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Utility and lower limits of frequency detection in surface electrode stimulation for somatosensory brain-computer interface in humans

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OBJECTIVE Stimulation of the primary somatosensory cortex (S1) has been successful in evoking artificial somatosensation in both humans and animals, but much is unknown about the optimal stimulation parameters needed to generate robust percepts of somatosensation. In this study, the authors investigated frequency as an adjustable stimulation parameter for artificial somatosensation in a closed-loop brain-computer interface (BCI) system.

METHODS Three epilepsy patients with subdural mini-electrocorticography grids over the hand area of S1 were asked to compare the percepts elicited with different stimulation frequencies. Amplitude, pulse width, and duration were held constant across all trials. In each trial, subjects experienced 2 stimuli and reported which they thought was given at a higher stimulation frequency. Two paradigms were used: first, 50 versus 100 Hz to establish the utility of comparing frequencies, and then 2, 5, 10, 20, 50, or 100 Hz were pseudorandomly compared.

RESULTS As the magnitude of the stimulation frequency was increased, subjects described percepts that were "more intense" or "faster." Cumulatively, the participants achieved 98.0% accuracy when comparing stimulation at 50 and 100 Hz. In the second paradigm, the corresponding overall accuracy was 73.3%. If both tested frequencies were less than or equal to 10 Hz, accuracy was 41.7% and increased to 79.4% when one frequency was greater than 10 Hz ($p = 0.01$). When both stimulation frequencies were 20 Hz or less, accuracy was 40.7% compared with 91.7% when one frequency was greater than 20 Hz ($p < 0.001$). Accuracy was 85% in trials in which 50 Hz was the higher stimulation frequency. Therefore, the lower limit of detection occurred at 20 Hz, and accuracy decreased significantly when lower frequencies were tested. In trials testing 10 Hz versus 20 Hz, accuracy was 16.7% compared with 85.7% in trials testing 20 Hz versus 50 Hz ($p < 0.05$). Accuracy was greater than chance at frequency differences greater than or equal to 30 Hz.

CONCLUSIONS Frequencies greater than 20 Hz may be used as an adjustable parameter to elicit distinguishable percepts. These findings may be useful in informing the settings and the degrees of freedom achievable in future BCI systems.

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KEYWORDS somatosensation; cortical stimulation; brain-computer interface; BCI; sensory feedback control; electrocorticography; ECoG; frequency

For patients with loss of function due to stroke or paralysis, the restoration of somatosensation has implications both for motor restoration[17,24] through brain-computer interface (BCI) systems[3,4,26,28] and as an independent aid for monitoring injury, pressure, and internal organ states. Direct electrical stimulation of the primary somatosensory cortex (S1) is a promising technique for generating artificial somatosensation in humans, having yielded reliable and safe outcomes.[2,5,13,14,16] Given the success of initial studies, the next step is to understand the limitations and parameters involved in leveraging artificial sensation in a closed-loop BCI system.

ABBREVIATIONS BCI = brain-computer interface; ECoG = electrocorticography; EMU = epilepsy monitoring unit; NHP = nonhuman primate; S1 = primary somatosensory cortex.

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TABLE 1. Participant demographics

Subject	Seizure Foci	Radiographic Abnormalities	Epilepsy Duration (yrs)	Age (yrs), Sex	Dominant Hand
S08	Lt amygdala & hippocampus	Lt mesial temporal sclerosis	3	21, F	Rt
S10	Lt mesial temporal	Lt mesial temporal sclerosis	45	50, F	Rt
S14	Rt temporal	Prior surgery for rt parietal cavernous malformation	3	25, F	Rt

Epilepsy patients underwent subdural ECoG implantation to localize their seizure foci, and an ECoG grid was placed over S1.

Studies in nonhuman primates (NHPs) with cortical stimulation in the S1 region have produced performance results comparable to those of real sensation in behavioral tasks.[18,27] Trained rhesus monkeys in an active exploration task are able to use artificial stimulation to discriminate between periodic pulse trains of intracortical microstimulation.[20] In a vibrational "flutter" discrimination task, monkeys achieved nearly the same degree of accuracy (80% accuracy with artificial stimulation vs 89% for mechanical stimulation) receiving either a physical stimulus or a cortical stimulus of 10 to 30 Hz.[22,23] Motor BCI has also shown performance improvements when paired with cortical stimulation feedback in a closed-loop BCI system.[12,19,26]

Preliminary work with NHPs has investigated the effects of electrode configuration and stimulation parameters on the detectability and discernibility of percepts arising from cortical stimulation.[10,11] However, despite the information gained from animal studies, the range of parameter changes that result in functionally useful percepts in humans is not clear. The frequency component of the stimulation pulse train is of particular interest as it has been shown, in humans, to be a parameter that can be altered independently, and may play a role in the coding of different types of sensory percepts[16] or alter the perceived intensity of a stimulus.[6,16] NHPs with microelectrodes were able to differentiate between sensory percepts arising from frequencies as low as 6 and 10 Hz,[22] suggesting 10 Hz as a lower limit of detection (it is not possible to tell if the monkeys felt a percept at 6 Hz or learned to interpret the absence of sensation as the lower frequency). The just-noticeable difference, that is, the lower limit of discerning between two frequencies at 75% accuracy, was 4.57 Hz, similar to that with mechanical trials (3.97 Hz).[22]

Based on these prior studies, it is reasonable to hypothesize that altering stimulation frequency will yield discernable percepts for humans as well. Indeed, while studies in humans have mostly focused on the effects of varying the amplitude of stimulation,[2,5] frequency has been successfully altered in somatosensory BCI systems. A recent high-density electrocorticography (ECoG) study modulated frequencies from 2 to 100 Hz sequentially and suggested a lower limit of detection around 20 Hz.[16] However, this was derived from the response generated by subjects and not in a paradigm of direct comparison. Another ECoG study did attempt to compare frequencies among 50, 65, 75, and 100 Hz in limited pair combinations and noted that participants could differentiate between evoked somatosensation.[9] These studies suggest that changing frequency alone is discernable to subjects; however, 2 important aspects are necessary to clarify use of frequency as a consistent and functionally useful parameter: first, to demonstrate that frequency is indeed a reliable parameter to provide feedback to a BCI participant over repeat stimulations, and second, to assess the lower threshold of detection.

Here, we assess the reliability of perceived changes in artificial somatosensation following changes in stimulation frequency and the detection thresholds of percepts generated with low stimulation frequencies. We investigated these properties of stimulation frequency using 2 experimental paradigms designed to compare frequencies both coarsely and with smaller differences between the frequencies. With this approach, we expand on the results of earlier studies and hope to provide insights into how frequency might be best utilized in a closed-loop BCI system.

Methods

Subjects and Implantation

Three participants (S08, S10, and S14) with intractable epilepsy undergoing subdural ECoG implantation for seizure localization, with access to S1, were recruited to this study (Table 1). This study was approved by the University of Southern California institutional review board, and all subjects provided written informed consent. Participants were without deficits in somatosensation and were of normal intelligence following preoperative neuropsychiatric testing. To identify the seizure focus, a craniotomy was performed for subdural ECoG grid placement, which also had access to the hand representation of S1. S08 had a seizure focus in the left hippocampus and amygdala, as well as sclerosis in the left mesial temporal lobe. S10 had a seizure focus in the left mesial temporal lobe, along with sclerosis in the same region. S14 had a seizure focus in the right parietal lobe and a history of surgery for a right parietal cavernous malformation; both regions were separate and distinct from S1 (Table 1).

Before surgery, anatomical landmarks were used to identify the hand representation of the motor cortex and the corresponding hand region in S1 based on preoperative MRI findings. While our surgical protocol has been previously described in detail,[16] briefly, a frontotemporoparietal craniotomy was performed. The S1 hand region was not always directly visualized, and the implanted ECoG grids were placed over this region using intraoperative navigation. For S08 and S10, grids were high-density, "mini"-ECoG grids with 2-mm contacts, with a 1.2-mm exposed surface of platinum-iridium electrodes between silastic sheeting, spaced 3 mm apart (FG64C-MP03, Ad-Tech Medical Instrument Corp.). For

S14, ECoG with standard spacing was implanted with 4-mm contacts, with a 2.4-mm exposed surface, spaced 1 cm apart (AU4X5P2, Integra Life Sciences Corp.). Following standard protocol, the dura was sutured closed, the bone was replaced, and the scalp was closed, with the lead tails tunneled out of the skin for attachment to the recording equipment and the stimulator. As part of the clinical monitoring, patients were placed in the epilepsy monitoring unit (EMU).

Experimental Setup

All testing occurred in the EMU on hospital day 6 or 7, after participants resumed their antiepileptic medications and under direct supervision by the treating epileptologist. While the participants were in the EMU, functional electrode locations were mapped with intracortical stimulation. The epileptologist stimulated the cortex using the FDA-approved Natus stimulator (Natus Neurology Inc.). Stimulation of electrode pairs was done with the following parameters: frequency of 50 Hz, pulse width of 250 μsec, duration of 1 second. The amplitude ranged from 0.5 mA to 12 mA at the discretion of the epileptologist. Generally, stimulation started at 2 mA and was steadily increased until one of the following categorizations was noted: "sensory" (somatosensation without any involuntary muscle movement), "motor" (visible motion, the feeling of motion without visible motion was considered proprioceptive sensory), "mixed motor-sensory" (both motion and somatosensation), and "no response" (when the amplitude reached 12 mA without a response). If concern for epileptiform activity was noted by the epileptologist (e.g., afterdischarges) the amplitude was stopped prior to reaching 12 mA. Once an electrode pair was determined to have somatosensory percepts only, the response was retested 25 times with the same parameters to ensure stability. If more than 1 pair met these criteria, the electrode pairs with a dermatome on the ventral side of the hand and those that occurred on the thumb, index, or middle finger were chosen.

To test discrimination between frequencies, subjects performed a target acquisition task: they moved the hand contralateral to the implanted ECoG grid over 2D targets and received intracortical stimulation over each target as the only feedback; following stimulation, they verbalized which target had the higher frequency. The frequencies used in these trials were dependent on which paradigm was tested. In the first paradigm, frequencies of 50 and 100 Hz were chosen for each target in a pseudorandom fashion to establish that reliable detection could be obtained between two frequencies for the purpose of locating hidden targets. Second, frequencies of 2, 5, 10, 20, 50, and 100 Hz were compared in a pseudorandom fashion to establish the lower and upper limits of detection and basic parameters for noticeable differences between frequencies. Paradigm 1 was performed on S08 and S10, with 50 trials each, and paradigm 2 was performed on S10 (50 trials) and S14 (25 trials). Due to limited testing time in the EMU, we were unable to perform all study paradigms in each participant. Statistical analysis was carried out with MATLAB software (MathWorks). Fisher's exact test was used to compare responses.

Results

Grid locations were assessed by fusing a postoperative CT scan to a preoperative MRI scan, and 3D representations were made using FreeSurfer and Statistical Parametric Mapping software SPM12 with the *img_pip* package (Fig. 1).[7] Stimulation was given at a pulse width of 250 μsec, pulse duration of 1 second, with square-wave pulses, and at the smallest amplitude that evoked consistent somatosensation during the 25+ stimulations while not resulting in a motor response. The amplitude was 1.5 mA for S08, 2 mA for S10, and 2 mA for S14. Dermatomes chosen were the ventral surface of the tip of digit 2 for S08, ventral surface of digit 4 for S10, and the medial surface of digit 5 for S14 (Table 2). Twenty-five trials were completed for S08 and S10 for paradigm 1. For paradigm 2, 50 trials were tested for S10, and 25 trials for S14 (limited by time constraints for testing in the EMU). After testing, the subjects were asked to describe the difference in frequencies. As the magnitude of the frequency of stimulation was increased, the difference in somatosensory percept was described as "faster" (S08), "more intense" (S10), and "faster buzzing" (S14). No subject reported a change in dermatomal area (e.g., larger area) with any of the tested frequencies, or over repeat stimulations. No adverse events occurred during testing.

In paradigm 1, S08 and S10 received cortical stimulation of either 50 or 100 Hz. Stimulation at both frequencies was successful in evoking somatosensory percepts, and the participants were able to correctly differentiate between the frequencies by stating the higher frequency with 98.0% accuracy (Fig. 2). In paradigm 2, S10 and S14 distinguished between somatosensation arising from cortical stimulation of 2, 5, 10, 20, 50, or 100 Hz. The higher frequency was identified with 73.3% accuracy (Fig. 2). The accuracy of trials testing each frequency pair is broken down in Fig. 3. To evaluate if the first stimulation altered the perception of the second, a comparison was made when the higher frequency was first versus when it was second. When the first frequency was greater than the second (n = 39), the accuracy was 72.2% (S10, 67.9%; S14, 90.9%) compared with 74.4% (S10, 69.5%; S14, 76.9%) when the first frequency was less than the second (n = 36, $p > 0.99$).

Next, to establish the lower limits of detection in an alternating forced-choice paradigm, we compared accuracy at the lower and higher frequencies tested. The accuracy of choosing the higher frequency, broken down by thresholds, is summarized in Fig. 4. The lower limit of accuracy above chance occurs around 20 Hz, where if both frequencies were 20 Hz or less (n = 27), accuracy was 40.7% (S10, 33.3%; S14, 55.0%), while when one frequency was greater than 20 Hz, accuracy increased to 91.7% (S10, 87.8%; S14, 100%; n = 48) ($p < 0.001$).

Accuracy decreased significantly when lower frequencies were tested. If both frequencies were less than or equal to 10 Hz (n = 12), accuracy was 41.7% compared with 79.4% when one frequency was greater than 10 Hz (n = 63, $p = 0.01$). Finally, if both frequencies were 50 Hz or less, accuracy was 59.6% (n = 47). In trials in which 50 Hz was the higher frequency (n = 20), accuracy increased to 85%, differing significantly from trials in which 10 Hz

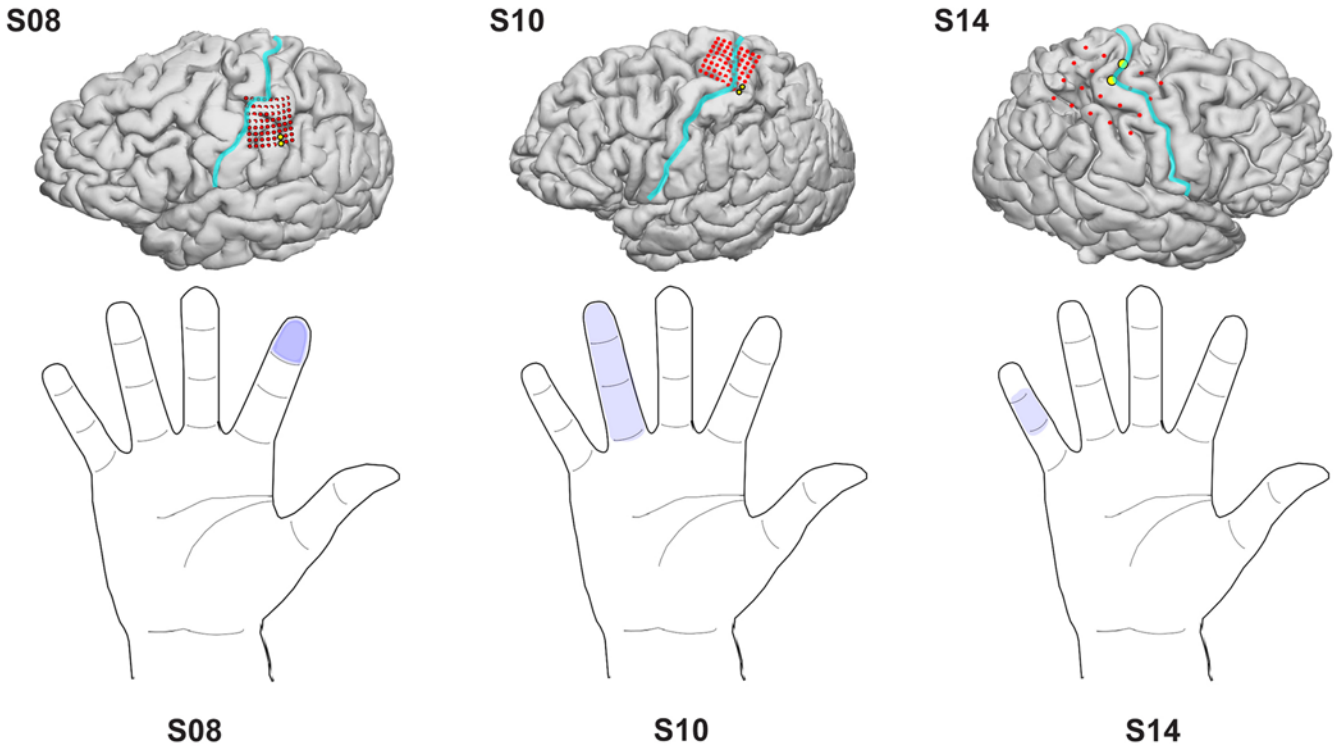

FIG. 1. ECoG grid placement and hand receptive fields. **Upper:** An ECoG grid was placed over S1 in epilepsy patients. Based on MRI findings, a 3D image was generated of each subject's brain with the electrode grid superimposed. The central sulcus is outlined in *green* and the electrodes are shown in *red*. The electrodes chosen for stimulation appear as *yellow dots*. The electrodes were placed 3 mm apart in S08 and S10 and 1 cm apart in S14 (center-to-center). **Lower:** Dermatomes associated with the chosen electrodes (*yellow dots* in the upper panel) for stimulation following mapping by an epileptologist.

($p < 0.05$) or 20 Hz ($p < 0.01$) was the higher frequency. In trials in which 100 Hz was the higher frequency ($n = 28$), accuracy was 96.4%, again significantly higher than trials with 10 Hz ($p < 0.01$) or 20 Hz ($p < 0.0001$) as the higher frequency. There was no significant difference between trials with the higher frequency at 50 Hz or trials with the higher frequency at 100 Hz ($p = 0.29$). Therefore, accuracy increased in trials with higher tested frequencies (20 Hz and above), while accuracy was close to chance in trials with lower tested frequencies (10 Hz and below). The greatest accuracy was noted in trials in which one frequency was either 50 or 100 Hz.

Next, we investigated the effect of stimulation differences on accuracy. We isolated and compared trials testing 10 Hz versus 20 Hz (frequency difference of 10 Hz) and 20 Hz versus 50 Hz (frequency difference of 30 Hz). When one stimulus was at 10 Hz and the other was at 20 Hz ($n = 6$), accuracy was 16.7%, compared with 85.7% in trials testing 20 Hz versus 50 Hz ($n = 7$, $p < 0.05$) (Fig. 5). When one frequency was 20 Hz and the other was 5 Hz (frequency difference of 15), accuracy was 66.7% ($n = 6$). Overall, summing the low frequency differences, when the difference was less than or equal to 40 Hz ($n = 39$), accuracy was 53.9%, compared with 94.4% accuracy when the difference was greater than 40 Hz ($n = 39$) ($p < 0.0001$) (Fig. 5). Accuracy was above chance at a frequency difference of 30 Hz or greater.

TABLE 2. Subjective stimulation qualities

Subject	Dermatome Chosen for Stimulation	Higher-Frequency Description	Effect of Repeat Stimulations & Larger Frequencies on Dermatomal Area
S08	Digit 2 ventral tip	"Faster"	No change
S10	Digit 4 ventral surface	"More intense"	No change
S14	Digit 5 medial surface	"Faster buzzing"	No change

Dermatomes used for stimulation were chosen on the basis of electrode pairs that elicited safe and reliable somatosensation over a consistent dermatomal area following repeat stimulation by the epileptologist. Subjects reported the subjective quality of percepts arising from higher frequencies. Repeat stimulation and stimulation at larger frequencies did not change the dermatomal area in all subjects.

Discussion

Here, we investigated the effects of stimulation frequency on the percepts evoked when electrically stimulating the S1. Expanding on previous work, this study sought to establish the plausibility and limitations of us-

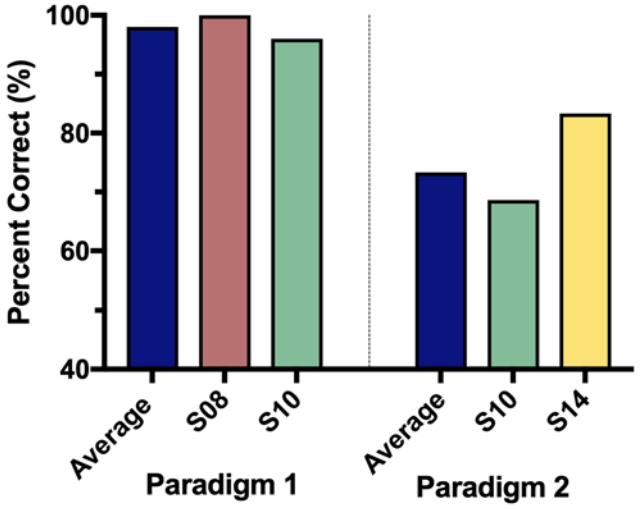

FIG. 2. Accuracy across both paradigms. Paradigm 1 tested frequencies of 50 Hz and 100 Hz and had an overall accuracy of 98.0% (S08, 100%; S10, 96%). Paradigm 2 tested frequencies of 2, 5, 10, 20, 50, and 100 Hz and had an overall accuracy of 73.3% (S10, 68.2%; S14, 83.3%).

ing frequency as an adjustable parameter for the sensory component of a closed-loop BCI system. Using ECoG grids over the S1 hand area, we were able to show frequency as a reliable and adjustable component in somatosensory BCI systems. Subjects distinguished between percepts arising from stimuli of 50 and 100 Hz with near-perfect accuracy, suggesting that frequency may be utilized as a degree of freedom with excellent reliability. In evaluating response accuracy as stimulation frequencies were adjusted over a range of 2–100 Hz, we found that frequencies below 20 Hz were unreliable, and a system with frequencies spaced out 30 Hz would lead to reliable detection.

Utilizing frequency as the only altered stimulation parameter, participants were asked to differentiate between two identical targets in a nontactile environment. We were able to show a high degree of accuracy for 50 versus 100 Hz (98.0%). This is not unexpected, as prior work has shown good differentiation of 50, 65, 75, and 100 Hz in humans;[9] however, the trial set was limited. We have previously shown that 10-Hz differences are detectable between 20 and 60 Hz but did not explore lower, or repeat, frequency stimulations to assess the threshold of absolute detection to inform stimulation parameters in BCI.[15] Here, we show that repetitive stimulation with the same two frequencies is easily distinguishable, suggesting the stability of frequency as a stimulation "degree of freedom" for somatosensory BCI. In the second paradigm, when one stimulus was 50 or 100 Hz, accuracy was 91.7%, compared with 40.7% when both stimuli were less than or equal to 20 Hz ($p < 0.001$). Although the lower ends—2, 5, and 10 Hz—may not have been detected at all, as participants made subjective comments to this effect, when the other frequency was 50 or 100 Hz, the subjects were able to reliably discern between the two frequencies. This may suggest that patients are perceiving some stimuli at lower tested frequencies that are not reaching conscious perception. Another possibility is that the absence of perception at a low frequency leads to the correct identification of the higher frequency by default, as only one stimulus is perceived.

We tested a range of frequencies from 2 to 100 Hz. Our results suggest that 20 Hz may be a lower limit of detection but not reliable enough to be functionally useful. Accuracy increased significantly (79.4%) when one tested frequency was 20 Hz or greater; however, if 20 Hz was the

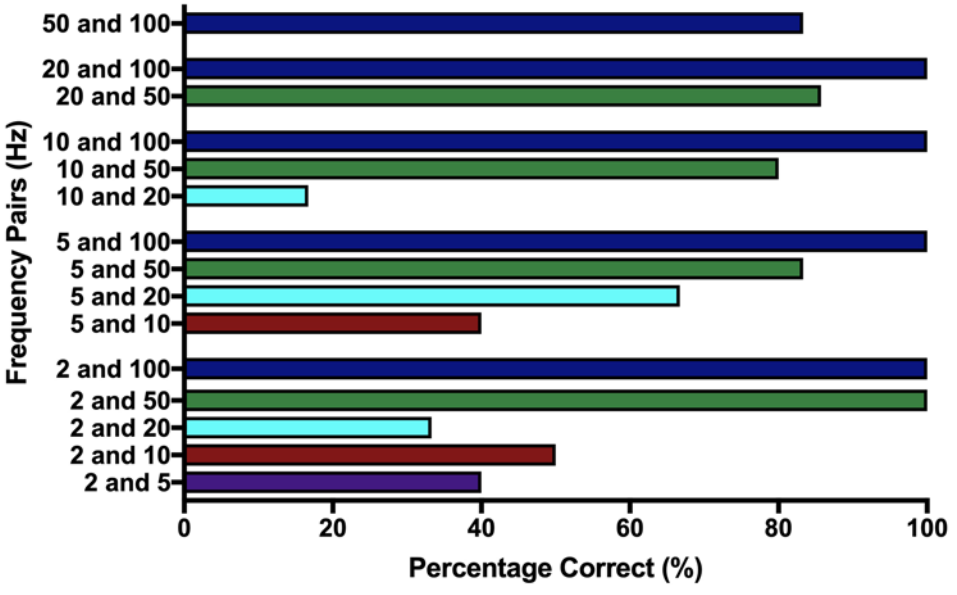

FIG. 3. Correct responses for different frequency pairs. Percentage correct for all trials tested. Accuracy increased when at least one frequency was greater than 20 Hz.

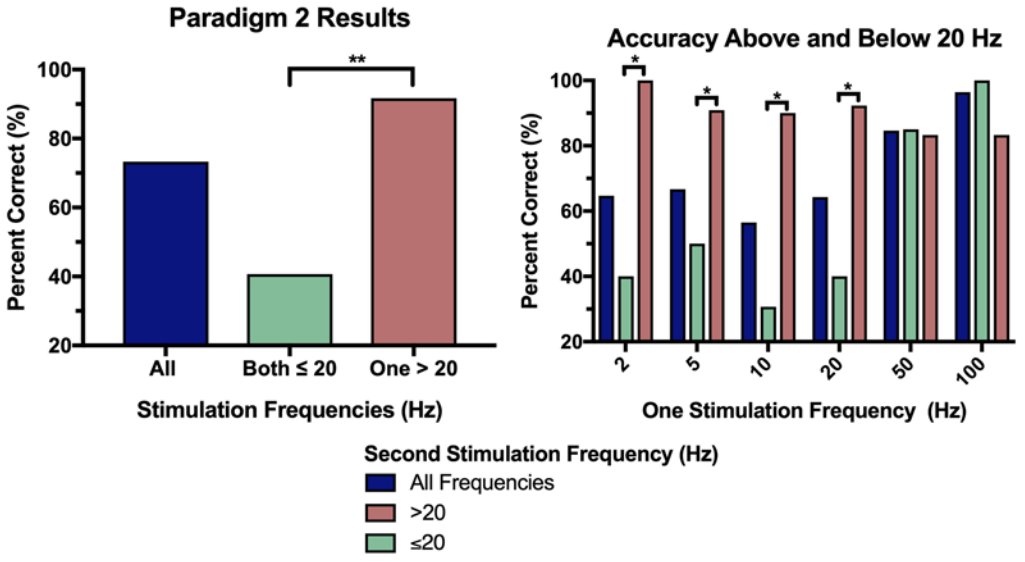

FIG. 4. Accuracy with frequencies above and below 20 Hz. **Left:** Accuracy when both tested frequencies were below or equal to 20 Hz versus when one frequency was above 20 Hz. Accuracy increased substantially when one frequency was above 20 Hz compared with when both frequencies were less than or equal to 20 Hz (91.7% and 40.7%, respectively), giving an overall accuracy of 73.3%. **Right:** Accuracy at all tested frequencies, when the second frequency was above or below 20 Hz. At lower frequencies (2, 5, 10, and 20 Hz), accuracy increased greatly when the second tested frequency was above 20 Hz versus when it was less than or equal to 20 Hz, likely indicating a lack of perception below 20 Hz. At 50 and 100 Hz, there was little effect on accuracy when the second frequency was greater than 20 Hz compared with less than or equal to 20 Hz. *p < 0.05; **p < 0.001.

higher frequency, accuracy was around chance (42.9%). Accuracy rose to 85% when one tested frequency was 50 Hz or greater. These findings are in agreement with our previous work using ECoG, in which the majority (56%) of participants first reported a sensation with 20-Hz stimulations.[16] In NHP microstimulation trials, monkeys were able to perceive and discern between stimulations as low as 10 Hz, suggesting that reliable somatosensation occurs at or below 10 Hz.[22] Our results indicate that stimulation below 20 Hz is not reliable. This discrepancy could result

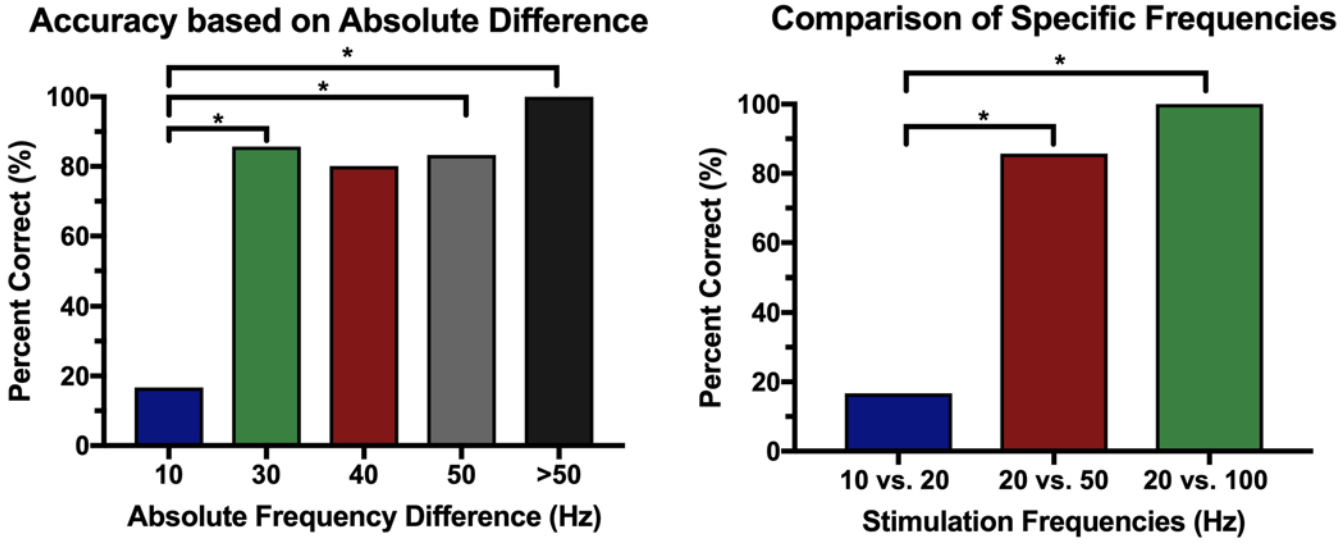

FIG. 5. Accuracy at tested frequencies organized by the absolute difference between the two. **Left:** Accuracy based on the absolute difference between tested frequencies. Accuracy increased when the frequency difference was 30 Hz or greater compared with 10 Hz. **Right:** Accuracy at specific frequencies. Trials in which the tested frequencies were 10 versus 20 Hz, 20 versus 50 Hz, and 20 versus 100 Hz were isolated and compared. Accuracy was low in trials testing 10 versus 20 Hz and increased significantly in trials testing 20 versus 50 Hz and 20 versus 100 Hz. *p < 0.05.

from a difference in species, study designs, stimulation devices, or all the above. We have previously suggested that high-density ECoG is a less-invasive approach to accessing more of the existing architecture in S1.[14] These results suggest that even if the stimulation parameters are less easily differentiated with ECoG compared with microelectrodes, detecting differences is still reliable and feasible in a relatively large range of acceptable stimulation parameters (20 to 100 Hz).[1,21,25,29]

Our findings suggest that reliable differentiation between frequencies may occur when the frequency difference is at least 30 Hz. We found that a frequency difference of 10 Hz led to a poor accuracy of 16.7%, whereas a frequency difference of 30 Hz led to a greatly improved accuracy of 85.7%. Previously, we have shown that a 10-Hz difference, between 20 and 100 Hz, is detected above chance;[15] however, here 10 Hz or smaller differences occurred at lower tested frequencies (2, 5, 10, or 20 Hz). These results likely reflect a lower detection threshold of around 20 Hz, rather than a just-noticeable difference. The low accuracy in trials testing 10 Hz versus 20 Hz (16.7%) indicates that participants reliably chose 10 Hz as the higher frequency; however, when only comparing 10 Hz and 20 Hz, the trial numbers were small (n = 6). Perhaps it reflects a reversal of somatosensation in this frequency range, but this hypothesis warrants further investigation.

Subjectively, we asked participants to describe the sensations comparing 2 frequencies. Across both paradigms, when both frequencies were perceived, the higher frequency was described as "faster" (S08), "more intense" (S10), and "faster buzzing" (S14), in line with previous studies (Table 2).[8,9,16] Below 20 Hz, subjects did not report somatosensation, and at 20 Hz, they described the stimulation as "inconsistent." Repeat stimulations and larger frequencies did not alter the dermatomal region that exhibited percepts (Table 2). This adds to our previous report establishing broad, unnatural feeling percepts from stimulation[16] and suggests more clearly that the speed of stimulation frequency is translated to the perception.

This study has several limitations. The sample size in each paradigm was limited to 2 participants, making the results difficult to generalize. The trials were performed in the EMU, limiting control and requiring clinical and time constraints, ultimately preventing more trials and paradigms. In addition, other stimulation parameters, such as amplitude, varied between participants, possibly making comparisons between subjects unreliable. We chose to keep the amplitude as low as possible while maintaining reliable detection (25 trials at the chosen amplitude and 50 Hz), but this may have introduced differences in responses. The subjects were diagnosed with epilepsy, a disease that may remodel cortical pathways in S1. However, they experienced consistent somatosensation in a localized region and had no known pathology affecting the hand representation of S1. The location on S1 was not consistent between subjects (i.e., location of percepts on the hand) due to variability in grid placement. It is possible that a difference in cortical or dermatomal representations of the areas used alters perception of cortical stimulation. Finally, the results of this study are not representative of chronic stimulation and its effects, as each session took place in 1 day.

Conclusions

We investigated the frequency component of cortical stimulation to understand the limitations, parameters, and plausibility of using this component as a degree of freedom in somatosensory BCI. We report frequency as a reliable stimulation parameter in ECoG-generated somatosensation, with near-perfect accuracy on multiple trials of 50 versus 100 Hz. Our results also imply a lower limit of detection around 20 Hz and suggest that a lower limit for reliable sensation occurs in the range between 20 Hz and 50 Hz. Thus, we suggest that frequencies larger than 20 Hz can be utilized as an adjustable parameter to evoke reliable, unique, distinguishable somatosensation.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Kramer, Liu, Kellis, Lee. Acquisition of data: Kramer. Analysis and interpretation of data: Kramer, Lamorie-Foote. Drafting the article: Kramer, Lamorie-Foote. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Statistical analysis: all authors. Study supervision: Kramer, Nune, Liu, Kellis, Lee.

Supplemental Information

Previous Presentations

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