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Injecting information in the cortical reach-to-grasp network is effective in ventral but not dorsal nodes

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SUMMARY

Although control of movement involves many cortical association areas, bidirectional brain-machine interfaces (BMIs) typically decode movement intent from the motor cortex and deliver feedback information to the primary somatosensory cortex (S1). Compared to the S1, the parietal and premotor areas encode more complex information about object properties, hand pre-shaping, and reach trajectories. BMIs therefore might deliver richer information to those cortical association areas than to primary areas. Here, we investigated whether instructions for a center-out task could be delivered via intracortical microstimulation (ICMS) in the anterior intraparietal area (AIP), dorsal posterior parietal cortex (dPPC), or dorsal premotor cortex (PMd) as well as the ventral premotor cortex (PMv) and S1. Two monkeys successfully learned to use AIP, PMv, or S1-ICMS instructions, but neither learned to use dPPC- or PMd-ICMS instructions. The AIP, PMv, and S1 may thus be effective cortical territory for delivering information to the brain, whereas the dPPC or PMd may be comparatively ineffective.

Graphical Abstract

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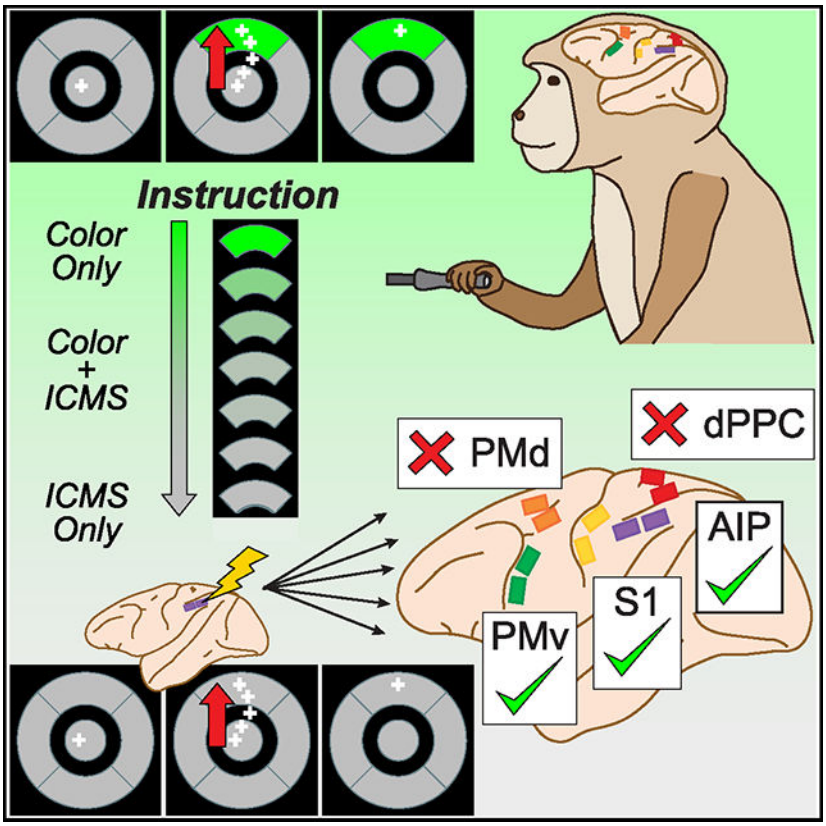
AUTHOR CONTRIBUTIONS

Conceptualization, M.H.S. and B.M.R.; methodology, B.M.R. and M.H.S.; software, B.M.R.; validation, B.M.R.; formal analysis, B.M.R.; investigation, B.M.R.; resources, M.H.S.; data curation, B.M.R. and M.H.S.; writing – original draft, B.M.R.; writing – review and editing, M.H.S. and B.M.R.; visualization, B. M.R.; supervision, M.H.S.; project administration, B.M.R.; funding acquisition, M.H.S. and B.M.R.).

DECLARATION OF INTERESTS

The authors declare no competing interests.



In brief

Ruszala and Schieber show that information can be delivered in the ventral, but not dorsal, association areas of the cortical reach-to-grasp network using low-amplitude intracortical microstimulation. Compared to ICMS in the primary somatosensory cortex, ICMS in ventral association areas may deliver richer information to the brain for future brain-machine interfaces.

INTRODUCTION

Brain-machine interfaces (BMIs) demonstrate great potential for restoring function after nervous system injury or peripheral amputation. An intact cerebral cortex can be interfaced with a robotic arm,[1,2] with the native arm through functional electrical stimulation,[3,4] or with a bridging device that bypasses the injured region within the central nervous system.[5] Most studies to date have decoded motor intent from the motor cortex.

To improve BMI control of neuroprosthetic limbs, some studies have started to investigate the utility of decoding from association cortical regions.[6,7] One study, for example, decoded imagined movements from neurons in the human posterior parietal cortex to drive a prosthetic limb.[8] In parallel, other studies have investigated the possibility of improving control of neuroprosthetic devices by making them bidirectional—concurrently decoding motor intent from neurons in the motor cortex (direction 1) and delivering feedback to the primary somatosensory cortex (S1) (direction 2). Delivering information to the S1 with intracortical microstimulation (ICMS) can improve the speed, accuracy, and precision

of BMIs.[9–13] Beyond the S1 and other primary sensory regions, association areas of the cerebral cortex process complex information that might not only be harnessed to decode motor intent but also to deliver information to the central nervous system. Neurons in the human posterior parietal cortex, for example, encode specific movement trajectories, such as imagined reaches toward the mouth versus the chin or ear[8] or visual and/or motor imagery of complex hand conformations (e.g., rock vs. paper vs. scissors).[14] Whether ICMS might be used to deliver information to association cortical regions remains unknown.

An early study found that intracortical electrical stimulation using currents of up to 700 μA delivered in different macaque frontal and parietal cortical regions could be used to condition food retrieval versus shock avoidance responses,[15] suggesting that information could be delivered in those cortical regions. In that study, however, the monkeys were not required to distinguish different stimuli delivered within the same cortical area. Interestingly, macaques can learn to use information on target direction and distance delivered through arbitrarily assigned electrodes implanted in the S1,[16] providing evidence that S1-ICMS through different microelectrodes produces distinguishable experiences. We recently found that monkeys could distinguish ICMS trains delivered through four different arbitrarily assigned electrodes in the ventral premotor cortex (PMv) as readily as through four different arbitrarily assigned electrodes in the S1.[17] In fact, the monkeys had slightly faster reaction times and higher success percentages with PMv-ICMS than with S1-ICMS. ICMS delivered in the macaque dorsal premotor cortex (PMd) subthreshold for affecting movements was found to increase reaction times,[18] but whether stimulation produced detectable and distinguishable experiences of which the subjects were aware remains unknown. Association cortical areas in which distinguishable experiences can be elicited with low-amplitude ICMS could be effective regions for delivering information to the brain from a BMI.

Here, we investigated whether low-amplitude ICMS in the anterior intraparietal area (AIP), dorsal posterior parietal cortex (dPPC), PMd, PMv, or S1 could be used to deliver information to the brain. We tested each cortical area separately by attempting to train rhesus monkeys to perform a center-out task using instructions delivered as low-amplitude ICMS pulse trains in each area. Each instruction for the four different movements in the task was delivered through a different set of electrodes. Successful training indicated (1) that ICMS elicited experiences (i.e., the monkey detected when to begin reaching toward a target) and (2) that experiences elicited by stimulation at different electrodes were distinguishable (i.e., the monkey chose the correct target).

RESULTS

We conducted series of daily sessions to train each of two rhesus monkeys to reach to 4 different targets in a center-out task (COT) instructed by ICMS trains delivered in each of five different cortical regions: the AIP, dPPC, PMd, PMv, or S1. We reasoned that, if ICMS trains delivered through different electrodes in a given cortical region evoked distinguishable experiences, then monkeys could report those different experiences by learning to associate them with different, arbitrarily assigned targets in the COT task. For the monkey to know when to leave the center and move toward a target, the experience evoked by ICMS could serve as a go cue. For the monkey to know which target to choose, ICMS delivered on

different electrodes would have to produce different experiences that could be distinguished from one another.

As detailed in the STAR Methods, prior to any ICMS training, each monkey was trained to perform the COT using only visual instructions until a daily success rate of >75% correct was achieved. The order in which ICMS training was undertaken in the five cortical areas was chosen randomly for each monkey; for monkey Q, that order was S1, PMv, AIP, dPPC, and PMd, and for monkey F, it was dPPC, S1, AIP, PMv, and PMd. Table S1 gives descriptive information on the sessions devoted to training each monkey to use ICMS instructions in each cortical area.

At the beginning of training with ICMS delivered in each cortical region, the monkey first performed the COT task with only visual instructions for several sessions to establish a baseline. Then, each of the visual cues (up, down, left, or right target) was paired with an ICMS pulse train delivered on a different, arbitrarily assigned set of four electrodes close to one another in the same cortical area (STAR Methods for details on electrode assignments). In the next few sessions, those ICMS pulse trains were delivered simultaneously with the visual cues to allow the monkey to begin forming associations between each target and the arbitrarily assigned ICMS instruction. During these early training sessions, we constructed triggered averages of electromyographic activity recorded from contralateral arm muscles and of extraocular movements to confirm that ICMS pulse trains did not evoke either muscle twitches or eye movements that could have served as instructions. Thereafter, the visual cues were desaturated gradually over multiple sessions until the ICMS trains served as the only instructions. Training with ICMS delivered in a given cortical region was considered successful if the monkey could perform the COT with a high percentage correct using only ICMS instructions.

ICMS evokes distinguishable experiences in ventral but not dorsal nodes

Figure 1 shows the time course of percent correct (top), reaction time (center) and movement time (bottom) in sequential training sessions as the visual cues were dimmed and monkey Q attempted to learn to use ICMS instructions delivered in the AIP (Figure 1A) or dPPC (Figure 1B). In both cases, as the green visual cues were progressively desaturated (beginning at the vertical dashed line marked “Dim”), the percentage correct eventually decreased and reaction time increased, whereas movement time remained relatively constant. These behavioral trends suggest that, as the visual cues became desaturated, the monkey became less certain of which target was being instructed and therefore made more errors and took longer to choose the target toward which to move. These trends were similar whether ICMS was being delivered in the AIP or in dPPC.

Behavior began to diverge as training progressed to the point where the palest visual cues were used (light green dots) and then no visual instructions at all were present (vertical dashed line marked “ICMS,” red dots), forcing the monkey to rely entirely on the ICMS instructions. For training with AIP-ICMS instructions (Figure 1A), in the absence of visual cues, the monkey’s performance stabilized well above chance (~80% correct), and reaction times decreased, indicating that the monkey had learned to associate the different experiences evoked by the ICMS instructions with the arbitrarily assigned targets.

We then began “dropping” electrodes (“Drop” sessions, blue); i.e., turning off the current delivered through individual electrodes until only one of the four electrodes initially used to deliver current for each instruction remained active (“Single” sessions, gray dots). Though percentage correct initially declined slightly and reaction time initially increased slightly, both subsequently recovered to the baseline levels present at the beginning of training when fully saturated visual cues had been available.

For selected sessions, the confusion matrices at the top of Figure 1 show the distribution of correct trials (main diagonal) and error trials (off diagonal) across all possible combinations of the target instructed (columns) and the target the monkey’s cursor entered (rows). For training with AIP-ICMS instructions (Figure 1A), confusion matrices illustrate that (1) when both visual and ICMS instructions were delivered concurrently, the monkey’s cursor entered the instructed target in almost every trial, indicated by dark blue cells along the main diagonal; (2) in the first session using AIP-ICMS and the palest visual cues, the monkey’s cursor still entered the instructed target most of the time, with errors scattered among various combinations of instructed and entered targets, indicated by light blue shades in off-diagonal cells; and (3) after 4 sessions with trials involving only AIP-ICMS instructions, performance remained well above chance.

With continued training and reduction of the AIP-ICMS instructions to single electrodes, performance with AIP-ICMS instructions eventually improved to near the level observed when visual cues had been available (Video S1 shows monkey Q’s performance with single-electrode AIP-ICMS). As a final control, we randomly interleaved some trials involving only fully saturated visual instructions with no simultaneous ICMS and other trials involving only single-electrode AIP-ICMS instructions with no simultaneous visual cue; monkey Q performed equally well with either type of instruction (Video S2). We thus infer that ICMS delivered through different single electrodes in AIP evoked distinguishable experiences that the monkey could learn to use as instructions for COT movements to the four different targets. Interestingly, performance with single-electrode AIP-ICMS instructions gradually improved to levels higher (~90% correct) than what had been achieved with four-electrode AIP-ICMS instructions (~80% correct between ICMS and Drop), raising the possibility that the experiences elicited might have become easier to distinguish when ICMS instructions were delivered on single electrodes.

Training with dPPC-ICMS (Figure 1B) progressed differently. When ICMS instructions were delivered concurrently with the palest visual cues (light green dots), monkey Q’s percentage correct fell lower and reaction times rose higher with dPPC-ICMS than with AIP-ICMS. Subsequently, when sessions included trials involving only dPPC-ICMS instructions with no simultaneous visual cue (red dots), performance fell to near chance levels (~25%) on such trials. Confusion matrix 6 (Figure 1B) then showed nearly random performance for each of the four instructed targets (columns), though the monkey’s cursor entered target 3 (row 3) less often than the other targets. None of the cells along the main diagonal were particularly dark, indicating that monkey Q had not learned any of the four dPPC-ICMS instructions. In a final, remedial attempt to train monkey Q to use dPPC-ICMS instructions, we tried reducing the number of targets being presented to 3 or 2 (Figure 1B,

red arrows, 3T or 2T, respectively), but performance remained near chance (33% or 50% correct, respectively).

To quantify these differences, we pooled (1) the counts of correct versus incorrect trials and (2) the reaction times from successful trials, each across the first four sessions with only AIP- or dPPC-ICMS instructions (red dots). Monkey Q's performance was significantly poorer with dPPC-than with AIP-ICMS (29% versus 78% correct, $p = 8.7e{-}24$, χ^2 test). Monkey Q's reaction times were also significantly longer with dPPC-ICMS than with AIP-ICMS (dPPC: median reaction time, 521 ms, interquartile range (IQR), 374–748 ms; AIP: median reaction time 332 ms, IQR 252–443 ms; $p = 8.7e{-}24$, Mann-Whitney U test). These differences suggest that, even in the first few sessions involving trials with no visual cues, monkey Q was learning to use AIP-ICMS but not dPPC-ICMS.

Though more complex than training monkey Q, training monkey F to use AIP-ICMS instructions was also successful. During the first few sessions after eliminating all visual cues (Figure 2A, red dots), monkey F performed poorly, falling to chance levels (25%). However, confusion matrix 1 (Figure 2A) revealed that monkey F was performing well with instruction 2 and that the overall near-chance performance was a result of confusing the other three instructions in addition to rarely moving the cursor into target 1. Because monkey F appeared to experience instruction 2, we continued training with AIP-ICMS instructions and took remedial steps. After several more sessions with only partial improvement, we temporarily omitted trials involving target 1 (Figure 2A, dotted orange line, No T1). Confusion matrix 2 (Figure 2A) then showed that monkey F continued to perform well with the instruction for target 2 but still confused the instructions for targets 3 and 4. Nevertheless, relatively short reaction times for both instructions 3 and 4 (data not shown) suggested that the AIP-ICMS pulse trains were eliciting experiences. We therefore reintroduced trials involving target 1 and omitted trials involving target 3 (Figure 2A, dotted orange line, No T3). This enabled monkey F to learn to use the ICMS instructions for targets 1 and 4 while continuing to perform well with instruction 2 (Figure 2A, confusion matrix 3). At this point, having seen that monkey Q achieved higher performance with single-electrode AIP-ICMS instructions compared to four-electrode instructions, we chose to drop electrodes from monkey F's AIP-ICMS instructions until they were delivered on single electrodes (Figure 2A, dotted blue line, Drop). Performance remained above chance with single-electrode instructions for targets 1, 2, and 4. We then considered the possibility that the experience elicited by original instruction 3 was not distinguishable from single-electrode instruction 4. Therefore, we introduced a new four-electrode instruction for target 3, which included one electrode that had been used previously for instruction 2 (Figure 2A, dotted orange line, Add T3), and subsequently reduced instruction 3 to a single electrode (Figure 2A, dotted blue line, Drop T3). The electrode originally used for instruction 2 proved to be the best single electrode for instruction 3. Performance with all 4 single-electrode instructions (Figure 2A, dotted gray line, Single All) continued improving until success rates were high for each of the four instructions (Figure 2A, confusion matrix 4). We confirmed that monkey F was relying on the AIP-ICMS instructions by randomly interleaving catch trials (every 10–15 trials) during which no ICMS or visual instructions were delivered. Performance remained high on the ICMS-instructed trials (83%) and dropped to chance (25%) on the no-instruction catch trials (Figure 2A confusion matrix Catch), confirming

that monkey F could successfully utilize all four single-electrode AIP-ICMS instructions. Moreover, during that session, the monkey had significantly prolonged reaction times during the catch trials as compared to the AIP-ICMS-instructed trials (median reaction times 1,240 vs. 385 ms, respectively; $p = 2.5e{-}6$, Mann-Whitney U test), indicating that the monkey was using the experiences evoked by AIP-ICMS not only as instructions regarding the correct target but also as go cues regarding when to begin moving.

Like monkey Q, monkey F was unable to learn to use dPPC-ICMS instructions (Figure 2B). Whereas in the fourth session using only AIP-ICMS instructions (without visual cues) monkey F had shown partial learning of instruction 2 (Figure 2A, confusion matrix 1), in the fifth session with only dPPC-ICMS instructions, monkey F demonstrated no learning and instead showed a strong bias to enter target 4 regardless of the target instructed (Figure 2B, confusion matrix 7), resulting in an overall performance of <25% correct. We quantified this difference in behavior by comparing percentage correct and reaction times (successful trials only) during the first four sessions with only dPPC- or AIP-ICMS instructions. (Note that, because there were no successful trials from the first session including only dPPC-ICMS instructions, there were no reaction time data from that session, so we included data from only dPPC-ICMS trials on the fifth session). In these sessions, monkey F's performance was significantly poorer with dPPC- than with AIP-ICMS instructions (13% versus 35% correct, $p = 1.1e{-}15$, χ^2 test), and his reaction times were significantly longer (dPPC: median 674 ms, IQR 300–1,000 ms; AIP: 321 ms, IQR, 178–594 ms; $p = 0.001$, Mann-Whitney U test). These differences suggest that ICMS delivered through different electrodes in the dPPC did not evoke distinguishable experiences that the monkeys could learn to use as instructions for COT movements.

For both monkeys, training with ICMS instructions in ventral versus dorsal premotor areas (PMv versus PMd) followed trends similar to those observed in ventral versus dorsal parietal areas (AIP versus dPPC), respectively. With fully saturated visual instructions delivered concurrently with either PMv-ICMS (Figures 3A and 3C) or PMd-ICMS instructions (Figures 3B and 3D), performance initially was high, and reaction times were short (Figure 3, black dots, confusion matrices 1, 4, 7, and 10). As the visual cues were desaturated (dark green dots), performance eventually declined, and reaction times lengthened. With the palest visual cues (Figure 3, light green dots), performance generally became poorer and reaction times longer, and confusion matrices (2, 5, 8, and 11) showed more blue cells off the main diagonal than the corresponding confusion matrices with fully saturated visual cues (matrices 1, 4, 7, and 10, respectively).

Behavior with PMv- versus PMd-ICMS instructions diverged substantially when visual cues were removed entirely (Figure 3, red dots, confusion matrix 3 versus 6 and 9 versus 12). With PMv-ICMS, by the fourth session involving trials with only ICMS instructions, percentage correct on those trials had recovered to ~70% with both monkeys (Figures 3A and 3C, confusion matrices 3 and 9) and continued to gradually recover to near-baseline levels with further training. Reaction times also decreased. With PMd-ICMS, however, percentage correct dropped to ~40% with monkey Q and ~25% with monkey F, increasing little, if at all, with further training for either monkey (Figures 3B and 3D, confusion matrices 6 and 12), and reaction times remained elevated for several sessions. For each

monkey, we quantitatively compared the performance (percent correct) and the reaction times in the first four sessions with only PMd-ICMS instructions versus the first four sessions with only PMv-ICMS instructions. For both monkeys, with PMd-ICMS instructions performance was significantly lower (monkey Q, PMd 34% vs. PMv 65%, p = 0; monkey F, PMd 26% vs. PMv 47%, p = 4.4e-18, χ^2-test), and reaction times were significantly longer (monkey Q: PMd 678 [IQR 506–879] ms, PMv 294 [IQR 234–399] ms, p = 4.9e-59; monkey F, PMd 903 [IQR 619–1254] ms, PMv 596 [IQR 392–832] ms, p = 1.4e-11, Mann-Whitney U-tests).

We noticed, however, that monkey Q's percentage correct did not fall entirely to 25% with PMd-ICMS instructions (Figure 3B, red dots). While this might have resulted simply from chance fluctuations in performance, we again attempted remedial training by reducing the number of instructions. For three sessions (labeled "3T"), we chose to omit instruction 1 because the monkey frequently chose target 1 following any of instructions 1, 2, or 3 (Figure 3B, confusion matrix 6). Nevertheless, with PMd-ICMS instructions for only three targets (i.e., only targets 2, 3, and 4), monkey Q's performance showed no further improvement. Overall, both monkeys were successful in learning to associate the PMv-ICMS instructions with each target but not the PMd-ICMS instructions. We thus infer that ICMS delivered through different electrodes in the PMv did evoke distinguishable experiences that the monkeys could learn to use as instructions for COT movements, whereas ICMS delivered in the PMd was much less effective (monkey Q) or ineffective (monkey F).

In a previous study, we found that monkeys could learn to use S1-ICMS as instructions in a reach-grasp-manipulate task.[17] We therefore trained both of the present monkeys to use S1-ICMS instructions in our COT as a positive control. Training with S1-ICMS instructions was slow in both monkeys, perhaps in part because S1 happened to be the first successfully trained area in both monkeys, even though we had randomized the order in which the five cortical areas were trained,. In our previous study, we similarly observed that training with ICMS instructions took longer in the first area trained—whether S1 or PMv—than in the second. Additionally, training with S1-ICMS in both present monkeys likely was slowed further because two of the four S1-ICMS instructions turned out to be indistinguishable.

Figure 4 shows the course of training with S1-ICMS for both monkeys. During the first session that included some trials with both the palest visual cues and S1-ICMS (light green dots) and other trials with only ICMS and no visual cues (red dots, red dotted line, ICMS), both monkeys performed poorly on ICMS-only trials. Nevertheless, in the corresponding confusion matrices 1 and 4 for monkeys Q and F, respectively, based solely on ICMS-only trials, the dark blue square (4,4) suggested that each monkey had begun to learn instruction 4, coincidentally the same target in both monkeys. With monkey Q (Figure 4A), after 8 more sessions, confusion matrix 2 showed improved performance with instructions 3 and 4 but persisting confusion of instructions 1 and 2. We therefore omitted instruction 2 (Figure 4A, orange dotted line, No T2), and performance continued to improve. Eventually we were able to drop electrodes (Drop) from each instruction until instructions 1, 3, and 4 each were delivered with S1-ICMS on a single electrode (Single), and the monkey performed well with each (Figure 4A, confusion matrix 3).

After training had plateaued with instructions 1, 3, and 4, in additional sessions (not illustrated with dots in Figure 4A), we attempted to reintroduce instruction 2 so that all four instructions could be used. We began by giving the monkey only trials involving instruction 2 for one full session. During the next session, we reintroduced trials involving instructions 3 and 4. The confusion matrix from this session (Figure 4A, confusion matrix No T1) shows a dark blue main diagonal, indicating that the monkey performed well with instructions 2, 3, and 4. We then presented all four instructions for two sessions, but the monkey still confused instructions 1 and 2. During the next session, we presented only instructions 1 and 2 (Figure 4A, confusion matrix No T3, T4), confirming that the monkey confused these two instructions. We concluded that monkey Q was unable to distinguish the experiences evoked by S1-ICMS instructions 1 and 2.

Monkey F similarly was unable to distinguish two S1-ICMS instructions. During an early training session, the monkey performed well with instructions 2 and 4 but poorly with instructions 1 and 3 (Figure 4B, confusion matrix 4). We therefore removed instruction 1, and the monkey learned to perform well with instructions 2, 3, and 4 (Figure 4B, confusion matrix 5). We then attempted to reintroduce instruction 1, but monkey F still confused instruction 1 with instructions 2 and 3 (Figure 4B, confusion matrix 6), so we again removed instruction 1 and continued training. Monkey F eventually learned to perform well with instructions 2, 3, and 4 delivered through single electrodes (Figure 4B, confusion matrix 7).

Performance sensitivity to ICMS amplitude, frequency, and pulse train duration

Having found that AIP-, PMv-, and S1-ICMS each produced distinguishable experiences that monkeys could learn to use as instructions to perform different movements, we swept the amplitude, frequency, and duration of pulse trains delivered on single electrodes to investigate how performance varied depending on these stimulation parameters. Psychometric performance curves fit to the data for each ICMS parameter (see STAR Methods, Equation 1, and fitted values in Table S3) were similar across cortical areas and monkeys (Figure 5). While there was relatively little data to fit each psychometric performance function (5–8 levels tested for each swept parameter, 1 session per level) and therefore low power for comparing the curves among cortical regions, the 95% confidence intervals of the estimated maximal performance (plateau), sensitivity to changing parameter (slope), and detection thresholds (horizontal shift) each overlapped for all swept stimulation parameters in each monkey (Table S3). We therefore infer that ICMS could be experienced in the AIP, PMv, and S1 at similar amplitudes, frequencies, and pulse train durations.

Though we identified no significant differences among the performance curves for these three cortical areas in either monkey, we note the following features. Across all parameter sweeps in monkey Q, performance plateaued as high as 90% with AIP-ICMS instructions, 92% with PMv-ICMS instructions, and 89% with S1-ICMS instructions. Monkey F's performance plateaued as high as 84% with AIP-ICMS instructions, 89% with PMv-ICMS instructions, and 82% with S1-ICMS instructions. S1-ICMS was most commonly detected at the lowest amplitudes, frequencies, and pulse train durations with some exceptions (amplitude for monkey Q and pulse train duration for monkey F). Notably, in S1 frequency sweeps, monkey Q's detection threshold was estimated to be single ICMS pulses, and in

pulse train duration sweeps, monkey Q's detection threshold was estimated at only 1–2 pulses (25 ms inter-pulse interval with 45 ms detection threshold). While performance tended to be most sensitive to changes in S1-ICMS parameters, followed by AIP-ICMS and then PMv-ICMS, any differences were small. Distinguishable experiences thus could be elicited from the AIP, PMv, or S1 with similar levels of stimulation. This result bodes well for translation to humans, where levels of S1-ICMS similar to those used here have been shown to be both effective for delivering information to the brain from neuroprosthetic devices[9,19] and safe for chronic use.[20]

Performance using visual versus ICMS instructions

How did performance using only single-electrode ICMS instructions compare with that when using fully saturated visual instructions? For the AIP, PMv, and S1 separately, we compared data pooled across the four best sessions (highest percentage correct) during the baseline period using fully saturated visual instructions versus data pooled across the four best sessions using only single-electrode ICMS instructions and no visual cue (including parameter sweep sessions). The number of successful and unsuccessful trials from the 4 baseline sessions or 4 single-electrode ICMS sessions were counted and compared using Fisher's exact test. Median reaction and movement times were compared with Mann-Whitney U tests. Values are given in Table S2.

Success percentages were significantly higher during baseline sessions with visual cues in all cases, though all differences were <5%. For monkey Q, median reaction times were significantly faster with single-electrode ICMS instructions delivered in each of the three cortical areas. Notably, with single-electrode PMv-ICMS instructions, median reaction times were 116 ms faster than the baseline sessions with visual instructions. Monkey F's reaction times with single-electrode S1-ICMS instructions were also significantly faster than in the baseline sessions with visual instructions, but his reaction times with either single-electrode PMv-ICMS or AIP-ICMS instructions were slower by 101 ms. Movement times were significantly faster during the baseline sessions with visual instructions than with single-electrode ICMS instructions delivered in any cortical area of either monkey. In general then, the two monkeys had slightly higher success rates and slightly shorter movement times with visual instructions but reacted faster with ICMS instructions. Differences between the two monkeys' performance metrics might reflect differences in factors such as attentiveness, motivation, and effort as well as differences in the intensity and distinctness of the experiences elicited by ICMS.

DISCUSSION

In both of the present monkeys, ICMS delivered in the AIP, PMv, or S1 evoked distinguishable experiences, as evidenced by the monkeys' ability to perform the COT (Figure 6) with instructions for different movement directions provided as trains of ICMS delivered through different single electrodes (Figure 7). In contrast, neither monkey learned to use ICMS delivered in the dPPC or PMd as instructions. We have shown previously that ICMS delivered through different electrodes in the macaque S1 or PMv elicits distinguishable experiences.[17] The present work now extends this finding, showing that

ICMS delivered through different electrodes in the macaque AIP also elicits distinguishable experiences, whereas ICMS in the dPPC or PMd does not.

Deciding whether ICMS did or did not elicit distinguishable experiences

We considered three factors in determining whether monkeys could learn to use ICMS in a given cortical area as instructions for different movement directions: (1) performance metrics for each individual target, (2) confusion matrices, and (3) empirical observation of the monkey's behavior.

Factor 1 (Performance metrics): Quantifying performance metrics (percentage correct, reaction time, and movement time) for each target separately allowed us to determine whether any given instruction was learned. Although overall percentage correct could be low and reaction times long if only one instruction was learned, a high percentage correct and short reaction time for that one instruction provided evidence that an experience was elicited consistently and had been associated with movement to a particular target. For example, we observed that monkey F performed well with the multielectrode AIP-ICMS instruction for target 2 only (Figure 2A, confusion matrix 1). We also observed low reaction times for the other three instructions, suggesting that those ICMS instructions were eliciting experiences, but the experiences were difficult to distinguish from one another. Based on that evidence, we provided remedial training, adjusting the other instructions so that the monkey eventually learned to perform well with all four instructions.

In contrast, performance metrics for individual instructions provided little to no evidence that any dPPC- or PMd-ICMS instructions were learned by either monkey. When the palest visual cues were paired with ICMS instructions, percentage correct was lower and reaction times were longer with dPPC- or PMd-ICMS than with AIP- or PMv-ICMS, respectively. When only ICMS instructions were delivered with no visual cues, reaction times remained elevated with dPPC- or PMd-ICMS, whereas reaction times gradually returned to baseline with AIP- or PMv-ICMS.

Factor 2 (Confusion matrices): Although we illustrate only selected confusion matrices, we constructed confusion matrices for each training session to view concisely which targets were chosen after each of the four instructions. For sessions that included both trials with and without visual cues, we constructed separate confusion matrices for trials of each type. Confusion matrices enabled us to differentiate whether poor performance reflected that the monkey was learning only 1 target (Figure 2A, confusion matrix 1), was guessing almost randomly (Figure 1, matrix 6), was habitually entering a particular target regardless of the instruction (Figure 2, matrix 7), or was consistently confusing two targets (Figure 4, matrix No T3, T4). We then could adjust our training protocol to attempt to remediate the problem identified. Such remedial training was successful with AIP-ICMS in monkey F (Figure 2). In contrast, attempts to resolve confusion between two S1-ICMS instructions were unsuccessful in each monkey (Figure 4).

Factor 3 (Empirical behavioral observations): During training sessions, the present monkeys appeared to express frustration by letting go of the joystick used to control the

cursor in the COT and/or slamming it against its physical stops. Such frustration behavior proved to be temporary when the monkey could learn to use ICMS instructions. When the monkey could not learn to use the ICMS instructions, a high level of frustration behavior persisted, and soon the monkey stopped attempting additional trials.

When, despite attempts at remediation, (1) performance metrics remained poor for all targets; (2) confusion matrices showed random guessing, habitual errors, or persistent confusion between targets; and (3) the monkey repeatedly showed a high level of frustration behavior, we decided that we were unable to train the monkey to use ICMS delivered through different sets of electrodes in that cortical area as instructions to move in different directions. As with all negative results, we cannot use such unsuccessful training to conclude that ICMS in the dPPC or PMd could not elicit distinguishable experiences under any circumstances. Nevertheless, we can conclude that, in the present study, ICMS in the dPPC or PMd was less effective in eliciting distinguishable experiences than ICMS delivered in the AIP, PMv, or S1.

Did short reaction times indicate that ICMS elicited experiences?

We used reaction time as a secondary indicator that trains of ICMS were evoking some experience that cued the monkey when to start movement. Indeed, in training the present monkeys, as in our previous report,[17] reaction times typically became longer as the visual cue was progressively desaturated and percentage correct declined, suggesting that the monkey was increasingly uncertain about which direction to move. Subsequently, when visual cues had been eliminated and percentage correct increased, reaction times returned toward baseline, suggesting that the monkey had learned to use the ICMS instructions. In conjunction with a high percentage correct, short reaction times indicated that the monkey confidently and quickly chose in which direction to move based on the learned ICMS instructions.

This was perhaps most evident when, after successfully training a monkey to use ICMS instructions in a given cortical region, we randomly interleaved catch trials during which no ICMS or visual instructions were delivered at all. During such no-instruction catch trials, still trying to earn rewards, the monkeys made COT movements without having had any visual instruction or any experience elicited by ICMS. On such catch trials, the monkeys performed at chance levels, which we illustrated only after training monkey F to use AIP-ICMS instructions (Figure 2, confusion matrix Catch). In that case, as in every case, median reaction times on no-instruction catch trials were longer than on ICMS-instructed trials (monkey F: AIP, 1,240 vs. 385 ms, $p = 2.5e{-}6$; PMv, 589 vs. 257 ms, $p = 2.4e{-}15$; S1 435 vs. 196 ms, $p = 2.8e{-}7$. Monkey Q: AIP, 478 vs. 314, $p = 2.5e{-}7$; PMv, 386 vs. 219, $p = 1.4e{-}7$; S1, 355 vs. 237 ms, $p = 1.8e{-}10$. Mann-Whitney U tests). We interpret these longer reaction times on no-instruction catch trials to indicate that the monkeys used the experiences evoked by ICMS instruction as go cues telling them when to begin moving, and after an ICMS instruction failed to arrive in an expected time frame, they attempted to earn a reward by moving to a random or habitually chosen target.

A different strategy, however, may have produced short reaction times even when ICMS training had been unsuccessful. Although the duration of the task's initial hold epoch was

varied randomly (Q, 750–1000 ms; F, 500–750 ms), the monkey still could have predicted when the longest time required to keep the cursor in the center target would have expired and then made a movement promptly to a target in an attempt to earn a reward. This strategy would have enabled the monkey to achieve rewards in the absence of any experience elicited by ICMS and would have resulted in short median reaction times, albeit with chance performance. Such a strategy would account for the combination of percentage correct at chance levels and short reaction times, as seen during sessions in which we reduced the number of ICMS-instructed targets in final, remedial attempts to train a monkey to use ICMS in the dPPC (Figures 1B, 2T and 3T, and 2B, 1T and 2T) or PMd (Figure 3B, 3T). Although we cannot be certain that no experience was elicited by dPPC- or PMd-ICMS, short reaction times under these circumstances do not necessarily indicate that dPPC- or PMd-ICMS did elicit an experience.

Experiences potentially evoked by cortical stimulation

Though our study was not designed to evaluate the nature of the experiences evoked by ICMS in the cortical areas we studied, considering what sort of experiences might have been evoked in the present monkeys may facilitate translating our findings to future human studies. ICMS delivered in the S1 is known to produce distinguishable somatosensory percepts. Monkeys can compare the frequency of S1-ICMS pulses accurately with the frequency of tactile mechanical vibration.[21] ICMS delivered in the human S1 elicits localized tactile percepts, described most often as pressure sensations organized somatotopically according to the location of the stimulating electrode,[19,22,23] as well as proprioceptive sensations described as rightward, forward, or upward movements.[24]

Less is known concerning experiences evoked by ICMS in the posterior parietal or premotor cortex. In humans, Penfield and Rasmussen described that electrical stimulation of the cortical surface in “elaboration” areas posterior to the postcentral gyrus or anterior to the precentral gyrus evoked no experience unless the patient was performing a behavior that engaged that particular area, in which case electrical stimulation arrested that behavior.[25] Stimulation of Broca’s area, for example, produced aphasic speech arrest if the patient was speaking, but the patient was otherwise “oblivious” to stimulation in these regions of the cortex. Linguistic errors produced by electrical stimulation continue to be used to investigate the roles of human cortical areas involved in language processing,[26–30] but if the patient is not engaged actively in appropriate language tasks, then neither the patient nor a blinded examiner would necessarily be aware that stimulation had been delivered.

In the present monkeys, neurons in the dPPC and PMd were presumably engaged in the present COT task,[31–36] yet 35 μA ICMS delivered along with visual cues did not disrupt performance, nor, in the absence of visual cues, did either monkey appear to have distinguishable experiences evoked by dPPC- or PMd-ICMS. Conceivably, our ICMS by chance might have activated dPPC or PMd neurons in patterns of covariance irrelevant to task performance and unrelated to distinguishable experiences, akin to the “output-null” neural population subspace of PMd and M1 neurons found during movement preparation, orthogonal to the “output-potent” subspace found during movement itself.[37] More sophisticated, biomimetic stimulation patterns might then be necessary to inject

information in output-potent subspaces and thereby elicit distinguishable experiences. Yet why the present ICMS trains should evoke output-null patterns of activation in the dPPC or PMd but output-potent patterns in the AIP or PMv in each of two monkeys remains unclear.

In comparison to our findings in monkeys, Penfield and Boldrey (their Figure 20) reported that, in humans, several sites stimulated posterior to the S1 or anterior to the M1 evoked either a sensation of movement or a desire to move.[38] A more recent study, however, found that surface electrical stimulation of the human PMd (superior Brodmann's area 6) evoked no experience.[39] Even when stimulation amplitude was increased to the point of evoking observable movement, patients denied that part of their body had moved. In contrast, distinguishable experiences were evoked by stimulation in the inferior posterior parietal cortex (Brodmann's areas 39 and 40). Though no movements were evoked, nor was muscle activation detected by EMG, patients described an intention or desire to move the arm and hand, lick the lips, or move the mouth to speak. We speculate that the present monkeys may have had similar experiences evoked by ICMS in the ventral regions but no experiences evoked by ICMS in the dorsal regions.

Ventral and dorsal streams in the reach-to-grasp network

These differences in the cortical areas where ICMS does or does not evoke distinguishable experiences also correspond to the difference between a more ventral stream of predominant information flow between the AIP and PMv versus a more dorsal stream between the dPPC and PMd.[40] The ventral AIP-PMv stream is thought to process information primarily on visually assessed object shape and the hand configuration required to grasp objects, while the dPPC-PMd stream is involved in integrating conditional instructions with target, eye, and hand position in space to reach to the selected target.[41,42]

In the ventral stream, AIP neurons discharge differentially depending on the shape, size, and orientation of the object to be grasped, whether the activity of the neuron is visual dominant, visuomotor, or motor dominant.[43] PMv neurons have large visual and somatosensory receptive fields and discharge most intensely when particular grasps or reaches are performed.[44–48] We therefore speculate that ICMS in either the AIP or PMv might evoke a visual or somatosensory percept of a particular object and/or a desire or intent to grasp a particular object.

In the dorsal stream, dPPC neurons encode target location with respect to the hand and eye, which then can be transformed into a movement vector.[49] PMd neurons also encode target locations with respect to hand and eye position[50,51] as well as the amplitude, direction, and speed of impending arm movements.[52] Our monkeys were actively engaged in a task that required reaching with a hand-held joystick to move a cursor to a target, yet we observed no disrupted reaches, movement arrest, or hijacking[53] during dPPC- or PMd-ICMS, as evidenced by the ability of both monkeys to perform well when visual cues were delivered concurrently with dPPC- or PMd-ICMS.

Though not producing any arrest of ongoing behavior, we cannot rule out the possibility that dPPC- or PMd-ICMS in our monkeys did elicit experiences, but the monkeys were unable to learn to use these experiences as instructions in the COT. PMd neurons play a role

in learning to associate arbitrary instructions with particular movements.[54,55] PMd-ICMS might have produced distinguishable experiences while at the same time disrupting the monkeys' ability to form associations between those experiences and particular targets. Furthermore, considering that the dPPC and PMd are heavily interconnected,[40] dPPC-ICMS might have produced enough modulation in the activity of PMd neurons to disrupt the formation of new conditional associations.

ICMS for BMIs

S1-ICMS is currently being developed to provide somatosensory feedback for BMIs.[9,56,57] The present results show that ICMS delivered in the same range of amplitude, frequency, and pulse train duration in the AIP or PMv also evokes distinguishable experiences. Remarkably, AIP-, PMv-, and S1-ICMS all could be detected at similar thresholds with similar sensitivities to changing amplitude, frequency, and pulse train duration. Furthermore, the psychometric functions obtained here based on performance of a COT were quite similar to those obtained previously using PMv-ICMS or S1-ICMS to instruct a reach-grasp-manipulation task.[17] S1-ICMS at amplitudes up to 80 μA has been shown to be safe and stable in monkeys for up to 160 weeks.[58] Given that AIP- and PMv-ICMS evoke experiences at amplitudes ≤50 μA, ICMS delivered in these two cortical areas can be expected to be similarly safe and stable if used in a human BMI. Design considerations would include timing the delivery of ICMS, using different combinations of electrodes, testing various pulse train parameters, and assessing any other variables that drive the activity of neural elements near the stimulating electrodes.

We speculate that AIP-ICMS might evoke experiences substantially more specific than the desire or intention to make movements evoked by stimulation of the cortical surface in human areas 39 and 40.[39] Neurons recorded in human posterior parietal association cortical regions (homologous to the macaque AIP and dPPC) encode the goal and trajectory of imagined movements.[8] One neuron, for example, encoded imagined movements of the hand to the mouth but not similar movements of the hand to the nearby cheek or forehead. Other neurons in these regions encode previously seen stimuli, decision confidence, and even speech.[59] One could envision, then, that AIP-ICMS (and perhaps PMv-ICMS as well) eventually might be used to deliver similarly rich, complex information to the brain as part of a bidirectional BMI. Such information might provide either feedback on the grasp configuration of a prosthetic hand or instructions to move the hand to a specific location, such as the mouth or cheek.

Limitations of the study

After successful training with 4-electrode AIP-, PMv-, or S1-ICMS instructions, we dropped electrodes until each instruction was delivered through a single electrode without hindering performance, raising the possibility that training might have been successful had we stimulated through single electrodes from the outset. In some instances, especially during S1-ICMS training, the present monkeys were unable to learn the ICMS instruction for a particular target while successfully learning to use other ICMS instructions. That behavior suggests either that certain electrodes produced experiences that were indistinguishable or that some electrodes did not produce any experience. In such instances, training with ICMS

instructions delivered through single electrodes from the outset might have been successful. However, trying different electrodes for each instruction until an effective electrode was found would have required lengthy searches not feasible in the present study designed to test training with ICMS in five different cortical regions in two monkeys. Further, multielectrode ICMS in the human S1 has been found to evoke sensations that are more readily perceived and localized than single-electrode stimulation.[19] Choosing to begin delivering each ICMS instruction through a group of 4 electrodes simultaneously was not only more efficient but increased the likelihood that the stimulation would elicit an experience. Future studies could focus specifically on training PMd- or dPPC-ICMS using only single-electrode ICMS.

As is the case with all negative results, the inability of monkeys to learn to use ICMS instructions delivered in the dPPC or PMd in the present study does not provide sufficient evidence to conclude that ICMS cannot be experienced in these cortical regions. Distinguishable experiences might have been elicited in these cortical regions with higher stimulation amplitudes, higher frequencies, or biomimetic pulse trains that emulated neural spike trains. Alternatively, by chance, we may have missed electrodes that would have been successful for training with dPPC- and PMd-ICMS. However, since neither monkey learned to use either dPPC- or PMd-ICMS while both learned to use AIP-, PMv-, and S1-ICMS, that latter possibility seems unlikely. Exhaustive exploration of the vast space of possible electrodes and stimulation parameters that might have been used in training the monkeys was not feasible in the present study. Future studies may attempt training with various stimulation parameters and/or biomimetic stimulation patterns to determine whether PMd- or dPPC-ICMS can elicit distinguishable experiences.

RESOURCE AVAILABILITY

Lead contact

Requests for further information, resources, and reagents should be directed to and will be fulfilled by the lead contact, Marc H. Schieber (mschiebe@ur.rochester.edu).

Materials availability

This study did not generate new unique reagents or other materials.

Data and code availability

- Original data used in this study are available upon request from the lead contact, Marc H. Schieber (mschiebe@ur.rochester.edu).
- Code used in this study is available at Github: https://doi.org/10.5281/zenodo.15043160.

STAR★METHODS

Detailed methods are provided in the online version of this paper and include the following:

EXPERIMENTAL MODEL AND STUDY PARTICIPANT DETAILS

Non-human primates: Two male rhesus macaque monkeys, Q and F, weighing 9 and 14 kg, and 7 and 10 years old, respectively, were trained in the present study. As only two males were studied, the influence of sex on the present findings cannot be evaluated. All procedures for the care and use of these nonhuman primates followed the Guide for the Care and Use of Laboratory Animals and were approved by the University Committee on Animal Resources at the University of Rochester, Rochester, New York, USA.

METHOD DETAILS

Initial training with visual instructions: Each monkey was trained for a single session each day. Initially, each monkey was trained to perform a center-out task using a hand-held joystick to move a cursor from a center target into one of 4 peripheral targets instructed with visual cues (Figure 6A). The monkey began each trial by moving the cursor to the center target and keeping it there through an initial hold epoch of variable duration (Q, 750–1000 ms; F, 500–750 ms). A peripheral target then turned green, and the monkey moved the cursor into that instructed target (instruction 1 = right, 2 = up, 3 = left, 4 = down), holding it there through a final hold epoch of variable duration (Q, 750–1000 ms; F, 500–750 ms). Targets were presented pseudo-randomly such that each four-trial "block" included one trial of each target, but the order of targets within each block was re-randomized at the beginning of that block. On successful trials, the monkey was rewarded with water and then an inter-trial interval of at least 1000 ms occurred before the next trial could begin. Potential errors included leaving the center or peripheral targets prematurely, entering a target other than the instructed target, taking too long to leave the center (>2000 ms), or taking too long to enter a peripheral target after leaving the center (>2000 ms). When any of these errors occurred, the current trial was aborted immediately, the display background turned red, and no reward was given. To prevent the monkey from rejecting trials involving particular targets, the same instructed target was repeated on subsequent trials until the monkey succeeded. Training with visual instructions alone continued until the monkey achieved a daily success rate of >75% correctly performed trials.

Microelectrode array implantation: Each monkey was implanted with floating microelectrode arrays (FMAs; Microprobes for Life Sciences, Gaithersburg, MD) in the ventral premotor cortex (PMv), dorsal premotor cortex (PMd), primary motor cortex (M1), primar y somatosensory cortex (S1), anterior intraparietal area (AIP), and dorsal posterior parietal cortex (dPPC) of the left hemisphere. Two 32-channel arrays were implanted in each cortical region in both monkeys Q and F, with an additional 16-channel array being implanted in M1 of monkey Q. Each FMA consisted of multiple Pt/Ir (70%/30%) microelectrodes with impedance of ~0.5 MΩ at the time of implantation, all mounted on a ~2×4 mm ceramic chip for 32-channel arrays or a ~2×2 mm chip for the 16-channel array. Electrode shaft lengths varied from 1 to 7 mm. Figure 7A illustrates the location of the arrays implanted in each monkey. Based on the lengths of our electrode shanks and their distances from major sulci, our AIP electrode tips, like those in other studies,[60] probably lay not only in AIP in the strict sense,[42,61,62] but also more superficially in adjacent area PF and/or PFG. Similarly, our dPPC electrode tips probably lay not only in area MIP, but also more superficially in areas PE and/or PEc.

ICMS training: ICMS training began several months after array implantation (see Table S1) and after the monkey had been well-trained on the center-out task using visual instructions. ICMS pulse trains for each instruction consisted of symmetric, biphasic, randomly jittered (12.5–30 ms inter-pulse intervals, or 33–80 Hz) pulses with an amplitude of 35 μA delivered simultaneously through 4 electrodes on the same array (Figure 7B). These initial parameters were chosen based on our prior study in which two monkeys had been trained successfully with PMv-ICMS.[17] That study also demonstrated that, whereas the monkeys were trained initially with rhythmic pulse trains at 50 to 225 Hz, they continued to perform well when switched to jittered pulse trains, eliminating the possibility of rhythmic entrainment of neural activity. Pulse trains were delivered with an IZ2 stimulator controlled through an RZ5 BioAmp Processor by an OpenEx Software Suite (Tucker Davis Technologies, Gainesville, FL, USA) running on a host PC.

In single daily sessions, each monkey was trained to use ICMS pulse trains as instructions for performing the center-out task. The series of daily training sessions generally proceeded as follows: i) To establish a performance baseline, the monkey completed 3 or more sessions using only visual cues as instructions, with no ICMS. ii) During the next 3 sessions, ICMS instructions were delivered concurrently with the visual-cue instructions to allow the monkey to begin associating experiences elicited by the ICMS instructions with their assigned targets. Each ICMS instruction was delivered simultaneously on a group of 4 microelectrodes located near one another on the same array implanted in the cortical region being investigated and assigned arbitrarily to instruct movement to 1 of the 4 targets. Electrodes were assigned to each group such that the 4 electrodes within a group were as close as possible to one another and the different groups were as spatially separated as possible (Figure 7B). The 16 electrodes used for ICMS in each cortical area were selected based on recorded spike activity confirming their intracortical location, and impedances low enough to deliver the desired currents (~35 μA) with the compliance voltage available from the stimulator. (In some cortical regions, although 64 electrodes had been implanted, these requirements constrained our ability to try a variety of four-electrode sets for a given instruction if the set initially chosen proved ineffective.) iii) In subsequent sessions, as ICMS instructions continued to be delivered concurrently with visual cues, the green color of the visual cues was desaturated gradually until the targets eventually remained the same gray as the background throughout the trials (Figure 6B). The last transition from the palest green visual cue to no visual cue was usually difficult for the monkey, initially causing the monkey to stop attempting further trials. Routinely, we therefore randomly interleaved trials with the palest green cue and trials with no visual cue to encourage the monkey to continue attempting more trials. Only a few such sessions were needed for cortical areas in which the ICMS instructions were learned quickly, but more were undertaken when the monkey had difficulty learning. Thereafter we progressively decreased the proportion of trials with the palest visual cue until there were no trials with any visual cue, leaving the ICMS pulse trains as the only instructions available throughout the daily session (Figure 6C). iv) The monkey remained at this stage of training with only ICMS instructions until success rates improved and stabilized, which typically required from 5 to 15 sessions. As detailed in the Results, if performance with ICMS instructions alone (no visual cues) did not improve over 3 successive days, the number of targets was reduced. If performance still remained

at chance levels for >2 additional days, it was concluded that ICMS delivered through different electrode groups at 35 μA was ineffective for evoking distinguishable experiences. v) If ICMS instructions were learned successfully, catch trials with neither ICMS nor visual cues were interleaved randomly every 5–15 trials to ensure the monkey was relying on the ICMS for instructions. Chance performance on catch trials with no ICMS instructions, along with above chance performance on trials with ICMS instructions, indicated the monkey was utilizing the ICMS instructions.

For each daily session throughout training, we formed a 4×4 confusion matrix in which the 16 cells represented the percentage of trials the monkey's cursor entered each of the 4 peripheral targets following each of the 4 instructions. For sessions in which trials instructed with concurrent visual cues and ICMS trains were interleaved with other trials instructed with only ICMS, the confusion matrices illustrated are based solely on ICMS-only trials. We additionally monitored 1) the monkey's success rate as the percentage of correctly performed trials in a session, 2) the median reaction time from instruction onset until the cursor began moving out of the center target, and 3) the movement time from the onset of cursor (joystick) movement until it entered a peripheral target. Each of these three measures could be evaluated collectively for all targets together, or separately for individual targets. In addition, we observed the monkey's general behavior in each session for signs of frustration such as letting go of the joystick used to control the cursor and/or slamming the joystick against its physical stops.

Dropping electrodes: For cortical areas in which a monkey learned to use ICMS instructions delivered simultaneously through 4 electrodes per target, we subsequently dropped electrodes from each instruction to determine whether ICMS needed to be delivered through multiple electrodes for the monkey to perform well. The order in which to drop electrodes was chosen randomly. Current was switched off to one electrode at a time, and performance was monitored for ~60 trials (15 repetitions of each target). If performance on trials involving the relevant target declined and did not recover promptly, current to that electrode was switched back on and current to another electrode was switched off. If performance did not decline or recovered promptly, that electrode remained off. We attempted to repeat this electrode dropping process until the four different instructions for the four targets each could be delivered with ICMS through only a single electrode.

Parameter sweeps: Parameter sweeps were undertaken once performance had reached a steady state with 1 electrode per instruction. Amplitude, frequency, and pulse-train duration each were varied between values that reduced performance to chance and values that demonstrated an asymptotic plateau. Parameter sweeps were completed with AIP-, PMv-, and S1-ICMS. Parameter sweeps could not be performed with dPPC- or PMd-ICMS in either monkey because the dependent measure of performance was the percentage of trials completed correctly, and percent correct never improved above chance with ICMS instructions delivered in dPPC or PMd.

ICMS parameters have been found to be interdependent (e.g., sensitivity to frequency is different at different amplitudes) in some cortical areas.[22] To minimize any interdependence, the present parameter sweeps were undertaken in the following sequence: Amplitude was

swept first, using the same inter-pulse intervals and pulse-train durations used during training. The frequency remained jittered (33–80 Hz) so that many frequencies were randomly included, and the pulse-trains were delivered for maximum duration (from instruction onset until a target was entered). Frequency (rhythmic, not jittered) was swept second, using an amplitude in the plateau region of the psychometric performance function for amplitude, but close to the roll-off. Pulse-train duration was swept third, using that same amplitude and a frequency likewise in the plateau region of the frequency psychometric performance function, but close to its roll-off.

For each parameter, the highest value was delivered first (largest amplitude, highest frequency, or longest pulse-train), and the value then was reduced progressively to the lowest level (smallest amplitude, lowest frequency, shortest pulse-train) in subsequent sessions. At each value tested, a minimum of 100 successful trials were collected for each target (400 total). Because the same target was instructed again following an error, only trials following a successful trial were analyzed to ensure the monkey had no prior information about the upcoming target.

QUANTIFICATION AND STATISTICAL ANALYSIS

All analyses were performed off-line using MATLAB (MathWorks, Natick, MA). Statistical details are provided in the Results.

Fitting psychometric performance functions: Data from each parameter sweep was fit to the following sigmoidal psychometric performance function[63]:

$$Y = 100 * (A - D) * \left(\frac{1}{(1 + e^{-B(x - C)})}\right) + D$$

(Equation 1)

where Y is performance expressed as the proportion of correctly performed trials (from 0 to 1) and multiplied by 100 to convert it to a percentage, x is the value of the swept stimulation parameter (amplitude, frequency, or pulse-train duration), A is the asymptote of the plateau indicating “maximal performance,” B is the “sensitivity” to changing values of x (steepness of the rise), C is the “detection threshold” value of x at which Y is midway between A and D, and D is chance performance (set to 0.25 for 4 targets, 0.33 for 3 targets).

Control studies: ICMS is known to be capable of evoking muscle twitches, overt limb movements, and extraocular movements.[47,48,64–72] Somatosensory or visual feedback from such evoked movements might provide experiences that could serve as instructions the monkeys could learn to associate with particular targets. To ensure that ICMS instructions were below threshold for eliciting muscle activity or eye movements, we performed the following studies prior to desaturating the visual cues for the ICMS training in each cortical area.

Stimulus-triggered averages of electromyographic activity: On the first day of ICMS training in each cortical area, in addition to the four standard trial types involving visual

instructions delivered concurrently with ICMS instructions at 35 μA, we included a fifth trial type in which ICMS was delivered in M1 instead of the area being trained. M1-ICMS was delivered at 35 μA simultaneously through 1–4 electrodes, all on a single M1 array, concurrently with the visual instruction for one of the four targets chosen at random. In these sessions, we routinely visually inspected and physically palpated muscles throughout contralateral arm (as well as the rest of the body) to detect any muscle contraction that the monkey might use as an instructional cue.

To provide more sensitive detection of evoked muscle twitches, surface electromyographic (EMG) activity was recorded from the triceps, biceps, forearm flexors, and forearm extensors of the right arm, contralateral to the left hemisphere in which ICMS was delivered. Bipolar signals were recorded from pairs of cup electrodes filled with electrolyte gel and spaced ~2 cm apart on the skin, passed through a hardware preamplifier (GRASS high-impedance headstages and P511 amplifiers, 5–200x gain, 300–3000 Hz band-pass; Astro-Med Inc.), and sampled at 30 kHz by the Grapevine Analog Module of a Trek data acquisition system (Ripple, Salt Lake City, UT, USA). The time of each ICMS pulse was recorded as a TTL pulse in the digital event stream by the Grapevine Digital I/O Module of the Trek data acquisition system or, if TTL pulses were not available, was extracted from the timestamp of ICMS pulse artifacts recorded in analog channels and discriminated offline using Off-Line Sorter (Plexon, Dallas, TX, USA).

Offline, snippets of EMG activity were taken from −20 ms to +40 ms before and after the time of each ICMS pulse, full-wave rectified, averaged, and smoothed using a flat 10-point finite impulse response filter. Linear regression then was performed to estimate any ramp in the average across the entire 60 ms timeframe. The estimated ramp was subtracted from the average, which then was z-scored through division by the standard deviation of the signal during the baseline period from −20 to 0 ms. Stimulation artifacts were sometimes present in the EMG signals and could begin before off-line discriminated ICMS pulse triggers. We therefore blanked the average from −2 to +4 ms relative to the trigger at time 0 ms, resulting in the final stimulus-triggered average (StimTA) of EMG. Previous studies have shown that the latency of significant facilitatory effects in such StimTAs of upper extremity muscles is consistently ≥5 ms.[73–75] We therefore considered any StimTA in which the signal surpassed ±3 standard deviations of its baseline for at least 1 ms beginning more than 4 ms after the trigger time to show a significant post-stimulus effect (PStE).

Figure S1 shows the StimTAs constructed from each of the four EMGs triggered on the pulses of each of the four AIP-ICMS instructions (blue, red, yellow, and purple traces) delivered in monkey Q and in monkey F. For monkey Q (Figure S1A), none of the StimTAs triggered on pulses from any of the four ICMS trains used to instruct the four different targets showed a significant PStE in any of the four EMGs. StimTAs triggered on ICMS pulses delivered in M1 catch trials (green traces) did evoke PStEs however, demonstrating that PStEs evoked by AIP-ICMS would have been detected. This observation applied to all AIP-, dPPC-, PMd-, and S1-StimTAs from monkey Q. Similarly for monkey F (Figure S1B), the StimTAs from none of the four AIP-ICMS instructions showed significant PStEs in any of the four EMGs, and the same was true of StimTAs triggered by ICMS pulses in dPPC, PMd, and S1. However, StimTAs from 35 μA PMv-ICMS in each monkey did show PStEs.

Consequently, we used lower amplitude PMv-ICMS for training in both monkeys (20 μA in monkey Q, 30 μA in monkey F). At these amplitudes, StimTAs showed that PMv-ICMS no longer evoked any significant PStEs (Figures S2 and S3.).

Triggered averages of extraocular movements: To exclude the possibility that extraocular movements evoked by ICMS or the resulting shift in gaze might be used by the monkeys as instructions, we recorded eye movements with an infrared camera system (Primate Eye-Tracking system, ISCAN, Woburn, MA, USA). Both the horizontal (X) and vertical (Y) positions of one eye were sampled continuously at 1 kHz and recorded using the Grape-vine Analog Module of the Trek data acquisition system. Prior to beginning a session of ICMS training, eye movement amplitude was calibrated by having the monkey fixate briefly on circular targets (radius 1° visual angle, VA), looking first at a center target and then at up, down, left, or right targets located 5° VA from the center. During the subsequent ICMS training session eye movements were unrestricted.

Offline, we constructed averages of the X (horizontal) and Y (vertical) eye position signals from −200 before to 500 ms after the first pulse of each ICMS train recorded during a session, forming separate averages for the trains instructing each of the four targets. Figure S4 illustrates examples for each of the four instructions from a session using AIP-ICMS, showing both overlapped individual trial traces (gray) and their average (black). Though saccades often occurred both before and after the onset of ICMS trains, we found no evidence of fixed-direction saccades evoked consistently at short latency by ICMS trains delivered in any of the cortical regions studied here.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Monkeys experienced ICMS in anterior intraparietal and ventral premotor cortex
- ICMS was not experienced in dorsal posterior parietal or dorsal premotor cortex
- Success rates and reaction times were similar with visual or ICMS instructions
- Behavioral sensitivity to ICMS parameters was similar among successful areas

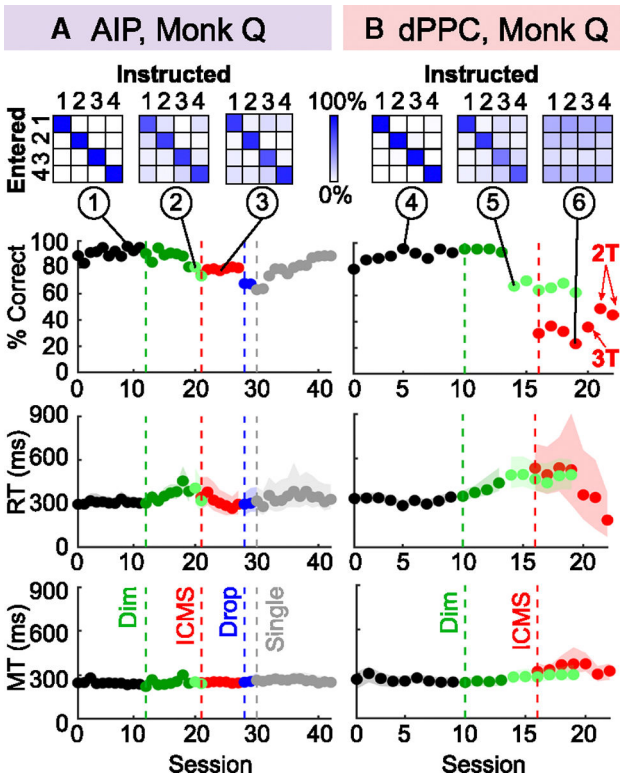

Figure 1. Training with AIP-ICMS or dPPC-ICMS instructions in monkey Q

Six confusion matrices are shown along the top: three from selected sessions during AIP-ICMS training (A; 1, 2, and 3) and three from dPPC-ICMS training (B; 4, 5, and 6). Each cell in a matrix represents a possible combination of the instructed target (*x* axis) and the entered target (*y* axis). The blue color of a square corresponds to the proportion of trials from the indicated session with that combination of instructed and entered target, ranging from 0% (white) to 100% (dark blue), as indicated by the color bar between matrices 3 and 4. For each plot below, black dots represent baseline sessions with fully saturated visual cues, and vertical dashed lines mark the following training milestones. (i) Dim (dark green dots): color desaturation of visual cues paired with ICMS begins (sessions involving the palest visual cues [red, green, blue (RGB): 190, 193, 190] are represented by light green dots). (ii) ICMS (red dots): only ICMS instructions remain. (iii) Drop (blue dots): dropping stimulating electrodes from each instruction. (iv) Single (gray dots): each instruction now delivered on a single electrode. Dots show the percentage of trials performed correctly (% correct, top), median reaction times (RTs; middle), and median movement times (MTs; bottom). Shading around reaction and movement times indicates the 25th–75th percentile range. On some days, trials with the palest visual cues (light green dots) and no visual cues (red dots) were interleaved to encourage the monkey to continue working. Note that confusion matrix 6 is based solely on such ICMS-only trials. After 4 days of near-chance performance with dPPC-ICMS instructions (25% with 4 targets), the number of targets was reduced to 3 and then 2 (red 3T and 2T), yet performance remained near chance. See text for additional description. See also Videos S1 and S2. Additional descriptive information on training sessions is given in Table S1. Best performance with single-electrode AIP-ICMS versus fully saturated visual cues is compared in Table S2.

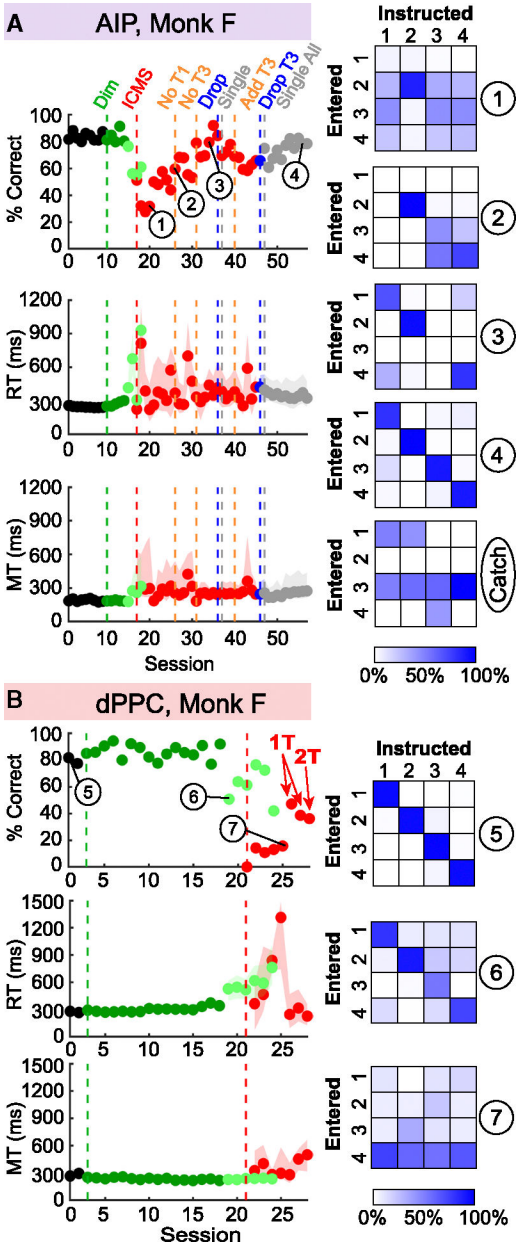

Figure 2. Training with AIP-ICMS or dPPC-ICMS in monkey F

(A) Training with AIP-ICMS instructions. Shown are percentage correct (% correct, top), median reaction times (RTs; middle), and median movement times (MTs; bottom) during AIP-ICMS training, formatted as described for Figure 1, with additional orange dashed lines indicating non-standard training adjustments as described in the text. Confusion matrices of key training sessions are shown on the right, including (1) an early session, at which point only instruction 2 had been learned; (2) a later session in which instruction 1 was removed because target 1 rarely had been entered; (3) a subsequent session after instruction 1 was added back and instruction 3 was removed because it was being confused with instruction 4; and (4) a session after each of the four instructions had been reduced to delivery on a single electrode, and performance had improved. Confusion matrices 1–4 are based entirely

on ICMS-only trials (red dots), and the Catch matrix represents catch trials in which no ICMS or visual instruction was delivered, causing percentage correct to drop to chance. (B) Training with dPPC-ICMS instructions. Confusion matrices show (5) strong performance with fully saturated visual cues, (6) degraded performance with the palest visual cues and ICMS instructions, and (7) poor performance with ICMS alone and no visual cues, with the monkey showing a habitual bias to enter target 4 regardless of the ICMS instruction. After 5 sessions of near-chance performance with dPPC-ICMS instructions (25% with 4 targets), in a final, remedial attempt to train monkey F to use dPPC-ICMS instructions, the number of targets was reduced to 1 or 2 (red 1T and 2T), yet performance remained poor.

Formatting is as described for Figure 1. See text for additional description. Additional descriptive information on training sessions is given in Table S1. Best performance with single-electrode AIP-ICMS versus fully saturated visual cues is compared in Table S2.

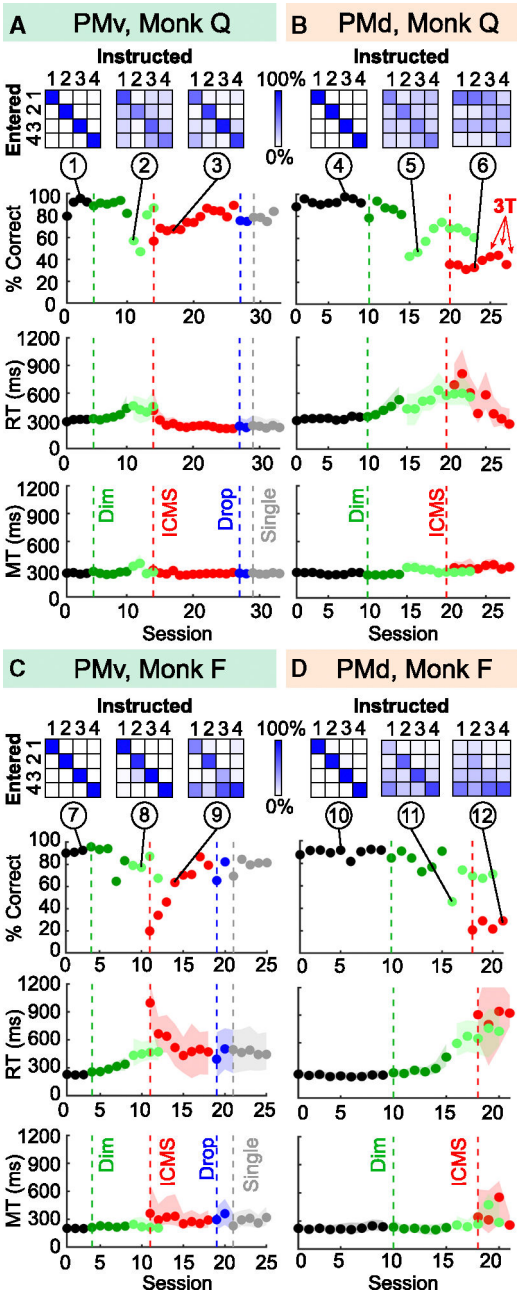

Figure 3. Training with PMv-ICMS or PMd-ICMS instructions in monkeys Q and F

In (A) and (B), six confusion matrices are shown along the top: three from sessions during PMv-ICMS training (1, 2, and 3) and three during PMd-ICMS training (4, 5, and 6) with monkey Q. Confusion matrices 3 and 6 are based solely on ICMS-only trials. In (C) and (D), the confusion matrices are from sessions during PMv-ICMS training (7, 8, and 9) and during PMd-ICMS training (10, 11, and 12) with monkey F. Plots below show percentage correct (% correct), median reaction time (RT), and median movement time (MT) throughout training.

Formatting is as described for Figure 1. See text for additional description. Additional descriptive information on training sessions is given in Table S1. Best performance with single-electrode PMv-ICMS versus fully saturated visual cues is compared in Table S2.

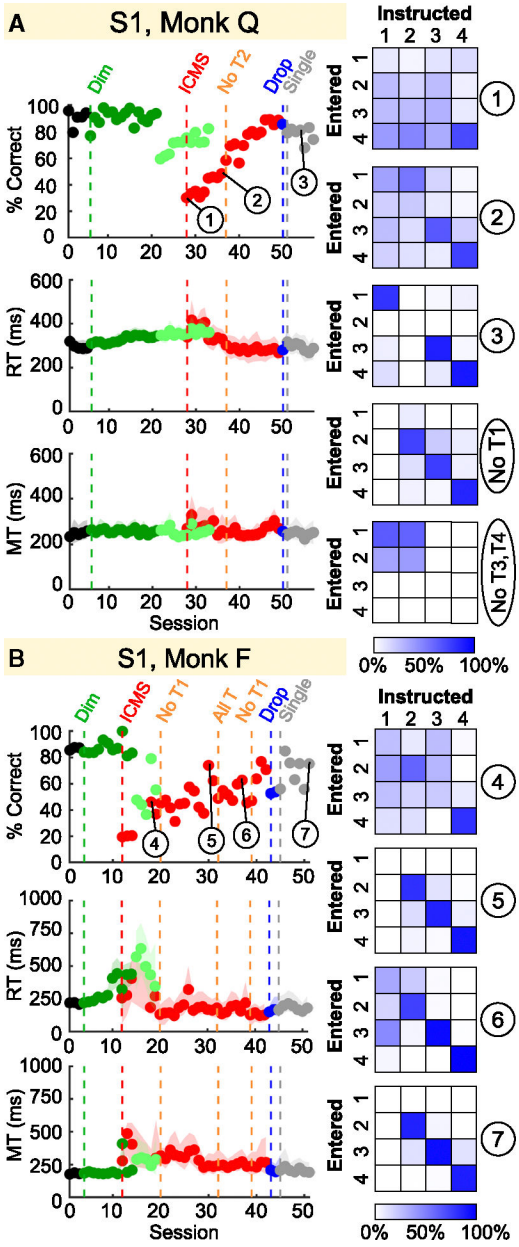

Figure 4. Training with S1-ICMS instructions in monkeys Q and F

Selected confusion matrices on the right and plots of percentage correct (% correct), median reaction time (RT), and median movement time (MT) throughout training on the left are all formatted as described for Figure 1. See text for additional description. Additional descriptive information on training sessions is given in Table S1. Best performance with single-electrode S1-ICMS versus fully saturated visual cues is compared in Table S2.

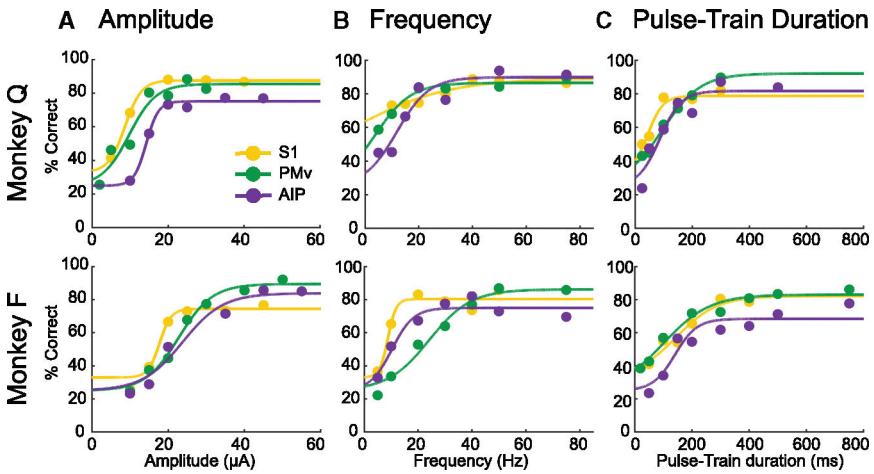

Figure 5. Parameter sweeps

We compared behavioral sensitivity to changing (A) amplitude, (B) frequency, and (C) duration of ICMS pulse trains delivered in the anterior intraparietal area (AIP; purple), ventral premotor cortex (PMv; green), and primary somatosensory cortex (S1; yellow). Curves were fit to a psychometric performance function with four parameters using MATLAB's nonlinear least squares method (see STAR Methods for the equation and Table S3 for parameter values, 95% confidence intervals, and R^2 value for goodness of fit).

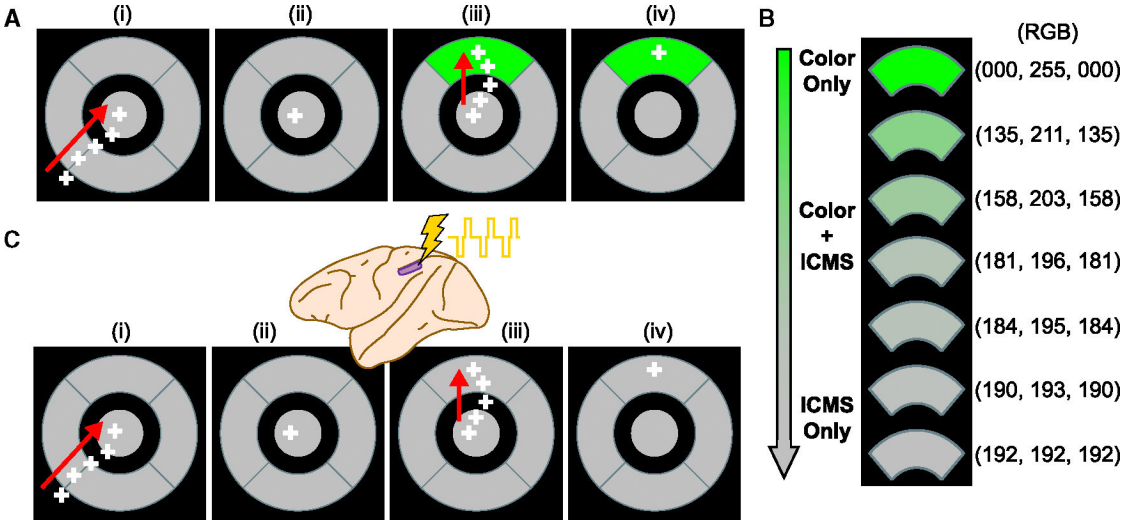

Figure 6. Center-out task

(A) Monkeys were initially trained to perform the center-out task (COT) using visual instructions only. Four frames from left to right illustrate (i) the cursor brought to the center target, (ii) initial hold in the center, (iii) appearance of a visual cue (green) and cursor movement into the cued target, and (iv) final hold in the instructed target. The white + marks in (A) and (C) illustrate a time series of cursor positions on the screen, representing example cursor trajectories during these four stages of a trial. For ICMS training, each of the four visual cues was paired with a unique, arbitrarily chosen ICMS instruction as described in the text.

(B) Over several sessions, the green visual cues then were desaturated gradually using the red, green, and blue (RGB) levels shown on the right. In the text, we refer to the RGB level (190,193,190) as the “palest” visual cue.

(C) Eventually, the targets remained gray (192,192,192) for the entire trial, and the monkey performed the COT using only ICMS instructions.

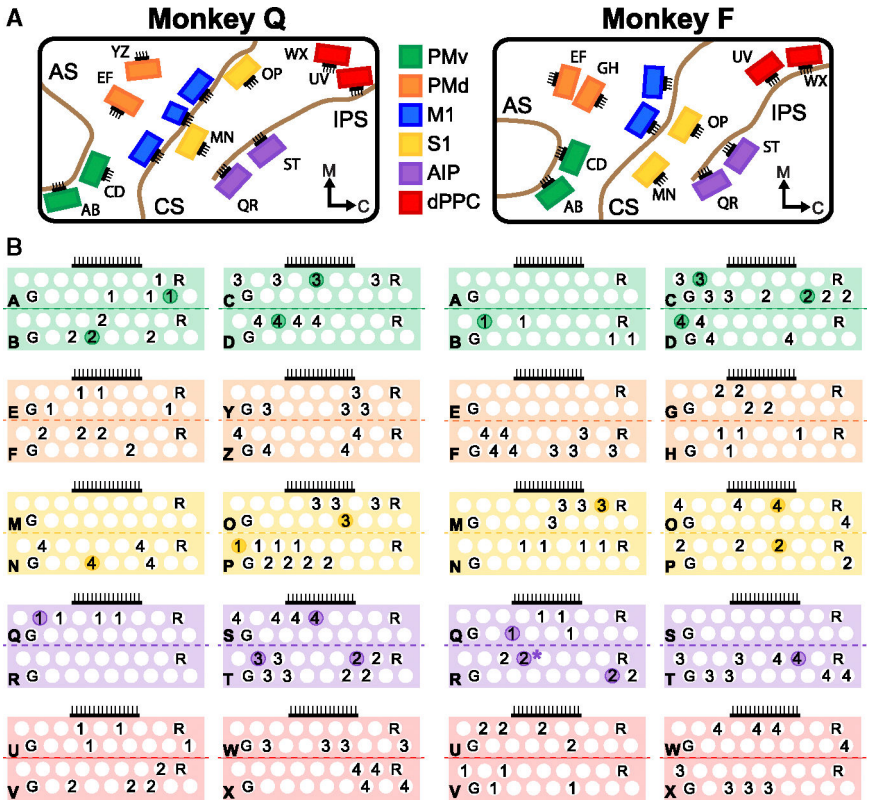

Figure 7. Microelectrode arrays

(A) Cortical locations of microelectrode arrays implanted in monkeys Q and F redrawn from intraoperative photographs. Two 32-channel arrays were implanted in the PMv (green), PMd (orange), M1 (blue), S1 (yellow), AIP (purple), and dPPC (red). AS, arcuate sulcus; CS, central sulcus; IPS, intraparietal sulcus; M, medial; C, caudal. In monkey Q, an additional 16-channel array was implanted in the M1. Black “combs” indicate the side from which wire bundles exited each array. B) Location of the individual electrodes used for each of the four ICMS instructions in each monkey. On a schematic layout of each implanted 32-channel FMA, the locations of the sets of four electrodes arbitrarily assigned to deliver ICMS instructions for each of the four targets are denoted by 1, 2, 3, or 4. A dashed, horizontal line separates each array into two banks, with separate low-impedance reference (R) and ground (G) electrodes; the latter was used to return current from electrodes within each bank. At the bottom left of each bank, A (A through X) corresponds to one of the double letters (e.g., EF or WX) labeling each of the arrays in (A). Color-filled circles indicate the locations of single electrodes used for ICMS instructions after dropping the other electrodes originally part of the four-electrode sets. Note that, as described under Results in relation to Figure 2, one of monkey F’s AIP electrodes (location denoted with an asterisk), originally part of the four-electrode set for instruction 2, eventually was used as the single-electrode for instruction 3.

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Software and algorithms		
MATLAB	MathWorks	https://www.mathworks.com/products/matlab.html
Trellis Software Suite	Ripple Neuro	https://rippleneuro.com/support/software-downloads-updates/
Offline Sorter	Plexon Inc.	https://plexon.com/products/offline-sorter/
OpenEx Software Suite	Tucker-Davis Technologies	https://www.tdt.com/component/openex-software-suite/
Custom code for data analysis	This study	Github repository: https://doi.org/10.5281/zenodo.15043160
Other		
Ripple Trek Data Acquisition System	Ripple Neuro	https://rippleneuro.com/ripple-products/trek-electrophysiology-system/
Primate Eye-Tracking System	ISCAN	https://iscaninc.com/standard-systems
Grass High-Impedance Headstages	Astro-Med Inc.	No longer available
P511 Amplifiers	Astro-Med Inc.	No longer available
IZ2 Stimulator	Tucker-Davis Technologies	https://wvww.tdt.com/component/iz2m-iz2mh-stimulator/
RZ5 BioAmp Processor	Tucker-Davis Technologies	https://www.tdt.com/component/rz2-bioamp-processor/
Floating Microelectrode Arrays (FMAs)	Microprobes for Life Sciences	https://www.microprobes.com/products/multichannel-arrays/fma