Long-term stability of sensitivity to intracortical microstimulation of somatosensory cortex

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Abstract

Objective. The dexterous manipulation of objects depends heavily on somatosensory signals from the limb. The development of anthropomorphic robotic arms and of algorithms to decode intended movements from neuronal signals has stimulated the need to restore somatosensation for use in upper-limb neuroprostheses. Without touch and proprioception, patients have difficulty controlling prosthetic limbs to a level that justifies the required invasive surgery. Intracortical microstimulation (ICMS) through chronically implanted electrode arrays has the potential to provide rich and intuitive sensory feedback. This approach to sensory restoration requires, however, that the evoked sensations remain stable over time. Approach. To investigate the stability of ICMS-evoked sensations, we measured the ability of non-human primates to detect ICMS over experimental sessions that spanned years. Main results. We found that the performance of the animals remained highly stable over time, even when they were tested with electrodes that had experienced extensive stimulation. Significance. Given the stability of the sensations that it evokes, ICMS may thus be a viable approach for sensory restoration.

Keywords: non-human primates, detection, electrode arrays, chronic stimulation, Utah electrode array, sensory feedback, neuroprosthetics

(Some figures may appear in colour only in the online journal)

Introduction

The development of sophisticated anthropomorphic robotic limbs and of methods to decode intended movements from motor areas of the brain [1–7] offer the possibility of restoring sensorimotor function to patients who have lost it [8]. While these are remarkable achievements, upper-limb neuroprostheses may not be clinically viable until they provide somatosensory feedback. Indeed, tactile and proprioceptive signals are critical for grasping and manipulating objects and performing activities of daily living [9]. One approach to restoring touch and proprioception consists of electrically stimulating somatosensory cortex through chronically implanted microelectrode arrays [4, 10–18]. For this approach to be successful, not only must the interface with the brain provide for bidirectional communication between sensorimotor areas and the prosthesis, it must do so for an extended period of time. That is, the arrays must provide stable recordings from motor structures [6, 19–24] and elicit stable percepts through intracortical microstimulation (ICMS) of sensory structures [25–31]. Indeed, electrode arrays can only be implanted once in a given area and must therefore last for the remainder of the patient’s life. While studies have shown...
that chronic ICMS is safe—that is, it causes negligible
damage to the stimulated tissue or electrodes [32, 33], but see [34]—the stability of the evoked percepts has been called into
question as sensitivity to ICMS has been found in some cases
to deteriorate over time [26].

In the present study, we investigated how sensitivity to
ICMS, delivered through chronically implanted arrays,
progresses over time. To this end, we tested the ability of non-
human primates to detect ICMS delivered to primary soma-
tosensory cortex (S1) from every electrode in the implanted
arrays over several multi-week periods (‘survey periods’) spaced at intervals over several years. We assessed not only the
degree to which detection performance changed over these
intervals but also whether changes in detection per-
formance, if any, depended on the amount of charge that had
been delivered in the lifetime of that electrode. We found that
sensitivity remained highly stable over time, and may, in fact,
have slightly improved, long after discriminable neuronal
waveforms had all but disappeared. Furthermore, detection
performance for electrodes that had been subjected to large
amounts of currents was equivalent to that for electrodes that
had received only limited stimulation.

Materials and methods

Animals

Two male Rhesus macaques (Macaca mulatta), 6 years of age
and weighing 10 Kg, participated in this study. Animal care
and handling conformed to the procedures approved by the
University of Chicago Animal Care and Use Committee.

Implants

Each animal was implanted with one Utah electrode array
(UEA, Blackrock Microsystems, Inc., Salt Lake City, UT) in
the left hand representation of area 1 (figure 1(A)). Each UEA
consists of 96 1.5 mm long electrodes, with tips coated with
iridium oxide, spaced 400 μm apart, and spanning a
4 mm × 4 mm area. Given the length of the electrodes, their
tips are likely to impinge upon the infragranular layers of
somatosensory cortex, as we have previously found to be the
case in postmortem histological analysis with other animals
instrumented with identical arrays [33]. We mapped the
receptive field of each electrode by identifying which areas of
skin evoked multiunit activity (monitored through speakers)
and confirmed that the receptive fields of neurons in
implanted cortex were on the hand.

In one animal (Monkey A), the original UEA remained
functional throughout the duration of the study. In the other
animal (Monkey B), the original array failed during the two
years following the first survey period, and another UEA was
implanted in the other hemisphere 115 weeks after initial
implantation. Only data from the second UEA in Monkey B
are included here as repeated measurements were only made
on this array in this animal. As a result, we report results of
three experiments conducted over a period of three years for
Monkey A and of two experiments conducted over a period of
approximately one year for Monkey B.

Detection tasks

Monkeys sat at the experimental table facing a monitor, with
their hand fixed palmar surface facing up to allow a custom-
designed tactile stimulator to indent their skin (figure 1(B)).
Eye movements were tracked with an optical eye-tracking
system (MR PC60, Arrington Research, Scottsdale, AZ).
Animals performed a detection task in a two-alternative
forced choice paradigm (figure 1(C)). Each trial comprised
two successive stimulus intervals, one of which contained a
stimulus (mechanical indentation of the skin or ICMS pulse
train applied to S1) and the other was empty. Animals
reported which interval contained the stimulus by making a
saccade to one of two targets to obtain a juice reward.

In the mechanical version of the detection task, stimuli
consisted of 1 s long trapezoidal indentations delivered to the
palmar surface of the hand using a high-precision custom-
made tactile stimulator (figure 1(B))(described in detail in
[14]). The stimulator tip (1 mm in diameter) was pre-indentated
500 μm into the skin. Without the pre-indentation, the
indentations could not be precisely controlled because the gradual shifts in hand position over time are of comparable magnitude to the indentations (on the order of tens or hundreds of microns). The afferent response to the pre-indentation decays away within 10–20 s, as does the resulting sensation, and afferent responses to further indentation of the skin are independent of the depth of pre-indentation [35]. In the present experiments, then, the perception of each indentation was relatively insensitive to gradual shifts in hand position as evidenced by the consistency of the animals’ performance across sessions. The set of stimulus amplitudes (beyond the pre-indentation) was adjusted for each animal to span the range from subliminal to reliably detectable. Amplitudes ranged from 25 to 350 μm and varied randomly across trials. Performance was computed as the proportion correct at each amplitude across skin locations (figure 2A). Mechanical stimuli were applied to multiple skin locations, each corresponding to the receptive fields of a subset of electrodes.

Monkey A was trained on mechanical detection for 11 weeks prior to implantation, and a further 14 weeks before its first ICMS survey period. Monkey B was trained on mechanical detection with its left hand for 3 weeks prior to the implantation of its first array (in the right hemisphere) and another 131 weeks before the first reported survey, which was carried out with an array in the left hemisphere. Following the implantation of the second array, Monkey B performed the mechanical detection task based on stimulation of its right hand, which was contralateral to the first (failed) array. For both monkeys, ICMS detection performance is reported over the periods indicated by the solid lines (week 14 to 160 for Monkey A, week 13 to 62 for Monkey B).

Figure 2. Mechanical detection experiments. (A) Psychometric functions derived from the animals’ detection performance (number of trials in chronological order: 2726, 2160, 1910 for Monkey A and 1700, 2256 for Monkey B). Curves of matching color indicate survey periods occurring within 5 weeks of each other. Time for each monkey is reported from array implantation date (for Monkey B, its second array). The horizontal dashed lines show threshold criterion, the vertical ones the resulting detection thresholds. (B) Progression of the overall proportion correct (left) and of detection thresholds (right) over time. The performance of Monkey A improved over time while that of Monkey B remained stable over the testing period. The dashed line denotes the period of time during which Monkey B performed the detection task based on mechanical stimulation of its left hand, which was contralateral to the first (failed) array. For both monkeys, ICMS detection performance is reported over the periods indicated by the solid lines (week 14 to 160 for Monkey A, week 13 to 62 for Monkey B).
hand (contralateral to the array). Task transfer from one hand to the other was immediate.

In the electrical version of the detection task, stimuli consisted of 1 s long 300 Hz trains of symmetric biphasic pulses (phase duration = 200 μs, inter-phase duration = 53 μs) delivered using a CereStim R96 (Blackrock Microsystems, Inc.). We had incorrectly assumed that cathodal phase leading was the default for the stimulator, given that it yields greater sensitivity [36–38]. However, this was not the case so pulses were anodal phase leading in the initial survey period for Monkey A. As soon as we discovered our mistake, we switched to cathodal phase leading stimulation for all subsequent experiments, including the later survey periods.

During survey periods, mechanical blocks were interleaved with ICMS survey blocks to monitor and maintain the animals’ familiarity with the task. ICMS amplitude was always 40 μA (corresponding to 8 nC/phase or 0.4 mC cm−2 assuming an exposed area of 2000 μm² as specified by the manufacturer). In initial surveys, we divided the array into 4 quadrants. During a given experimental block, stimulation was delivered through each electrode in a single quadrant, in random order, a total of four times. Quadrants were interleaved randomly from block to block. In later survey periods, we abandoned the quadrant structure and delivered stimulation once to every electrode in the array in each experimental block, again in pseudorandom order. Animal performed between two and four experimental blocks each day so two to four weeks were required to obtain 40 behavioral trials for every electrode on the array (for a total of 40 blocks or 3840 trials). The first survey was performed 14 and 13 weeks after implantation of the arrays for Monkeys A and B, respectively (in the case of Monkey B, his second array), then 23 and 34 months later for Monkey A and 11 months later for Monkey B. The timing of the testing is reported with respect to the date of array implantation (for Monkey B, his second). Between survey periods, both monkeys participated in other experiments that involved making perceptual judgments about ICMS. In these experiments, ICMS varied over a wide range: frequency from 50 to 1000 Hz, pulse width from 50 to 400 μs, and duration from 50 to 500 ms [14, 39]; in some experiments, stimulation was delivered through multiple electrodes simultaneously [12]. Throughout these studies, we tracked how much charge was delivered through each electrode (see below). The length of time separating survey periods was determined by the duration of the intervening experiments.

Between the penultimate and final survey periods for each monkey, several additional detection experiments were carried out in which ICMS parameters were identical except for the amplitude, which took on one of seven values, varying randomly across trials and ranging from 5 to 80 μA (1 to 16 nC/phase; 0.05 to 1.6 mC cm−2). In these experiments, stimulation was delivered through a single electrode throughout each experimental block and at least 20 trials were obtained at each amplitude, distributed over several blocks. Performance was computed as the proportion correct at each amplitude with each electrode.

**Stimulation history**

While the survey experiments involved equivalent stimulation of all electrodes in the array, many other stimulation experiments were carried out with these arrays between survey blocks. These other experiments typically involved a small subset of electrodes, which were thus subjected to much more stimulation than the others. To gauge the degree to which stimulation history might affect the progressions of sensitivity over time, we computed the cumulative charge that had been delivered through each electrode by the time each survey experiment was carried out.

**Pulse polarity**

Pulse polarity (anodal versus cathodal phase leading) has been previously shown to affect sensitivity to ICMS [36–38]. Because pulse polarity changed part way through the study, we needed to account for any differences in performance that might be attributable to polarity. To this end, we had animals perform the detection task described above, with pulse polarity varying from trial to trial. We were thus able to compare the detectability of stimuli that differed only in their polarity.

To account for the switch in pulse polarity from the first survey session to subsequent ones, we computed a correction for any polarity-related differences. Specifically, we computed the ratio of the performance with cathodal phase-leading to that with anodal phase-leading, both at 40 μA, the amplitude used in the survey experiments. To ensure we did not underestimate the effect, we subtracted the standard error of the mean from the mean performance with anodal phase leading, and added the standard error of the mean to the mean performance with cathodal phase leading before we computed the correction factor. Performance from the initial survey was then multiplied by this correction factor, thereby yielding the performance that would have been obtained had the experiments been carried out with cathodal phase-leading (perhaps slightly overestimating it). We could then compare the performance in this initial block to that in subsequent, polarity-reversed experiments.

**Results and discussion**

We trained two non-human primates to perform a detection task using a two-alternative forced-paradigm. Animals were seated in front of a computer monitor with their hand fixed, palmar surface facing upward (figure 1B). On each trial, they indicated which of two sequential intervals contained the stimulus by saccading to a left or right target (figure 1C). Animals were first trained to perform this task based on indentations of the skin, delivered with a high-precision tactile stimulator (figure 1B). When the animals had learned to perform the mechanical version of the task, they performed the same task based on ICMS delivered to S1 through chronically implanted arrays (figure 1A).
Progression of tactile sensitivity and task familiarity

As mentioned above, the animals performed the mechanical detection task before they were implanted with electrode arrays and continued to perform this task (interleaved with its electrical counterpart) throughout the duration of the study. We assumed that any improvements in performance on the mechanical task reflected greater familiarity with the task rather than increased sensitivity to cutaneous stimulation. Indeed, the limits to tactile sensitivity have been shown to be set by the sensitivity of cutaneous mechanoreceptive afferents [40], which is not likely to increase over time.

We could then gauge the extent to which changes in performance on electrical trials might be due to task familiarity rather than sensitivity to ICMS. While the performance of Monkey B was relatively stable over the one-year testing period (Kruskal Wallis ANOVA: \( \chi^2 (1, 53) = 0.8, p > 0.1 \)), that of Monkey A improved considerably over the three-year period (Kruskal Wallis ANOVA: \( \chi^2 (2, 70) = 46.9, p < 0.001 \)) (figure 2).

Figure 3. Results of the survey experiments. (A) Heat map showing the performance of Monkey A in the three survey periods (14, 114, and 160 weeks after implantation) along with scatter plots of performance in two successive surveys. (B) Heat maps and scatter plots of the performance of Monkey B in the two survey periods (13 and 62 weeks after implantation). During each survey period, a minimum of 40 trials was collected for each of 96 electrodes.
nearly perfect performance on others yielding performance that ranged from chance on some to electrodes. As we and others have previously reported, sensitivity to detect 40 μA ICMS delivered through each of the 96 electrodes. As we and others have previously reported, sensitivity to ICMS varied from electrode to electrode [41–43], yielding performance that ranged from chance on some to nearly perfect performance on others (Figure 3). Furthermore, these across-electrode differences tended to be conserved over time: poorly performing electrodes tended to remain that way, as did the well performing ones (Figure 3). More importantly, performance levels improved over time for both animals (Friedman test: \( \chi^2(2, 287) = 41.6 \) and \( \chi^2(1, 191) = 63.4 \) for Monkeys A and B, respectively; \( p < 0.0001 \)).

Improvements in performance might be attributable to greater task familiarity as these seem to mirror improvements in the mechanical task. The improvement in performance may also reflect learning to recognize ICMS-evoked percepts. Indeed, detection of ICMS to primary sensory cortex has been found to improve with practice [44]. The improvements are gradual, which suggests that the ability to perceive the stimulus is acquired incrementally, as in perceptual learning [45]. Whether or not the animals actually got better at detecting ICMS over time, our results demonstrate that sensitivity to ICMS delivered through chronically implanted electrode arrays can be maintained over multiple years.

One might argue that probing detectability at a single stimulus amplitude (a 40 μA pulse train) provides a low resolution measure of sensitivity to ICMS over time. For example, if performance were bimodal, with some electrodes consistently yielding chance performance and the rest yielding perfect performance, we might not be able to detect changes in sensitivity over time. To test this possibility, we used data from experiments carried out between survey periods to compare detection performance across a range of amplitudes at different time points with a subset of electrodes (Figure 4). This analysis replicated the general trend of improving detection performance and decreasing detection thresholds over time.

Our results stand in contrast with those of previous studies on ICMS stability, in which thresholds were found to remain stable [25], or to increase progressively over time [26, 27, 29]. Our study differed from these previous ones in a variety of ways. First, we used electrodes coated with iridium oxide, rather than platinum [29], platinum iridium, platinum tungsten [25], or iridium [27], each of which involves different types of Faradaic charge transfer than does iridium oxide (used here) [46], which may affect the stability of the interface. Second, we capped our stimulation amplitude at 20 nC/phase or 1 mC cm\(^{-2}\) (unlike in [26]), thereby limiting possible electrically induced damage to the tissue or electrodes, third, differences across studies may also reflect differences in the length of electrodes. Indeed, ICMS thresholds have been found to be lower and more stable in the deep layers of rat auditory cortex [37] and monkey visual cortex [47].

**Effect of cumulative charge on performance**

While all electrodes were stimulated approximately equally in the survey experiments, a subset of high performing electrodes were used in a variety of other experiments investigating the detectability and discriminability of ICMS trains [14, 18, 48]. The heterogeneity in the stimulation regimes tested with the various electrodes gave us the opportunity to examine the degree to which sensitivity to ICMS was dependent on stimulation history. We found that change in performance from one survey to the next with highly stimulated electrodes was not significantly different from that with sparingly stimulated electrodes (Kruskal Wallis ANOVA: \( \chi^2(2, 95) = 2.9 \) and \( \chi^2(3, 95) = 5.4 \) for week 14 to 114 and 114 to 160 for Monkey A, \( p > 0.1 \), and \( \chi^2(2, 95) = 6.0, p = 0.05 \) for Monkey B) (Figure 5). One might argue that the performance with the highly stimulated electrodes did not improve as much as that with the others for Monkey B, but this is likely a result of the selection process: for both monkeys, electrodes that yielded poor performance in the initial survey experiments were not used in subsequent experiments.
ICMS through chronically implanted arrays has been shown to elicit percepts over months or years in human visual cortex [30], macaque visual cortex [25, 26, 31], rat auditory cortex [27], cat auditory cortex [29], and to elicit EMG responses in cat motor cortex [28]. In some studies, thresholds increased progressively with time [26], whereas in others, they were stable [25] or exhibited more complex patterns of change [27, 29]. We show that sensitivity to ICMS remains stable over years, even when delivered through electrodes that have been extensively used. The stability of sensitivity to ICMS stands in contrast to that of neuronal recordings obtained through chronically implanted arrays, which, while occasionally retaining the ability to resolve single-unit responses over several years, tend to deteriorate over time [6, 19–24]. Given the stability of the sensations that it evokes, ICMS may be a viable approach for sensory restoration.

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**Figure 5.** Effect of stimulation history on detection performance. (A) Monkey A, 14 to 114 weeks after implantation (84, 4, and 8 electrodes were in the low, medium, and high charge groups). (B) Monkey A, 114 to 160 weeks after implantation (85, 4, 2 electrodes). (C) Monkey B, 13 to 62 weeks after implantation (80, 13, and 3 electrodes). Performance with often-used electrodes was thus subject to a ceiling effect, with initial performance already very high.
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