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How Fast Is Too Fast? Boundaries to the Perception of Electrical Stimulation of Peripheral Nerves

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Abstract—Transcutaneous electrical stimulation is a promising technique for providing prosthetic hand users with information about sensory events. However, questions remain over how to design the stimulation paradigms to provide users the best opportunity to discriminate these events. Here, we investigate if the refractory period influences how the amplitude of the applied stimulus is perceived. Twenty participants completed a two-alternative forced choice experiment. We delivered two stimuli spaced between 250 ms to 450 ms apart (inter-stimulus-interval, isi). The participants reported which stimulus they perceived as strongest. Each stimulus consisted of either a single or paired pulse delivered transcutaneously. The inter-pulse interval (ipi) for the paired pulse stimuli varied between 6 and 10 ms. We found paired pulses with an ipi of 6 ms were perceived stronger than a single pulse less often than paired pulses with an ipi of 8 ms ($p = 0.001$) or 10 ms ($p < 0.0001$). Additionally, we found when the isi was 250 ms, participants were less likely to identify the paired pulse as strongest, than when the isi was 350 or 450 ms. This study emphasizes the importance of basing stimulation paradigms on the underlying neural physiology. The results indicate there is an upper limit to the commonly accepted notion that higher stimulation frequencies lead to stronger perception. If frequency is to be used to encode sensory events, then the results suggest stimulus paradigms should be designed using frequencies below 125 Hz.

Index Terms—Electrical stimulation, sensory feedback, neural behavior, prosthetic control.

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I. INTRODUCTION

MODULATING the peripheral and central nervous system is central to bioelectronic medicine and neuroprosthetics [1]–[6]. Established examples include: cardiac pacemakers, spinal cord stimulators, deep brain stimulators, and cochlear implants [2]. These devices electrically stimulate the nervous system to treat diseases, or restore lost function [4]. To best design stimulation protocols for the desired application, it is important to understand the effects of electrical impulses on neural behaviour. Additionally, in cases where the stimulation aims to transfer information through perception changes, verification on a perceptual level is required.

The perception of the magnitude of sensory stimuli is influenced by a combination of the firing rate of the sensory nerve fibres, and how many nerves are firing (recruitment) [6]–[8]. Increases in perception amplitude can be acquired through increasing stimulation amplitude, pulse width, or stimulation frequency (f_s) [7], [9]–[17]. Previous research has shown that increases in f_s mainly lead to increases of nerve firing frequency, while increases in pulse width or amplitude result in an increased nerve fibre recruitment [6], [7], [16], [18]. When focusing on f_s , an analysis of previous literature on sensory feedback for limb prostheses shows that studied stimulation paradigms mostly include frequencies under 200 Hz [7], [19]–[24], but some go up to 500 Hz [9], [10], [25] or even 1000 Hz [16]. This broad range of stimulation paradigms suggests a lack of consensus on the optimal settings. While most of these studies include intraneural stimulation, recent work by George *et al.* (2020) shows that discrimination of pulse frequency is similar for transcutaneous and intraneural stimulation [17], allowing the comparison between invasive and non-invasive work.

The membrane potentials of nerves show a characteristic hyperpolarising pattern after firing, which can last up to 5–8 ms [26]–[30]. Until the end of this hyperpolarisation phase, it is more difficult to evoke another action potential (AP). Early human neural recordings have shown a refractory period of about 5 ms [26]–[28], which was confirmed in models of the electrical behaviour of sensory fibres [29], [30]. A recent animal study in rats using intraneural stimulation showed that sensory fibres needed 8 ms to completely recover from a conditioning pulse [30]. None of these studies investigated if the duration of the refractory period is reflected in sensory perception.

Figure 1a presents our hypothesis. In this figure, f_r represents the stimulation frequency at which the pulses are

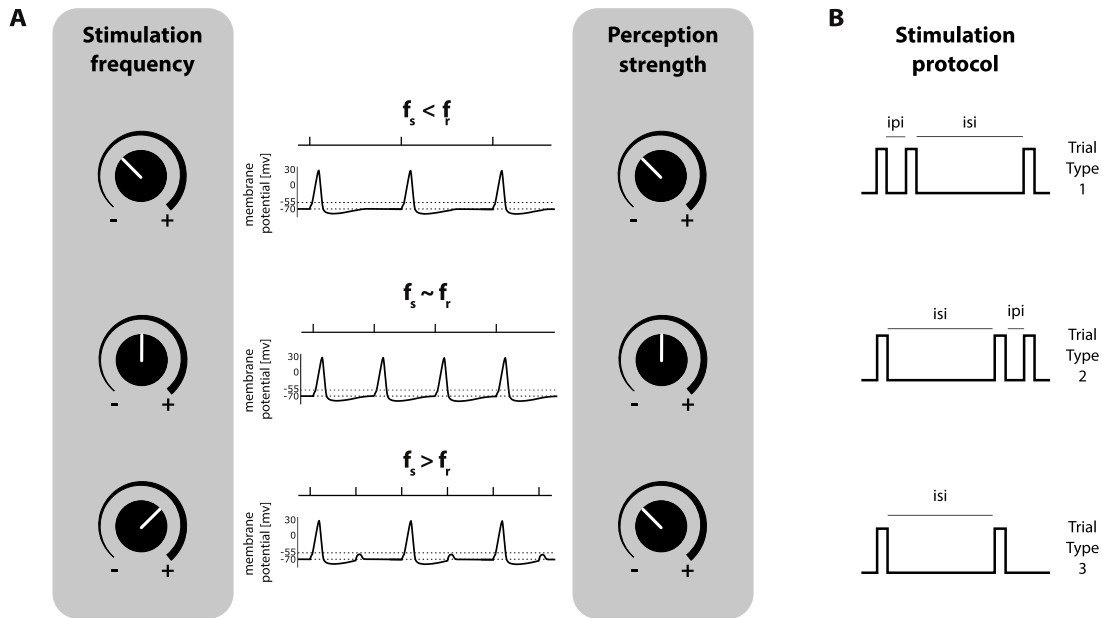


Fig. 1. (A) Diagram representing our hypothesis. Stimuli can fail to generate an AP in the sensory nerves when the stimulus is delivered during the refractory period of the fibre. Therefore, increasing the stimulation frequency above f_r leads to a reduction in perceived strength. (B) Illustration of the stimulus pairs included in the experiment. All stimuli were rectangular and monophasic.

delivered at the exact moment when the membrane potentials of nerves reach their resting threshold again after firing, that is the end of the refractory period. We hypothesise that a stimulation frequency above f_r leads to a decreased perception amplitude due to the inability of some stimulation pulses to generate an AP. The lower panel in figure 1a shows the worst case scenario, in which all stimuli during the refractory period fail to activate the nerve. However, even a subset of stimulation pulses not activating the nerve will lead to a lower amplitude perception than expected based on f_s . In this case, the commonly accepted notion that an increase in f_s leads to an increased perceived amplitude does not hold, therefore failing to deliver the intended information that is encoded in the stimulation.

To test our hypothesis, we implemented a two-alternative forced choice task containing single and paired pulses, with the inter-pulse interval (ipi) between the paired pulses ranging from 6 ms to 10 ms. Two different stimulation amplitudes were included to test if our hypothesis holds at different amplitude levels. The inter-stimulus-interval (isi) was varied from 250 ms to 450 ms to check if the second stimulus was influenced by the preceding stimulus on a longer time scale. In this paper, we will use ‘stimulus’ for stimulation patterns leading to independent perceptions, while we use ‘pulse’ to describe the pattern of electrical stimulation delivered. As a result, a stimulus can consist of either a single or paired pulse (see Figure 1b).

II. METHODS

A. Participants

Twenty participants took part in the study, which was approved by the local ethics committee at Newcastle University (19-NAZ-043). All participants provided written informed

consent before participating in the study. Participants had no known neurological condition.

B. Experimental Setup

Participants sat in an experimental chair, where the arm rest was adjusted to individual participants to ensure comfort. A pair of surface electrodes (MedTAB, Medgraphics Ltd, UK) delivered pulses of transcutaneous electrical stimulation to the left wrist. To target the ulnar nerve, the electrodes were positioned proximal to the wrist, with an inter-electrode distance of 20 mm and the anode contact placed distally. The pulses were delivered with a DS7A Constant Current High Voltage Stimulator (Digitimer Ltd, UK), and were rectangular, monophasic pulses with a fixed width of 200 μ s.

Sensory thresholds were determined for all participants. The threshold was determined using the staircase procedure, which was concluded when participants could detect 5 out of 10 stimuli [31]. Participants were divided in two groups based on the stimulation intensity during the experiment, with one group receiving pulses with an amplitude of 120% sensory threshold, while the other group received pulses with an amplitude of 160% sensory threshold.

Participants reported they felt all stimuli during the experiment. We did not systematically collect information related to sensation location and type. Different people experienced the stimulation differently, describing it as ‘tingling in the palm of the hand at the side of the little finger’ and ‘the feeling of mouse clicks underneath the electrodes’. No participants mentioned changes in the type of sensation.

C. Experimental Design

Participant perception was studied through the use of a two-alternative forced choice task, in which participants had

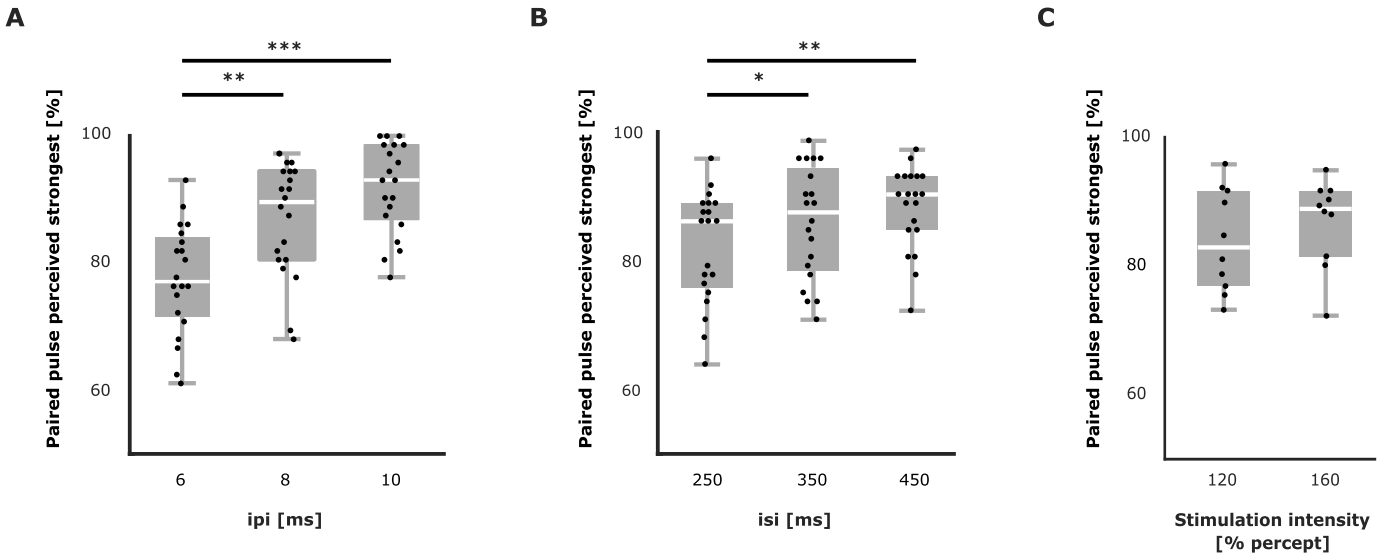


Fig. 2. (A) Inter-pulse-interval analysis. Trials with a 6 ms ipi led to the lower identification of the paired pulse as the strongest perception. This suggests that the second pulse of these paired pulses might fall within the refractory period of the nerve fibres that are being stimulated. $N=20$, averaged over 72 trials for each participant. (B) Stimulus interaction analysis. Stimuli with 350 and 450 ms isi led to higher identification of the paired pulse as the strongest perception. This indicates that shorter inter-stimulus intervals also reduce the likelihood that a participant would be able to discriminate between two different stimuli. $N=20$, averaged over 72 trials for each participant. (C) The stimulation intensity had no significant effect on the perception of the paired pulse. $N=10$, averaged over 216 trials for each participant. Each filled dot represent the average for one participant. The white lines in the plots represent the medians; the box spans from the 25th percentile to the 75th percentile; and the whiskers represent the full range of the data.

to report which of the two consecutive stimuli they perceived as being the strongest stimulus. From here forward, two consecutive stimuli will be referred to as a trial. Three types of trials were presented to each participant:

- Trial Type 1 - a paired-pulse followed by a single pulse
- Trial Type 2 - a single pulse followed by a paired pulse
- Trial Type 3 - catch trial where a single pulse is followed by another single pulse

Participants did not have an option to communicate that both pulses felt the same. The ipi and the isi were varied during the experiment. [Figure 1b](#) depicts the stimulation protocol.

The changes in perception related to the refractory period were tested by varying the ipi (6, 8, and 10 ms). These values were chosen based on refractory period literature [26]–[28], and previous rodent work [30]. Interaction of stimuli at a longer time scale were studied by using different isi of 250, 350, and 450 ms. Values of isi were determined during pilot experiments, and were narrowed down from isi ranging from 100 ms to 500 ms. The order of single and paired pulses, the ipi, and the isi were balanced and randomised within each block of the experiment. This resulted in a $3 \times 3 \times 2$ design (ipi \times isi \times leading pulse), and each type of trial was repeated twice per block. Each block also included 6 catch trials (2 repetitions of 3 isi). This resulted in blocks of 42 trials. All participants completing 6 blocks.

D. Analysis

Perception of the stimuli was analysed by calculating the percentage of trials in which the paired pulse was perceived as a stronger perception than the single pulse. Type A order effect exists when participants have a preference for either the first or second stimulus regardless of the type of pulse [32], and was analysed by determining the percentage of catch

trials in which the first pulse was perceived as the strongest. Type B order effect, which studies if participants perceived the stimuli differently based on which stimulus was presented first [32], was analysed by studying the difference in amplitude perception when the paired pulse either leads or lags.

A multi-way analysis was used to determine if any interactions were present between the independent variables: pulse amplitude, ipi, isi, and leading pulse. Non-parametric statistical analysis was used throughout the study as the normality analysis (Shapiro-Wilk normality test) showed that not all data was normally distributed. When the Friedman test showed significant differences at group level, then Mann-Whitney U-tests with Bonferroni corrections were used for the post-hoc analysis. All presented descriptive statistics represent median and interquartile range, unless stated differently.

III. RESULTS

A. Inter-Pulse Interval

The perception related to the duration of the ipi is analysed by comparing how often the paired pulse is perceived as the stronger stimulus for the different ipi. If the participant cannot discriminate the difference between a single or paired pulse, participants would perceive the paired pulse stimulus as being stronger approximately 50% of the time. If the participant finds it easy to discriminate between the single and paired pulse, then the participant would identify either the single or paired pulse as being stronger 100% of the time.

The Friedman test uncovered a statistical difference in how often the paired pulse is identified as stronger ($p < 0.0001$; see [Figure 2A](#)). Post-hoc analysis showed statistical differences between paired pulses with an ipi of 6 ms ($77.08 \pm 12.50\%$) and those with an ipi of 8 ms ($89.58 \pm 13.89\%$; $p = 0.001$) and between those with an ipi of 6 ms and 10 ms ($93.06 \pm$

11.81%; $p < 0.0001$). No statistical difference was found between the trials with an ipi of 8 ms and 10 ms ($p = 0.112$). This indicates that it is easier for participants to discriminate a paired pulse from single pulse when the ipi is 8 or 10 ms, than it is discriminate the paired pulse from a single pulse when the ipi is 6 ms.

B. Inter-Stimulus Interval

Participants are more likely to be able to discriminate consecutive stimuli when they are spaced far enough apart in time. During the experiment, participants reported that they felt all stimuli, suggesting that the inter-stimulus intervals included in this study surpassed the discrimination threshold. However, it is not known if stimuli interact beyond this discrimination threshold. If the paired pulses are identified less often, it would mean that stimulus interaction is present.

The results show that the isi had a significant influence on the likelihood of the paired pulse being perceived as stronger; with shorter isi leading to a lower rate of participants identifying the paired pulse as strongest ($p = 0.0002$; see Figure 2B). Post-hoc analysis showed a difference on the perception of the paired pulse between isi of 250 ms ($86.11 \pm 13.19\%$) and 350 ms ($87.50 \pm 15.97\%$; $p = 0.009$); and 250 ms and 450 ms ($90.28 \pm 8.33\%$; $p = 0.0002$). There was no significant difference for trials including isi of 350 ms and 450 ms ($p = 0.97$).

C. Stimulation Intensity

Two stimulation intensities were used in the study, 120% and 160% of the perception threshold. A two-tailed Mann-Whitney U-test showed that the stimulation intensity did not influence the perception difference between single and paired pulses. The paired pulse led to a stronger perception in $82.87 \pm 14.81\%$ of trials with 120% stimulation, and $88.89 \pm 10.19\%$ trials for 160% stimulation ($p = 0.57$; see Figure 2C).

D. Supporting Analysis

1) *Multiway Analysis*: The previous refractory period and interaction results showed clear, statistically significant trends with increasing ipi and isi. As the full study included four changing variables, namely, ipi, isi, stimulation intensity, and leading pulse, there is a possibility that conducting the analysis one variable at a time would disguise more complex underlying patterns where the analysis of one variable depends on the state of a different variable. To account for this, a multiway analysis was performed prior to sections III-A - III-C to determine if interactions existed between any of the variables. The outcome of the interaction analysis is presented in the supplementary materials, and shows that no significant interactions were present.

2) *Catch Trial Analysis*: Prior to conducting the main analysis (sections III-A - III-C), we verified whether any biases influenced the participants' answers. The analysis of Type A order effect, which was present if participants had a bias towards either the first or second pulse, was made possible by the inclusion of the catch trials. The type B order effect shows

participants perceive a difference in stimuli dissimilarly when the stimuli are presented in the opposite order. We investigated whether this bias was present when two different stimuli were presented. Type B order effect was tested by comparing the results for Trial Type 1 and Trial Type 2. The full analysis is in the supplementary materials. We observed a Type A order effect: participants perceived the first of two single pulses as stronger $62.83 \pm 21.29\%$ of the time ($p = 0.003$ when compared to expected value of 50 %). The analysis of the Type B order effect showed that there was no difference based on which pulse was leading, with the paired pulse being perceived stronger in $85.18 \pm 12.04\%$ of the trials when the single pulse is leading, and $89.81 \pm 11.11\%$ when the paired pulse is leading ($p = 0.11$). These results, combined with the fact that the leading pulses were balanced, suggest that our main analysis was not influenced by any bias.

3) *Performance Over Time*: Studying the perception difference between single and paired pulses over time could tell us if participants needed to learn to differentiate these stimuli. Analysis showed no statistical difference between the different blocks ($p = 0.41$; see Figure 1 in the supplementary materials), indicating that the perception difference between the single and paired pulses is innate.

IV. DISCUSSION

In this study, we aimed to determine how modulating the temporal pattern of electrical stimulation may influence the perceived amplitude of a given stimulus. Our results provide evidence that (1) perception of the strength of a stimulus can be modulated by changing the ipi of the stimulus, mirroring findings from neural recordings that examined refractory periods; (2) the perception of a stimulus' strength is also influenced by the timing between two consecutive stimuli; and (3) these findings are stable over different stimulation intensities. Importantly, the findings of this study show that there is a limit to the speed at which two stimuli can follow each other and reliably produce a consistent perception of stimulus intensity. This result implies there is an upper limit to the commonly accepted notion that increasing stimulation frequency leads to an increase in the perceived amplitude of a stimulus.

Our hypothesis stated that stimulation frequencies above f_r would lead to a decreased perception amplitude due to the inability of stimulation pulses to generate an AP during the refractory period. The lower panel of figure 1A depicted the scenario in which none of the pulses during the refractory period resulted in an AP. However, the refractory period is divided in an absolute refractory period, and a relative refractory period. During the former, no new APs can be generated, while the generation of APs is more difficult - but not impossible - during the latter. Neural measurements show that the absolute refractory period is limited to 1 ms [26]–[28], indicating that the pulses used in this study fall within the relative refractory period. If all second pulses of the paired pulse failed in generating APs, participants would have perceived these trials as two single pulses, leading to an identification of the paired pulse at/close to chance

level (50%). Our results show that this was not the case, which confirms that the second pulse of the paired pulse did not fall within the absolute refractory period. However, the decreased rate of paired pulse identification with an ipi of 6 ms indicates that at this ipi, the second pulse failed to generate an AP more often than when the ipi was set at 8 or 10 ms. Therefore, it is likely that the second pulse of the paired pulse falls within the relative refractory period with an ipi of 6 ms.

Our results show that there is an upper limit to increasing the perceived amplitude of an applied stimulus through increasing f_s . We found that increasing the f_s above 125 Hz, i.e. an ipi less than 8 ms, made it less likely that a participant would identify a paired pulse as being stronger than a single pulse. Our results are in line with previous refractory period measurements [26]–[30]. Similarly, perceptual responses measured in response to microstimulation of the somatosensory cortex of a human participant showed that in over half the tested electrodes, stimulus trains with pulse frequencies between 20 and 100 Hz were perceived as the most intense, with the intensity decreasing with further increases of f_s [33]. These findings are also in line with the maximum spiking frequencies found in human sensory nerve fibres resulting from both painful [34], and pleasant touch [35]. As perception is based on a combination of the firing frequency and recruitment of sensory nerves [6]–[8], one could always increase perception through increasing either the stimulation intensity and/or pulse width. As we were interested in the relative discrimination of stimuli, i.e. whether participants can distinguish one stimulus from the other, each trial consisted of only one stimulation amplitude. The inclusion of the two stimulation amplitudes showed that an increase in stimulation amplitude of all pulses during the protocol did not influence the ability of participants to discriminate stimuli.

The refractory period is not the only mechanism that influences the perception of electrical stimulation. Neural adaptation, a decay of the cumulative firing rate in response to a constant stimulus [36], leads to a reduction of the perceived intensity of continuous electrical stimulation. This common phenomenon has previously been studied in the context of invasive electrical stimulation for prosthetics, showing a process that happens during a period of 50-100 seconds [37]. Different adaptation mechanism can lead to a decrease in spiking, and can happen at different time scales. However, the common factor in these mechanisms is that inhibitory processes lead to the reduction in spiking, i.e. increased inhibitory connections or an increase in the firing rate of inhibitory neurons leads to a lower firing frequency at the output level [36]. This is a distinctly different process than the refractory period, allowing the two processes to occur simultaneously. We limited the influence of neural adaptation in this study by using single and paired pulses instead of constant stimuli, and limiting trials to a maximum of 500ms. We found similar results for both stimulation intensities in the study, showing that the refractory period has the same effect irrespective of the amount of nerve fibres firing, suggesting that the effect of the refractory period will be similar throughout the adaptation process.

This study was performed to inform future prosthetic sensory feedback studies. Including sensory feedback as part of prosthetic has been shown to have advantages ranging from improved hand control [9], [16], [25], [38], to increased prosthesis embodiment [25], [38], [39], and a reduction in phantom limb pain [25], [40]. In these studies, wide ranging stimulation paradigms were used, indicating that there is no consensus yet on the optimal parameters. Our study suggests that modulation of perception through changes in f_s should be limited to frequencies below 125Hz. Indeed, a study investigating linear frequency and amplitude modulation, which included f_s values up to 1000 Hz, found that linear frequency modulation did not allow participants to continuously modulate their grip pressure based on the feedback [16]. A study including frequencies up to 500 Hz found a linear relationship between the frequency in a logarithmic scale and perception amplitude, indicating that the rate of increased perception amplitude decreased for higher frequencies [10]. Similarly, George *et al.* [17] showed that intensity discrimination was better at lower f_s (12.5 - 87.5 Hz) than higher frequencies (50 - 200 Hz). A recent study into the influence of intraneural stimulation frequency and pulse width found that participants were able to discriminate frequencies in the range of 2 - ~50 Hz, but that ability broke down beyond a stimulus frequency of 60 Hz [41]. One other study including f_s up to 500 Hz did find a linear relationship between f_s and perception magnitude [9]. However, this paradigm included varying pulse width during the stimulation, therefore not allowing to disentangle if the increased magnitude was purely based on the increased f_s . Graczyk *et al.* [7] found a linear relationship between f_s and perception amplitude in a study including frequencies up to 175 Hz.

Implementations for prosthetic control vary, with some - such as discrete event related feedback [42] - requiring the perception of distinct stimuli. In this framework, stimulation paradigms are not aimed at creating biomimetic sensations, but towards stimuli that are easily distinguishable relative to each other to encode discrete events. For example, one pattern might indicate ‘force increase’, while another indicates ‘object contact’ [43]. The lack of influence by the stimulation intensity on the discrimination between stimuli in our study is therefore encouraging, as it indicates that the relative difference is stable. The participants also experienced different types of sensations, from in-loco sensation (e.g. ‘the feeling of mouse clicks under the electrodes’) to somatotopic sensations (e.g. ‘tingling in the palm of the hand’). The type of sensation participants experienced did not impact their ability to complete the task.

Previous research has shown that discrimination of consecutive stimuli is possible when the isi between the stimuli is at least 100 ms [44]. Others have shown that each of these stimuli can transfer information such as prosthesis movement or object characteristics through modulation of the stimuli [43]. However, it was not clear if one stimulus could alter the perception of the following pulse when an isi over 100 ms is included. Our results show that this interaction is present for consecutive stimuli with isi greatly exceeding the discrimination threshold of 100 ms. Therefore, to transfer additional information through modulation of the perceived amplitude with f_s , an isi of at least 350 ms should be

respected. The stimulus interaction for isi of 250 ms was unexpected, as participants were able to discriminate the stimuli. This finding warrants further investigation. It would also be interesting to determine if modulation of perception through the modulation of pulse width or amplitude requires the same isi.

Integration of the underlying neurophysiology in our experimental design demonstrates the neural basis for previous findings where no linear relation could be found between f_s and perception amplitude when higher frequencies were included [10], [16], [17]. Avoiding the inclusion of stimulation frequencies above 125 Hz will allow for the temporal encoding of the desired information in the fields of bioelectronic medicine and neuroprosthesis. If frequency encoding does not allow for the desired modulation within these parameters, then perceived amplitude can additionally be modulated by changing fibre recruitment through adaptation of the stimulation intensity and/or pulse width [18]. The relayed information will be application-dependent, and may range from grip strength, proprioceptive information, or temperature in upper limb prosthetics, to visual information in visual prostheses.

While this study was performed to inform future prosthetic feedback strategies, no limb impaired participants took part in the study. Previous research has shown that perception modulation based on frequency changes is similar for transcutaneous stimulation in limb intact participants, transcutaneous stimulation of reinnervated skin, and intraneural microstimulation [17]. These findings, in conjunction with the literature on neural recordings of the refractory period [26]–[28], and the perception modulation through intracortical microstimulation [33], suggest that these results will also hold for limb different participants receiving either transcutaneous stimulation or intraneural microstimulation. While we saw different sensation locations and types during this experiment, we do not think this influenced the results, as the underlying neural phenomenon was previously shown in a wide range of studies, from intraneural microstimulation [33], during invasive refractory period measurements [26]–[28], and in rodents [30].

This study examined the influence of three independent variables, namely, ipi, isi, and stimulation intensity. No interaction between these variables was found, and the analysis showed that ipi and isi influenced the likelihood a paired pulse would be perceived as stronger than a single pulse, while stimulation intensity did not effect this likelihood. The inclusion of three independent variables limited the number of values of each variable we could incorporate in this study. The fact that we found a statistical effect for both isi and ipi suggests that the correct ranges of values were included in this study. The results investigating the perceptual effect inter-pulse-interval also mirrored the exact timings found for stimulus interactions in neural recordings in rodents [30], affirming our findings.

V. CONCLUSION

We showed that there is a boundary to increasing f_s to increase the perceived amplitude. This boundary matches the time necessary for nerve fibres to completely recover after the generation of an action potential, and was stable for

multiple stimulation amplitudes. These results demonstrate the importance of understanding the underlying physiology and anatomy when designing biomedical engineering solutions to restore or replace missing function.

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