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Selective Facial Muscle Activation with Acute and Chronic Multichannel Cuff Electrode Implantation in a Feline Model

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Abstract

Objectives: Facial paralysis is a debilitating condition with substantial functional and psychological consequences. This feline-model study evaluates whether facial muscles can be selectively activated in acute and chronic implantation of 16-channel multichannel cuff electrodes (MCE).

Methods: Two cats underwent acute terminal MCE implantation experiments, 2 underwent chronic MCE implantation in uninjured facial nerves (FN) and tested for 6 months, and 2 underwent chronic MCE implantation experiments after FN transection injury and tested for 3 months. The MCE were wrapped around the main trunk of the skeletonized FN, and data collection consisted of EMG thresholds, amplitudes, and selectivity of muscle activation.

Results: In acute experimentation, activation of specific channels (ie, channels 1-3 and 6-8) resulted in selective activation of *orbicularis oculi*, whereas activation of other channels (ie, channels 4, 5, or 8) led to selective activation of *levator auris longus* with higher EMG amplitudes. MCE implantation yielded stable and selective facial muscle activation EMG thresholds and amplitudes up to a 5-month period. Modest selective muscle activation was furthermore obtained after a complete transection-reapproximating nerve injury after a 3-month recovery period and implantation reoperation. Chronic implantation of MCE did not lead to fibrosis on histology. Field steering was achieved to activate distinct facial muscles by sending simultaneous subthreshold currents to multiple channels, thus theoretically protecting against nerve damage from chronic electrical stimulation.

Conclusion: Our proof-of-concept results show the ability of an MCE, supplemented with field steering, to provide a degree of selective facial muscle stimulation in a feline model, even following nerve regeneration after FN injury.

Level of evidence: N/A

Keywords

facial nerve, neuroprosthetic, facial paralysis, cuff electrode, EMG

Introduction

Permanent facial paralysis and paresis (FP) is a debilitating condition caused by damage to the facial nerve (FN), which controls muscles responsible for facial expression, proper enunciation and communication, blink function, corneal protection, and maintenance of oral competency.[1] FN damage can lead to a loss of muscle tone, and over time, cause muscle atrophy and scar tissue development. FP can arise from a variety of causes including tumor, surgery, trauma, or infection, and may result in problems such as eye irritation, visual impairment, drooling, proper retention of intraoral food, and cosmetic deformaties.[2] FP has an incidence of approximately 70 per 100 000, with 127 000 new cases diagnosed annually in the United States alone.[2,3] While the majority of patients recover some function, some develop significant dysfunction such as facial asymmetry, synkinesis, and spasms. Several surgical interventions, including

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static and dynamic options, have been described for patients with unilateral FP and are utilized by otolaryngologists and plastic surgeons worldwide.[4] In cases of irreversible denervation and flaccid paresis, nerve reconstruction can be attempted. Beyond that, static options introduce non-muscular material to the face to aid in function or cosmesis, and dynamic options such as the gracilis myoneurovascular free tissue transfer, restore some degree of volitional muscular function.[5,6] However, each of these interventions only address specific parts of the face, may require multiple procedures or reoperation, and can have a 10% to 15% failure rate.[7,8]

Previous works have suggested that neuroprosthetic technologies may be efficacious in the treatment of FP in animal models.[9-11] Functional restoration of paretic or paralyzed FN activity (in the case of intact and still functional FN and distal musculature) requires selective stimulation of the fascicle, which then subsequently activates specific muscles. Here, we test the ability of a multichannel cuff electrode (MCE) to selectively activate feline facial muscles in both acute and chronic settings, and in both uninjured and injured FN. We also demonstrate the ability to utilize *field steering*, a process by which multiple stimulation sources enable programmable and directed current flow through tissue. This is done to reduce the total charge per pulse sent to the nerve tissue while maintaining adequate facial muscle activation as measured by electromyography (EMG).[12]

Materials and Methods

Animals

All procedures were conducted in accordance with the National Institute of Health Animal Welfare Guidelines and with a protocol ethically approved by the University of California, Irvine Institutional Animal Care and Use Committee. Six female domestic shorthaired cats (*Felis catus*) were obtained from a research breeding colony. Two cats underwent acute terminal experiments, 2 underwent chronic implantation experiments where the implanted MCE was tested for a period of 6 months, and the last 2 underwent chronic implantation experiments after nerve transection where the implanted MCE was tested for a period of 3 months.

Anesthesia

In the acute experiments and during the biweekly testing of the implanted MCE, a light level of anesthesia was induced with an intramuscular injection of 0.7 mL of ketamine (20 mg/kg) and 0.3 mL of acepromazine (1 mg/kg); with a booster dose of 0.3 mL of ketamine given when necessary to maintain stable sedation. Intravenous pentobarbital was also used in the terminal experiments to maintain sedation.

MCE Specifications

A custom 8-channel MCE (MicroProbes for Life Science, Gaithersburg, MD) with an inner diameter of 1.5 mm was used. The MCE contained 2 "rings" of electrodes with each ring containing 4 individual 100 μm rectangular (tripolar) platinum contacts housed within a silicon enclosure (Figure 1). Each electrode was positioned at 0, 90, 180, and 270 degrees around the ring. This configuration allowed for monopolar stimulation of 4 discrete anatomical locations within each ring, which ultimately allowed for 8 individual contact points with the nerve. The charge injection capacity was calculated to be ~164 $\mu C/cm^2$ at 1 mA and 82 μs per phase in duration (0.5-1.5 μC/phase) with electrode impedance of 0.5 kΩ at 1000 Hz. Field steering (ie, stimulation of 2 contacts simultaneously) allowed for numerous stimulation permutations.

Stimulus Generation

Electrical pulses were generated by a custom optically isolated 16-channel current source controlled by 16-bit digital-to-analog converters (RX8, Tucker-Davis Technologies (TDT; Alachua, FL). Each channel had a maximum output of 1 mA and 4 different current intensity were tested: ~1, ~0.5, ~0.3, and 0.1 mA. In order to better investigate EMG responses, in this phase of our study we presented only a single biphasic pulse every second rather than a continuous train of pulses. This allowed us to have EMG with minimal artifact, as the stimulus artifact was confined to the first ~1 ms of data. Stimuli were single charge-balanced biphasic electrical pulses, initially cathodic, 82 μs per phase, with response stimulus charge levels of 26 to 41 nC per phase.

Electromyography (EMG)

Following biphasic current delivery to a MCE channel, EMG activity from concentric muscle contraction in the feline hemiface was detected and recorded with sub-dermal electrodes by using System III hardware from Tucker-Davis Technologies (TDT; Alachua, FL) controlled by custom MATLAB software (The Mathworks; Natick, MA). Four sub-dermal electrodes were used to record from 4 different facial muscles: *levator, orbicularis oris, orbicularis oculi*, and *nasalis*. The reference and the ground were placed in the lateral/long *triceps* head on the front limb of the cat. Ten sweeps per condition were collected. The sampling frequency was 24 414 Hz. A high-pass digital filter with a cut-off frequency at 10 Hz was applied online to the raw data, the signal was down-sampled in real-time to 3052 Hz and then the average of the 10 sweeps was band-pass filtered offline using a 4th order, band-pass Butterworth filter (100-1500 Hz).

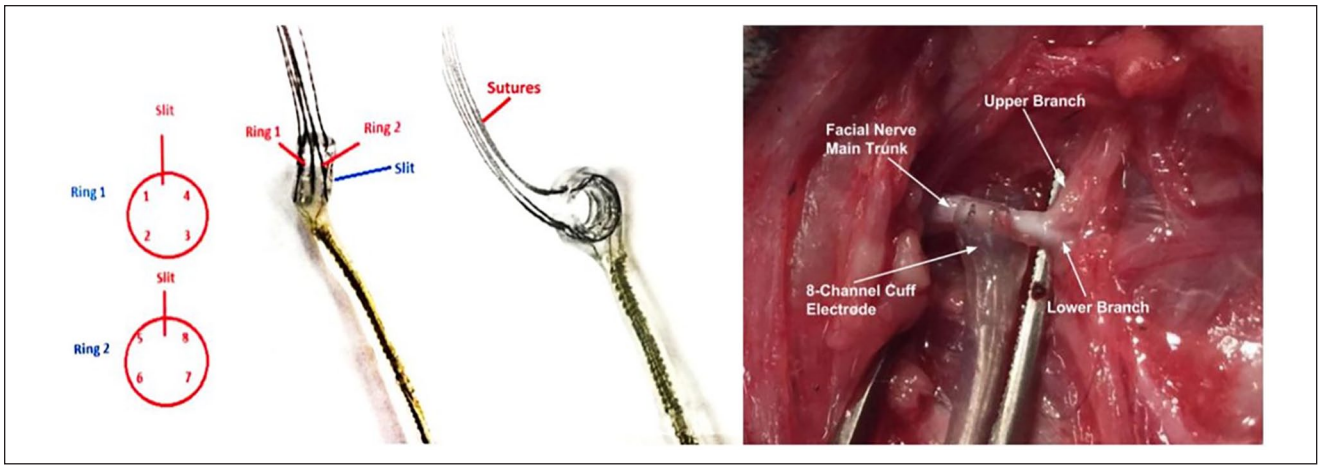

Figure 1. (Left) 8-channel MCE with 2 electrode "rings," each with 4 rectangular (100 μm) platinum electrodes in a silicon enclosure spaced 90° apart from one another. The current source is controlled by a 16-channel digital-to-analog converter (TDT RX8) that delivers biphasic electrical pulses (82 μs in duration per phase, initially cathodic). (Right) Intraoperative image of implanted MCE.

Acute Experiments

EMG needle electrodes were inserted into 4 facial muscles, including the *orbicularis oris, orbicularis oculi, nasalis*, and *levator auris longus*. For MCE implantation, an infraauricular incision was performed and the parotid gland was dissected through until the extratemporal FN trunk was identified and skeletonized. The MCE was subsequently positioned on the main trunk of the FN (positioning was not pre-determined and was dictated by surgical exposure and access to the nerve), and each of the 8 MCE channels was individually stimulated while EMG responses from each facial muscle were recorded.

Chronic Experiments with Uninjured FN

For chronic nerve implantation surgeries in 2 anesthetized cats, a preauricular incision was made under sterile conditions and dissection through the parotid gland proceeded until the FN trunk was identified and skeletonized. The MCE was positioned at the main trunk of the FN and secured with incorporated nylon sutures. The positioning of the cuff electrode (ie, site and angle of contact) was dictated by the surgical anatomy and FN access. The MCEs wire connectors were tunneled subcutaneously along the side of the head and fastened through to a skull mounted Omnetics (Minneapolis, MN) connector that was housed within a stainless-steel cylinder with a screw-on cap. After 6 months, both facial nerves were harvested for histological processing (hematoxylin and eosin [H&E] and trichrome stains) and analysis.

Chronic Experiments with Injured FN

To produce a standardized FN injury, a pre-auricular incision was made, and the FN trunk was identified and skeletonized. The nerve was then intentionally damaged by a complete transection with scissors and reapproximating of nerve endings to contact without suturing, thus producing a Sunderland fifth degree neurotmesis injury. The incision was closed in layers. Immediate and complete unilateral FP was observed in all cats that received a transection-reapproximating injury. Eye ointment was routinely applied to protect the cornea. In a second surgery 3 months post-injury, the FN trunk was again identified, and an MCE was implanted following the procedures detailed previously.

Results

Acute Experiments

In acute animal experiments and normal nerves, activation of individual channels resulted in differential activation of facial muscles (Figure 2). Namely, activation of channels 1-3 and 6-8 resulted in robust activation of *orbicularis oculi*, whereas activation of channels 4, 5, or 8 led to stronger activation of *levator auris longus*.

Chronic Experiments

MCE implantation in *cat A* resulted in stable and selective activation of facial musculature EMG thresholds and amplitudes over a 5-month implantation period (Figure 3 and Supplemental Figure 1). This selectivity is visually demonstrated in Supplemental Video 1. After 6 months the EMG response seemed to deteriorate, possibly due to debris that accumulated on the cup connector that interfered with conductivity of current. Interestingly, a relatively stable response was particularly observed up to 5 months at 1 and 0.5 mA in the *levator* (channel 1) and in the *nasalis* (channels 2 and 7). Minor variability was seen in the other electrodes, possibly due to variation in the exact placement of

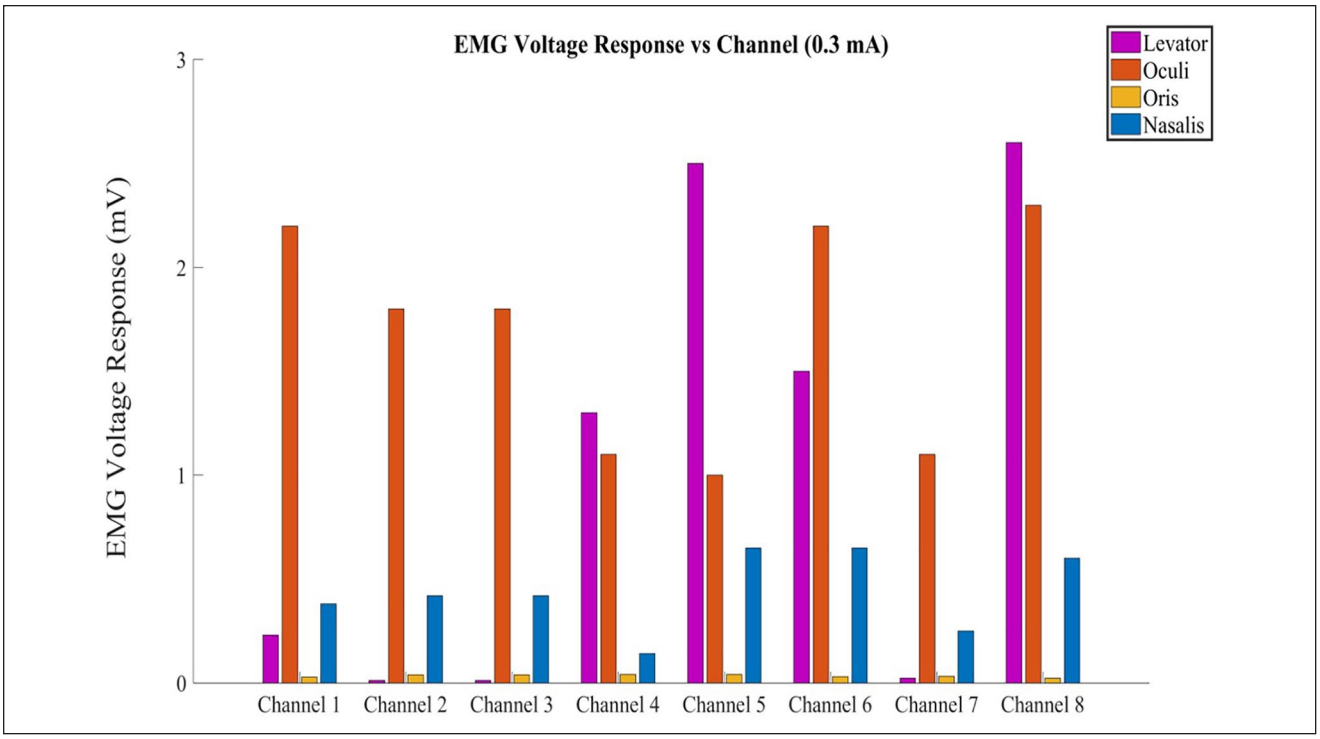

Figure 2. Representative feline data of acute experimentation. Activation of channels 1-3 and 6-8 resulted in robust activation of *orbicularis oculi*. Activation of channels 4, 5, or 8 led to stronger activation of *levator auris longus*.

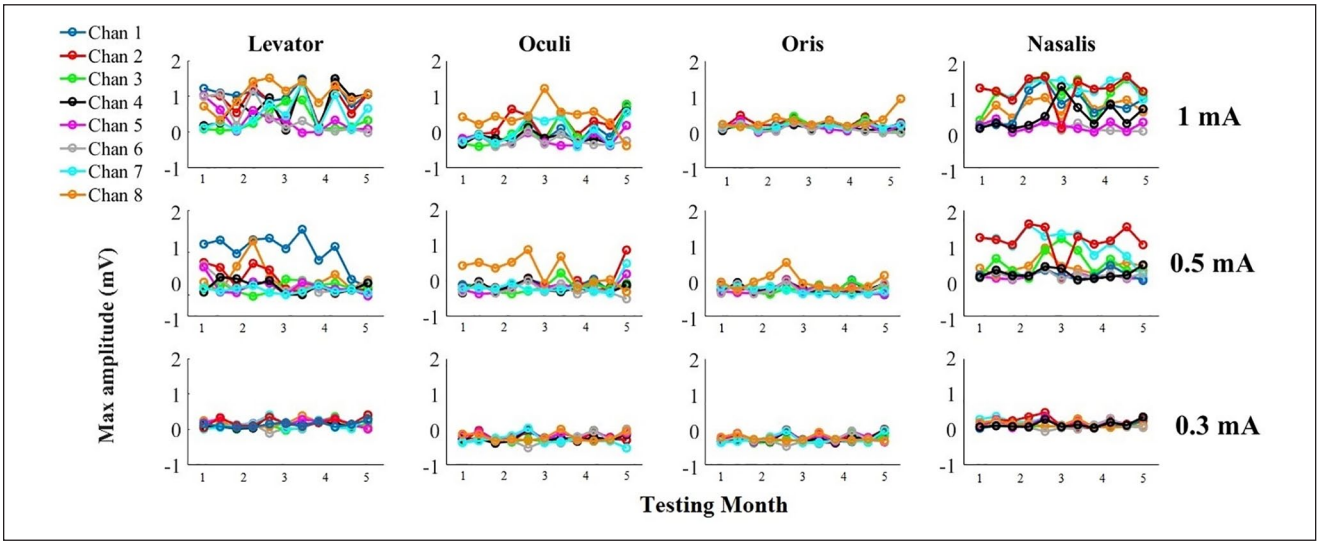

Figure 3. Representative feline data of chronic experimentation. Max EMG amplitude extracted for each electrode tested at each of the testing day. A relatively stable response was particularly observed up to 5 months at 1 and 0.5 mA in the levator (channel 1) and in the Nasalis (channels 2 and 7).

the electrodes in the muscles. In *cat B*, the surgical implantation of the MCE resulted in a stretch injury that temporarily paralyzed the FN. Following recovery of facial movement, the implanted MCE was partially functional over a 6-month implantation period, although stimulation of the various channels did not result in selectivity in any of the channels tested (Supplemental Figure 2). On histological examination, no marked increase in fibrosis was visualized in the chronically implanted facial nerve compared to the contralateral normal nerve (Figure 4).

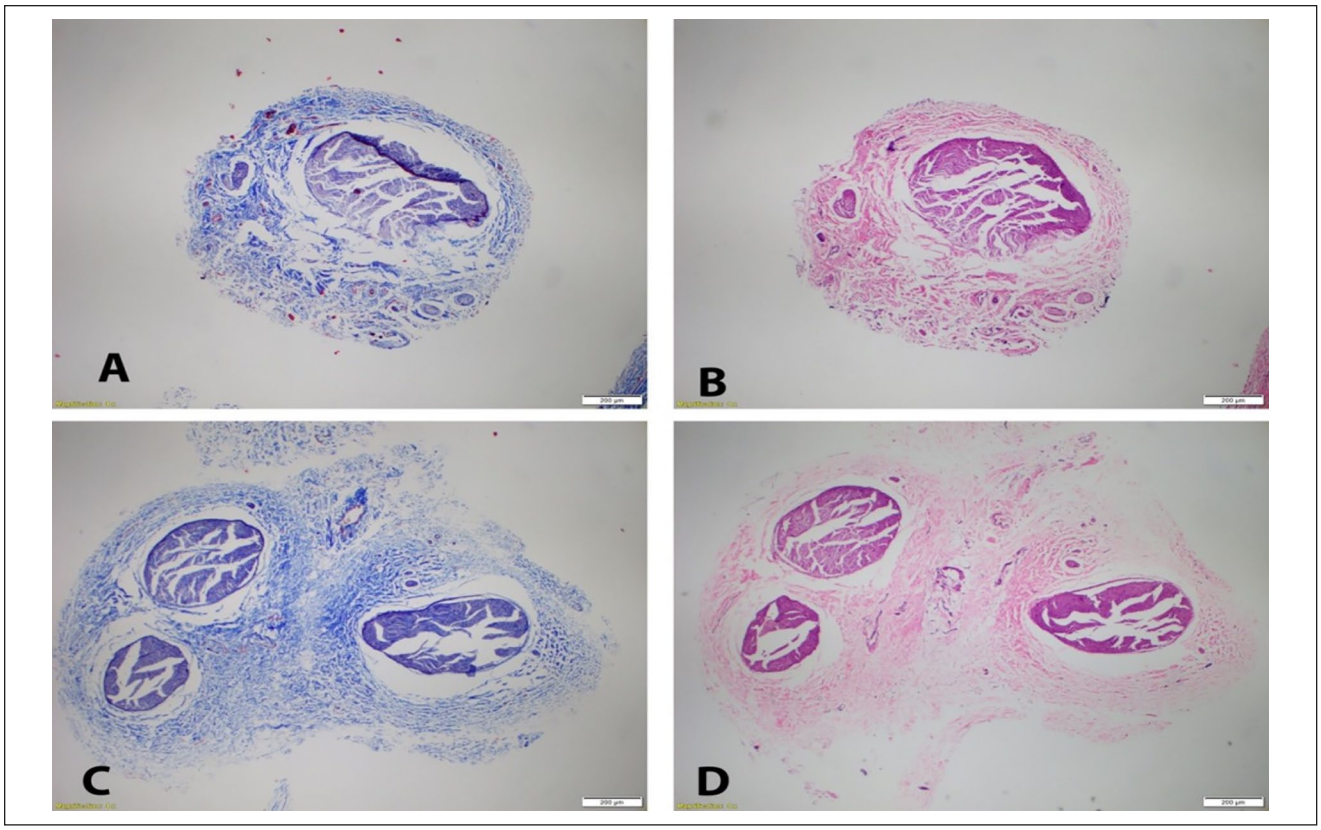

Figure 4. Representative feline data of chronic experimentation. Light microscopic histological images of implanted nerves at 4× magnification. (A) Cross section of the FN chronically implanted with the MCE evaluating epi- and peri-neural fibrosis (trichome stain, 4× magnification). (B) Section of the facial nerve chronically implanted with the MCE demonstrating no significant increase of fibrosis (hematoxylin and eosin [H&E] stain, 4× magnification). (C) Section of normal FN evaluating epi- and peri-neural fibrosis (trichome stain, 4× magnification). (D) Section of normal FN demonstrating no significant increase of fibrosis (H&E stain, 4× magnification).

Field Steering

Field steering was achieved to activate distinct facial muscles by sending subthreshold current to 2 channels simultaneously, which is demonstrated in Figure 5. By reducing the current levels being delivered to any individual electrode from 1 or 0.5 mA to 0.3 mA, we were able to achieve the same functional muscle movement using field steering (Supplemental Video 2). This allowed delivering of current below the threshold at which nerve damage from chronic electrical stimulation can be observed (ie, Shannon criteria k values decreased from 2.8 to 1.8).[13]

Chronic Experiments after FN Injury

MCE implantation after complete FN transection injury resulted in similar selectivity results. Both cats with implanted MCE's after FN transection-reapproximating achieved stable and selective activation of individual facial muscles over a 3-month implantation period. These results were achieved through individual channel activation and through field steering, the latter of which resulted in optimal selective facial stimulation (Supplemental Video 3). Similar to our previously describe chronic experiments without nerve injury, the EMG responses of these experiments did deteriorate after approximately 6 months, likely due to the observed accumulating debris collecting within the cap and connector, and resulting interference with conductivity of current.

Discussion

In this study, we demonstrated the ability of a MCE to provide a degree of selective stimulation and activation of individual facial muscles in the acute and chronic feline-model experiments. Selective muscle activation was obtained even after a complete transection-reapproximating nerve injury after a 3-month recovery period. We were able to demonstrate field steering to activate distinct facial muscles by sending simultaneous subthreshold currents to multiple channels. Chronic implantation of MCE did not lead to fibrosis on histology, and although the MCE implanted in *cat B* was functional, the lack of selectivity was likely due to the stretch injury and an increase in impedance of the

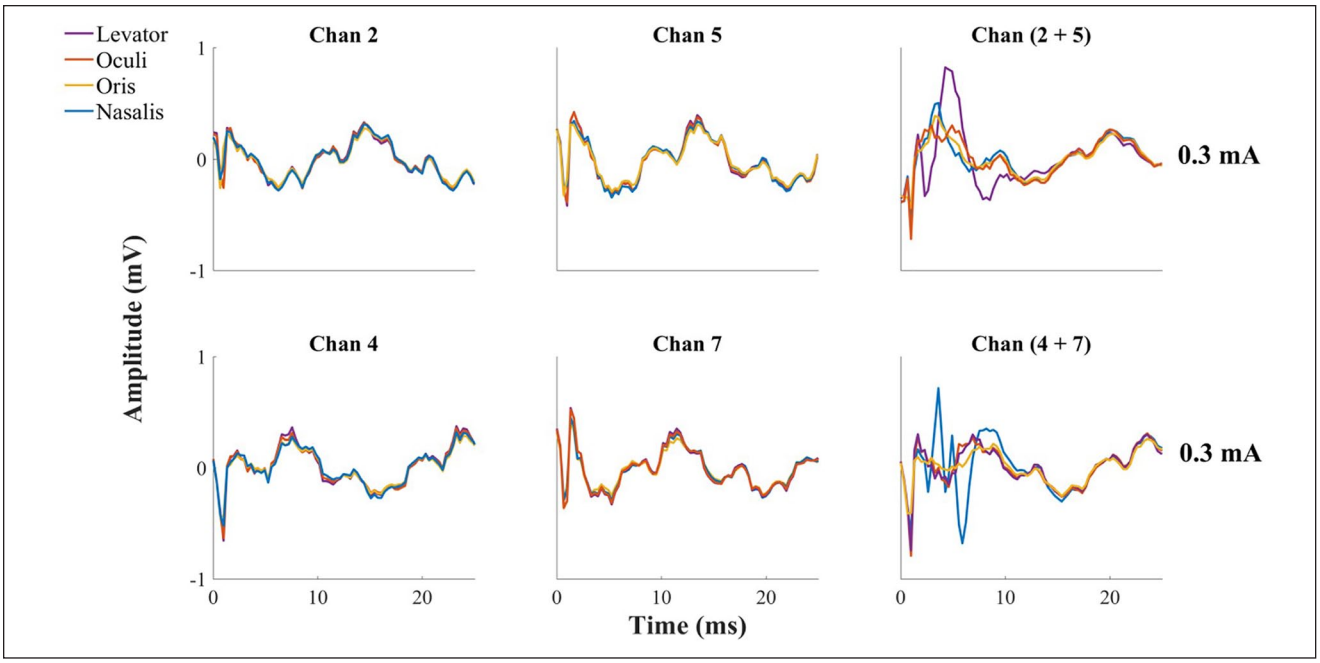

Figure 5. Effect of field steering. Sending 0.3 mA of current to channels 2, 4, 5, or 7 alone did not elicit a detectable EMG response in any of the recorded muscles (Left and middle figures). Simultaneous activation of channels 2 and 5, or channels 4 and 7, resulted in selective activation of *levator* or *nasalis*, respectively.

implanted Omnetics connector due to a buildup of debris and tissue within the female contacts. The proposed selective stimulation of the facial muscles is clinically relevant even when considering the possibility that it is often the undesirable action of antagonist muscles that restrict movement in aberrantly regenerated states, because this methodology can be paired with kilohertz electrical stimulation (KES) technology for conductive nerve blockage, as we are doing in a current study, to provide a multi-faceted approach to proper and selective muscle activation. This work also demonstrates the ability of neuroprosthetic technology, specifically MCE's, to maintain a consistent ability to stimulate individual facial muscles after complete FN injury. These results bode well for a possible translation of this technology into a novel clinical treatment of FN injury.

Previous work has demonstrated the utility of a penetrating microelectrode array (MEA), when inserted into the FN, to stimulate movement and contraction in specific muscles in a feline model.[9,10,13] However, the histological reaction and electrode migration that ensued following chronic implantation warranted the investigation of alternative electrodes that would mitigate the fibrotic response and have enhanced stimulation characteristics when chronically implanted. These results have led to the exploration of the ability of a MCE to selectively activate facial muscles. Classically, cuff electrodes activate nerves in an "all-or-none" fashion, with minimal selectivity of fascicular activation. However, by delivering low levels of current to discrete anatomical locations of the FN epineurium, rather than stimulating the entire FN, we demonstrate the ability to subsequently active discrete facial muscles.

It has been suggested that there is little to no somatotopic organization of the human facial nerve at the main trunk. Moreover, if a patient undergoes a facial-hypoglossal anastomosis for facial tone, new axons originating from the hypoglossal nucleus extending into the distal facial nerve will unlikely have any degree of bundling or organization at the level of the anastomosis. Nevertheless, neuroprosthetic device could in principle still have application for facial reanimation for several reasons. First, cuff electrodes could be designed with even smaller and more numerous contact points to provide far more discrete activation of more limited numbers of axons than we were able to achieve with our off-the-shelf cuff array with large electrode-to-nerve surface area ratios. Furthermore, an array with a combination of penetrating and surface electrodes could provide far more precise stimulation of discrete neural fibers. Second, an implant with multiple cuff electrodes could be placed at more distal branches, including or instead of the main trunk, and programmed to provide more specific stimulation of different regions of the face. Third, in the setting of total facial paralysis, some degree of non-specificity of elicited facial movements would likely be tolerated by patients. For instance, if there is some degree of brow elevation or platysma contraction during an electrically-evoked smile, and the smile provides a desirable degree of symmetry with motion, the extraneous movements of the face could be acceptable.

As mentioned, by refining the electrode design and optimizing stimulation parameters, the selectivity of muscle activation can be improved even further. It has been shown that spatial selectivity can be improved using MCEs, as each channel is able to stimulate neighboring muscle fascicles that are in close proximity to the stimulation contact site while reducing current spread.[14-16] Selectivity has also shown to be improved using a monopolar versus tripolar cuff electrode configuration. Briefly, the monopolar configuration has 4 contacts, 4 sets of monopolar contacts, while the tripolar configuration has 12 contacts, 4 sets of tripolar contacts, that are equidistant from each other surrounding the nerve-cuff electrode[17] Prior work has demonstrated the application of a monopolar 4 contact nerve-cuff electrode for selective and independent activation of either of the 4 motor fascicles in the sciatic nerve irrespective of the placement of the channels with respect to the specific motor fascicle.[18] Selectivity is further improved in a more practical manner using multi-contact stimulation and the "field steering" phenomenon, which creates novel excitation regions at sites other than the target region of the stimulated channel.[19]

The application of neuroprosthetic technologies to the FN, such as the MCE, may allow for a facial reanimation system that could augment or replace current therapies. For example, by selectively activating the *frontalis, orbicularis oculi* and *oris*, and *depressor anguli oris* muscles in humans, therapeutic goals for FP could be accomplished in a single, outpatient surgery without facial incisions. These goals include: (1) providing a baseline level of stimulation to provide tone and bulk to the muscles and facial symmetry at rest, (2) regular and timed stimulation of the *orbicularis oculi* to routinely blink and protect the cornea, and (3) detection of muscle contraction on the contralateral (normal) side and consequent, simultaneous, and effort-matched stimulation of the same muscles on the paralyzed side (ie, a closed-loop system). The results presented in this study are in the setting of MCE implantation in both normal and injured feline nerves. However, the MCE results presented in this study are pre-clinical and clearly do not constitute validation of the MCE in selectively activating human facial muscles. Future studies are warranted to refine and eventually translate this technology towards clinical implementation.

One limitation of the study was that all the functional movements were not quantified; however, the supplemental videos qualitatively demonstrate the evoking selectivity of facial displacement. Another limitation was a lack of nerve histomorphometry to assess axonal integrity and occult neural insult, in addition to the standard histology that was already performed. Moreover, the proposed MCE will likely not work in a patient with permanent flaccid facial paralysis with chronic neurodegeneration and distal muscle atrophy. Despite these limitations, the presented manuscript provides valuable proof-of-concept results demonstrating a modest degree of selective activation of feline facial muscles via MCE stimulation of the FN, warranting further studies in human subjects. Ultimately, the application of MCE technology to selectively stimulate motor nerve fibers/fascicles could have further clinical applications to other peripheral or cranial motor nerves. Aside from FP, paralysis/paresis of cranial and peripheral motor nerves is a debilitating and widespread problem that results from complete or partial injury at the level of the nerve. Each year in the U.S., nearly 5.4 million people, or 1.7% of the population acquire a new motor nerve deficit.[20] Bioelectronic approaches are readily available to restore function in numerous clinical pathologies, however, the application of neuroprosthetic devices to restore function or augment endogenous recovery has only recently grained traction as a therapeutic option in motor nerve dysfunction.[20-23] Furthermore, since high grade insult to the facial nerve can lead to aberrant regeneration, our group is currently developing a compatible KES system for the facial nerve that would avoid aberrant regeneration and resulting synkinesis.

Conclusion

The application of neuroprosthetic technologies, such as the MCE, may be useful in the setting of FP. This work demonstrates that acute MCE implantation in a feline model consistently produced selective functional facial muscle activation with stable EMG amplitudes, thresholds, and selectivity, while the chronic experiment demonstrated promising results for further investigation. Furthermore, this work indicates similar selective facial muscle activation in a feline model after complete FN injury. Optimal field steering was also demonstrated by activating distinct facial muscles via simultaneous subthreshold currents to multiple channels. These results suggest possible translational application of this technology for a novel clinical treatment of FN injury in humans.

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Declaration of Conflicting Interests

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Supplemental Material

Supplemental material for this article is available online.

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