

A Robust Encoding Scheme for Delivering Artificial Sensory Information via Direct Brain Stimulation

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Abstract—Innovations for creating somatosensation via direct electrical stimulation of the brain will be required for the next generation of bi-directional cortical neuroprostheses. The current lack of tactile perception and proprioceptive input likely imposes a fundamental limit on speed and accuracy of brain-controlled prostheses or re-animated limbs. This study addresses the unique challenge of identifying a robust, high bandwidth sensory encoding scheme in a high-dimensional parameter space. Previous studies demonstrated single dimensional encoding schemes delivering low bandwidth sensory information, but no comparison has been performed across parameters, nor with update rates suitable for real-time operation of a neuroprosthesis. Here, we report the first comprehensive measurement of the resolution of key stimulation parameters such as pulse amplitude, pulse width, frequency, train interval and number of pulses. Surprisingly, modulation of stimulation frequency was largely undetectable. While we initially expected high frequency content to be an ideal candidate for passing high throughput sensory signals to the brain, we found only modulation of very low frequencies were detectable. Instead, the charge-per-phase of each pulse yields the highest resolution sensory signal, and is the key parameter modulating perceived intensity. The stimulation encoding patterns were designed for high-bandwidth information transfer that will be required for bi-directional brain interfaces. Our discovery of the stimulation features which best encode perceived intensity have significant implications for design of any neural interface seeking to convey information directly to the brain via electrical stimulation.

Index Terms—Brain-computer-interface, cortical neuroprosthesis, electrical stimulation, sensory perception, sensory stimulation.

I. INTRODUCTION

CORTICAL neuroprostheses offer a unique tool to improve health and function via direct communication

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with the brain. Cortical stimulation is being explored to convey visual [1]–[5], auditory [6]–[8], and somatosensory information [9]–[16]. In order for these devices to faithfully deliver high-bandwidth information to the brain, we must understand how to reliably encode information within the stimulation signals.

Although early studies demonstrated somatosensory feedback [11], [17]–[20], recent advances in neural recording and decoding have largely outpaced progress in sensory feedback. Current brain computer interfaces (BCIs) decode neuronal activity, enabling subjects to complete a variety of tasks [21]–[29]. Recent improvements to BCIs incorporate higher channel counts [30], [31] and machine learning algorithms [32] to control biomimetic robotic arms in real-time [33], [34]. As a result, human BCI users are able to achieve control of 7–10 degrees of freedom [35], [36]. These open-loop controllers, however, rely on slow visual feedback pathways and may realize greater improvements by incorporating closed-loop sensory feedback [37], [38].

Achieving coordinated, dexterous control using a BCI will likely require a short-latency, high-fidelity feedback signal [39]. However, the optimal design of this signal is the topic of much debate [40]. Biomimetic signal designers have delivered electrical stimulation patterns similar to the neural signals expected by the sensory cortex [11], [41]. By recording neural activation patterns of a sensation elicited via mechanical stimuli, electrical stimulation mimicking those recorded patterns can evoke similar sensations, which at times may be indistinguishable from natural sensation [18], [42]. This technique is important for verifying the quality of the elicited sensory percepts; unfortunately, it excludes typical BCI users, whom may no longer receive natural sensory input to their brain due to spinal cord injury or stroke.

Sensory substitution relies on the plasticity of the brain to “substitute” an incoming artificial signal for a physical sensation [43]. This second approach presents stimulation first and measures the evoked sensation afterwards [20], [44]. By exploiting cortical adaptation, electrical stimulation has artificially evoked a variety of sensations, utilized by rodents [19], primates [17], [45] and human patients [46] to solve sensorimotor tasks. Rather than answer this debate conclusively, the purpose of this paper is to address a more fundamental question. Regardless of the cortical region stimulated or the sensation elicited, the community does not yet understand the fundamentals of how individual stimulation parameters

affect an evoked percept. Prior to incorporating any designed high-resolution sensory feedback signal in bi-directional neuroprostheses, we seek to understand which parameters can rapidly encode discriminable information.

The basic building blocks of a stimulation pattern are five characteristic parameters: amplitude, pulse-width, frequency, number of pulses, and train interval. By modulating these parameters, intra-cortical micro-stimulation (ICMS) can convey sensory information delivered to primary sensory cortex. Information can be encoded by modulating amplitude [18], [20], pulse-width [16], frequency [11], [19], [47], and temporal spike trains [48], [49]. Our comprehensive comparison aims to determine the highest resolution parameters.

Prior experiments focused on discrimination of two disparate stimulation patterns rather than exploring the entire parameter space. Early work in ICMS concluded discrimination was possible at very low frequencies ($<44\text{Hz}$), but temporal resolution was poor [50]. Later work found discrimination between two discrete frequency patterns possible, but this required changing several other parameters to control for consistent pulse delivery over the specified time period [17]. A comprehensive examination of amplitude discrimination was completed in the primate model, but it did not measure discriminability of any other parameters [16].

To directly test the fidelity of artificial cortical sensory encoding, we compared the ability of rodent subjects to utilize artificial sensory stimulation in the same behavioral task while we systematically modulated each stimulation parameter. Our primary goal was to identify the cortical stimulation patterns which animals could discriminate during a forelimb exploration task. We chose to deliver stimulation within the sensorimotor cortex of rats in order to provide an intuitive comprehension of the incoming signal. By measuring just-noticeable-differences of five different parameters encoding sensory feedback, we determined which parameters maximize information transfer. We also compared the perceptual resolution of each parameter using the same task and animals to enable direct comparisons between parameters.

We tested the ability to discriminate different cortical stimulation patterns using a modified rodent center-out task [51]. Rather than cue the animal for a particular target, stimulation provided feedback of the joystick position within one of three targets. We used performance of the task as a measure of comprehension of the feedback signal.

To convey the maximum sensory information per time, we tested stimulation trains that were brief. Our goal was to determine whether short bouts of stimulation could be perceived by the brain on the timescale of the sensory feedback loop during a motor task ($<50\text{ms}$) [52]. We also wanted to test stimulation trains which could both be perceived by the brain and updated much faster than visual feedback ($>200\text{ms}$) [53].

We found clear differences between stimulation parameters modulating spatial and temporal features. Our findings suggest there is a lower subspace or plane used by the brain to interpret electrical stimulation within the high dimensional manifold of stimulation parameters measured. The individual discrimination curves obtained from modulating amplitude and pulse-width showed the highest resolution. Further experiments

revealed both parameters may be modulating the same latent variable, charge-per-pulse. Surprisingly, measurements from temporal parameters such as frequency resulted in very low resolution. These results have significant implications for the design of high-bandwidth neural interfaces aiming to convey sensory information to cortical networks via electrical stimulation.

II. METHODS

A. Animal Care

Nine adult female Long-Evans rats (Charles River, 200-300g) were trained to perform a modified center-out task [51]. Animals were housed 1-3 per cage during initial training. The housing room light cycle was set to a 12-hour day/night cycle, shifted such that the housing and behavior room was dark from 9am-9pm. This permitted training/testing to take place during the animals' active, dark cycle. Ad libitum access to food was allowed throughout the training, but animals were restricted from water in their home cages. Free water was given for 1/2 hour each day after their training/testing sessions. For correctly completing a trial during the behavioral task sessions, drops of apple juice were administered as a liquid reward (0.05ml). On weekends, each animal was given free access to water. Animals were weighed each day of restriction to ensure proper maintenance of body weight. All procedures were approved by University of Washington IACUC.

B. Modified-Center-Out Task

Each animal followed a 16 step protocol developed to train rats to perform the modified center-out task [51]. Using a 3D printed joystick, rats explored three targets within the workspace. A light cue illuminated when the rat entered the desired target, while no light cue was presented when the rat was exploring non-desired targets. Subjects received a liquid reward for dwelling 1.25s in the illuminated target. If a rat dwelled for 1.25s in a non-desired target, a timeout penalty of 5s was assessed.

Animals completing over 200 trials per session with above 75% success rate were deemed proficient at the task. They were then implanted with cortical stimulating electrodes and direct cortical electrical stimulation replaced the light cue.

C. Implant

Each rat was implanted with a 16 channel micro-wire array in sensorimotor cortex (Fig. 1), targeting layer 4-5. An 8x2 tungsten micro-wire array was soldered to a custom printed-circuit-board (PCB) with mating connector (DF30) to vias placed on the bottom of the PCB. Each micro-wire was $30\mu\text{m}$ in diameter covered with $5\mu\text{m}$ thick insulation. The rows were separated by 1.2mm, while the pitch between each electrode in a row was $400\mu\text{m}$ (Fig. 1d).

The implant was lowered using a stereotaxic manipulator (Kopf) within the cranial window to 1.5mm depth. Ground wires were wrapped around several skull screws. The array was secured in place using 2-part dental acrylic (C.B. Metabond), exposing the DF-30 connector on top of the

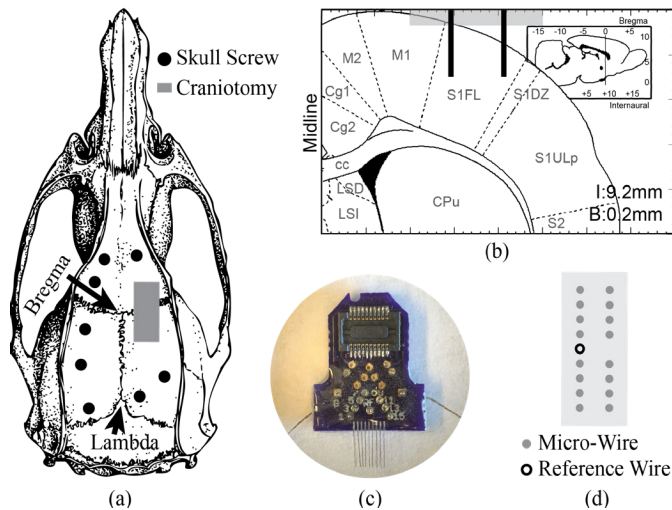


Fig. 1. A micro-wire array was implanted in the left forelimb sensorimotor cortex. (a) Placement of seven skull screws (black dots) are overlaid on cranial landmarks with location of craniotomy over sensorimotor cortex (grey: 5mm \times 3mm). (b) Coronal slice of the targeted cortical implant location. Image adapted from [61]. (c) Hand-built 16 channel cortical stimulating array. (d) Layout of array.

array for attachment to cables for delivering stimulation to, and/or recording from, each electrode.

D. Selection of Electrode Site

In each animal, a stimulation site was chosen corresponding to sensory activity related to the left forepaw, the limb used to control the joystick. The activation of both sensory and motor areas was measured prior to selecting the electrode for each experiment to confirm that our stimulation site did not trigger muscle activity or movement.

E. Sensory Evoked Potentials

In each animal, we measured sensory evoked potentials (SEPs) and event related potentials (ERPs) to verify final electrode location within the implanted cortical region. Animals were lightly sedated using ketamine and xylazine. The left forearm was shaved and two skin electrodes attached one either side of the bicep muscles. We recorded Local Field Potentials (LFPs) at a range of bicep stimulation amplitudes to test for proportional neural responses, such as decreases in onset latency and increasing amplitude to larger inputs. Biphasic electrical pulses were delivered to the left bicep muscle with amplitudes from 0.25mA – 2.0mA. Based on conduction velocities, the cortical SEPs are expected to show a graded, biphasic responses to stimulation about 20ms after the pulse (Fig. 2a). Some sites showed no correlated activity, with little variation in response to the changing stimulation amplitudes. A heat map shows peak neural responses (Fig. 2b) on each of the 16 electrodes in response to the same stimulus pulse. We selected an electrode with a robust sensory response and no motor activity or significant task correlated activity. Channel 2 was chosen for this example animal in Figure 2.

F. Event Related Potentials

To identify any potential motor activity, animals performed the center-out task using light cues while we captured neural

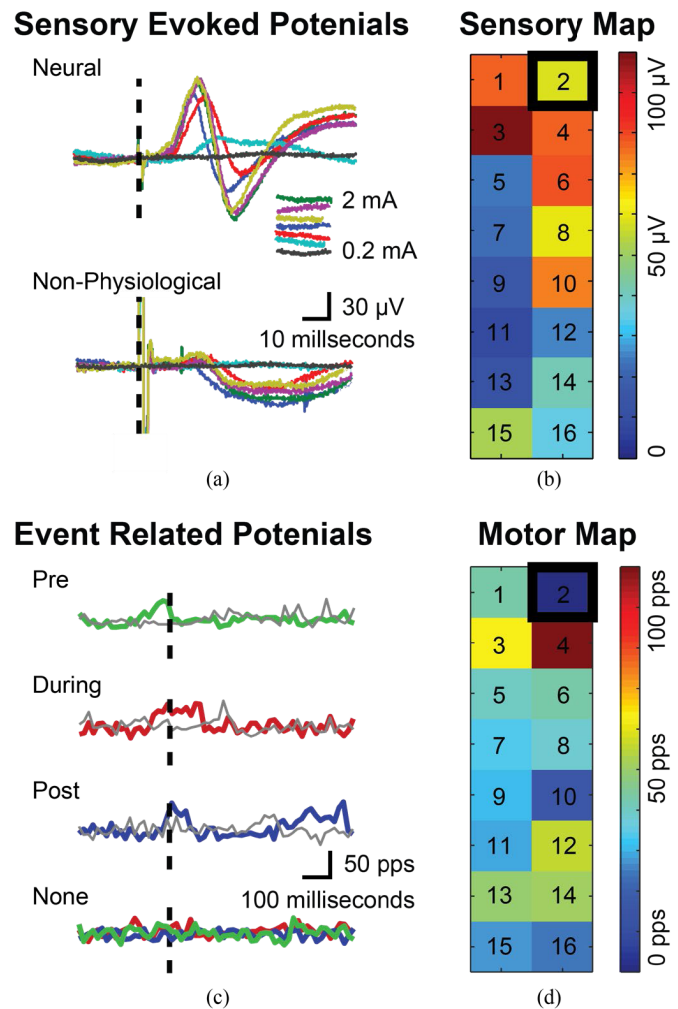


Fig. 2. Sensory Evoked Potentials (SEPs) and Event Related Potentials (ERPs) were used to map cortical implant locations. (a) Recorded cortical LFP waveforms were evoked from biphasic stimulation delivered to the bicep muscle on the left forearm at amplitudes from 0.25mA – 2mA. (b) A heat map shows peak sensory evoked responses. (c) Recorded averaged ERPs for Pre, During, or Post activity for behavioral events such as entering a particular target. Light cues were used for task feedback during these recordings. (d) Heat map corresponding to the strength of response above baseline, to visualize electrode sites dominated by motor correlated activity. In this example, electrode 2 (black square) was selected for stimulation due to high sensory (b) and low motor (d) activity.

activity. Event-related-potentials (ERPs) were recorded for various behavioral events occurring during the task (Fig. 2c). Single unit activity was thresholded and their firing rates smoothed. The firing rates were averaged over behavioral features, such as entering/exiting a target and initiating a movement. The majority of sites showed no correlation.

Similarly to our SEP analysis, a heat map corresponding to the strength of response above baseline indicated electrodes dominated by correlated motor activity (Fig. 2d). If activity was detected such as excitation post-event, sustained activity during event or pre-event, these sites were excluded from possible selection for the experiment. Finally, only electrodes with impedance between 50-500kOhms were included.

G. Task Training With Stimulation

Once animals completed their initial recording sessions, they were retrained to perform the task with stimulation cues

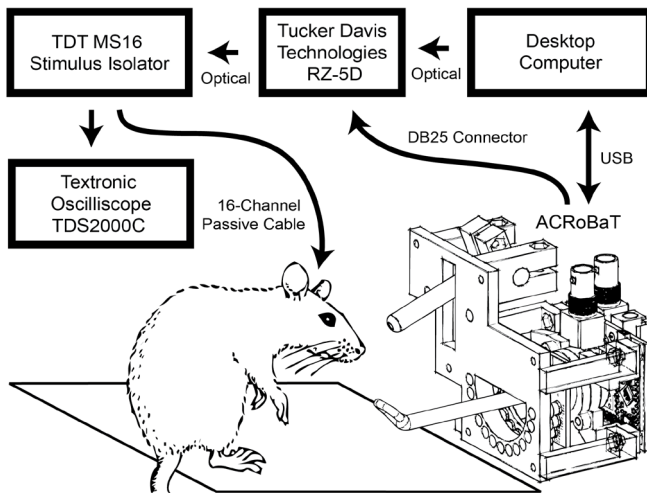


Fig. 3. Experimental block diagram. A desktop computer initiated each session's parameters, the ACROBaT system measured behavioral actions and triggered stimulation while the TDT system generated waveforms and delivered sensory stimulation to the animal, or recorded neural activity.

instead of light cues [47, steps 17-23]. A baseline stimulation pattern was substituted for the light cue. This training allowed the animals to become familiar with the stimulation. Since the stimulation is presented as only feedback to the joystick manipulation, we could see if the stimulation evoked visible movements. If so, a different electrode site was chosen.

H. Experimental Setup

Our behavioral data collection system (Fig. 3) consisted of the ACROBaT training system [51], a desktop computer, and a benchtop stimulator (Tucker Davis Technologies). Our ACROBaT system integrated data from several sources, synchronized timing variables, and output stimulation parameters in real-time. The desktop computer logged behavioral variables and sent session parameters to ACROBaT's onboard microprocessor. The benchtop stimulator received real-time stimulation parameters via a custom serial protocol from the ACROBaT system. A 16 channel passive cable connected the stimulus isolator (TDT MS16) to the implanted array on the animals' head and allowed it to freely move around the arena.

I. Stimulation Parameters

We defined a set of five features (Fig. 4) to describe our stimulation paradigm: amplitude, pulse width, pulse frequency, train interval, and number of pulses [11], [16], [17], [20], [48], [54]. We varied each parameter individually around a base pattern with amplitude of $70\mu\text{A}$, pulse-width of 200ms, train interval of 100ms, pulse frequency of 300Hz, and five pulses per train.

We defined corresponding ranges of each of these parameters for both safety [55]–[57] and ability to recruit cortical neural populations. Amplitude defines the height of each pulse, within a range from 5-120 μA . Pulse Width defines the width of each pulse, within a range from 50-500 μs . Frequency defines the rate of each stimulus pulse within a train, within a

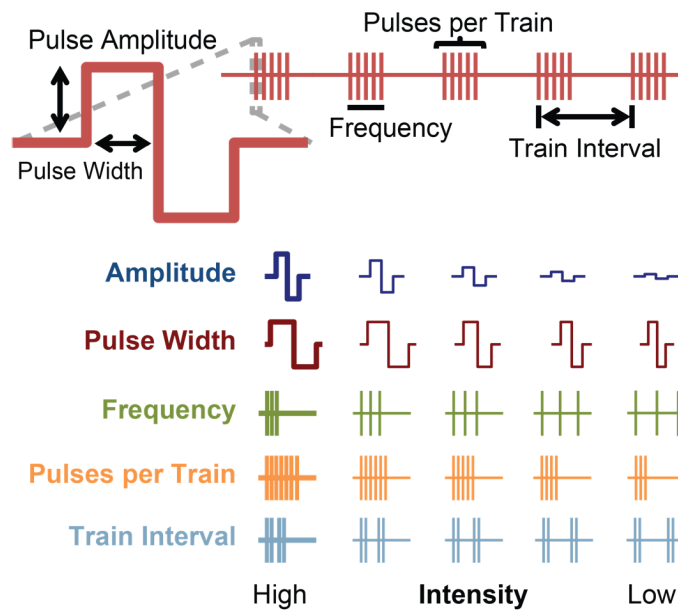


Fig. 4. Five cortical stimulation parameters were independently modulated to measure perceptual sensitivity. Each stimulation pulse was constant current, bi-phasic and symmetrical. Amplitude refers to the height of each pulse phase, and pulse width the width of each phase. Frequency is the rate of the pulses in a train. Pulses per Train is the number of pulses in each train. Train Interval is the time between the start of each train. These parameters were varied individually and in some cases concurrently.

range from 50-400Hz. Pulse per Train defines the length of a stimulation train (range of 5-20 pulses per train) and the Train Interval defines the time between the start of stimulation trains (varying from 50-400ms).

All stimulation pulses were bi-phasic, symmetrical, and constant-current to prevent any charge build-up around the electrode tip from damaging the surrounding tissue [55]–[57]. Current was delivered through the selected electrode and a common reference wire, consistent with a bi-polar stimulation protocol. The anodic phase was first delivered through the selected electrode. Since both electrodes have similar impedance, this definition is somewhat arbitrary.

J. Parameter Range Detection

The final step was to determine the lowest possible amplitude and pulse width that animals could perceive. A threshold detection task assessed whether animals could discriminate between a stimulation pattern and sham pattern. Using the task design outlined in Section B, three targets were presented in each trial, with only one containing the stimulation pattern. Animals were trained to explore the workspace and dwell in the target delivering stimulation. By varying the amplitude and pulse width on each trial, we determined the lowest perceivable parameter values. Animals could perceive any value in our defined range for the other three parameters.

K. Just-Noticeable-Differences

To reliably compare the resolution of each parameter, the Just-Noticeable-Difference (JNDs) was explicitly measured.

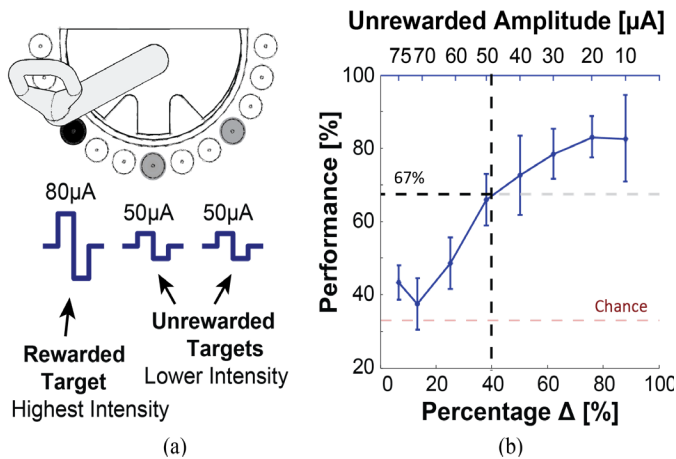


Fig. 5. A three-alternative forced-choice (3AFC) task was used to assess discriminability. (a) A high intensity parameter value (such as $80\mu\text{A}$ amplitude) was chosen as the rewarded pattern, while a variety of lower intensity parameters (70, 60, 50, 40, $30\mu\text{A}$, etc.) were presented as unrewarded patterns. The rewarded target was randomly chosen for each trial, and both the other targets assigned the same lower intensity value. (b) Discriminability is plotted as the performance of identifying the high intensity parameter vs the lower value distractors. In this example, when the difference between the rewarded parameter and the unrewarded parameter is greater than $30\mu\text{A}$, the animal was able to correctly identify the higher value parameter more than 67% of the time. Chance for a three-choice task is 33%.

The JND measurement is the magnitude of change required for the animal to detect a difference between two signals. By using this method to determine resolution of a signal, each pattern was modulated until the animal could reliably discriminate between rewarded and unrewarded patterns.

For simplicity, the rewarded pattern was nominally a “higher intensity” pattern, corresponding to higher amplitude, longer pulse width, shorter train intervals, higher pulses-per-train, and higher frequency (Fig. 5). Conversely, unrewarded patterns were “lower intensity”.

We used the three-alternative forced-choice (3AFC) task described in Section B to measure sensory discriminability (Fig. 5a). Animals were trained to explore the three targets in the workspace, and rewarded for dwelling in the correct target. When entering a target, stimulation pattern was delivered as feedback. Performance, the percentage of correct trials, is used to build a psychometric curve demonstrating the ability of the animal to distinguish between the two stimulation patterns. In this example (Fig. 5b), the JND, or the difference between the rewarded amplitude and the unrewarded amplitude is $30\mu\text{A}$ or a 40% change (Fig. 5b, bottom x-axis).

The target location of the two unrewarded and the single rewarded pattern were randomized each trial (Fig. 5a). The sensory threshold is nominally halfway between chance (33%) and 100% [58], resulting in a threshold of 67%.

While only a two-choice task may have sufficed, the three-choice task was preferable given the tendency for animals to repeatedly visit only one target. To encourage a more random search strategy, a 20-trial history negatively biased the selection of the location of the reward target from targets where the animal successfully accomplished the task previously.

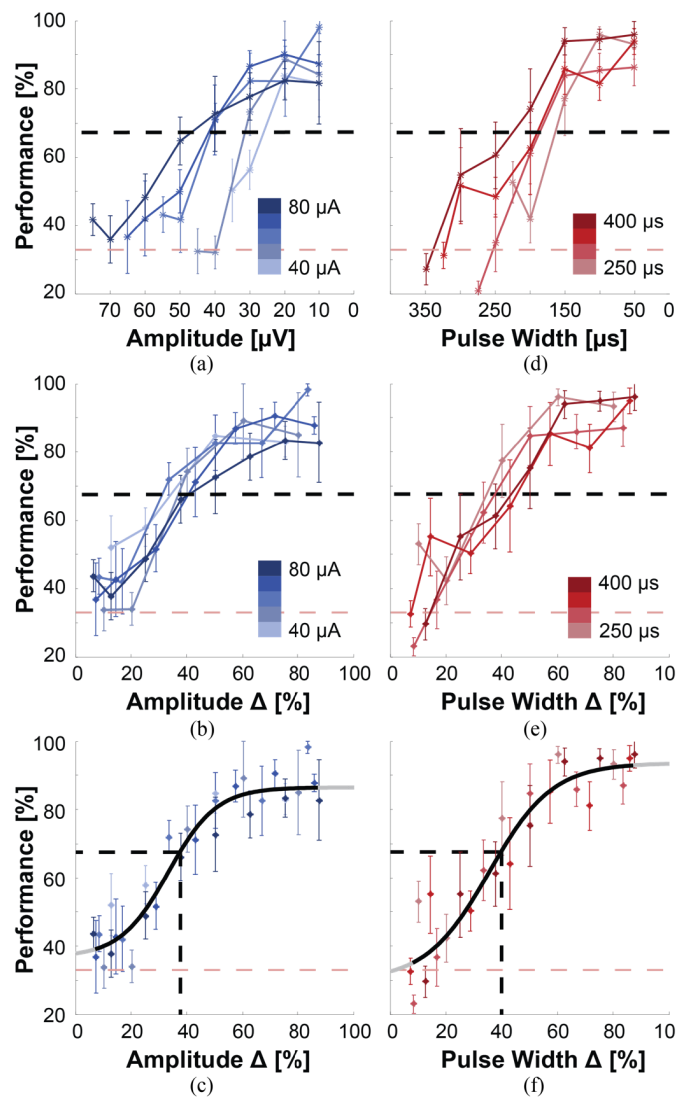


Fig. 6. Psychometric curves capture performance of discrimination between the rewarded “high intensity” pattern (shown in the legends) vs the unrewarded value (plotted on the x axis). A range of 50-100 trials were collected for each individual data point. (a) We measured individual psychometric curves throughout the perceivable range of stimulus amplitude. Here, we show an example of five curves collected when the rewarded intensity value ranged from 40 - $80\mu\text{A}$. Within a single session, the rewarded value was fixed. (b) The same results as (a) are normalized to the percentage difference between the rewarded amplitude value and the unrewarded amplitude value. (c) All the data in (b) are used to fit a sigmoidal curve. These psychometric curves are calculated individually for each animal. The JND measurement is calculated as the point which this sigmoidal curve crosses the sensory threshold, 67% (dotted black line). (d-f) Examples for the parameter pulse-width. Note the similarities between (c) and (f).

This adaptive algorithm was highly successful in preventing repetitive movements to a single target location.

L. Normalization

To measure the resolution at the low, middle and high values of the each parameter’s range, we collected several different JND measurements. Since each parameter had a different magnitude from min to max value (Section I), and in order to directly compare paradigms, we normalized each parameter range as a function of percent change (Fig. 6b,e). For example,

if the rewarded value was $80\mu\text{A}$, and the unrewarded value was $30\mu\text{A}$, normalization would set the percentage difference at 62.5%.

We plot psychometric curves for a variety of amplitudes and pulse-widths as an example in Fig. 6a,d. Normalized psychometric curves are generated by plotting amplitude and pulse width as a function of the percentage of the rewarded parameter value. For each animal, these individual psychometric curves were fit by a single sigmoidal curve (Fig. 6c,f) for comparison across animals. The JND measurement, calculated as percentage change required to cross the sensory threshold (67%), was used to compare sensitivity across parameters and animals. The normalized JND measurement can also be called a Weber Fraction.

III. RESULTS

We compared the resolution of multiple stimulation parameters applied to the same cortical electrode toward our goal of developing a high-resolution sensory feedback signal delivered via electrical stimulation to the sensorimotor cortex.

A. Just-Noticeable-Differences

We determined the just-noticeable-difference (JND) for a variety of stimulation encoding paradigms, allowing us to quantify perceptual resolution across the parameter space. We modulated the intensity of a single stimulation parameter, and fixed all other parameters at perceivable values.

To capture JND resolution across the entire range of perceivable intensities, we equate discriminability with performance. By measuring each animal's ability to discriminate between a high intensity sensation vs a lower intensity sensation, each parameter's perceptual resolution is found.

B. Single Parameters

Sensitivity of each parameter was calculated as the inverse of the just-noticeable difference across all animals (Fig. 7a). The highest resolution parameters pulse-width ($n=5$) and amplitude ($n=8$) measured JND of $30\%\pm 3$ and $34\%\pm 6$, respectively (Fig. 7b,c). In other words, a $\sim 30\%$ change in either parameter is required for the animal to reliably recognize two patterns as distinct. This corresponds to a sensitivity of $\sim 70\%$ (Fig. 7a). These were the lowest single parameter JND's measured. Interestingly, for both amplitude and pulse-width, each of the individual psychometric curves overlapped when normalized.

The measured resolution when modulating frequency was surprisingly inconsistent (Fig. 7e), measuring a JND of $86\%\pm 7$ (sensitivity of 14%). Three of six animals tested were unable to discriminate between even the highest (400Hz) and lowest (50Hz) values of our range. Even the best performing animal had only moderate success at frequency discrimination, requiring a 60% change in frequency to discriminate different stimulus trains (40% sensitivity) (Fig. 7e). The only discriminable frequency pairs occurred when the lower frequency was below 100Hz (see Discussion). Our conclusion is that lower frequencies may be discriminable, but performance declines when higher frequencies are used.

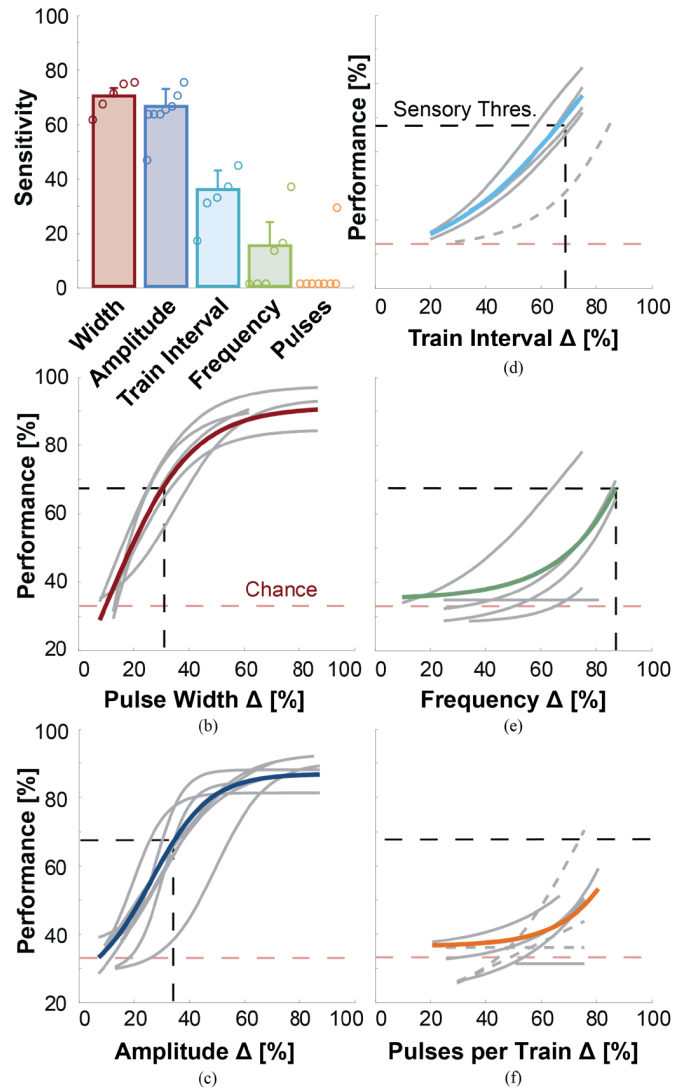


Fig. 7. Just-Noticeable-Difference (JND) curves for measuring perceptual sensitivity of modulating each parameter individually. (a) Sensitivity is a direct measure of the perceptual resolution of each parameter. The JND is calculated by the percentage difference required to cross the sensory threshold (67%). This value is subtracted from 100% to yield our sensitivity measure. Bars summarize where colored sigmoid curves cross the sensory threshold, while error bars capture the standard deviation of where each grey line crosses the sensory threshold. Pulse Width has 2971 trials across 5 subjects, with 43 ± 12 trials per data point. Amplitude has 6283 trials across 8 subjects, with 56 ± 30 trials per data point. Train Interval has 1965 trials over 5 subjects, with 57 ± 26 trials per data point. Frequency has 2174 trials across 6 subjects, with 54 ± 31 trials per data point. Pulse per Train had 2194 trials over 7 subjects with 56 ± 33 trials per data point. (b-f) A fitted sigmoid curve in color shows the average response across all animals. In grey, each animal's individual data are shown as a fitted sigmoidal curve. Dotted lines show data where the animal was asked to identify the lower intensity value. Pulses per train is the only parameter which never crosses the sensory threshold, thus its sensitivity score is 0. Y-axis shows percentage correct of trials and x-axis show the percent change between the rewarded higher intensity pattern and the unrewarded lower intensity patterns. Amplitude and pulse-width modulation have the highest sensitivity to changes, while the other parameters require the magnitude of change to be two times or greater for the same discriminability performance.

Measurements of resolution for train interval revealed moderate, but consistent, sensitivity. The measured JND was $65\%\pm 7$ ($n=5$). This corresponds to a 35% sensitivity for

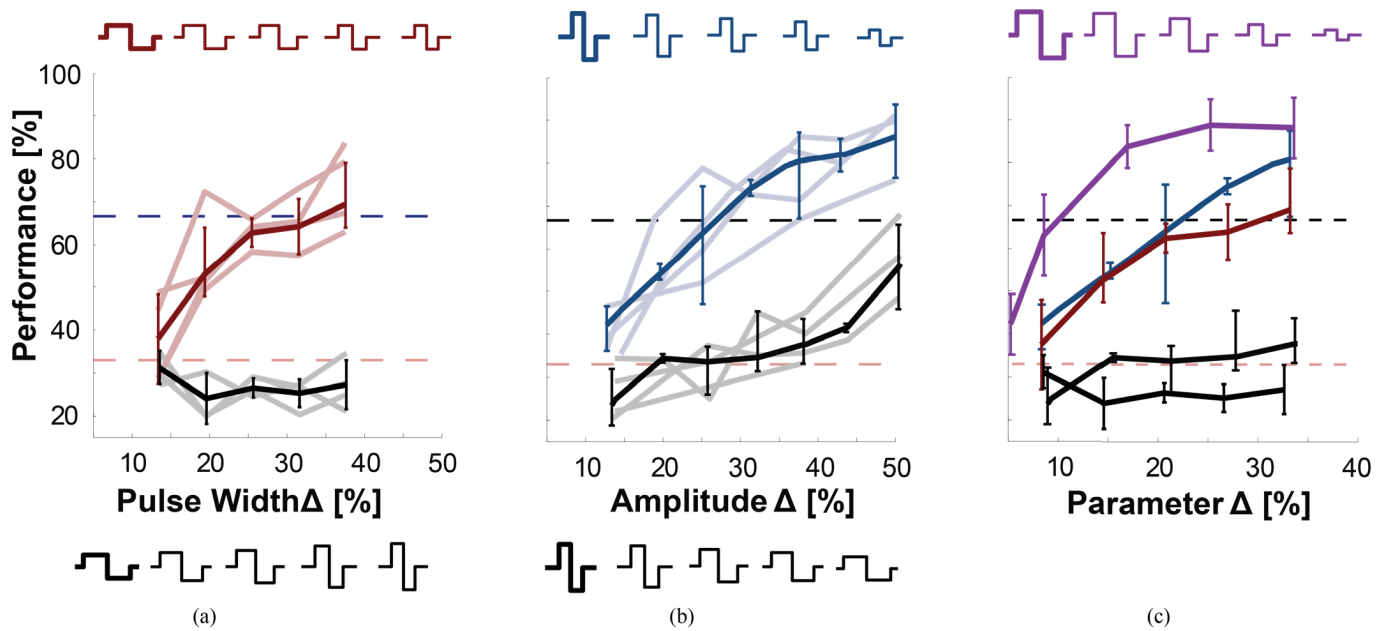


Fig. 8. To explore the effects of charge per pulse (CPP) we varied amplitude and pulse-width inversely, constraining the charge per pulse to be equal. (a) In the black, we varied pulse-width negatively and amplitude positively such that the rewarded pattern had a wide pulse-width and small amplitude. Unrewarded patterns had a shorter pulse-widths and higher amplitudes such that the charge, or area under the curve, was constrained. 3365 trials were recorded across 5 subjects. (b) In the black, we modulated amplitude negatively and pulse-width positively. The rewarded pattern had high amplitude and short pulse-width, while the unrewarded patterns had lower amplitudes and longer pulse-widths. We recorded 2316 trials across 4 subjects. (c) Here we combine amplitude and pulse-width positively. As expected, we see a significant boost in sensitivity. Shown in purple, this psychometric curve crosses the sensory threshold at 11%. 245 trials were recorded in a single animal for purple curve. Total trial count for the panel was 5926 across all conditions and 5 subjects.

train interval (Fig. 7a,d). We also measured an animal’s JND discriminating (Fig. 7d, dotted line) between patterns when stimulation pulses were delivered continuously, or pulses were delivered grouped into trains (Fig. 4). This experiment revealed that pulse trains occurring at a rate of faster than 100ms per train were perceived as tonic, continuous stimulation, setting a lower bound for perception of distinct pulse trains. Thus, modulation of train interval is a reliable way to modulate intensity, however, there are only a few discriminable steps possible between the max. and min. of the tested range.

Modulation of the parameter pulses-per-train (PPT) yielded little perceptible change. Six of seven animals could not discriminate between the highest (20 pulses) and lowest (5 pulses) number of pulses (Fig. 7f).

Since most animals were unable to discriminate between the maximum and minimum values of PPT, we flipped the experimental paradigm to test if the lower value was perceived differently (Fig. 7f, dotted line). We rewarded the animal for locating the lowest intensity sensation (5 pulses per train) and discriminating between several higher unrewarded conditions of 10, 12, 15, and 20 pulses per train. Only one animal was able to succeed for a single pair of stimuli (5 vs 20 ppt).

In summary, pulse-width and amplitude have the greatest sensitivity and allow animals to easily discriminate between the rewarded intensity and the unrewarded intensities (Fig. 7a). Temporal parameters such as train interval, frequency, and pulses per train demonstrated surprisingly low sensitivity during direct brain stimulation. Pulse-width and amplitude therefore permit the highest resolution encoding scheme.

C. Charge-Per-Pulse (CPP)

Our discovery of the high sensitivity parameters for amplitude and pulse-width informed two follow-up experiments to further disentangle the effects of modulating charge-per-pulse. In the first experiment, we held charge constant by reciprocally modulating pulse-width and amplitude (Fig. 8a, black pulses). Specifically, the product of the two parameters pulse-width and amplitude was set to a constant value (16nC). When comparing this psychometric curve with single parameter modulation (red line in Fig. 8a), the animal is no longer able to discriminate between any values in the encoded range (Fig. 8a, black line). We repeated the experiment by rewarding the “higher intensity” pattern as large amplitude values (Fig. 8b). Here, the rewarded “high intensity” sensation was encoded as a short pulse-width, high amplitude pulse and the unrewarded “low intensity” values were a longer pulse-width, lower amplitude pulse (Fig. 8b, black line). With charge-per-pulse held constant, the animal couldn’t discriminate any values over nearly the entire range.

This evidence suggested sensory cortex is responding to the underlying variable charge-per-pulse. From this line of reasoning, it follows that modulating this variable directly would produce the highest JND, or highest resolution encoding scheme. We tested this hypothesis and found a two-fold improvement in sensitivity (Fig. 8c). When high intensity was encoded as a long pulse-width, high amplitude pulse and low intensity was encoded as a short pulse-width, low amplitude pulse (Fig. 8c, purple line), only an 11% change was required

for discriminability compared to nearly a 30% change required when amplitude or pulse-width were modulated individually.

In summary, we find the most discriminable parameters to be charge-per-pulse, pulse-width, and amplitude. These parameters require changes of only 11%, 30% and 34%, respectively. Train interval is also reliable, but requires a 65% change to be detected as different. Frequency is an unreliable parameter for conveying sensory information, as half of our animals were unable to interpret any change in frequency when the charge-per-time is carefully controlled. Modulating pulse-per-train also seemed to have little effect on perception, possibly due to the small number of events (5-20 pulses) and the short intervals per train.

IV. DISCUSSION

Our goal was to determine the most effective and efficient parameters to convey information directly to cortical networks via electrical stimulation. We directly compared the perceptual resolution of different stimulus parameters using the same task, animals and electrode sites. Our results demonstrate that modulating either amplitude or pulse-width requires only a 30% change to discriminate between two different stimuli. Modulating amplitude and pulse width concurrently is even more effective, requiring only an 11% change in stimulus charge. These paradigms for encoding intensity have the highest sensitivity and therefore the greatest bandwidth for information transfer. Therefore, the charge-per-pulse (CPP) is a primary means for conveying information directly to cortex.

A. Unreliable Frequency Discrimination

Surprisingly, we find discrimination between high frequency pulse trains to be an unreliable way to convey sensory feedback. Five out of six animals were completely unable to discriminate between any frequency tested ($n=3$) or only able to discriminate between the highest and lowest frequencies in the range ($n=2$).

Given the historical emphasis on frequency modulation in the sensory stimulation literature, we seek to reconcile our findings. Specifically, several studies suggested frequency discrimination was not only possible, but likely the most promising feedback method [17], [19], [47], [50]. Below, we carefully compare our results to prior work.

Romo conducted experiments to measure discriminability between mechanical flutter stimuli applied to a fingertip and different low frequency ICMS (less than 44Hz). Non-human primates were reliably able to substitute sensations caused by mechanical flutter stimuli with low frequency tonic stimulation [46, Fig. 1d]. Frequencies ranging from 10Hz to 30Hz adequately mapped to the same range of mechanical stimuli. However, the task became more difficult when discriminating between two different low frequency ICMS patterns [46, Fig. 5c, grey line]. The primate could discriminate between ICMS at 20Hz and 30Hz, but this represents a 50% difference in frequency. It would be highly impractical to deliver artificial sensory feedback at such a low rate due to the resulting low bandwidth. Furthermore, frequency discrimination was highly sensitive to cortical depth and proper

localization of the receptive field. This suggests that only particular brain networks are sensitive to changes in stimulation frequency.

A prior study using a brain-machine-brain interface provided direct cortical feedback in response to exploration of a three target workspace [17]. Primates were rewarded for discriminating between two different stimulation frequencies and a third target with no stimulation. This successful demonstration of interleaved decoding of motor intent and delivery of sensory feedback indicated that animals might be able to discriminate between 200Hz vs. 400Hz stimulation. The different stimulation trains were carefully designed to interleave with recording blocks, and deliver the same amount of total charge over a 500ms window. This, however, meant frequency was not the only parameter modulated. When frequency doubled over the same train length, the number of pulses also doubled, and the train-interval doubled as well. Our data suggest that animals in this study may have cued on the change in train-interval, perhaps more so than the difference between these high frequency trains.

In a related study, rats chose from one of three water ports based on the frequency of electrical stimulation delivered to the whisker representation of S1 [19]. Stimulation was delivered in a continuous train with frequency proportional to their orientation towards the correct target, with a maximum of 300Hz. These rats performed the task well when the ports were located at disparate locations throughout the circular arena. When the ports were closer than 60 degrees from each other, however, the animals' performance significantly declined. Although the paper does not provide the exact mapping from target location to stimulation frequency, based on our results we predict that stimulation frequency was below 100Hz when the animal was facing more than 60 degrees from the correct port. With such low stimulation frequencies, the total charge-per-time delivered during these trains of stimulation would also be decreased, providing an additional cue.

Separate experiments in the non-human primate measured the just-noticeable-difference (JND) of different amplitudes of stimulation [16]. The authors explored different pulse-widths, frequencies and pulse train lengths while they tested for stimulus amplitude discrimination. Their results demonstrate no significant change in amplitude JNDs across a frequency range from 50Hz to 500Hz, suggesting the frequency component does not contribute to a perceived stimulus intensity [16, Fig 4b]. Our data reinforce this interpretation since our animals were unable to discriminate between similar high frequency stimulation trains.

We carefully examined the data from our single animal that appeared to adequately discriminate frequency. The most likely explanation of higher performance in this animal is that the particular cortical network activated was quite sensitive to stimulation at 75Hz. This animal could reliably distinguish between 75Hz and nearly every other frequency, but was unable to discriminate between similar percentage differences between higher frequencies in the range.

Synthesizing prior work with our current findings, we conclude that lower frequency discrimination may be possible for frequencies below approximately 100Hz.

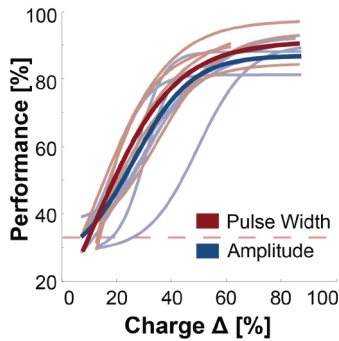


Fig. 9. Overlapping JND curves for all animals tested on amplitude and pulse-width modulation ($n = 13$). 9254 trials represented.

Performance significantly degrades, however, when using higher frequencies to convey sensory feedback. The inability to perform frequency discrimination when charge-per-time is fixed could be evidence of a fundamental upper limit on the brain's ability to discriminate between higher stimulus frequencies. We also emphasize the rarity of finding a location sensitive to any changes in frequency, both in our data and prior work [50]. This suggests that only a few particular networks in the sensory cortex are sensitive to frequency, rather than the wide-spread sensitivity to charge observed here.

B. Modeling of Neural Network Activation

It would be advantageous to be able to accurately model the selective activation of sensory regions, and use it to explore the effects of electrical stimulation on perception. Given the high dimensional stimulation parameter space, computational models could reduce the substantial workload to experimentally test all stimulation conditions and their interactions. While the field has yet to coalesce upon a verified model, a leaky integrator model of delivered charge can successfully predict perceived intensity [47], reinforcing our findings that charge is the primary variable for modulating perception intensity.

In this prior work, a model was experimentally validated by selecting several fixed points in the stimulation parameter space (varying frequency, amplitude, and train duration). The parameters of the model were estimated through threshold detection tasks, and it accurately predicted trained rodent behavior discriminating between several fixed points in the space. This model, however, was separately fit with different parameters for each set of comparisons that varied along each dimension, making it difficult to generalize.

C. Weber's Law

We see significant evidence that perceived intensity of ICMS may follow Weber's Law [60] for amplitude and pulse-width modulation (Fig. 9), in contrast to previous findings [16]. Weber's Law predicts that perceived intensity will be proportional to the percent change of a stimulus, rather than an absolute unit of value (such as micro-amps). When normalizing to percent change of amplitude and pulse-width, each resulting psychometric curve overlaps (Fig. 6b,e).

Thus, normalized JND, or Weber fractions, are relatively constant throughout the entire dynamic range. This finding has important implications for feedback using stimulation design, since we identify the highest sensitivity at the lower end of the range.

D. Implications for Neural Interface Design

The goals of our experiments were to determine the sensory resolution and to maximize the band-width of direct brain stimulation parameters. Given that most BCI technology uses visual feedback as the primary mechanism for guiding control strategies, our ICMS feedback patterns were designed to improve on the slow visual feedback pathway (~ 200 ms delay). Therefore, we explored relatively short train-intervals (nominally 100ms) and a small number of pulses-per-train (< 20) so that future applications could achieve feedback rates of 10Hz. In comparison, others who have studied electrical stimulation have used relatively long pulse trains (200–1000ms) and a large number of pulses (> 50 -100 pulses per train) [11], [14], [47], [54]. These differences in stimulus train length may also help to explain the differences between our results and previous studies. We emphasize that longer pulse trains may compromise the temporal resolution of rapid sensory feedback, especially in real-time neural interface applications. Co-adaptive learning effects of long-term use of feedback may also improve discrimination performance.

Few prior studies have directly compared stimulation parameters in the same animal and brain region. We chose the rodent model and a high-throughput behavior task [51] in order to test these encodings in the same cortical circuit of each animal. This allowed us to collect thousands of trials to robustly compare the sensory discrimination of different parameters. Although differences in stimulus perception may exist between the rodent and primate brain, our results provide guidance for testing promising sensory encoding schemes in non-human primates and human subjects.

V. CONCLUSION

In conclusion, we have determined the most promising parameters to deliver high-resolution sensory feedback via electrical stimulation to the cortex. We find that animals are most sensitive to changes in amplitude and pulse-width, which modulate the charge of the delivered pulses. Surprisingly, animals showed little ability to discriminate frequencies above 100 Hz. Finally, animals were able to detect train-intervals but not the number of pulses in the train.

With the knowledge of which features animals can detect in an artificial electrical stimulation pattern, we can now design stimulation encoding models to maximize resolution of an input signal. With the goal of delivering high band-width information directly to the brain, we validated stimulation parameters which could be updated and interpreted quickly. We recommend using the parameters amplitude and pulse-width to modulate intensity of a given percept (Fig. 8c, purple line). If further input range is needed, we also recommend modulating train interval, although future experiments

are required to determine orthogonality of these parameters. In summary, modulating charge-per-phase reliably encodes information via direct electrical cortical stimulation in the rapidly expanding field of cortical neuroprostheses.

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