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The functional consequences of chronic, physiologically effective intracortical microstimulation

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Abstract

Many studies have demonstrated the ability of chronically implanted multielectrode arrays (MEAs) to extract information from the motor cortex of both humans and nonhuman primates. Similarly, many studies have shown the ability of intracortical microstimulation to impart information to the brain via a single or a few electrodes acutely implanted in sensory cortex of nonhuman primates, but relatively few microstimulation studies characterizing chronically implanted MEAs have been performed. Additionally, device and tissue damage have been reported at the levels of microstimulation used in these studies. Whether the damage resulting from microstimulation impairs the ability of MEAs to chronically produce physiological effects, however, has not been directly tested. In this study, we examined the functional consequences of multiple months of periodic microstimulation via chronically implanted MEAs at levels capable of evoking physiological responses, that is, electromyogram (EMG) activity. The functionality of the MEA and neural tissue was determined by measuring impedances, the ability of microstimulation to evoke EMG responses, and the recording of action potentials. We found that impedances and the number of recorded action potentials followed the previously reported trend of decreasing over time in both animals that received microstimulation and those which did not receive microstimulation. Despite these trends, the ability to evoke EMG responses and record action potentials was retained throughout the study. The results of this study suggest that intracortical microstimulation via MEAs did not cause functional failure, suggesting that MEA-based microstimulation is ready to transition into subchronic (<30 days) human trials to determine whether complex spatiotemporal sensory percepts can be evoked by patterned microstimulation.

Keywords

micro-electrode array; motor cortex; feline; electromyogram; impedance; microstimulation

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Introduction

Multielectrode arrays (MEAs) are a promising technology for use in intracortical neuroprosthetics. For such devices to be clinically successful in recording applications, MEAs must be able to acquire sufficient neural data to control an effector device, such as a prosthetic arm, for the life span of the patient. While the action potential recordings currently obtained using MEAs are not stable over these timeframes (Dickey et al., 2009; Linderman et al., 2006; Suner et al., 2005), studies have shown that having well-isolated action potential recordings is not necessary for successfully decoding movements (Fraser et al., 2009; Rivera-Alvidrez et al., 2010). Numerous studies have also demonstrated the utility of MEAs for intracortical motor prosthetic applications in nonhuman primates (Aggarwal et al., 2009; Musallam, 2004; Nicolelis, 2003; Santhanam et al., 2006; Schwartz et al., 2006; Taylor, 2002; Wessberg, 2000). Further, chronically implanted MEAs have been used to control a variety of effectors in human patients (Hochberg and Donoghue, 2006; Hochberg et al., 2006; Serruya et al., 2002).

MEAs can also potentially be used as a high-resolution interface for the injection of charge directly into brain tissue. Such electrical microstimulation activates neurons, which can generate or modulate a neurophysiological process, such as sensory perception or movement. Numerous studies have evaluated the effects of acute microstimulation on different neural systems. These studies include experiments in the auditory system of rodents (Otto et al., 2005a; Rousche et al., 2003), and the somatosensory system (Romo et al., 1998), visual system (DeYoe, 2005; Murphey and Maunsell, 2007, 2008; Tehovnik, 2006; Tehovnik and Slocum, 2009), and motor system (Cooke, 2003; Fitzsimmons et al., 2007; Graziano, 2005; Graziano et al., 2002; Salzman et al., 1990; Schmidt and McIntosh, 1990) of nonhuman primates. Only a few studies, however, have investigated the consequences of chronic intracortical microstimulation to effect through a chronically implanted MEA (Bradley, 2004; Rousche and Normann, 1999). Human studies have demonstrated the ability to evoke percepts through intracortical microstimulation, but these experiments have been limited to intraoperative time frames (Bak et al., 1990) or to a single chronically implanted patient (Schmidt et al., 1996). Significant insight into the perceptual effects of microstimulation was obtained in these few human experiments, suggesting that further studies utilizing microstimulation via highdensity MEAs in subchronic clinical trials will be valuable. Prior to transitioning such research into human patients, however, the functional effects of microstimulation must be evaluated in a nonhuman system to demonstrate both safety and efficacy over chronic timescales.

The consequences of chronic microstimulation are disputed. *In vitro* stimulation studies and investigations of the histological response of brain tissue to microstimulation have shown that damage to both device and tissue can arise from microstimulation (Cogan, 2004; McCreery et al., 2010; Merrill et al., 2005; Negi et al., 2010; Troyk et al., 2004). Intracortical stimulating macroelectrodes, such as deep brain stimulating electrodes, have also been shown to cause tissue reactivity with the application of stimulation (Moss, 2004). Despite the damage caused by stimulating macroelectrodes, however, such devices can deliver functional stimulation for years, especially when stimulation is titrated to effect (Deuschl et al., 2006). While histological markers, including antibodies for reactive

astrocytes and neurons can indicate that tissue is damaged, histology cannot indicate whether or not stimulation was effective or whether tissue response would have had an effect on performance. Additionally, histology can only be collected at experimental end points, which means that tissue response cannot be tracked through the course of multiple months of implantation and microstimulation without the sacrifice of many animals at several time points. In order to analyze the performance of microstimulation via microelectrodes over the course of a multiple-month implantation, electrophysiological markers of performance, rather than histological markers of safety, must beused. Electrophysiological markers, such as recorded action potentials, can demonstrate not only the viability of tissue in the vicinity of electrodes, but also that device integrity is maintained.

In this study, we investigate the *in vivo* performance of sputtered iridium oxide film (SIROF) metalized MEAs used to deliver chronic, physiologically effective intracortical microstimulation. Four felines were implanted with MEAs and two were stimulated to physiological effect, as measured by electromyogram (EMG). Functionality was evaluated using impedance measurements, electrophysiological recordings, and the ability of microstimulation to evoke EMG responses, to determine if device and/or tissue damage occurred with periodic microstimulation. Using these measures, we found that microstimulation efficacy could be maintained after several months of implantation and many microstimulation sessions. Further, we found that microstimulation did not appear to adversely impact either impedances or the ability to perform electrophysiological recordings over the course of the study.

Methods

Surgical procedures

Implantations and all other procedures were performed in accordance with protocols approved by the University of Utah Institutional Animal Care and Use Committee. Four felines (Felis catus) were used in this study. Felines each had an array implanted in motor cortex (Ghosh, 1997) so that applied stimulation would result in motor response measurable by EMGs recorded in either forelimb or hindlimb muscles. All implants were performed by the same clinical neurosurgeon to ensure consistency of implant technique and array placement. Anesthesia was induced using ketamine/xylazine and then continued using Isoflurane. Under sterile conditions, a midline incision was performed, and a craniotomy over the targeted area was made by means of a neurosurgical drill. The dura was reflected, and the array was pneumatically inserted into motor cortex (Rousche and Normann, 1992). Following implantation, the titanium percutaneous connector was attached to the skull using bone screws. A dural replacement (DuraGen, Integra Life Sciences, Plainsboro, NJ) was used to cover the array, and silicone polymer (Kwik-cast, World Precision Instruments, Sarasota, FL) was used to fill the craniotomy, if necessary. The scalp was sutured closed and the animal given at least 24 h to recover before data acquisition was attempted.

Electrode arrays

For Felines 1 and 2, arrays were obtained from Cyberkinetics, Inc. (Salt Lake City, UT) with electrode tips that had been coated by EIC Laboratories (Norwood, MA) with SIROFs. For

Felines 3 and 4, 96-electrode SIROF Utah Electrode Arrays were commercially obtained from Blackrock Microsystems, Inc. (Salt Lake City, UT). Arrays were manufactured as described elsewhere (Jones et al., 1992) under Design Controls specified by the United States Food and Drug Administration. Electrodes were 1 mm long and spaced 400 μm apart. The SIROF used to coat the conductive electrode tips increased the charge injection capacity of the electrodes and reduced the possibility of electrode dissolution (Cogan, 2008; Cogan et al., 2009). Active electrode tips were ~40 μm in length, yielding ~4000 μm^2 of SIROF surface area per electrode (Negi et al., 2010; VanWagenen, 2004). The remainder of the array was coated with Parylene-C insulation for electrical isolation and biocompatibility. A summary of arrays used is presented in Table 1.

Data acquisition

A 128-channel Cerebus data acquisition system (Blackrock Microsystems) was used to acquire neural data. The 96 channels of electrode data from the UEA were fed to a front-end amplifier using a Cereport patient cable.

Impedance measurements—One kilohertz (kHz) impedance measurements were made using a routine in the Cerebus data acquisition system. Briefly, a small sinusoidal current at 1 kHz was passed through a reference electrode, and impedance was simultaneously computed on all electrodes. Chronic impedance readings were taken throughout the multiple-month course of implantation in all four felines. Acute impedance readings were also taken pre- and post-stimulation for each microstimulation session in Felines 3 and 4.

Electrophysiological recordings—Neural recordings were obtained from awake felines to examine device performance over time both with and without the application of microstimulation. Felines were placed in a pet carrier inside an electrically shielded chamber to minimize noise, and connected to the Cerebus. Recordings were made at least weekly in all felines, as well as prior to and following every stimulation session in Felines 3 and 4. Recordings were made in several-minute sessions using band-pass filter settings of 0.3 Hz–7.5 kHz and sampled at 30 kHz in Felines 1–3, and band-pass filter settings of 0.3 Hz–2.5 kHz sampled at 10 kHz in Feline 4 to reduce file size.

Electromyography—EMGs were used periodically in Felines 3 and 4 to test the ability to evoke physiological responses via intracortical microstimulation. Following a control neural data recording, the animal was anesthetized with Telazol administered intramuscularly at 0.01 mg/kg. Sterile, clinical fine-wire electrodes were placed in the biceps femoris muscle of Feline 3 and either the triceps or extensor carpi muscle of Feline 4. Reference electrodes were placed subcutaneously near the intramuscular electrode. EMG activity in response to stimulation was recorded at 2 kHz using the Cerebus data acquisition system described above. For the EMG sessions performed prior to 29/Sep/2009, a MA300-18-002 commercial EMG system (Motion Lab Systems, Baton Rouge, LA) was used. For subsequent EMG sessions, a one-channel AC differential amplifier (DAM 80, World Precision Instruments) was employed. Stimulus markers were output to Cerebus using in-house LabView code (National Instruments, Austin, TX).

Microstimulation

Six daisy-chained RX-7 stimulators (Tucker-Davis Technologies Inc., Alachua, FL) were used for microstimulation. These stimulators are capable of applying current-controlled waveforms with a voltage excursion of −24 to 24 V. Stimulation was controlled with in-house Matlab (The Mathworks, Natick, MA) and LabView code. Microstimulation was applied to Felines 3 and 4.

Stimulus waveforms—Stimuli were applied in charge-balanced square waveforms to prevent charge buildup (Merrill et al., 2005). For each session, pulses of a square, charge-balanced, biphasic waveform at 0.2 ms per phase were applied in trains of 25, 50, or 100 pulses at 100 Hz, settings chosen for their efficacy at evoking responses in perceptual microstimulation studies (Table 5). Trains of pulses were applied in rounds such that every electrode was stimulated at a given amplitude before the current used to stimulate was increased.

All-channel stimulation—Stimulation was periodically applied to the feline on all 96 electrodes in sequence in rounds of each indicated amplitude in order to determine whether stimulation across all channels affected functionality. In none of these sessions did the feline respond in any manner (e.g., vocalizations or movements) that would indicate an adverse reaction to stimulation while awake (listed as all-channel sessions in Table 2). All-channel stimulation was also performed with the feline anesthetized in order to perform EMG (listed as all-channel EMG sessions in Table 2). Microstimulating current was increased in rounds over the course of the session to determine the threshold current required to evoke EMG responses on each electrode.

Test of parallel stimulation—To test the effects of synchronous stimulation on multiple electrodes, such as might be applied during a failure of patterned microstimulation, stimulation was applied simultaneously at 25 μA via 72 electrodes. The animal was disconnected from the experimental apparatus following five trains of stimulation.

Chronic stimulation—Chronic stimulation sessions were applied in two paradigms, low (15/20 μA) and high (20/25/30/25 μA), on 15 selected electrodes of the MEA in Felines 3 and 4 (Table 2). These specific 15 electrodes were chosen for microstimulation based on two factors: (1) Spatial distribution of charge application. (2) To stimulate on some electrodes which recorded action potentials and some electrodes which did not (Figs. 5a and 5c). Chronic microstimulation was applied at amplitudes ranging from 15 to 35 μA over the course of several months (Table 2). Stimulation levels were adjusted based on the results of EMG sessions.

Data analysis

All analyses and statistical tests were performed using custom Matlab code.

Impedance data—Electrodes which recorded 1 kHz impedance values over 2 MΩ on all days were considered to be out-of-specification and not included in any further analyses. Impedance values over 2 MΩ on a single day were replaced with a 2 MΩ ceiling value. *Z*-

scored impedances were computed by electrode in each feline. The value for an impedance reading of a single electrode in a single dataset was compared to mean value for that electrode across all datasets, and then divided by the standard deviation of all values recorded on that particular electrode. *Z*-scores were averaged across all electrodes for each dataset. For pre- and poststimulation session impedance readings, median impedances and standard errors were computed. Wilcoxon's signed rank test was applied to demonstrate significant drops in median impedance values immediately pre- and post-all-channel-stimulation in Feline 3. The Komolgorov–Smirnov test was applied in Feline 4 due to the small number of pre/post-stimulation datasets. Wilcoxon's signed rank test was used to demonstrate the significance of acute impedance drops on 15 stimulated channels in both Felines 3 and 4. In Feline 3, the median impedance drops between the first and second chronic stimulation paradigms were compared using Wilcoxon's signed rank test on the last 20 datasets of the first paradigm and all 20 datasets of the second paradigm. Wilcoxon's signed rank test was also used to determine significance of drops in impedance over time. Impedances for the first and last 30 datasets were compared in Felines 1, 3, and 4, and the first and last 10 datasets were compared in Feline 2 due to the lower number of recording sessions.

Electrophysiological recording data—Action potential recordings were sorted using a PCA-based *t*-distribution algorithm (Shoham, 2003). A threshold for action potentials was subsequently imposed at 70 μV. *t*-tests were performed to quantify changes in the number of electrodes which recorded well-isolated action potentials over time (using the first and last 30 datasets in Felines 1, 3, and 4 and the first and last 10 datasets in Feline 2). Student's *t*-test was also applied to acute pre- and poststimulation number of electrodes which recorded action potentials. The distribution of number of electrodes which recorded action potentials across all microstimulation sessions during pre-stimulation recordings was compared to the immediate post-stimulation distribution for Felines 3 and 4.

Electromyographic data—EMG data was rectified, and a boxcar filter (size 50 ms, stepped per sample) was applied across all recorded twitches evoked by a given amplitude of stimulus via a given electrode on EMG response traces to demonstrate the population-level response to a train of stimulation. The Komolgorov–Smirnov test was applied to the rectified averaged EMG data at −400 to −100 ms prior, and the +100 to +400 ms following, the application of microstimulation.

Results

Chronic 1 kHz impedance

Impedances followed a pattern of increasing after implantation to a peak within the first month in all felines (Figs. 1 and 2). This increase was followed by a decrease over time. The first 30 impedance measurement datasets had higher mean impedance than the last 30 datasets in Felines 1, 3, and 4 ($p<0.001$, Wilcoxon's signed rank test). Due to the smaller number of datasets in Feline 2, only the 10 first and last datasets were compared, with the same result ($p<0.05$, Wilcoxon's signed rank test). A summary of impedances is included in Table 3. Impedances over 2 MΩ were considered to be out-of-specification. In Feline 1,

three electrodes were out-of-specification. In Feline 4, seven electrodes were out-of-specification. Felines 2 and 3 did not have any out-of-specification electrodes.

Pre- and post-stimulation impedance

Median 1 kHz impedance decreased acutely on 19 of 23 days with the application of daily microstimulation (low paradigm) on 15 electrodes in Feline 3 ($p<0.01$, Wilcoxon's signed rank test, $n=23$ sessions; Fig. 3a), as well as acutely on 20 out of 20 days when stimulation (high paradigm) was not consistently applied on consecutive days ($p<0.01$, Wilcoxon's signed rank test, $n = 20$ sessions; Fig. 3b). Median acute impedance drops were larger during the high chronic stimulation paradigm than the low paradigm ($p<0.01$, Wilcoxon's signed rank test). Parallel microstimulation on 72 channels of the MEA in Feline 3 also led to an acute decrease in median impedance ($p<0.001$, Wilcoxon's signed rank test, $n = 96$ electrodes) on all electrodes of the MEA. Median impedance across the 96 electrodes of the MEA decreased when stimulation was applied simultaneously on 72 electrodes in Feline 3 (Feline 3, $p<0.05$, $n = 8$ sessions, Wilcoxon's signed rank test). In Feline 4, only five impedance readings were made following all-electrode stimulation sessions. Median impedance decreased following all-electrode stimulation (Komolgorov–Smirnov test, $p<0.01$, $n = 5$ sessions). Median impedance also decreased significantly on the 15 electrodes that passed current during the three applications of the 25 μA stimulation paradigm in Feline 4 ($p<0.001$, Wilcoxon's signed rank test, 15 electrodes over three sessions, $n = 45$).

Action potential recordings

In both nonstimulated and microstimulated felines (Figs. 4 and 5), the number of action potentials recorded from motor cortex followed a previously observed pattern of initially increasing followed by a decrease in numbers over the course of months (Suner et al., 2005). This chronic pattern of action potential recordings was similar between microstimulated and non-microstimulated felines. In nonstimulated Feline 1, the number of action potentials recorded during the plateau period (sessions 30–60) was greater than that recorded during the fade-out period (last 30 datasets, $p<0.05$, Student's two-sample t-test). This same observation was made in the microstimulated Felines 3 and 4 ($p<0.05$, Student's two-sample t-test). In non-microstimulated Feline 2, in which only 39 data acquisition sessions were performed, there was no significant change in the number of action potentials recorded between the first and last 10 datasets. All-electrode microstimulation, for example, for feline response tests and EMG sessions, did not lead to an acute decrease in the number of well-isolated action potentials recorded in either microstimulated feline ($p<0.05$, onetailed Student's t-test; Feline 3, prestimulation mean=5 action potentials, poststimulation =8 action potentials, $n=8$ sessions; Feline 4, prestimulation mean=60 action potentials, poststimulation=70 action potentials, $n =6$ sessions). The number of action potentials recorded prior to multielectrode synchronous stimulation in Feline 3 was 12, while the number recorded poststimulation was 13, demonstrating that acute parallel synchronous stimulation did not preclude recording ability. A summary of action potential recording data in all four felines is included in Table 4.

Microstimulation in awake felines

For awake stimulation sessions in both Felines 3 and 4, microstimulation was applied to one electrode at a time without anesthesia. No adverse behavioral or physiological responses to such stimulation were observed. For multichannel parallel stimulation in Feline 3, stimulation was synchronously appliedto72electrodes of the MEA (Table 2;07/Sep/2009). A bilateral, tonic seizure of <1 min duration resulted from this microstimulation paradigm. Full ambulatory recovery occurred within 5 min of ictus. The animal exhibited neither behavioral deficits nor spontaneous seizures in the 5 months between seizure induction and termination of the experiment.

Microstimulation to effect

Chronic stimulation was applied on the same 15 electrodes (shown in Fig. 5a) for a total of 43 days in Feline 3 (Table 2). It was possible to evoke EMG responses via an electrode that performed chronic microstimulation, both after it delivered 23 sessions of stimulation at 15 μA, and after 20 sessions at 30 μA (Fig. 6a), though this electrode did not record action potentials between EMG sessions. Of the 15 electrodes used for chronic stimulation in Feline 3, four recorded action potentials during the time that chronic stimulation was applied. EMG responses could also be evoked several months apart in time via electrodes that recorded action potentials in both microstimulated felines (Fig. 6b and c), though these electrodes did not deliver chronic microstimulation (three electrodes in Feline 3, two electrodes in Feline 4). In Feline 3, 13 electrodes evoked electromyographic responses at 10–35 μA on 14/Aug/2009, seven electrodes evoked responses between 20 and 40 μA on 04/Dec/2009, and 11 electrodes evoked responses at 100 μA on 14/Jan/2009 ($p<0.05$, Komolgorov–Smirnov test). While responses were evoked at currents of <40 μA during the second month of implantation in Feline 3, 100 μA current was required to evoke responses during the sixth month of implantation. Currents higher than 100 μA were not tested due to the voltage excursion limitation of the stimulator. Of the electrodes which evoked responses in Feline 3, two consistently evoked responses throughout all EMG sessions. In Feline 4, eight electrodes evoked EMG responses at 60–80 μA on 01/Oct/2010, two electrodes evoked responses at 60 μA on 28/Oct/2010, and eight electrodes evoked responses at 60–100 μA on 22/Dec/2010. Of the electrodes that evoked EMG responses in Feline 4, two retained the ability to evoke responses throughout the experiments performed.

Discussion

Many studies have shown that intracortical microstimulation to effect can be performed in nonhuman primate, feline, and other model systems for many sensory modalities (see Table 5). In most of these studies, stimulation was performed acutely on a single electrode in order to evaluate behavioral responses to stimulation. Few of these studies examined the chronic response to stimulation, and still fewer evaluated the long-term consequences of stimulation in a functional context. In this study, we found that chronic, intracortically implanted MEAs could stimulate to effect on multiple electrodes over the course of several months. By evaluating device performance using electrophysiological data, stimulation ability, and 1 kHz impedance, we found that effective stimulation via chronically implanted MEAs did not appear to destroy either the device or underlying cortical tissue.

The stimulation applied in this study was in the 5–100 μA range. While this exceeds the stimulus amplitudes that have been used in many *in vitro* studies that reported electrode damage with long-term pulsing, and several rodent studies that evoked behavioral response (Cogan, 2004; Houweling and Brecht, 2007; McCreery et al., 2010; Tehovnik, 1996), it is equivalent to the stimulus amplitudes that have been used to evoke perceptual or other effects in felines, macaques, and humans (see Table 5), as well as in other rodent studies (Otto et al., 2005b; Tehovnik, 1996). Some of these studies have noted damage to the tissue surrounding the electrodes using histological markers. While these histological markers indicate that tissue surrounding the electrodes reacted to stimulation, they cannot demonstrate whether or not stimulation affected device performance. By using electrophysiological markers such as recorded action potentials and ability to evoke physiological responses, we were able to demonstrate sustained functionality, including action potential recording, which implies tissue viability in the recording radius of the microelectrode tips.

The chronic changes in impedance observed in our experiments followed a pattern which has been previously noted in the literature. Mean impedance of passively implanted microelectrodes tends to increase over the first weeks of implantation, followed by a decrease over time (Williams et al., 2007). The causes of this pattern remain unclear, though it could result from ongoing processes of the tissue response to implanted devices. We observed this trend during the first weeks of implantation, followed by a continued decrease in impedance throughout the duration of the experiments in both passively implanted felines. The same phenomenon has also been observed in deep brain stimulation studies, where current was applied via chronically implanted macroelectrodes over time (Lempka et al., 2009). Important to note is that the impedances of both microstimulated and nonstimulated felines followed the same general pattern over time. The application of microstimulation did not drive electrode impedances out-of-specification, that is, >2 MΩ, as might be expected in the case of device failure or catastrophic tissue damage over time.

We also observed short-term decreases in impedance on stimulating electrodes with the application of microstimulation, which are reported to occur both *in vivo* and *in vitro* (Otto et al., 2006). These changes in impedance could reflect tissue response, for example, disruption of the glial scar by microstimulation. Impedance changes may also reflect processes of device damage known to occur with stimulation, such as dissolution of metallization or damage to electrode insulation. Finally, decreases could also indicate processes of electrochemical activation, which would change the valence state of the stimulating SIROF. The repeatability of the short-term impedance drops, with subsequent recovery, suggests that reversible electrochemical activation rather than cumulative damage may be reflected by these short-term changes in impedance values. The second chronic microstimulation paradigm in Feline 3 yielded larger acute impedance drops. This could be a result of either the increased current used to stimulate, or the increased time between stimulation sessions which would allow impedances to return to baseline. This further supports the idea that reversible electrochemical processes, rather than damage, contribute to observed impedance drops. Further, the maintained ability to stimulate and record indicates that any damage that may have occurred with microstimulation did not preclude device

functionality. Importantly, catastrophic changes in impedance, which might indicate device damage or tissue death, did not occur with the application of stimulation.

The microstimulation amplitudes used in this study never evoked seizure-like or aberrant electrical activity when performed on a single electrode. Further, no adverse behavioral responses occurred with the application of microstimulation in awake animals at 50 μA. However, a seizure did result from multielectrode simultaneous stimulation (Table 2; 07/Sep/2009) at 25 μA. Though no long-term device performance or physiological deficits were noted following this simultaneous multielectrode microstimulation, clearly the induction of a seizure event is unacceptable for any neural prosthetic application. In order to evoke complex spatiotemporal sensory percepts, interleaved multielectrode stimulation will need to be performed; it remains unknown how many electrodes can be simultaneously used without adverse physiological consequences. Patterns of stimulation can be sparsely distributed in both space and time, but must also be able to convey useful sensory information. An acceptable, safe balance between spatiotemporal patterns of microstimulation which convey useful sensory information and those which result in seizure must be found. Additionally, mechanisms to prevent unacceptably dense microstimulation will need to be implemented in the stimulation control electronics for human sensory prostheses to ensure that this failure mode does not occur.

It is unclear if complex spatiotemporal percepts can be evoked by patterned intracortical microstimulation. Testing patterned microstimulation in nonhuman primates is challenging (Bradley, 2004; Torab et al., 2011). It will be more efficiently addressed by means of psychophysical experiments conducted in human volunteers. Our ability to stimulate to effect and record electrophysiological data over multiple months demonstrated that tissue in the recording radius of the MEA remained viable after many months, and that the device maintained functionality over this time. These results suggest that microstimulation is ready for the next step in the development of sensory prosthetics, namely subchronic clinical trials in human subjects. Such trials will allow researchers to optimize stimulation parameters that are best at evoking sensory percepts, and will greatly speed the development of devices for the benefit of human patients.

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Abbreviations

EMG	electromyogram
MEA	multielectrode array
SIROF	sputtered iridium oxide film

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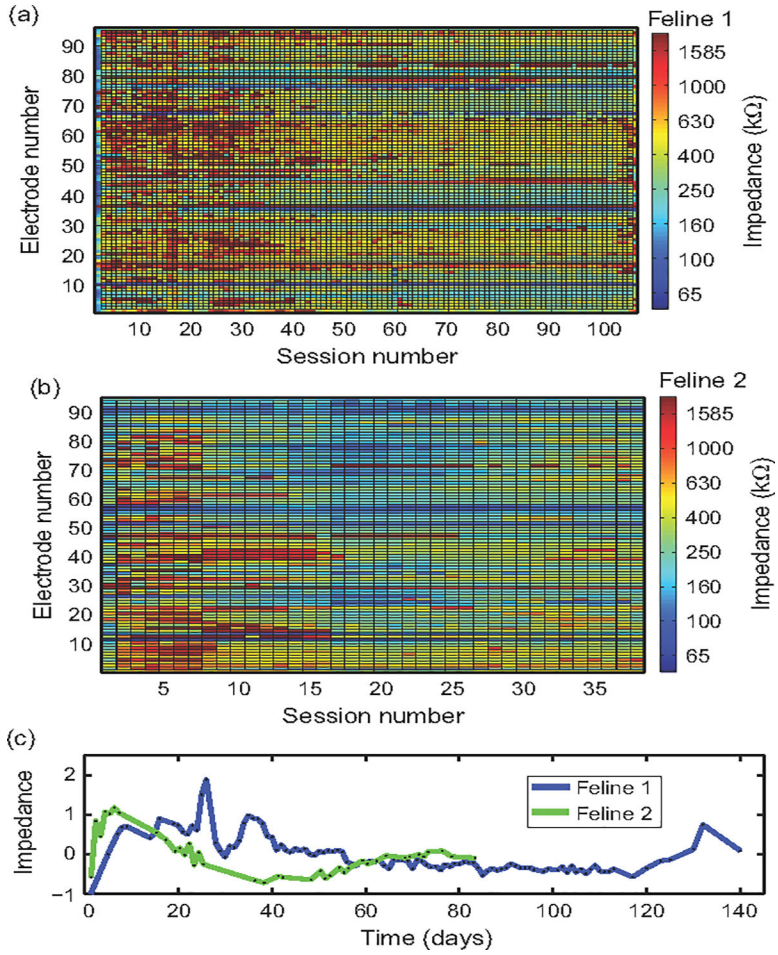


Fig. 1.

1 kHz impedance is variable over chronic timescales. (a, b) 1 kHz impedance measurements were made in the two nonstimulated felines over 8 and 3 months of implantation, respectively. Shown are impedance measurements colored by value. (c) Mean *Z*-scored impedance over time, in days, for both felines. Both felines exhibited a pattern of increase in impedance following implant that peaked within the first month, followed by a decrease toward preimplantation values ($p<0.01$, Wilcoxon's signed rank test).

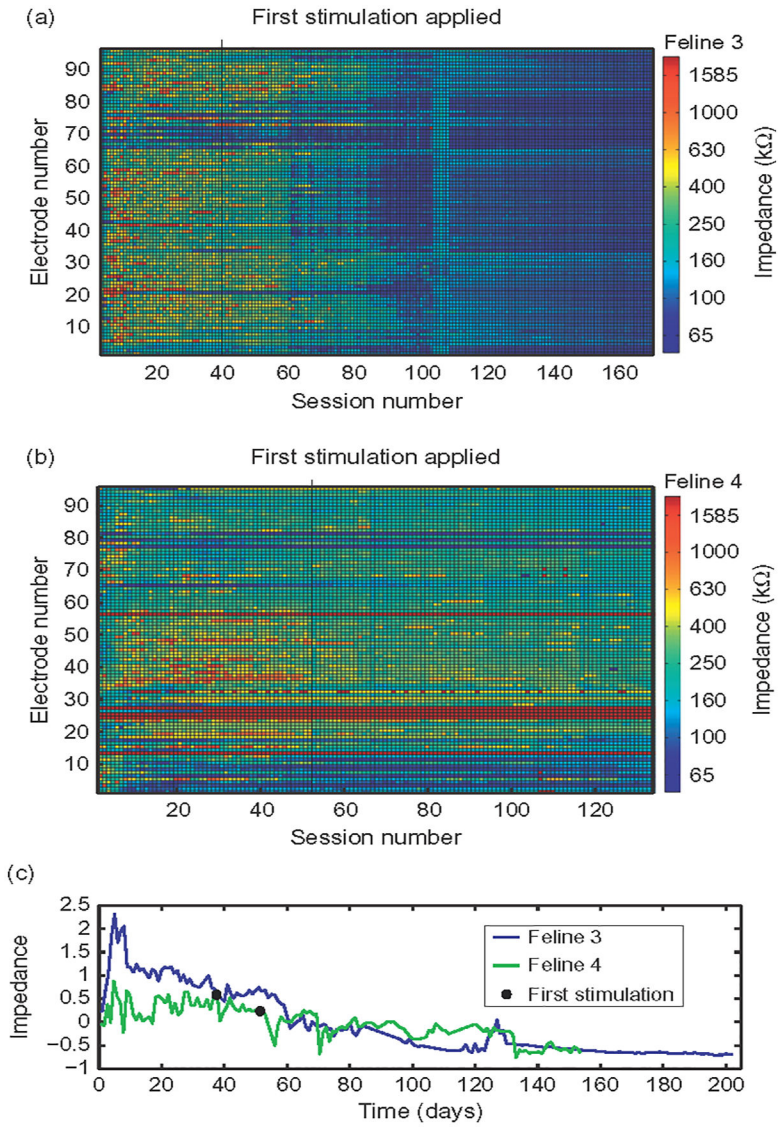


Fig. 2.

Microstimulation did not change 1 kHz impedance patterns. (a, b) 1 kHz impedance measurements, colored by value, across all 96 electrodes of the MEA in Felines 3 and 4. Black lines and circles indicate the first application of stimulation. (c) Mean *Z*-scored impedance over time (prestimulation values shown) over time in days. In both Feline 3 (blue) and Feline 4 (green), impedances dropped toward baseline over time ($p<0.01$, Wilcoxon's signed rank test).

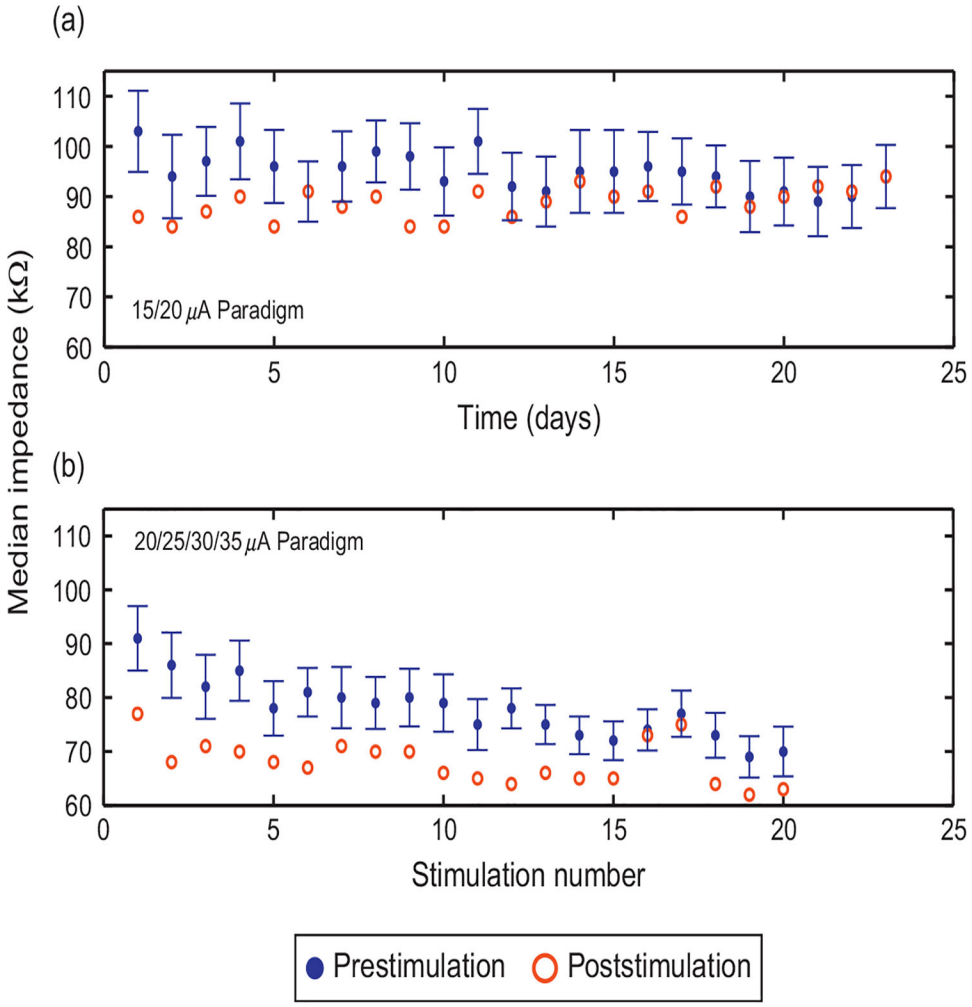


Fig. 3.

Microstimulation leads to acute drops in 1 kHz impedance. Median impedance before (blue, with standard error bars) and after (red) microstimulation on the 15 electrodes that passed current into tissue is shown for (a) the low stimulation paradigm, applied daily for 23 days and (b) the high stimulation paradigm, applied 20 times over a 6-week course. Impedance decreased significantly following microstimulation for both stimulus paradigms ($p<0.01$, Wilcoxon's signed rank test). Impedances drops were larger for the second paradigm ($p<0.01$, Wilcoxon's signed rank test).

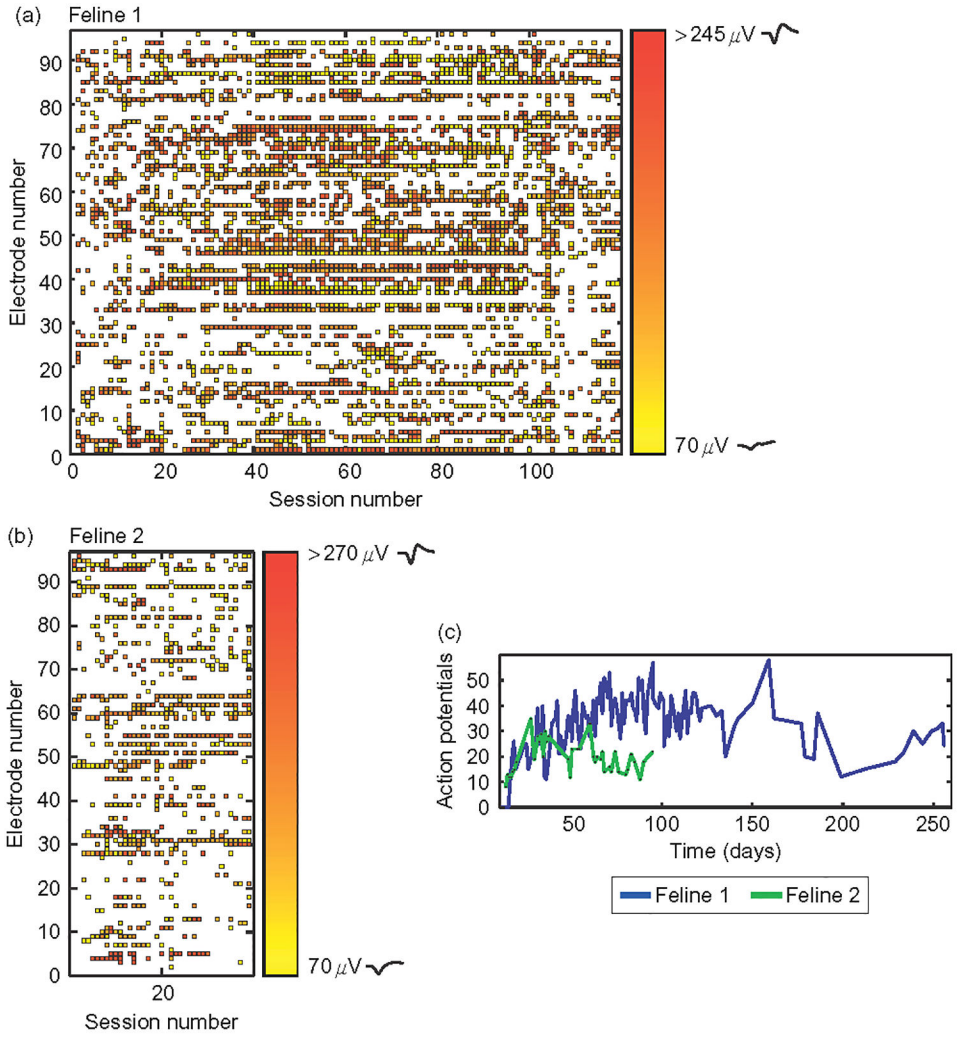
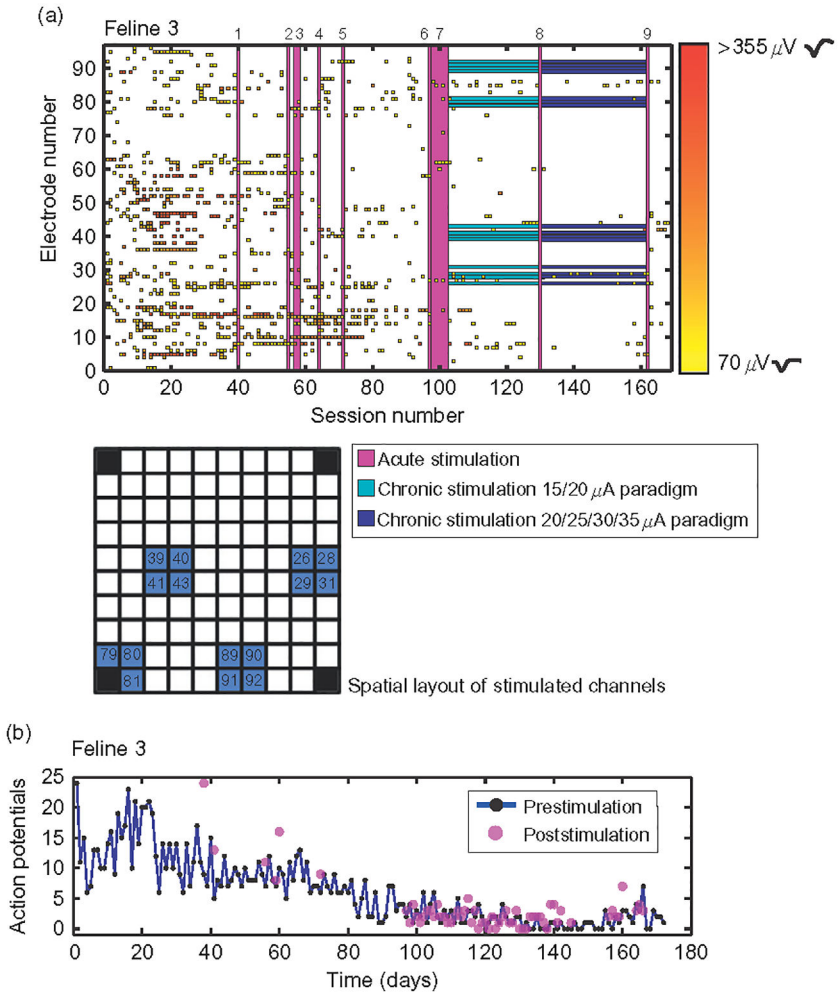


Fig. 4.

Action potential amplitudes over chronic timescales. (a and b) Raster plots of thresholded, sorted action potential recordings across the array for the duration of the study for Felines 1 and 2. Each square represents the mean of the furthest cluster from noise as isolated by principle component analysis. Waveforms shown on color bar are samples of action potential shapes isolated at low and high amplitudes. (c) Number of isolated action potentials recorded over time in days. There was an initial increase in the number of action potentials recorded, followed by a significant decrease in Feline 1 by the end of the 8 months of implantation ($p<0.01$, Student's t-test).



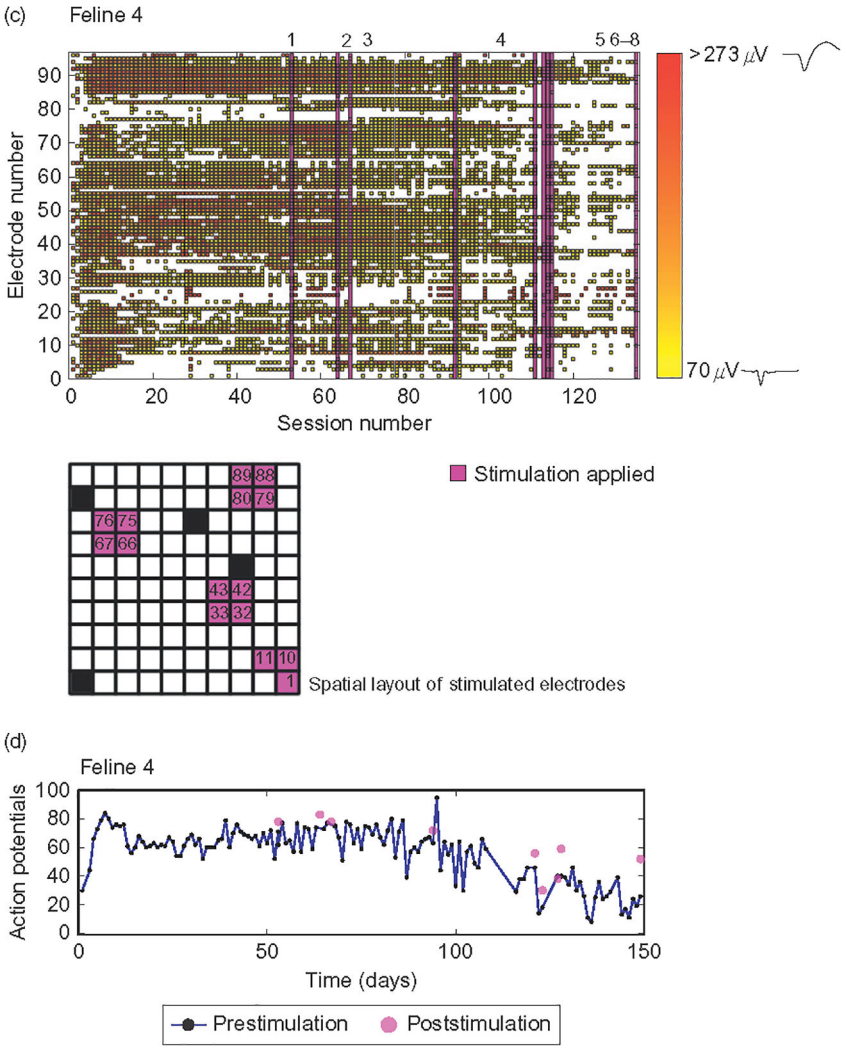


Fig. 5.

Microstimulation did not have a clear effect on the number or distribution of action potentials across the array over chronic timescales. (a and c) Raster of action potentials in Felines 3 and 4, color coded by amplitude over recording sessions. Purple bars represent an acute stimulation session, detailed by number in Table 2. Teal bars in Feline 3 represent chronic stimulation at the low stimulation paradigm listed in Table 2, while blue bars represent the high stimulation paradigm applied to the 15 electrodes highlighted. Grids show the spatial layout of electrodes stimulated, blue in Feline 3 and purple in Feline 4. Waveforms shown on color bar are samples of action potential shapes isolated at low and high amplitudes. (b, d) Number of action potentials recorded both over time before (blue) and after (purple) microstimulation in Felines 3 and 4. While the number of action potentials overall did decrease significantly by the end of the experiment in both felines ($p<0.01$, Student's t-test), the number of action potentials isolated acutely, that is, before and after individual stimulation sessions, did not decrease ($p<0.05$, Student's t-test).

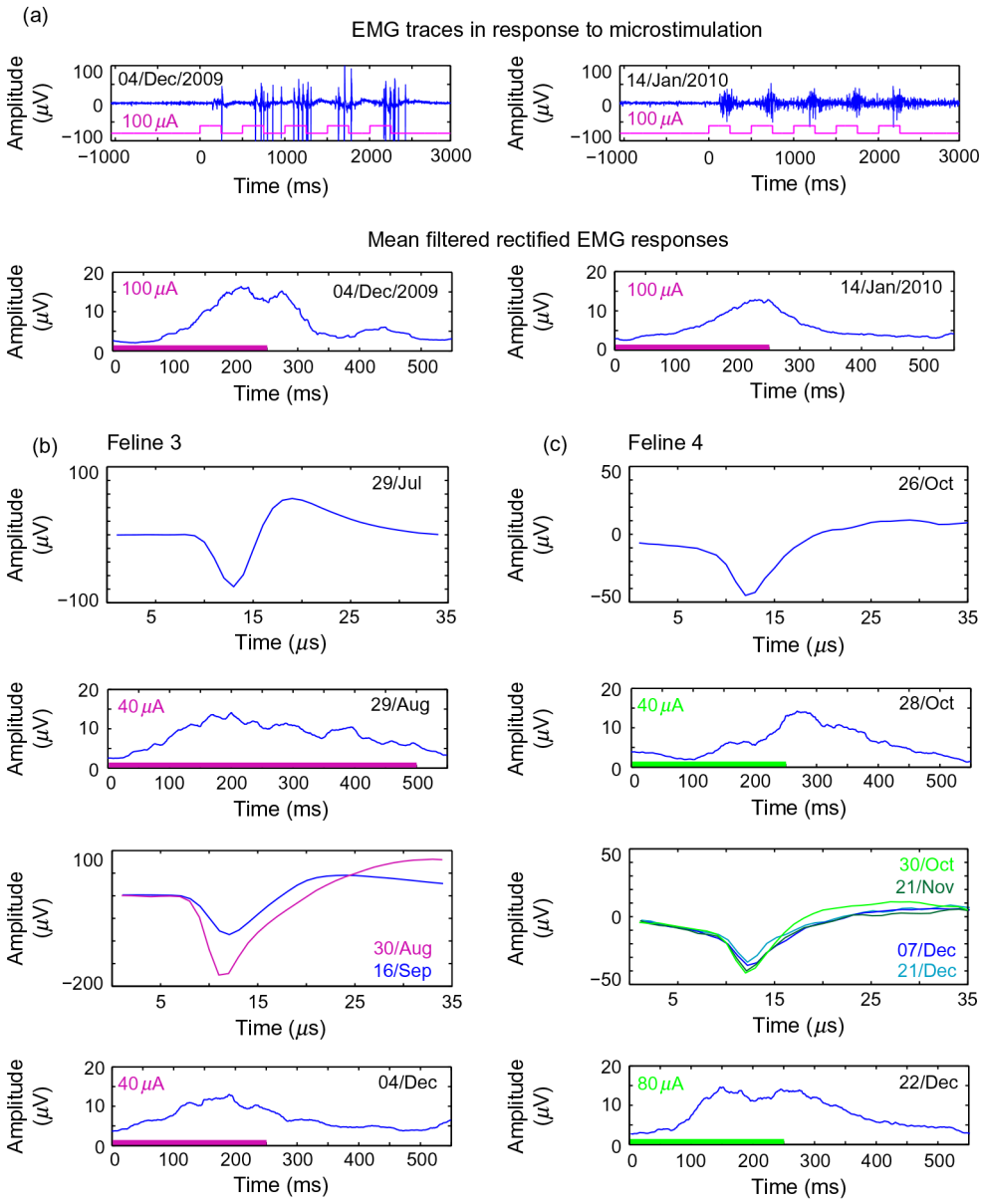


Fig. 6.

Chronically stimulated electrodes maintained the ability to stimulate to effect for multiple months. (a) Sample EMG recordings from both 04/Dec/2009 and 14/Jan/2009 evoked by stimulation on and electrode which applied current at 15 and 30 μA, according to the chronic paradigms detailed in Table 2, with the respective filtered mean rectified EMG responses below. Blue represents the recorded EMG response, while purple represents the pulses applied. (b) Sample action potentials recorded before and between electromyographic sessions during which responses were evoked at 40 μA in Feline 3. Colored bars along the time axis mark the application of microstimulation. (c) Sample action potentials recorded before and between EMG sessions in Feline 4. Dates of action potential recordings or stimulation and amplitude of stimulation applied are noted in each panel.

Table 1.

Arrays used

Animal	Array material, manufacture date, location	Implant date	Preinsertion impedances (kΩ)
Feline 1	SIROF 2006, Cyberkinetics/EIC	January 2007	Mean 16, Median 11, Min 4, Max 110
Feline 2	SIROF 2006, Cyberkinetics/EIC	October 2008	Mean 23, Median 14, Min 5, Max 160
Feline 3	SIROF 2009, Blackrock Microsystems	July 2009	Mean 50.4, Median 50, Min 42, Max 74
Feline 4	SIROF 2010, Blackrock Microsystems	July 2010	Mean 46.9, Median 47, Min 40, Max 63

Four SIROF arrays were chronically implanted in feline motor cortex. Felines 3 and 4 were microstimulated, while Felines 1 and 2 were used to obtain comparison recording-only data for long-term patterns of 1 kHz impedance and electrophysiological measures of chronic performance.

Table 2.

Summary of microstimulation sessions

Feline	Figure label (Fig. 5a or c)	Date	Description	Stimulus parameters	Amplitudes	Electrodes
3	1	14/Aug/2009	All-electrode (EMG efficacy test)	5 trains, 50 pulses	5–50 μA in steps of 5 μA	All
3	2	29/Aug/2009	All-electrode (EMG efficacy test)	5 trains, 50 pulses	5–35 μA, steps of 1-μA	43,78,84
3	3	01/Sep/2009 02/Sep/2009	All-electrode stimulation	2 rounds, 5 trains, 25 pulses	20/30, 30/35 μA	All
3	4	07/Sep/2009	Test of parallel stimulation	5 trains, 25 pulses	25 μA	Distributed pattern of 72 electrodes
3	5	14/Sep/2009	All-electrode stimulation	5 trains, 25 pulses	20–35 μA in steps of 5 μA	All
3	6	30/Oct/2009	All-electrode (EMG efficacy test)	10 trains, 25 pulses	20–40 μA in steps of 5 μA	All
3	7	31/Oct/2009–09/Nov/2009	15/20 μA on seven electrodes	100 trains of 25 pulses	15/20 μA	88,89,90,91/79,80,81
3	15/20 μA (Teal bars)	11/Oct/2009–03/Dec/2009 (23 sessions)	15/20 μA paradigm	200 trains (two rounds), 25 pulses	15 or 20 μA	20 μA—Electrodes 79,80,81 15 μA—Electrodes 26,28,29,31,39,40,41,43,89,90,91,92
3	8	04/Dec/2009	All-electrode (EMG efficacy test)	5 trains of 25 pulses	20–40 μA in steps of 5 μA	All
3	20/25/30/25 μA (Blue bars)	05/Dec/2009–13/Jan/2009 (20 sessions)	20/25/30/25 μA paradigm	200/electrode (two rounds), 25 pulses	20, 25, 30, or 35 μA	20 μA—Electrodes 39,40,41,43 25 μA—Electrodes 79,80,81 30 μA—Electrodes 89,90,91,92 35 μA—Electrodes 26,28,29,31
3	9	14/Jan/2010	All-electrode (EMG efficacy test)	5 trains of 25 pulses	100 μA	All
4	1	17/Sep/2010	All-electrode (EMG efficacy test)	5 trains of 25 pulses	5–50 μA in steps of 5 μA	All
4	2	28/Sep/2010	Test for feline response	5 trains of 25 pulses	5–50 μA in steps of 5 μA	All
4	3	01/Oct/2010	All-electrode (EMG efficacy test)	5 trains of 25 pulses	50–100 μA in steps of 10 μA	All
4	4	28/Oct/2010	All-electrode (EMG efficacy test)	5 trains of 25 pulses	20–60 μA in steps of 10 μA	All
4	5–7	24/Nov/2010–30/Nov/2010	25 μA paradigm	100 trains of 25 pulses	25 μA	1,10,11,32,33,42,43,66,67,75,76,79,80,88,89
4	8	01/Dec/2010	All-electrode (EMG efficacy test)	5 trains of 25 pulses	40–100 μA in steps of 10 μA	All
4	9	22/Dec/2010	All-electrode (EMG efficacy test)	5 trains of 25 pulses	50–100 μA in steps of 10 μA	All

Microstimulation was applied to Felines 3 and 4 according to several different stimulus paradigms depending on the goals of microstimulation, for example, to evaluate efficacy or to determine the effects of periodic stimulation on device functionality.

Table 3.

Summary of impedances during implantation

Feline	Mean (kΩ)	Median (kΩ)	Standard deviation (kΩ)	Recording sessions	Electrodes
1	462	353	144	107	93
2	358	285	161	39	96
3	157	91	78	168	96
4	244	99	73	134	89

Impedance values were used as a measure of device performance over the course of implantation and microstimulation. Shown here is summary data on impedances from all four MEAs used in this study.

Table 4.

Summary of thresholded action potential amplitudes

Feline	Number of recording sessions	Mean number of electrodes which recorded action potentials, all sessions	Mean number of electrodes which recorded action potentials, first 30 sessions	Mean number of electrodes which recorded action potentials, last 30 sessions
1	123	34	38	33
2	39	20	18 (first 10 sessions)	17 (last 10 sessions)
3	168	6	9	2
4	135	57	73	40

Electrophysiological data recorded from each MEA was used as a chronic measure of device performance. Shown are summary statistics for all four MEAs used in this study.

Table 5.

Summary of selected intracortical microstimulation studies

Citation	Model system	Electrode type	Reporter of efficacy	Current range applied	Frequency (Hz)	Impedance range 1 kHz	Damage?
Murphey and Maunsell (2008)	Macaque	Platinum/iridium, single electrode	Behavioral task (visual)	Up to 50 μA	200	0.2–1.5 MΩ	No
Murphey and Maunsell (2007)	Macaque	Platinum/iridium, single electrode	Behavioral task (visual)	3–12 μA	200	0.2–1.5 MΩ	No
McCreery et al. (2010)	Feline	Activated iridium, 16 microelectrode array	N/A	10–20 μA	50	Not reported	Yes
McCreery et al. (2002)	Feline	Activated iridium, 16 microelectrode array	Evoked potentials in medulla	0–32 μA	50	0.2–1.5 MΩ	No
Graziano (2005)	Macaque	Tungsten, single microelectrode	Arm movements	5–100 μA	100–250	1–2 MΩ	No
Graziano et al. (2002)	Macaque	Tungsten, single microelectrode	Arm movements	Up to 150 μA	200	0.5–2 MΩ	No
Tehovnik et al. (2003)	Macaque	Platinum/iridium, single microelectrodes	Behavioral task (visual)	Up to 30 μA	200	1–2 MΩ	No
Tehovnik et al. (2002)	Macaque	Platinum/iridium, single microelectrodes	Behavioral task (visual)	Up to 40 μA	200	1–1.5 MΩ	No
Romo et al. (2000)	Macaque	Platinum/tungsten, seven microelectrodes	Behavioral task (flutter discrimination)	65–100 μA	50–200	1–1.5 MΩ	No
Romo et al. (1998)	Macaque	Platinum/tungsten, seven microelectrodes	Behavioral task (flutter discrimination)	65–100 μA	50–200	1–1.5 MΩ	No
Rousche and Normann (1999)	Feline	Platinum, 96 electrode Utah Electrode Array	Behavioral task (auditory)	100 μA	25–2000	30–149 kΩ	No
Torab et al. (2011)	Macaque	SIROF, 96 electrode Utah Electrode Array	Behavioral task (visual)	0–96 μA	200	40 kΩ−2 MΩ	No
Bradley (2004)	Macaque	Iridium, 192 electrode array	Behavioral task (visual)	12–20 μA	200	80 kΩ−1.6 MΩ	No
Bak et al. (1990)	Human	Iridium, arrays of 1–3 electrodes	Verbal report (visual percepts)	20 μA-2 μA	100	Not reported	No
Schmidt et al. (1996)	Human	Iridium, 12 single electrodes, 13 paired electrodes	Verbal report (visual percepts)	1–80 μA	200	Not reported	No

The stimulus amplitudes and parameters applied in this study were similar to those used in other microstimulation experiments which evoked sensory percepts. Shown are sample studies for comparison.