Effects of Intracortical Microstimulation on Neural Activity in Distant Cortical Regions

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Summary

Intracortical microstimulation (ICMS) is the injection of weak (microampere) electrical pulses into cortical gray matter. Though commonly assumed to excite only local neurons and axons, the effects of ICMS are predominantly transsynaptic – clearly demonstrated by contractions in distal forelimb muscles caused by ICMS delivered in primary motor cortex. Given that those ICMS effects traveled far distances from the stimulating electrode, we investigated whether ICMS delivered in primary somatosensory cortex (S1) modulated neurons in two distant cortical areas: the primary motor cortex (M1) and the premotor cortex (PM). Information about distant ICMS effects could be used to help improve decoding accuracy of bidirectional brain-computer interfaces considering that they typically deliver ICMS feedback to S1 and decode M1 activity.

We studied distant modulation by recording from M1 and PM as rhesus macaques used S1-ICMS as instructions for arbitrarily assigned movements. Offline we constructed peri-stimulus time histograms (PSTHs) of each neuron's spike activity surrounding the ICMS pulses. These PSTHs demonstrated that S1-ICMS excited and/or inhibited many neurons in M1 and PM, which we call direct modulation. Further analysis showed that S1-ICMS effects converged onto individual M1 and PM neurons from wide territories in S1 and diverged from each S1-array to wide territories in M1 and PM. Our results show that S1-ICMS not only affects distant cortical regions, but can modulate a majority of the neural populations in M1 and PM.

Methods

Array Implantation

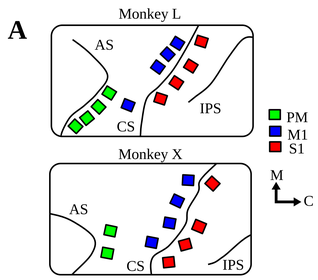


Figure 1. A) Floating microelectrode arrays (FMAs) were implanted in primary somatosensory cortex (S1 – red), premotor cortex (PM – green), and primary motor cortex (M1 – blue) in monkey L and monkey X. AS: Arcuate Sulcus. CS: Central Sulcus. IPS: Intraparietal Sulcus. M: Medial. C: Caudal. **B)** Cortical diagram outlining estimated boundaries of each implanted region for general rhesus macaque brain.

Reach-Grasp-Manipulate Task

We trained two rhesus macaques (L, X) to perform a reach, grasp, and manipulate task (RGM). Monkeys were instructed to turn a sphere, push a button, pull a coaxial cylinder, and pull a perpendicular cylinder. After initially being trained using LEDs to instruct the correct target object on each trial, each monkey learned to use ICMS delivered via 3-4 electrodes on four different arrays in S1 (S1-ICMS) as instructions for the four different objects.

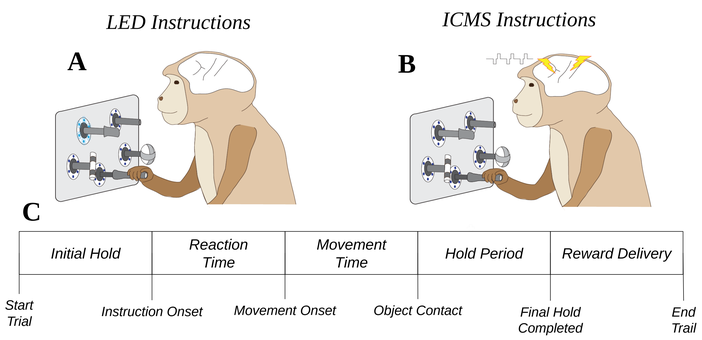


Figure 2. A) RGM task instructed with visual LED cues only. **B)** RGM task instructed with ICMS delivered in S1 only. ICMS training progressed by pairing S1-ICMS trains with the LED visual cues, and then gradually dimming the LED cues until ICMS served as the only instruction. **C)** Breakdown of the trial epochs during the RGM task

Intracortical Microstimulation Parameters

Table 1. Stimulation Parameters after Training

	Monkey L	Monkey X
Number of Electrodes	4 – 6	3 – 5
Waveform Shape	Biphasic, 200µs/phase, cathodal-leading, symmetric	
Pulse Frequencies	100 Hz	75, 100, 150, 225 Hz
Amplitudes	20 – 60 µA	25 – 55 µA

S1-ICMS: Instructions delivered in primary somatosensory cortex

Results

Direct Modulation in Peri-Stimulus Time Histograms

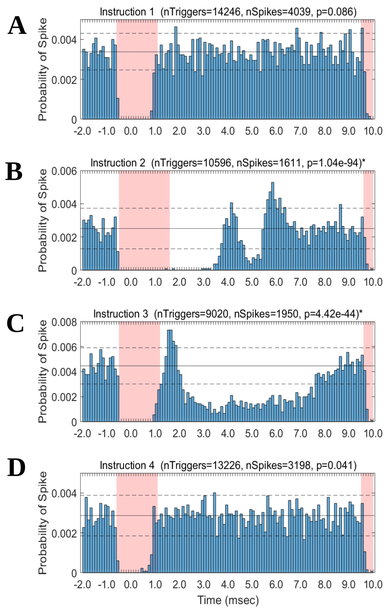
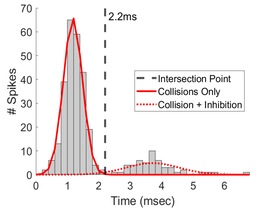


Figure 3. Peri-Stimulus Time Histograms (PSTHs) triggered on ICMS artifacts from each object instruction. All four PSTHs show spikes from the same definite single neuron from M1 triggered on ICMS artifacts from the **A)** button, **B)** sphere, **C)** perpendicular cylinder, or **D)** coaxial cylinder instructions. Bin counts were normalized by the number of triggers, so they represent the probability of a spike occurring in each time bin after a stimulation pulse. The pale red rectangles represent the ICMS artifact window during which spikes could not be sorted reliably offline due to collision with the ICMS artifact. Significantly non-uniform distributions were considered evidence of modulation resulting directly from the S1-ICMS pulses (KS goodness of fit test, p<0.01). In significantly modulated PSTHs, peaks and troughs were identified using a threshold of +/- two standard deviations (dashed black lines) from the mean baseline firing rate (solid black lines) for 3 or more consecutive bins.

Key Takeaways

- The same neuron had different responses to S1-ICMS delivered on different arrays ("neuron-array pairs").
- Excitatory and inhibitory effects could occur for the same neuron-array pair (Fig. 3B,C).
- Low spike counts occurring more than 2.2ms after the triggering ICMS artifact were attributed to inhibition rather than collisions with ICMS artifacts (see Fig. 4).

Figure 4. Earliest Recorded Spikes after ICMS Artifacts. Low spike counts due to collisions with ICMS artifacts could not always be distinguished from low spike counts due to inhibition elicited by the ICMS pulses. We therefore collected the earliest spike recorded after the onset of the artifact window from every PSTH. The distribution (binned in 0.2ms steps) appeared bimodal, so a generalized Gaussian mixture model with two components was fit to the data. We interpreted the earlier peak as spikes that resumed immediately after the artifact (Fig. 3C, above) and the later peak as spikes occurring after an inhibitory period that immediately followed the artifact (e.g. Fig. 3B, above). The intersection of the two components was therefore considered to be the maximum possible artifact duration (2.2ms). Low spike counts beyond 2.2ms were considered evidence of inhibition.



Direct Modulation Summary

Table 2. Prevalence of direct modulation

	PM-Neurons	M1-Neurons
Monkey L		
Number of Units	42	39
Units Modulated by ≥ 1 Array	62%	98%
Units Modulated by all Arrays	10%	49%
Total Neuron-Array Pairs	168	156
Pairs with Direct Modulation	34%	72%
Monkey X		
Number of Units	33	36
Units Modulated by ≥ 1 Array	91%	81%
Units Modulated by all Arrays	3%	33%
Total Neuron-Array Pairs	99	108
Pairs with Direct Modulation	43%	58%

NOTE: PSTHs constructed from pulse trains at 225Hz were excluded from analysis in monkey X. ICMS artifacts up to 2.2ms long combined with short inter-pulse-intervals (4.4ms) resulted in too few spikes being captured for reliable assessment of direct modulation.

Key Takeaways

- Over 62% of PM neurons and 81% of M1 neurons were directly modulated by S1-ICMS from at least one S1-array.
- Up to 49% of M1 neurons and 10% of PM neurons were directly modulated by S1-ICMS from all S1-arrays.

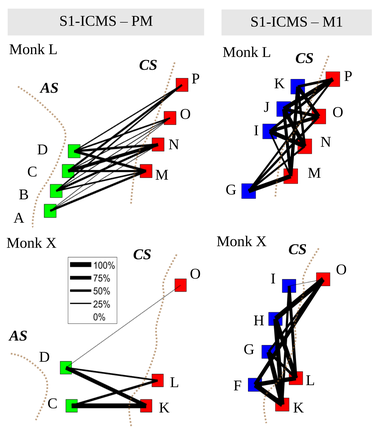


Figure 5: Topography of Direct Modulation Effects. Each square represents an FMA in PM (green), M1 (blue), or S1 (red). Brown dotted lines show sulci in the brain serving as landmarks: Arcuate Sulcus (AS) and Central Sulcus (CS). The solid black lines are proportional to the percent of M1 or PM neurons on each array that were directly modulated by ICMS delivered on the corresponding S1-ICMS array.

Results

Divergence and Convergence of S1-ICMS Effects in PM and M1

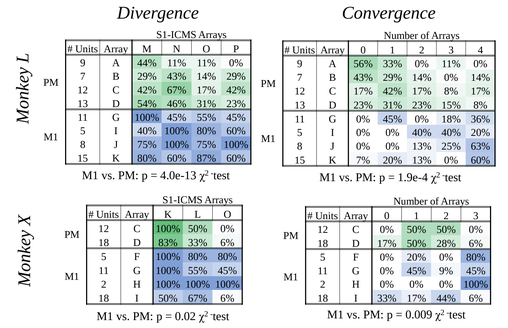


Figure 6. Divergence and Convergence of S1-ICMS onto PM and M1 neurons. Tables show the percentage of neurons modulated by each S1-ICMS array **(divergence, left)** and the number of S1-ICMS arrays modulating each neuron **(convergence, right)**. Darker colors denote higher percentages. The neuron counts underlying the percentages were compared between M1 (blue) and PM (green) using a χ^2-test ($p<0.05$). Both monkeys had significantly higher divergence and convergence between S1 – M1 than S1 – PM.

Key Takeaway

- Divergence and convergence were both significantly greater between M1 – S1 than PM – S1.

Characteristics of Excitatory and Inhibitory Effects

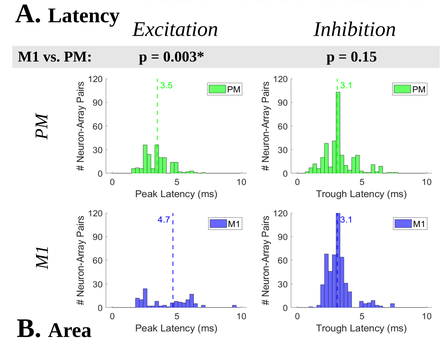


Figure 7: Properties of excitatory and inhibitory effects observed in PM (green) and M1 (blue) neurons. Separate histograms are shown for identified peaks (left column) and troughs (right column) in PSTHs from both monkeys combined. Dotted lines indicate the median of each distribution. Mann-Whitney U-tests were used for comparisons ($p<0.05$)

A) Latencies were calculated as the time from the ICMS artifact onset to the maximum of peaks or minimum of troughs. Excitation reached PM significantly earlier than M1 ($p=0.003$), but there was no significant difference for inhibition ($p=0.92$).

B) Peak/Trough Areas were calculated by integrating the PSTH above/below the baseline mean, respectively. Histogram bin size is $1.5x10^{-4}$ total spike probability change. Both peaks ($p = 0.004$) and troughs ($p=5.8e-6$) were smaller for PM neurons than M1 neurons.

Key Takeaways

- Excitation latencies were significantly shorter in PM than M1. Inhibition latencies were not significantly different, although some PM troughs occurred earlier than any M1 troughs.
- Multiple peaks in the latency histograms suggest multiple waves of excitation/inhibition arriving in PM and M1 after S1-ICMS pulses.
- Peaks/troughs had significantly larger areas in M1 than in PM

Discussion

- Low-amplitude ICMS delivered in S1 (20 – 60µA, 75 – 150Hz) directly modulated the firing activity of many neurons in both distant cortical regions, PM and M1.
- Up to 98% of M1 neurons and 88% of PM neurons were modulated by 1 or more S1-ICMS instructions.
- S1-ICMS delivered on different arrays produced different effects on the same neuron.
- Effects reached PM faster than M1, which may reflect the context of the S1-ICMS – an instruction. Information from the S1-ICMS would thus be relevant for movement planning before execution.
- Shorter latencies and narrower peaks/troughs in PM than M1, as well as known cortical connectivity, suggests many ICMS effects followed the cortical circuit of SI → SII → PM → M1. Evidence also suggests some ICMS effects went more directly SI → M1 or SI → SII → M1, without reaching PM first.

Future Directions

- How does distant modulation change over time as the monkey learns to interpret the ICMS instruction?
- What distant effects are produced by ICMS in other cortical areas – PMd, AIP, dPPC?
- Can distant modulation effects of ICMS delivered by brain-machine interfaces be used to improve learning efficiency ?

Acknowledgments

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