions

ELG designed the study, collected the data, analyzed the data, interpreted the results, and wrote the manuscript. BPC collected the data, analyzed the data, and wrote the manuscript. QH analyzed the data and wrote the manuscript. DJT advised on result interpretation and revised the manuscript. SJB designed the study, interpreted the results, and wrote the manuscript.

Competing Interests statement

The authors declare no financial competing interests. DJT has patents on the electrodes (US Patent #6456866B1) and stimulation patterns related to sensory restoration (US Patent #9421366B2). ELG, DJT, and SJB also have a patent application on stimulation patterns related to sensory restoration (PCT/US2017/056070).

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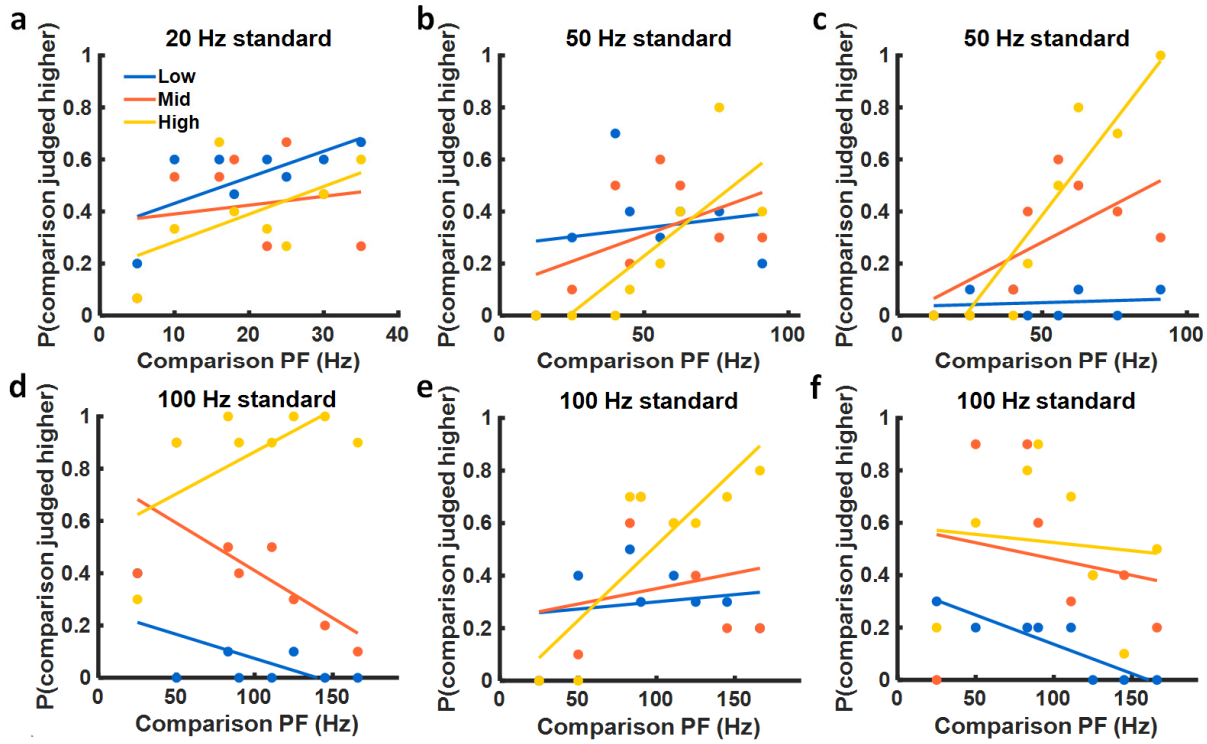
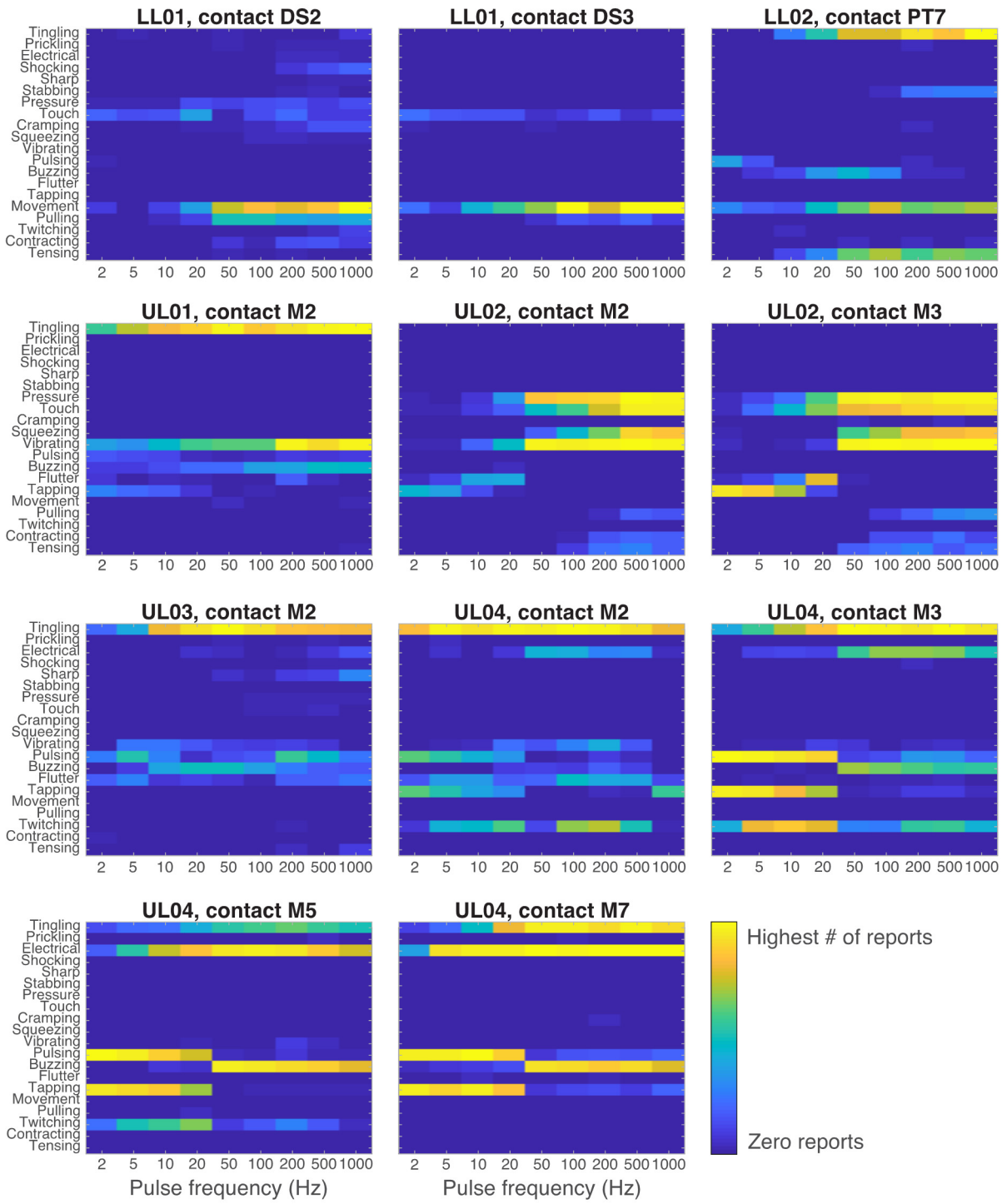
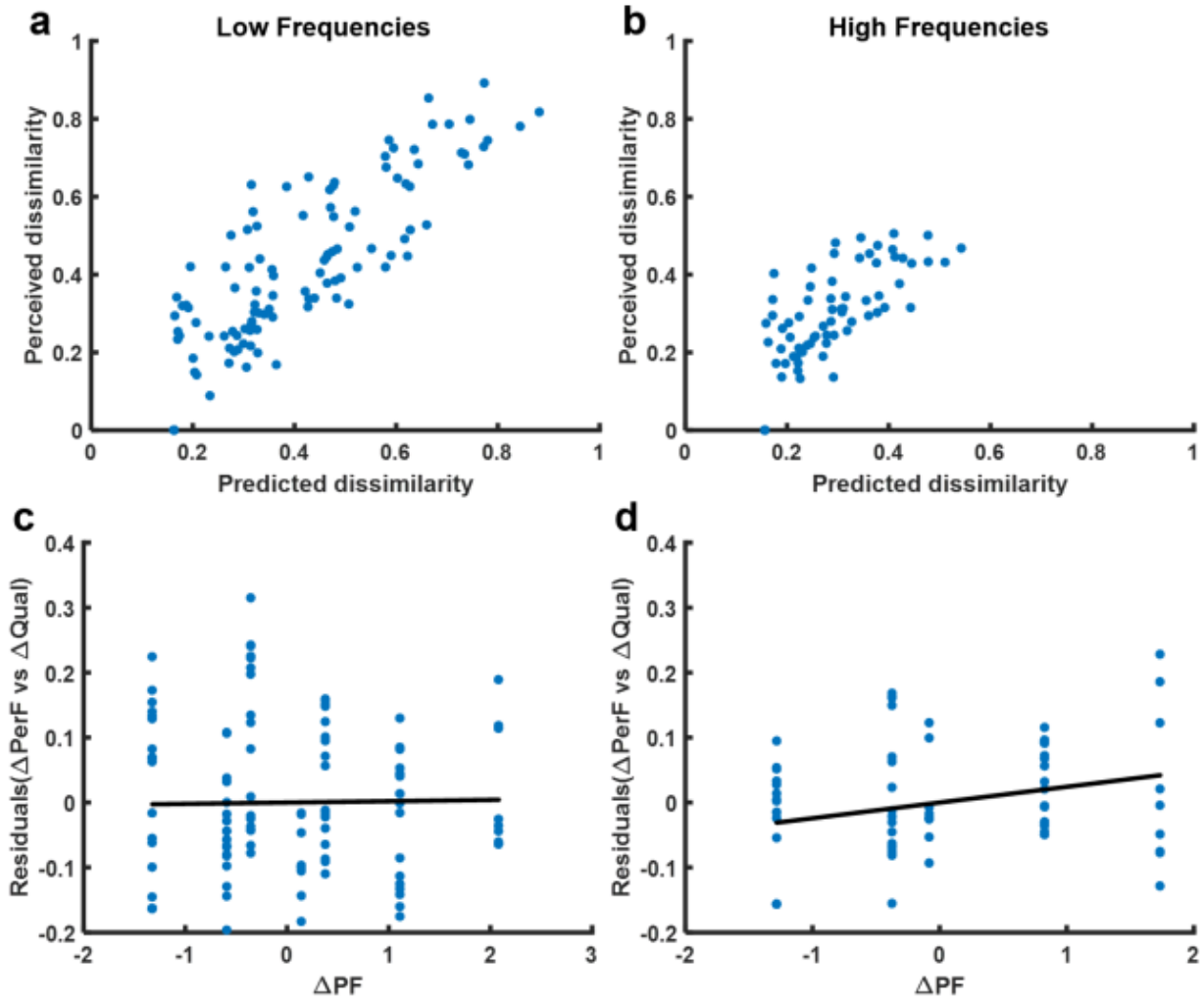
SUPPLEMENTARY FIGURES



Supplementary Figure 1. Examples of electrode contacts with poor frequency discrimination performance. Each panel depicts one contact in which the participant did not reach criterion performance. Lines are fitted to different comparison PWs (blue for low PW, orange for mid PW, and yellow for high PW). a) Contact G4 of participant LL02. b) Contact M2 of UL04. c) Contact M3 of UL04. d) Contact M3 of UL04. e) Contact M5 of UL04. f) Contact M2 of UL04.



Supplementary Figure 2. Effect of PF on qualitative reports for all participants and contacts (n=11). Each qualitative descriptor is a separate row. The color indicates the proportion of perceived trials at each stimulation PF in which the descriptor was reported.



Supplementary Figure 3. Effect of PF on perceived dissimilarity after removing the influence of perceived frequency. A univariate regression predicting quality dissimilarity based on perceived frequency was performed for low (a) and high (b) frequency stimuli. a,b) Perceived dissimilarity versus a linear prediction based on differences in perceived frequency. c,d) Residuals of the regression (shown in a and b) versus (z-scored) ΔPF. Solid black lines denote the regression of the residuals on to ΔPF. c) At low frequencies, the influence of ΔPF on dissimilarity was not significant after accounting for perceived frequency (p = 0.8). d) At high frequencies, ΔPF significantly impacted dissimilarity, even after accounting for perceived frequency (p = 0.001), but the effect was modest.