Short reaction times in response to multi-electrode intracortical microstimulation may provide a basis for rapid movement-related feedback

Joseph T Sombeck\textsuperscript{1,2,\ast} and Lee E Miller\textsuperscript{1,2,3,4,\dag}

\textsuperscript{1} Department of Physiology, Northwestern University, Chicago, IL, United States of America
\textsuperscript{2} Department of Biomedical Engineering, Northwestern University, Evanston, IL, United States of America
\textsuperscript{3} Department of Physical Medicine and Rehabilitation, Northwestern University, Chicago, IL, United States of America
\textsuperscript{4} Shirley Ryan AbilityLab, Chicago, IL, United States of America
\textsuperscript{5} Author to whom any correspondence should be addressed.
E-mail: lm@northwestern.edu

Keywords: brain–machine interface, intracortical microstimulation, somatosensory sensory feedback, microelectrode array

Abstract

Objective. Tetraplegic patients using brain–machine interfaces can make visually guided reaches with robotic arms. However, restoring proprioceptive feedback to these patients will be critical, as evidenced by the movement deficit in patients with proprioceptive loss. Proprioception is critical in large part because it provides faster feedback than vision. Intracortical microstimulation (ICMS) is a promising approach, but the ICMS-evoked reaction time (RT) is typically slower than that to natural proprioceptive and often even visual cues, implying that ICMS feedback may not be fast enough to guide movement. Approach. For most sensory modalities, RT decreases with increased stimulus intensity. Thus, it may be that stimulation intensities beyond what has previously been used will result in faster RTs. To test this, we compared the RT to ICMS applied through multi-electrode arrays in area 2 of somatosensory cortex to that of mechanical and visual cues. Main results. We found that the RT to single-electrode ICMS decreased with increased current, frequency, and train length. For 100 \mu{}A, 330 Hz stimulation, the highest single-electrode intensity we tested routinely, most electrodes resulted in RTs slower than the mechanical cue but slightly faster than the visual cue. While increasing the current beyond 100 \mu{}A resulted in faster RTs, sustained stimulation at this level may damage tissue. Alternatively, by stimulating through multiple electrodes (mICMS), a large amount of current can be injected while keeping that through each electrode at a safe level. We found that stimulation with at least 480 \mu{}A equally distributed over 16 electrodes could produce RTs as much as 20 ms faster than the mechanical cue, roughly the conduction delay to cortex from the periphery. Significance. These results suggest that mICMS may provide a means to supply rapid, movement-related feedback. Future neuroprosthetics may need spatiotemporally patterned mICMS to convey useful somatosensory information.

Novelty & Significance

Intracortical microstimulation (ICMS) is a promising approach for providing artificial somatosensation to patients with spinal cord injury or limb amputation, but in prior experiments, subjects have been unable to respond as quickly to it as to natural cues. We have investigated the use of multi-electrode stimulation (mICMS) and discovered that it can produce reaction times as fast or faster even than natural mechanical cues. Although our stimulus trains were not modulated in time, this result opens the door to more complex spatiotemporal patterns of mICMS that might be used to rapidly write in complex somatosensory information to the CNS.
Introduction

Efferent brain–machine interfaces (BMIs), which decode motor intent from recorded brain activity, can allow a tetraplegic patient to move a robotic arm (Hochberg et al 2012, Collinger et al 2013) or even their own arm, using functional electrical stimulation (FES) to cause their paralyzed muscles to contract (Ethier et al 2012, Bouton et al 2016, Aijboye et al 2017). These BMIs typically rely solely on visual feedback to guide movement, despite the considerable movement deficits suffered by patients without somatosensation (Rothwell et al 1982, Ghez et al 1995). Without cutaneous sensations, subjects exert forces larger than necessary, often crushing delicate objects (Monzée et al 2003), and dexterous manipulation of small objects becomes almost impossible (Johanson and Flanagan 2009). Patients who have lost proprioception are for the most part wheelchair bound, and make large reaching errors due to an inability to plan and rapidly update ongoing reaches (Ghez et al 1990, Sainburg et al 1995). The relatively slow speed of visual feedback is one of the reasons that it is an inadequate replacement for somatosensation. Additionally, somatosensation is important for prosthesis embodiment (Antfolk et al 2013). Thus, restoring somatosensation is a critical, yet unmet component of BMI development.

Intracortical microstimulation (ICMS) has the potential to restore somatosensation, having been shown to elicit conscious perceptions in rats (Fridman et al 2010, Deveciouş and Güçlü 2017, Öztürk et al 2019), monkeys (Romo et al 2000, London et al 2008, O’Doherty et al 2011, Tabot et al 2013) and humans (Flesher et al 2016, Salas et al 2018). Stimulation in tactile cortical areas provides sensations of flutter at a frequency that matches the stimulation frequency (Romo et al 2000). Consequently, ICMS has been used to provide artificial texture feedback, enabling monkeys to learn to select rewarded virtual objects based on their ‘feel’ (O’Doherty et al 2011). Additionally, the virtual location of the sensation elicited in tactile areas corresponds to the receptive field of neurons in that area (Tabot et al 2013), enabling a spinal cord injured patient to identify which of multiple robotic fingers were touched (Flesher et al 2016).

Replicating the sensations corresponding to the more distributed and complex receptive fields of proprioceptive neurons has not been as successful. In an experiment that relied on the ability to learn the meaning of an abstract stimulus, monkeys were able to reach to unseen targets using ICMS feedback about the error vector between the changing hand position and target position (Dadarlat et al 2015). This interface, though, required months of training, in contrast to the more rapidly learned, biomimetically-inspired, mapping in tactile areas (Flesher et al 2016). The long training time required was probably due to the complex learning problem associated with mapping an abstract stimulus to limb state. In an effort to provide a more natural proprioceptive sensation, thereby reducing training time and possibly providing more informative feedback, our group stimulated on small sets electrodes, selected because of their mutually similar responses recorded during arm movements (Tomlinson and Miller 2016). This biomimetic approach predictably biased one monkey’s perception of the direction of a coincident mechanical perturbation without any learning, suggesting that it had indeed, evoked a sensation like that of the natural perturbation. However, the effect could not be replicated in subsequent monkeys, for reasons that remain unclear.

In addition to evoking meaningful sensations, afferent interfaces also need to provide fast feedback, like that of somatosensation. Patients without proprioception make their largest errors during rapid movements, in part, because the slow speed of visual feedback limits correction of these movements (Ghez et al 1990, Sainburg et al 1995). Slow feedback also limits its successful embodiment of a prosthesis (Shimada 2009). It is reasonable to assume that ICMS could provide very rapid feedback, as it bypasses the conduction latency from the periphery. However, the response time to single-electrode stimulation in tactile areas is typically slower than that to either tactile or visual cues (Godlove et al 2014). Critically, if ICMS is no faster than natural vision, it is unlikely to replace it for guiding rapid reaches or enabling embodiment.

In this paper, we used a reaction time (RT) paradigm as a rapid, sensitive mean to compare the latency of ICMS applied through multi-electrode arrays implanted in area 2 of somatosensory cortex to that of perturbations applied to the hand and to visual cues. Consistent with earlier studies, we found that single-electrode ICMS (sICMS) typically resulted in RTs that were slower than limb perturbations and slightly faster than the visual inputs. On the other hand, multi-electrode ICMS (mICMS) elicited RTs even faster than limb perturbations. We investigated the effect of number of electrodes, total current, and distance between electrodes on the RT to mICMS. The use of many electrodes simultaneously may also allow the more complex spatial patterns of cortical activity typical of natural proprioceptive inputs to be elicited. Our results show that mICMS may be a suitable approach for providing fast feedback in future afferent interfaces.

Methods

Monkeys

All procedures in this study were performed in accordance with the guide for the care and use of laboratory animals and were approved by the institutional animal care and use committee of Northwestern University under protocol #1500000367. The experiments were performed using two male rhesus macaques (Monkey H: 12.9 kg, Monkey D: 9.8 kg).
Reaction time task
Monkeys held the handle of a two-link planar robotic manipulandum which controlled a cursor on an LCD screen in front of them (figure 1(a)). In the RT task, monkeys reached to a target in response to a go cue consisting of either a mechanical perturbation of the hand, a change in the color of the targets on the screen, or ICMS in area 2. Each trial began when the monkey moved the cursor into a target at the center of the workspace (figure 1(b)). At this point, the goal target appeared 9 cm from the center target, so that the monkey could plan where to reach. The cursor then disappeared, to avoid providing visual feedback about the mechanical cue. Monkey H made reaches to the right and monkey D made reaches forward, as these were the directions in which they each moved most rapidly. On 85% of trials for monkey H, a go cue was provided at a random time between 500 and 1500 ms after the goal target appeared. For monkey D, a go cue was provided on 75% of trials between 500 and 2000 ms after the goal target appeared. If the monkeys reached the goal target within a short time window (750 ms for monkey H and 800 ms for monkey D) after go cue onset, they received a water reward. In the rest of the trials, no cue was presented, and the monkeys were rewarded for not moving from the center target. These trials were included to reduce the rate of false starts.

The mechanical cue was a force applied to the hand for 120 ms, including 20 ms rise and fall times. We used a short duration so that the perturbation did not affect the monkey’s subsequent reach. There was a white noise audio mask throughout each experiment to prevent monkeys from hearing the motors during mechanical cues. The direction of the mechanical perturbation was perpendicular to the reach direction to simplify determination of movement onset. Stimulation in area 2 likely elicits both proprioceptive and tactile sensations, as area 2 is known to integrate information from both muscle and cutaneous receptors (Hyvärinen and Poranen 1978, Pons et al 1985, Weber et al 2011). After becoming proficient at the RT task, each monkey was implanted with a 1-mm long, 96-electrode, sputtered iridium-oxide Utah multi-electrode array (Blackrock Microsystems, Salt Lake City, UT) in the proximal arm area of somatosensory cortical area 2. In surgery, we found the arm representation by recording from the cortical surface while manipulating the arm and hand. For more details on surgical techniques, see (Weber et al 2011). After the implant surgery, we performed sensory mappings to confirm that recorded neurons had receptive fields corresponding to the proximal arm. On ICMS trials, electrodes were stimulated with pulse trains consisting of cathodal–first, biphasic, 200 μs pulses, using a Cerestim R96 (Blackrock Microsystems, Salt Lake City, UT). There was 53 μs between phases in each pulse. In experiments where we stimulated more than 16 electrodes, the electrodes were stimulated in two equal-size groups,
separated by a 100 µs lag, because the stimulator was limited to simultaneous stimulation of 16 electrodes. To control for any potential effect due to asynchronous stimulation in applicable experiments, all sets of electrodes were separated into two groups, regardless of how many electrodes were within each group.

A Cerebus system (Blackrock Microsystems, Salt Lake City, UT) was used to collect handle kinematics and cue onset times. Handle kinematics were recorded at 100 Hz using encoders on the manipulandum joints. Stimulation onset was determined through the sync line from the Cerestim R96 (Blackrock Microsystems, Salt Lake City, UT), and visual cue onset was determined by a photodiode placed near the screen, both sampled at 30 kHz. Mechanical cue onset was defined as the time of the command signal to the servo motors.

Experiments with monkey H began 30 months after array implantation, and 1 month after monkey D was implanted. Experiments were performed once a day for 6 months with monkey H (total of 34 sessions), and for 1.5 months (18 sessions) with monkey D. There were 15.2 ± 6.8 (mean ± standard deviation) successful trials per condition for monkey H and 18.9.0 ± 6.8 for monkey D across all conditions and sessions.

Data analysis
RT was defined as the time from cue onset to movement onset. To find movement onset, we first found the time of peak acceleration in the direction of the goal target after cue presentation. We then found movement onset by backtracking until the acceleration dropped below 35 cm s$^{-2}$, roughly two standard deviations above the mean acceleration measured during the hold period. The same threshold was used for all cue modalities across all sessions for both monkeys. RTs above or below two standard deviations from the mean were removed as outliers. There were a small number of outliers for each condition, mostly due to false starts, which resulted in extremely fast RTs, as well as extremely slow RTs, likely due to the monkeys not paying attention during some trials.

Statistical analysis
We used two-sided Welch’s t-tests to compare RTs to the mechanical and visual cues within sessions, and to compare sICMS at 100 µA for each electrode to the mechanical cues within the same session. We also used Welch’s t-tests to compare the mean RT across all electrodes when stimulated at 100 µA to the mean RT in response to the mechanical cue, the mean RT to sICMS at 200 µA and the mechanical cue, and the RT to mICMS and the mechanical cue. We used paired t-tests to compare the RT to sICMS and mICMS and to adjacent and non-adjacent electrode groups. The effect of amplitude, frequency, or train length on the resulting sICMS RT and the effect of total current and number of electrodes on the resulting mICMS RT were compared with an analysis of variance (ANOVA), with data aggregated across monkeys. We also used an ANOVA to test the effect of electrode position on the RT to sICMS at 100 µA for each monkey individually, generating two models. We used an F-test of the significance of the models and each individual parameter, when relevant.

Results

Reaction time in response to natural proprioceptive and visual cues
Monkeys performed an RT task in which they reached from a center target to an outer target when cued with either a mechanical or visual go cue (figure 1). We tested perturbation forces ranging from 0.1 to 1.0 N in monkey H, which caused a displacement of the monkey’s hand from roughly 0.1 to 0.5 cm forward, and from 0.5 to 4.5 N in monkey D, which moved the monkey’s hand to the right from 0.75 to 10 cm. Figure 2 shows the mean RTs in response to mechanical cues of different magnitudes for two representative sessions for each monkey, as well as the mean RT to the visual cue (black dashed line). As anticipated from many earlier studies across sensory modalities (Pins and Bonnet 1996), RT decreased with increasing
perturbation magnitude, reaching an asymptotic value at about 160 ms for a 1 N pulse in monkey H and 180 ms for a 3 N pulse in monkey D. We used only these forces for subsequent experiments in the respective monkeys. Across all sessions, the mean RT in response to the mechanical cue was 162 ± 14 ms for monkey H and 186 ± 23 ms for monkey D. For the visual cue, the mean RT for monkey H across all sessions was 250 ± 48 ms, and for monkey D, 380 ± 39 ms. In every session for both monkeys, the mean RT to the mechanical cue was significantly faster than that to the visual cue (p < 0.01, Welch’s t-test).

**Reaction time in response to single-electrode ICMS**

We tested sICMS with a wide range of current amplitudes, frequencies, and train lengths. The range of amplitudes (20–100 µA) and frequencies (50–500 Hz) included parameters commonly used in ICMS experiments. Initially, we used a maximum of 100 µA, as this was the largest current tested in earlier ICMS safety studies (Chen et al 2014, Rajan et al 2015). We also tested a range of train lengths (75–300 ms) with a maximum longer than the mean RT to ICMS found previously (Godlove et al 2014). Thus, we expected the RT to settle for a train length within the range tested. In one series of experiments, we kept two of these parameters constant and measured the RT while varying the third. The RT to stimulation on two representative channels in monkey D for varied train lengths is shown in figure 3(a). Figures 3(b) and (c) show the effect on RT of varied frequency and amplitude respectively. Results in monkey H were similar to these. We used an ANOVA to determine the effect of each parameter on RT. Aggregated across both monkeys, we found that increasing each parameter resulted in significantly faster RTs (amplitude: F(1,30) = 67; frequency: F(1,33) = 46; train length: F(1,27) = 17.8; p ≪ 0.01 for all). The RT stopped decreasing for train lengths above about 120 ms for monkey H and 200 ms for monkey D (with a frequency of 200 Hz). The RT stopped decreasing at a frequency of about 330 Hz (with 250 ms train length for monkey H and 200 ms for monkey D) for both monkeys. However, the RT continued to decrease for amplitudes up to 100 µA. Therefore, we used this frequency and these train lengths in later experiments and varied amplitude to change stimulation intensity, unless otherwise noted.

We measured the RT for each electrode at 100 µA across numerous sessions. The mean RT for each electrode in the order they were tested is shown in figures 4(a) and (c) for each monkey. Within each session (divided by vertical dashed lines), we also measured the mean RT in response to the mechanical cue (black solid line) and the visual cue (black dashed line). We compared the single-electrode RT for each electrode to the mechanical cue RT, as this was the fastest natural stimulus. Stimulation on 93 of the 192 individual electrodes resulted in significantly slower RTs than the mechanical cue while 9 electrodes evoked RTs significantly faster than the mechanical cue (p < 0.05, two-sided Welch’s t-test, Bonferroni correction). Seventy-nine electrodes resulted in RTs that were not significantly different than the mechanical cue. The monkeys did not react to stimulation on nine electrodes. Two electrodes caused monkey D to vocalize and were not tested further. Mean RTs for all electrodes and mean RTs to the mechanical cue and visual cue pooled across sessions are summarized in figures 4(b) and (d) for each monkey. The mean single-electrode RT across all electrodes was 199 ± 39 ms for monkey H and 225 ± 53 ms for monkey D. For both monkeys, the RT to single-electrode stimulation across electrodes was significantly slower than that to the mechanical cue in the corresponding session (p ≪ 0.001, Welch’s t-test).

The location of the electrode on the array may change the depth of the electrode in cortex, or the apparent location of the sensation on the arm, and thus affect the RT. The position of each array in cortex is shown in figure 5(a), with labels indicating the central sulcus (CS) and intraparietal sulcus (IPS). The color of each electrode in figure 5(b) corresponds to the RT measured when that electrode was stimulated at 100 µA. Black X’s indicate electrodes that the
monkeys did not respond to, red X’s indicate electrodes that caused the animal to vocalize, and white boxes indicate electrodes that were not connected (by design, four on each array). We fit a linear model for each monkey to predict the RT from the position along medial–lateral and anterior–posterior axes of the array, approximately parallel and perpendicular to the IPS respectively. This model was statistically significant in both monkeys ($p < 0.001$, F-test), suggesting that the resulting RT depended on the position of the electrode in cortex. The resulting vector of maximal decrease in RT is shown by the arrows in figure 5(a). For monkey

![Figure 4](image-url) Figure 4. Reaction time to single-electrode stimulation for many electrodes. The mean reaction times (RT) to single-electrode stimulation (circles) are shown in the order that electrodes were tested across multiple sessions for (a) monkey H and (c) monkey D. The mean RTs to the mechanical cue (black solid line) and to the visual cue (black dashed line) are shown for each session. The parameters of the mechanical cue were the same as those of figure 2. Vertical grey dashed lines denote different sessions. Electrodes were stimulated with 100 $\mu$A at 330 Hz for 120 ms for monkey H and for 200 ms for monkey D. Error bars show standard deviation. RT data across electrodes is summarized for (b) monkey H and (d) monkey D. The mean RTs to the mechanical cue (black horizontal line) and the visual cue (black dashed line) across sessions and the pooled standard deviation are shown for comparison.

![Figure 5](image-url) Figure 5. Dependence of reaction time to single-electrode stimulation on electrode position. (a) Schematic of the arrays in cortex for the two monkeys. The purple dashed square shows the array for monkey H, and the green solid square shows the array for monkey D. CS is central sulcus, IPS is intraparietal sulcus, A is anterior, and L is lateral. (b) The reaction time (RT) during single-electrode stimulation for each electrode is shown for monkey H (top) and monkey D (bottom). The color of each electrode denotes the RT to stimulation through that electrode. White squares represent electrodes that were not connected. The monkeys did not respond to stimulation through electrodes denoted with black X’s. Red X’s denote electrodes which resulted in vocalization.
H, the RT decreased for more lateral electrodes. The RT decreased for posterior electrodes for monkey D.

**Reaction time in response to high-amplitude sICMS**

A possible explanation for the slow RT in response to ICMS is that the evoked sensation is rather weak, like that of a small force-pulse perturbation. As in our results for the mechanical cue and sICMS, reaction time is typically a saturating function of stimulus intensity for all parameters (figures 2 and 3) (Pins and Bonnet 1996). While large currents may lead to a faster RT, there is a limit to the current that can be delivered safely through any given electrode. To test the effect of even larger currents on RT, we used currents up to 200 µA on single electrodes, near the maximum of our stimulator. The RT for currents from 40 to 200 µA is shown for two example channels in monkey D (figure 6(a)). RT decreased with increased current as it did for all channels, approaching that of the mechanical cue (black line). Figure 6(b) shows the RT to sICMS at 200 µA across all electrodes compared to that of the mechanical cue in the corresponding session. Across electrodes, the mean RT to sICMS at 200 µA was about 4 ms slower than that to the mechanical cue for monkey H, and about 29 ms slower for monkey D. The RT to 200 µA stimulation was not significantly different than the RT to the mechanical cue in either monkey (p = 0.38 for monkey H, p = 0.11 for monkey D, Welch’s t-test), though we performed only a small number of experiments to limit any damage done to the tissue surrounding the electrodes.

**Reaction time in response to multi-electrode stimulation**

Because the RT continued to decrease for currents up to 200 µA during sICMS for at least some of the channels, it may be that increasing the stimulation amplitude further would reliably elicit RTs as fast as or faster than...
the mechanical cue. However, since the current was already at the limit of what is considered safe for the electrode-tissue interface (Chen et al. 2014), we did not want to increase it further. Instead, we stimulated on multiple electrodes simultaneously in order to inject a large amount of total current while keeping the current through each electrode small. We randomly selected sets of 16 electrodes in each monkey and measured the RT to this mICMS. We used a train length of 120 ms for both monkeys, matching the duration of the mechanical cue. RTs for representative sets of electrodes at various total currents (160–800 µA) are shown in figures 7(a) and (b). Insets show the locations of the electrodes on the array, oriented as in figure 5. For every set of electrodes in monkey H, RT decreased with increasing total current. For monkey D, the RT decreased up to a total current of 480 µA. Unexpectedly, the RT began to increase for currents above 480 µA for 3 out of 4 electrode sets tested.

The mean RT for each set of electrodes compared to the mean RT to the mechanical cue in the corresponding session is shown in figure 7(c) for each monkey. For each electrode set, the fastest mean RT across the tested total currents is shown. For monkey H, stimulating with 16 electrodes resulted in significantly faster RTs than the mechanical cue ($p = 0.0037$, Welch’s t-test), with a mean difference of 27 ms. There was no significant difference between the RT to 16-electrode stimulation and the mechanical cue in monkey D ($p = 0.965$, Welch’s t-test).

Interestingly, neither monkey responded to stimulation with 80 µA distributed over 16 electrodes, even though 80 µA was typically detected during single-electrode stimulation. This implies that total current does not fully predict the resulting RT. We investigated the effect of total current and number of stimulation electrodes more thoroughly (figure 8). On each trial, we chose a random number of electrodes (4, 6, 8, 12, and 24) and total current (240, 360, and 480 µA). Then, we chose a random set of electrodes and distributed the total current equally across those electrodes. Because our stimulator was limited to 16 simultaneous channels, we stimulated the electrodes in two groups, separated by a 100 µs lag, even when stimulating on fewer than 16 channels. Again, we used a train length of 120 ms to match the duration of the limb perturbation. Resulting RTs to all combinations of electrodes and currents are shown in figure 8 for four sessions for monkey H and two sessions for monkey D. The RTs to the mechanical cue (black solid line) and the visual cue (black dashed line) pooled across sessions are also shown for each monkey. We used an ANOVA, combining data across monkeys, total currents, and number of electrodes, to determine the effect of these parameters on the resulting RT. RT consistently decreased when we stimulated with more current for the same number of electrodes ($F(1,26) = 17.5$, $p = 2.9 \times 10^{-4}$). Interestingly, the RT increased as the number of electrodes increased ($F(1,26) = 19.7$, $p = 1.5 \times 10^{-4}$), an effect that was more pronounced at smaller total currents.

### Comparison of mICMS to sICMS

We wanted to determine whether the apparent advantage of mICMS might be eliminated when compared to the single most sensitive electrode in the group. To test this, we measured the RT to stimulation on groups of 2 or 3 electrodes at 100 µA per electrode. We compared the resulting mICMS RT to the fastest 100 µA sICMS RT within each group (figure 9(a)). sICMS RT was measured in sessions 1–2 weeks prior to the corresponding mICMS RT in monkey H and less than a week prior in monkey D. We used a train length of 120 ms for monkey H and 200 ms for monkey D to match the train lengths used when testing sICMS. Across both monkeys, we found that mICMS resulted in significantly faster RTs than sICMS ($p < 0.001$, paired t-test).

### Effect of inter-electrode distance on mICMS reaction time

Previous experiments showed that the distance between electrodes does not affect how they interact...
J T Sombeck and L E Miller

However, this may not be true when stimulating with the large currents in this study, which will activate a larger population of neurons surrounding each electrode (Stoney et al 1968). To test this, we paired the groups of electrodes from figure 9 (a), such that one group contained only adjacent electrodes, while the other was composed of non-adjacent electrodes. These groups were tested in adjacent blocks to decrease any intra-sessional effect. Electrodes within paired groups were matched to have approximately equal RTs during sICMS, and we measured the RT when stimulating all electrodes within a group at 100 µA per electrode and 120 ms (monkey H) and 200 ms (monkey D).

Figure 9(b) shows the RT to stimulation of adjacent groups of electrodes and the corresponding non-adjacent groups. Across multiple sessions, both monkeys, and 30 pairs of electrode groups, the mean RT to stimulation on adjacent electrodes was 7 ms slower than the mean RT to stimulation on non-adjacent electrodes, a difference which was not significant ($p = 0.071$, paired $t$-test).

Discussion

Summary of results

In a series of experiments in two monkeys, we investigated the RT in response to both sICMS and mICMS applied through multi-electrode arrays implanted in area 2 of somatosensory cortex. We found that the RT to sICMS typically decreased with increased stimulation amplitude, frequency, and train length. Even at large stimulation parameters, the RT for most individual electrodes was slower than to mechanical cues. Increasing the stimulation amplitude to 200 µA resulted in RTs only slightly slower than that to mechanical cues, though currents this large may cause damage to tissue surrounding the electrodes. However, mICMS elicited RTs as fast as or faster than mechanical cues with safe levels of current through each electrode. Together, these results suggest that it may be possible to use mICMS to provide fast, artificial feedback, and thereby restore proprioception.

Reaction time to single-electrode stimulation

For most modalities, RT decreases with increased stimulus intensity, settling at some minimum latency (Pins and Bonnet 1996) (figure 2). We found that increasing the stimulation amplitude, frequency, and train length of ICMS all resulted in faster RTs (figure 3), consistent with their effect on detection thresholds (Butovas and Schwarz 2007, Kim et al 2015a). Nonetheless, the RT to sICMS remained slower than that to limb perturbations (figure 4), implying that the evoked sensation for many electrodes was still weaker than natural stimuli. We wanted to determine a rough estimate of the magnitude of sensation caused by sICMS. To do so, we assumed that the magnitude of sensation caused by sICMS was roughly equal to that of the mechanical cue which resulted in the same RT, after adding 20 ms to account for the conduction delay between the periphery and cortex. The mean RT to sICMS at 100 µA corresponded to a 0.2 N mechanical force for monkey H and 0.7 N for monkey D, moving the hand about 0.1 and 1.5 cm respectively. This rough estimate implies that sICMS does not cause a large sensation. This direct comparison is difficult for a variety of reasons, including the fact that the mechanical cues move the whole arm while sICMS may elicit a sensation only about a small part of the arm (Salas et al 2018).

While sICMS with large currents might provide fast feedback (figure 6), this approach may damage tissue and cause neural loss surrounding the stimulated electrodes (McCreery et al 2010). McCreery et al found that stimulation at even 20 µA applied eight hours a day for 30 d caused loss of neurons around the stimulated electrodes. The amount of damage depended on the

Figure 9. Effect of distance between electrodes on multi-electrode reaction time. (a) The mean reaction time (RT) to simultaneous stimulation on pairs (filled circles) or triplets (large open circles) of electrodes with 100 µA per electrode is compared to the fastest RT during single-electrode stimulation at 100 µA for electrodes within the group of electrodes. (b) The mean RT to simultaneous stimulation on groups of adjacent electrodes compared to non-adjacent electrodes. Groups of electrodes were paired such that the RT to single-electrode stimulation for electrodes within each pair was approximately the same.
current, as 10 µA applied for the same duration did not cause significant neural loss. In contrast, a recent study found that ICMS applied daily for four hours, five days per week, for six months, caused only a small amount of neural loss, even at 100 µA (Rajan et al 2015). Instead, most of the tissue damage was due to implanting, residence, and explanting the array. Results from the 100 µA condition in that study should be interpreted cautiously, as only a few tissue samples were analyzed. Overall, while sICMS with large currents might feasibly provide fast feedback, the safety of this approach is a concern which warrants further study.

Furthermore, large currents may reduce the effectiveness of feedback, well before causing damage. Stimulation applied to area MT, an area involved in processing visual motion, has been used to predictably bias a monkey’s report of the direction of a noisy motion signal (Murasugi et al 1993). With increasing stimulation amplitude, the bias became larger, up to currents of about 80 µA. At that point, the monkeys’ ability to identify the correct direction of motion dropped to chance. Since increasing the stimulation current leads to direct activation of neurons farther away from the stimulated electrode (Stoney et al 1968), this result is most likely explained by the increased activation of neurons with differing receptive field properties.

Effect of electrode location on sICMS reaction time
In both monkeys, the location of the electrode affected the RT (figure 5). One possible explanation for the change in RT across the array might be the depth of the electrode tips, the result of the array not conforming perfectly to the curved cortical surface. In that case, we would expect that any depth-related changes would be primarily in the anterior–posterior direction, with increasing distance from the greater convexity of the IPS. In monkey D, we observed that electrodes nearer the IPS had faster RTs, electrodes which would likely be shallower compared to more distant electrodes. This result stands in contrast with studies where stimulation in deeper cortical layers resulted in lower detection thresholds than in shallower layers (Tehtovnik and Slocum 2009, Koivuniemi and Otto 2011), though one study observed the opposite effect (DeYoe et al 2005). Computational models of cortical stimulation predict that neurons in layer 5 have a lower activation threshold than those in layer 2/3, implying that stimulation in deeper layers would activate more neurons than stimulation in shallower layers (Aberra et al 2018). The depth of the electrode tip would probably not explain the medial-lateral gradient in monkey H. Because our arrays are in the proximal arm area, it may be that more lateral electrodes elicited sensations closer to the hand than did medial electrodes. Perhaps monkey H responded faster to cues near his hand than on his arm. It is likely that a combination of factors, including electrode depth and sensation location, affect RT. More experiments will be required to determine those factors.

Reaction time to multi-electrode stimulation
By stimulating on multiple electrodes simultaneously, we were able to evoke RTs in monkey H about 27 ms faster, on average, than the mechanical cue, roughly the conduction delay between the periphery and cortex (figure 7). In monkey D, there was no difference between the mechanical cue RT and mICMS at 480 µA. Unexpectedly RT increased for total currents beyond 480 µA. We have no clear explanation for this observation, but speculate that it might be due to eliciting something like a startle response, or the result of mICMS actually delaying the monkey’s reach planning, in a manner similar to stimulation in pre-motor cortex (Churchland and Shenoy 2007). This effect may also be due to increased activation of inhibitory circuits at higher currents, as interneurons likely have higher activation thresholds than do pyramidal neurons (Overstreet et al 2013). We used random sets of electrodes during mICMS. It may be that choosing electrodes based on the sensation they elicit would have resulted in faster RTs in monkey D. Regardless, the mean mICMS RT in monkey D was considerably faster than sICMS. Even at 200 µA, sICMS RT was about 30 ms slower than in response to the mechanical cue.

While mICMS can elicit fast RTs with relatively low current through each electrode, there could still be the concern that tissue damage may be caused by the summed current at a return electrode. In our study, the current was returned through a large titanium pedestal placed on the monkey’s skull, and the current density through the pedestal was very low. mICMS has also induced effects such as discomfort (suggested by vocalization of the animal), muscle twitches, and seizures in previous studies (Parker et al 2011, Chen et al 2014). In these studies, transient effects occurred when a large amount of charge was injected simultaneously, or when electrodes were damaged before implantation. We did not induce any such adverse behavioral effects in our experiments during mICMS, possibly because the current we injected was smaller than in the reported cases, where at least 1600 µA total was required to induce such effects. Two individual electrodes did cause monkey D to vocalize. Since these two electrodes were positioned next to each other, it may be that this area of the array was damaged or happened to be in a sensitive region of cortex. The former explanation seems unlikely as one of the electrodes was actively recording from a neuron, the impedances of these electrodes were similar to other electrodes on the array (~50 kOhm), and electrodes surrounding these two did not elicit any similar effects.

Effect of number of stimulation electrodes and total current
We found that mICMS did decrease the RT compared to sICMS (figure 9(a)). This is consistent with previous studies measuring the detection threshold due to stimulation in area 3b/1 (Kim et al 2015a) and area
2 (Zaaimi et al 2013). However, at a constant total current, we found that increasing the number of electrodes resulted in slower RTs (figure 8). This effect may be due to the current on some electrodes falling below an activation threshold required to contribute to the overall sensation. This seems to conflict with our earlier observation that sub-detection threshold currents on multiple electrodes sum supralinearly (Zaaimi et al 2013). Instead, our result may be more similar to what Kim et al found: each electrode had an independent effect on sensitivity, even for sub-threshold currents (Kim et al 2015b). However, it is difficult to compare the current study to that of either Kim et al or the earlier sub-threshold detection study of Zaaimi et al, as our current study did not measure detection thresholds during single-electrode stimulation. It is apparent that the current-per-electrode needs to be carefully considered when designing stimulation patterns, as current that is too high may damage tissue while too low a current may not provide robust sensation.

**Effect of distance between electrodes**

At the largest currents in our study, adjacent electrodes may have activated overlapping populations of neurons. This might be expected to cause weaker sensations than from non-adjacent electrodes. However, previous studies have suggested that this is not the case (Zaaimi et al 2013, Kim et al 2015b). We found that groups of electrodes that were adjacent elicited slightly, though not significantly, slower RTs than non-adjacent groups of electrodes (figure 9(b)), consistent with the earlier studies. With at least 400 µm between electrodes, as with a Utah array, the distance between electrodes does not seem to be an important consideration when designing stimulation patterns.

**Implications for neuroprosthetics**

Current BMIs rely solely on visual feedback to correct movements, which is too slow to update rapid reaches (Ghez et al 1990, Sainburg et al 1995). Restoring fast somatosensory feedback to users should improve prosthetic control (Shanechi et al 2017) and may enable users to develop a stronger sense of embodiment of the prosthesis (Shimada 2009). Even though sICMS and stimulation through mini-electrocorticography arrays can elicit sensations spanning quite a range of different qualities (Flesher et al 2016, Lee et al 2018, Salas et al 2018), these approaches may not be able to provide fast somatosensory feedback (Godlove et al 2014, Caldwell et al 2019). We show that mICMS can be used to trigger movement at very short latencies, making it potentially suitable for providing rapid somatosensory feedback.

In addition to the more robust sensations it appears to provide, mICMS seems well suited to recreating the spatially complex patterns of cortical activity that are characteristic of the somatosensory response to limb movement (Soso and Fetz 1980, Prud’homme and Kalaska 1994, Tomlinson and Miller 2016). One such proprioceptive interface provided target-proximity feedback, using eight electrodes with arbitrarily assigned ‘preferred direction’ (error) vectors (Dadarlat et al 2015). Two monkeys learned to use the system, but required months of training and still made movements that were much slower than typical. A different, more biomimetic approach from our group used stimulation on small sets of electrodes with similar directional tuning properties in an effort to elicit naturalistic sensations of limb movement. This approach caused a predictable bias of a monkey’s perception of a coincident mechanical perturbation without any training (Tomlinson and Miller 2016). However, it failed to do so in three other monkeys. Although there is justifiable concern that synchronous stimulation of many neurons with mICMS may evoke artificial sensations (Tan et al 2014), it is hard to imagine, given existing methods, an alternative means to activate the cortical circuits needed to mimic the spatially complex patterns of neural activity evoked by limb movements. Unlike the paradigms that have been used in an effort to mimic tactile stimulation with single electrodes (Romo et al 2000, O’Doherty et al 2012, Tabot et al 2013), multiple electrodes will likely be required to provide useful proprioceptive feedback.

Most applications of ICMS for touch have used single electrodes to deliver simple, punctate sensations (O’Doherty et al 2011, Tabot et al 2013). However, any realistic object manipulation or haptic exploration will result in many contacts across the hand and fingers, possibly even the forearm. To provide robust cutaneous sensations about the whole hand, stimulation could be applied through multiple sets of electrodes, where each set elicits a localized sensation. This approach was tested recently in a spinal cord injured patient, where force applied to the fingers of a prosthetic hand was mapped to stimulation of sets of electrodes that evoked sensations in the corresponding finger of the patient (Flesher et al 2016). With this interface, the patient could correctly identify which robotic fingers were touched, even when they were touched in pairs, although the latter was less accurate. This approach was extended to provide haptic feedback while a patient controlled movement of the prosthesis (Flesher et al 2019). With haptic feedback provided by mICMS and visual feedback, the patient was able to grasp objects faster than with visual feedback alone. Whether for touch or proprioception, future neuroprosthetic devices will most likely need spatially and temporally patterned mICMS to provide natural, robust somatosensory sensation. Such results will likely be necessary to improve motor control.

**Acknowledgments**

We would like to thank Tucker Tomlinson and the rest of the Miller Limb Lab for useful discussions that
greatly improved this work. This research was funded by National Institute of Neurological Disorders and Stroke Grant No. NS095251 and National Institute of Health Grant No. T32 HD07418.

ORCID iDs

Joseph T Sombeck  https://orcid.org/0000-0001-5108-8901
Lee E Miller  https://orcid.org/0000-0001-8675-7140

References

Aberra A S, Peterchev A V and Grill W M 2018 Biophysically realistic neuron models for simulation of cortical stimulation J. Neural Eng. 15 066023

Ajiboye A B et al 2017 Restoration of reaching and grasping movements through brain–controlled muscle stimulation in a person with tetraplegia: a proof-of-concept demonstration Lancer 389 1821–30

Antolík C, D’Alonzo M, Rosén B, Lundborg G, Sebelius F and Cipriani C 2013 Sensory feedback in upper limb prosthetics Expert Rev. Med. Devices 10 45–54

Bouton C E et al 2016 Restoring cortical control of functional movement in a human with quadriplegia Nature 533 247–50

Butovas S and Schwarz C 2007 Detection psychophysics of intracortical microstimulation in rat primary somatosensory cortex Eur. J. Neurosci. 25 2161–9

Caldwell D J, Cronin J A, Wu J, Weaver K E, Ko A L, Rao R P and Ojemann J G 2019 Direct stimulation of somatosensory cortex results in slower reaction times compared to peripheral touch in humans Sci. Rep. 9 3292

Chen K H, Dammann J F, Boback J L, Tenore F V, Otto K J, Gaunt R A and Bensmaia S J 2014 The effect of chronic intracortical microstimulation on the electrode–tissue interface J. Neural Eng. 11 026004

Churchland M M and Shenoy K V 2007 Delay of movement caused by disruption of cortical preparatory activity J. Neurophysiol. 97 346–59

Collinger J L, Woodringer B, Downey J E, Wang W, Tyler-Kabara E C, Weber D J, McVordy A J C, Velliste M, Boninger M L and Schwartz A B 2013 High-performance neuroprosthetic control by an individual with tetraplegia Lancer 381 557–64

Dadarlat M G, O’Doherty J E and Sables P N 2015 A learning-based approach to artificial sensory feedback leads to optimal integration Nat. Neurosci. 18 138–44

Devecioglu L and Guçlü B 2017 Psychophysical correspondence between vibrotactile intensity and intracortical microstimulation for tactile neuroprostheses in rats J. Neural Eng. 14 016010

DeYoe E A, Lewine J D and Doty R W 2005 Laminar variation in threshold for detection of electrical excitation of striate cortex by macaques J. Neurophysiol. 94 3443–50

Ethier C, Oby E R, Bauman M J and Miller L E 2012 Restoration of grasp following paralysis through brain-controlled stimulation of muscles Nature 483 366–71

Flesher S N, Collinger J L, Folds S T, Weiss J M, Downey J E, Tyler-Kabara E C, Bensmaia S J, Schwartz A B, Boninger M L and Gaunt R A 2016 Intracortical microstimulation of human somatosensory cortex Sci. Transl. Med. 8 361ra141

Flesher S N, Downey J E, Weiss J M, Hughes C L, Herrera A J, Tyler-Kabara E C, Boninger M L, Collinger J L and Gaunt R A 2019 Restored tactile sensation improves neuroprosthetic arm control (https://doi.org/10.1101/653428)

Fridman G Y, Blair H T, Blaisdell A P and Judy J F W 2010 Perceived intensity of somatosensory cortical electrical stimulation Exp. Brain Res. 203 499–513

Ghez C, Gordon J and Ghilardi M F 1995 Impairments of reaching movements in patients without proprioception. II. Effects of visual information on accuracy J. Neurophysiol. 73 361–72

Ghez C, Gordon J, Ghilardi M F, Christakos C N and Cooper S E 1990 Roles of proprioceptive input in the programming of arm trajectories Cold Spring Harbor Symp. Quant. Biol. 55 837–47

Godlove J M, Whaite E O and Batista A P 2014 Comparing temporal aspects of visual, tactile, and microstimulation feedback for motor control J. Neural Eng. 11 046025

Hochberg L R, Bacher D, Jarosiewicz B, Masse N V, Simeral J D, Vogel J, Haddadin S, Liu J, Cash S S and Van Der Smagt P 2012 Reach and grasp by people with tetraplegia using a neurally controlled robotic arm Nature 485 372

Hyvärinen J and Poranen A 1978 Receptive field integration and submodality convergence in the hand area of the post-central gyrus of the alert monkey J. Physiol. 283 539–56

Johansson R S and Flanagan J R 2009 Coding and use of tactile signals from the fingertips in object manipulation tasks Nat. Rev. Neurosci. 10 1345

Kim S, Callier T, Tabot G A, Gaunt R A, Tenore F V and Bensmaia S J 2015a Behavioral assessment of sensitivity to intracortical microstimulation of primate somatosensory cortex Proc. Natl. Acad. Sci. 112 15202–7

Kim S, Callier T, Tabot G A, Tenore F V and Bensmaia S J 2015b Sensitivity to microstimulation of somatosensory cortex distributed over multiple electrodes Front. Syst. Neurosci. 9 47

Koivunen A S and Otto K E 2011 Asymmetric versus symmetric pulses for cortical microstimulation IEEE Trans. Neural Syst. Rehabil. Eng. 19 468–76

Lee B K, Kramer D, Armenta Salas M, Kells L, Brown D, Dobrea T, Klaes C, Heck C, Liu C and Andersen R A 2018 Engineering artificial somatosensation through cortical stimulation in humans Frontiers Syst. Neurosci. 12 24

London B M, Jordan J C R and Miller L E 2008 Electrical stimulation of the proprhoceptive cortex (area 3a) used to instruct a behaving monkey IEEE Trans. Neural Syst. Rehabil. Eng. 16 32–6

McCready D, Pikov V and Troyk P R 2010 Neuronal loss due to prolonged controlled-current stimulation with chronically implanted microelectrodes in the cat cerebral cortex J. Neural Eng. 7 036005

Monzée J, Lamarr Y and Smith A M 2003 The effects of digital anesthesia on force control using a precision grip J. Neurophysiol. 89 672–83

Murasaki C, Salzman C and Newsome W 1993 Microstimulation in visual area MT: effects of varying pulse amplitude and frequency J. Neurosci. 13 1719–29

O’Doherty J E, Lebedev M A, Ifti P J, Zhuang K Z, Shokur S, Bleuler H and Nicolecis M A L 2011 Active tactile exploration using a brain–machine–brain interface Nature 479 228–31

O’Doherty J E, Lebedev M A, Zheng L and Nicolecis M A L 2012 Virtual active touch using randomly patterned intracortical microstimulation IEEE Trans. Neural Syst. Rehabil. Eng. 20 85–93

Overstreet C K, Klein J D and Helm S Tillery S J 2013 Computational modeling of direct neuronal recruitment during intracortical microstimulation in somatosensory cortex J. Neural Eng. 10 066016

Ozurtürk S, Devecioglu I, Bégyi M, Atasoy A, Mutlu S, Ozkan M and Guçlü B 2019 Real-time performance of a tactile neuroprosthesis on awake behaving rats IEEE Trans. Neural Syst. Rehabil. Eng. 27 1053–62

Parker R A, Davis T S, House P A, Normann R A and Greger B 2011 The functional consequences of chronic, physiologically effective intracortical microstimulation Prog. Brain Res. 194 145–65

Pins D and Bonnet C 1996 On the relation between stimulus intensity and processing time: Piéron’s law and choice reaction time Perception Psychophys. 58 390–400
Pons T P, Garraghty P E, Cusick C G and Kaas J H 1985 The somatotopic organization of area 2 in macaque monkeys J. Comparative Neurol. 241 445–66
Prud'homme M J and Kalaska J F 1994 Proprioceptive activity in primate primary somatosensory cortex during active arm reaching movements J. Neurophysiol. 72 2289–301
Rajan A T, Boback J L, Dammann J F, Tenore F V, Wester B A, Otto K J, Gaunt R A and Bensmaia S J 2015 The effects of chronic intracortical microstimulation on neural tissue and fine motor behavior J. Neural Eng. 12 066018
Romo R, Hernández A, Zainos A, Brody C D and Lemus L 2000 Sensing without touching: psychophysical performance based on cortical microstimulation Neuron 26 273–8
Rothwell J, Traub M, Day B, Obeso J, Thomas P and Marsden C 1982 Manual motor performance in a deafferented man Brain 105 515–42
Sainburg R L, Ghilardi M F, Poizner H and Ghez C 1995 Control of limb dynamics in normal subjects and patients without proprioception J. Neurophysiol. 73 820–35
Salas M A et al 2018 Proprioceptive and cutaneous sensations in humans elicited by intracortical microstimulation elife 7 e32904
Shanechi M M, Orsborn A L, Moorman H G, Gowda S, Dangi S and Carmena J M 2017 Rapid control and feedback rates enhance neuroprosthetic control Nat. Commun. 8 13825
Shimada S, Kensuke F and Kazuo H 2009 Rubber hand illusion under delayed visual feedback PloS One 4.7 e6185
Soso M and Fetz E 1980 Responses of identified cells in postcentral cortex of awake monkeys during comparable active and passive joint movements J. Neurophysiol. 43 1090–110
Stoney S D, Thompson W D and Asamuma H 1968 Excitation of pyramidal tract cells by intracortical microstimulation; effective extent of stimulating current J. Neurophysiol. 31 659–69
Tabot G A, Dammann J F, Berg J A, Tenore F V, Boback J L, Vogelstein R J and Bensmaia S J 2013 Restoring the sense of touch with a prosthetic hand through a brain interface Proc. Natl Acad. Sci. USA 110 18279–84
Tan D W, Schieber M A, Keith M W, Anderson J R, Tyler J and Tyler D J 2014 A neural interface provides long-term stable natural touch perception Sci. Transl. Med. 6 257ra138
Tehovnik E J and Slocum W M 2009 Depth-dependent detection of microampere currents delivered to monkey V1 Eur. J. Neurosci. 29 1477–89
Tomlinson T and Miller L E 2016 Toward a proprioceptive neural interface that mimics natural cortical activity Progress in Motor Control vol 957, ed J Luczko and M L Latash (Berlin: Springer) pp 367–88
Weber D J, London B M, Hokanson J A, Ayers C A, Gaunt R A, Torres R R, Zaaimi B, Rose and Miller L E 2011 Limb-state information encoded by peripheral and central somatosensory neurons: implications for an afferent interface IEEE Trans. Neural Syst. Rehabil. Eng. 19 501–13
Zaaimi B, Ruiz-Torres R, Solla S A and Miller L E 2013 Multi-electrode stimulation in somatosensory cortex increases probability of detection J. Neural Eng. 10 056013