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Selective Stimulation of Facial Muscles With a Penetrating Electrode Array in the Feline Model

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Objectives/Hypothesis: Permanent facial nerve injury is a difficult challenge for both patients and physicians given its potential for debilitating functional, cosmetic, and psychological sequelae. Although current surgical interventions have provided considerable advancements in facial nerve rehabilitation, they often fail to fully address all impairments. We aim to introduce an alternative approach to facial nerve rehabilitation.

Study Design: Acute experiments in animals with normal facial function.

Methods: The study included three anesthetized cats. Four facial muscles (*levator auris longus, orbicularis oculi, nasalis,* and *orbicularis oris*) were monitored with a standard electromyographic (EMG) facial nerve monitoring system with needle electrodes. The main trunk of the facial nerve was exposed, and a 16-channel penetrating electrode array was placed into the nerve. Electrical current pulses were delivered to each stimulating electrode individually. Elicited EMG voltage outputs were recorded for each muscle.

Results: Stimulation through individual channels selectively activated restricted nerve populations, resulting in selective contraction of individual muscles. Increasing stimulation current levels resulted in increasing EMG voltage responses. Typically, selective activation of two or more distinct muscles was successfully achieved via a single placement of the multi-channel electrode array by selection of appropriate stimulation channels.

Conclusion: We have established in the animal model the ability of a penetrating electrode array to selectively stimulate restricted fiber populations within the facial nerve and to selectively elicit contractions in specific muscles and regions of the face. These results show promise for the development of a facial nerve implant system.

Key Words: Facial nerve, facial nerve implant, facial stimulation, multi-channel electrode array.

Level of Evidence: N/A.

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INTRODUCTION

The facial nerve conducts voluntary neural input to the muscles of the face, which are of critical importance in the demonstration of human emotions, proper enunciation, and maintenance of oral competency. It moreover provides for proper blink function, which importantly protects the cornea. Permanent facial paralysis is a difficult challenge for both patients and physicians because it often results in substantial functional and psychological deficits for the patient; surgical options for full restoration of spontaneous, volitional, and symmetric facial motion are currently very limited. Patients with facial paralysis from all causes, including birth, tumor, surgery, trauma, or infection, often suffer from debilitating functional problems with dry eye, visual impairment, drooling, intraoral food retention, and demoralizing cosmetic deformities of a readily apparent, asymmetrically flaccid, and paralyzed face. The annual incidence of facial paralysis has been estimated to be approximately 70 cases per 100,000, and an estimated 127,000 new cases of permanent facial paralysis are diagnosed annually in the United States alone.[1,2]

In recent decades, considerable efforts have been undertaken to care for this patient population. Several surgical interventions, including static and dynamic options, have been described for patients with unilateral facial paralysis and are in frequent use by otolaryngologists and plastic surgeons worldwide. Static options introduce nonmuscular material to the face to aid in function or cosmesis. Conversely, dynamic options such as the gracilis myoneurovascular free tissue transfer restore some degree of volitional muscular function. Because each of these interventions only address specific parts of the face and can have a 10% to 15% failure rate,[3,4] oftentimes multiple procedures involving multiple sites are required to accomplish functional and cosmetic goals. Although functional goals can often be achieved and quality of life is significantly improved,[5] the cosmetic results are infrequently fully satisfactory as

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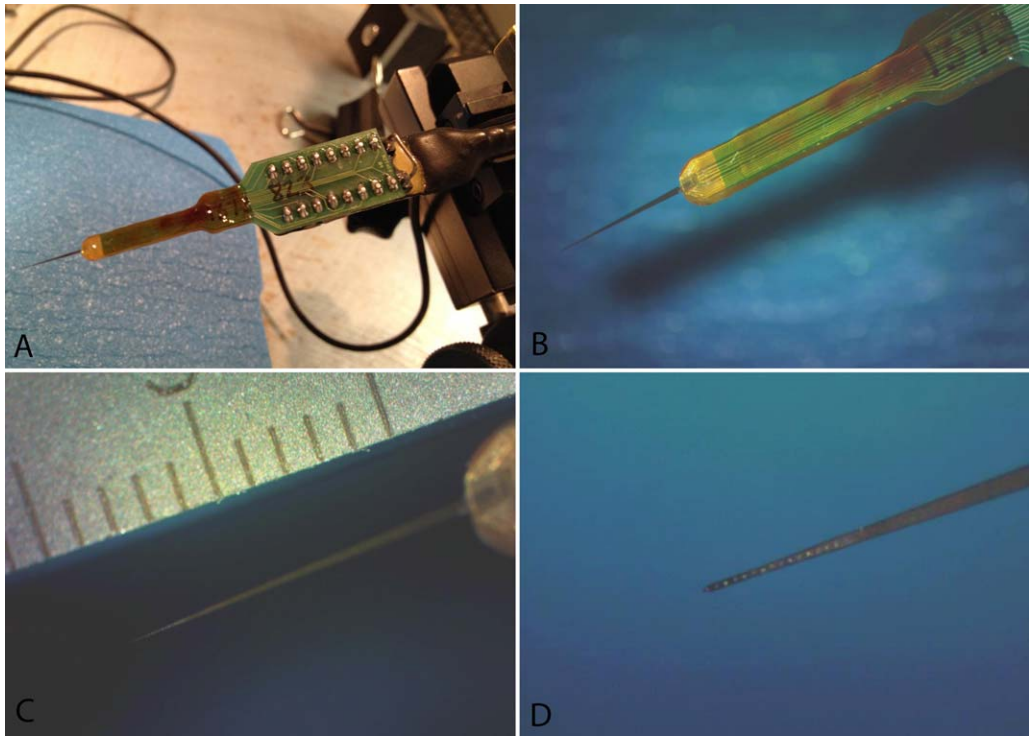

Fig. 1. (A) Photograph of a NeuroNexus 16-channel stimulating electrode array (NeuroNexus, Ann Arbor, MI) in position on a micropositioner. (B) Microscopic picture of the shank and distal board. (C) The silicon-substrate shank with a metric ruler-size reference. (D) High-magnification microscopic photograph of the distal end of the penetrating shank. The 16 electrode sites can be seen. Superficial or proximal electrodes are those furthest from the tip of the array (to the right in this picture), whereas deep or distal electrodes are those closest to the array tip (to the left). [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

compared with the resting and dynamic states of the face prior to facial paralysis onset.

Our group has recently demonstrated the utility of a penetrating multichannel electrode array to selectively stimulate highly specific neural fibers within the cochlear nerve.[6–8] In the present study, we sought to demonstrate the ability of the electrode array, when inserted into the facial nerve, to stimulate movement and contraction in specific regions and muscles of the face of a cat. This work serves to establish a novel approach to rehabilitation of permanent facial palsy and paralysis and to circumvent the shortcomings of current surgical interventions, while providing insight into the anatomy of, as well as the neuroprosthetic interfacing with, the facial nerve. Ultimately, this work serves to expand understanding of neuroprosthetic appliances, and it may lead to improved treatments for permanent facial paralysis and allow for clinically viable approaches for managing other neurological deficits and disorders.

MATERIALS AND METHODS

Electrode Array and Stimuli

The multichannel intraneural stimulating electrode arrays (NeuroNexus Technologies, Ann Arbor, MI) have 16 iridium-plated sites, 703-μm^2 in area, arrayed at 100-μm intervals spanning a distance of 1.5 mm along a single, 15-μm-thick silicon-substrate shank (Fig. 1). System 3 equipment from Tucker-Davis Technologies (TDT; Alachua, FL) and custom software running in MatLab (The MathWorks, Natick, MA) were used for stimulus presentation. Electrical stimulus pulses were generated by a 16-channel current source controlled by a 16-channel digital-to-analog converter (TDT RX8). Stimuli were single charge-balanced biphasic electrical pulses, initially cathodic, 41 or 82 μs per phase. The illustrated responses were obtained with stimulus charge levels of 26 to 41 nC per phase.

Surgery

All procedures were performed with the approval of the University of California at Irvine Institutional Animal Care and Use Committee according to the National Institutes of Health guidelines. We conducted acute, terminal experiments in three barbiturate-anesthetized cats. Small incisions were made over four facial muscles, including the *orbicularis oris*, *orbicularis oculi*, *nasalis*, and *levator auris longus*, and each muscle was exposed. Needle electromyographic (EMG) electrodes were inserted into each muscle. An infraauricular incision was made, and the trunk of the extratemporal facial nerve was identified as it exits the temporal bone by the external auditory canal. The dense epineurium was penetrated with a 30-gauge needle, and the array was introduced into the facial nerve proximal to the bifurcation into the dorsal and ventral rami[9] with the aid of a micropositioner and with the goal of inserting all 16 stimulating sites in neural tissue. The site and angle of insertion were not programmed or pre-determined; positioning of the array was dictated by the surgical anatomy and access to the nerve with the micropositioner. The electrode array was advanced until resistance was detected. Each of the intraneural sites was stimulated, one at a time, and EMG voltage responses from the four selected facial muscles were recorded by the nerve integrity monitoring

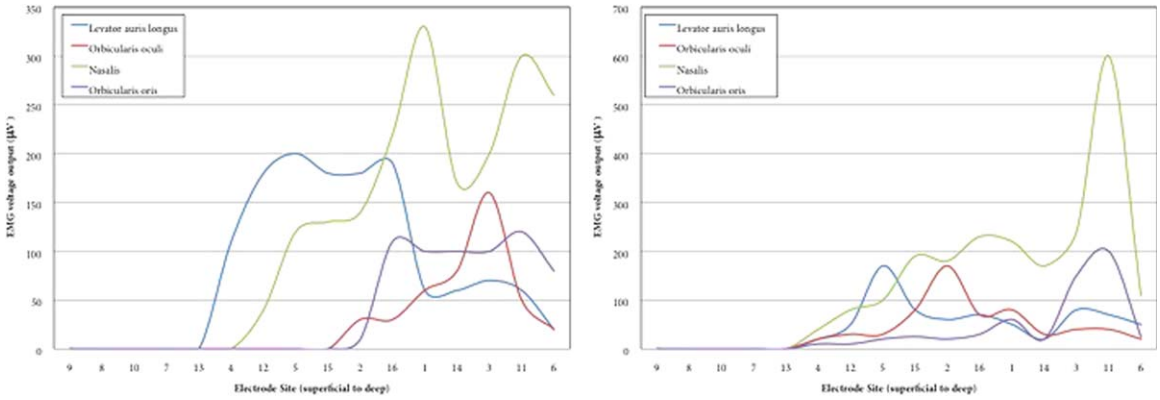

Fig. 2. Graphic representation of successive stimulation of channels from superficial (electrode 9) to deep (electrode 6) electrodes, from left to right on the *x*-axis, and the corresponding electromyographic voltage response of distinct muscles on the y-axis. Stimulation through the most superficial channels failed to elicit any substantial neural activity, likely due to the channels being out of the nerve. On the left (cat 2, position 1), the middle channels robustly stimulated the *levator auris longus* muscle, whereas the deeper channels activated the *orbicularis oculi*, *nasalis*, and *orbicularis oris* (current level: 35 dB re 1 μAmp; phase duration: 41 μs; pulse duration: 200 μs). At a different insertion site on the right (cat 2, position 3), a unique pattern of stimulation was recorded (current level: 45dB re 1 μAmp; phase duration: 41 μs; pulse duration: 200 μs).

system (NIM Response 2.0; Medtronic Inc., Minneapolis, MN). To vary the neural populations stimulated, the stimulating electrode array was removed and replaced into the nerve in varying trajectories and angles along the course of the exposed facial nerve trunk, and each electrode site was again stimulated.

RESULTS

Stimulation through individual electrodes activated nerve populations selectively, often resulting in EMG activity in individual muscles. Typically, selective activation of two or more distinct muscles was successfully achieved via a single placement of the multichannel electrode array by selection of appropriate stimulation channels. Figure 2 (cat 2, position 1) shows representative data of EMG voltages from individual channel stimulation of the main trunk of the facial nerve. Stimulation through the most proximal/superficial channels failed to elicit any substantial neural activity, which was the consequence of the superficial electrodes being out of the nerve. The middle channels of the array most robustly stimulated the *levator auris longus* muscle, while the deepest channels activated the remaining three muscles to varying, stronger degrees. A similarly diverse pattern of maximal and minimal stimulation responses was found in a subsequent insertion of the array into the facial nerve in a different location and angle (Fig. 2; cat 2, position 3). Supporting Video content 1 through 3 show representative movement of the auricle, lateral face, and upper lip, albeit with different insertions of the array into the nerve. We also demonstrate in Figure 3 (cat 3, positions 1 and 2) that increasing stimulation current levels resulted in increasing EMG voltage responses. Furthermore, we show that graded stimulation of one electrode

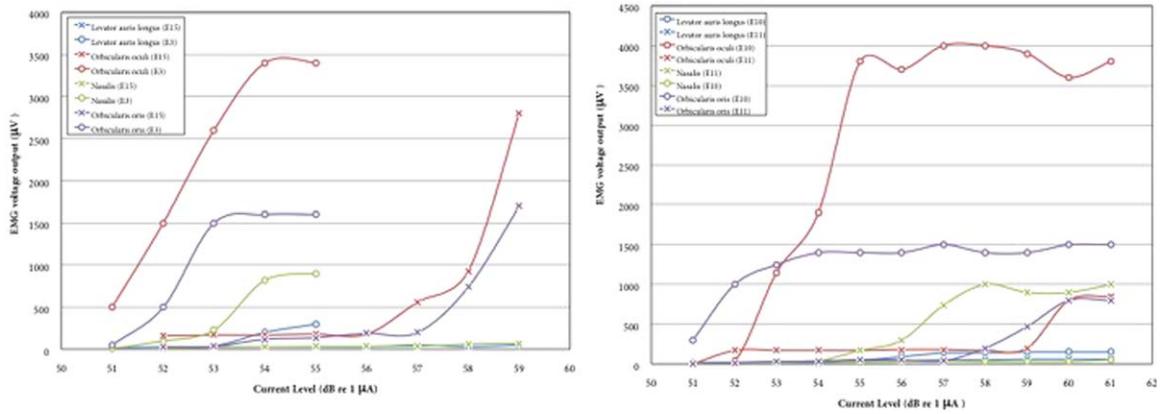

Fig. 3. Graphic representation of escalating stimulation current levels of a single electrode on the *x*-axis, with correspondingly increasing electromyographic voltage responses on the *y*-axis. Also demonstrated is the distinct voltage responses of different muscles to graded stimulation of a superficial electrode (electrode 15) compared to a distant, deeper electrode (electrode 3; cat 3, position 1). At high levels of muscular contraction, gross movement of the head of the cat will endanger the fragile stimulating array residing in the facial trunk, and accordingly electrode 3 could only be stimulated up to 55 dB re 1 μAmp. On the right is a similar plot from stimulation of electrode 10 and electrode 11 at a different array insertion site (cat 3, position 2).

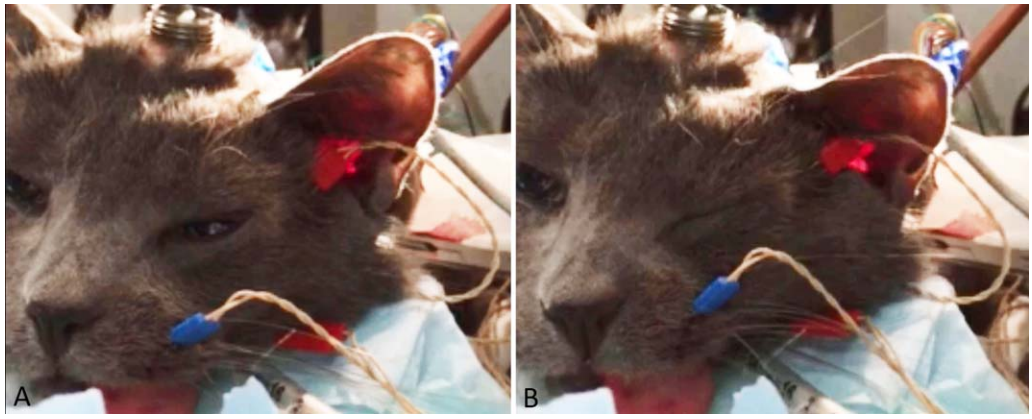

Fig. 4. Video still images of relaxed left facial muscles (A), prior to sustained facial contraction with three-second-long, high-level current pulses delivered to a single electrode on the intraneural array (B). [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

(electrode 3, 10, respectively) will elicit voltage responses of different muscles to different extents when compared to those from stimulation of a distant electrode (electrode 15, 11, respectively). Supporting Video content 4 demonstrates fine contractions of the face with delivery of short but high levels of current that activates several facial muscles, whereas Supporting Video content 5 shows sustained facial contraction with 3-second-long, high-level current delivery to the nerve (also shown in Fig. 4).

DISCUSSION

In this descriptive study, we report the ability of an intraneural multichannel electrode array to selectively stimulate neural populations that innervate distinct facial muscles. The concepts and technique used in this study are analogous to recent work using the penetrating array in the auditory nerve, with stimulation sites in intimate contact with nerve fibers. Studies in short-term animal experiments showed that this intraneural stimulation, compared to the conventional intrascalar cochlear implant (CI) electrode array, offered more precise excitation of frequency-specific nerve populations, access to the entire frequency range of hearing, greatly reduced interference among channels, substantially lower thresholds, and improved transmission of temporal fine structure.[6–8] All of these observations bode well for potential clinical use of intraneural stimulation in other cranial nerves, including the facial nerve. Although in the current study, the majority of individual electrode discharges often resulted in the stimulation of more than one facial muscle, refinements in the electrode material and surface area, and current characteristics (among other variables) will likely improve the selectivity of stimulation. Furthermore, this is not a proposed intervention with intent to regenerate the facial nerve or optimize neuromuscular junction physiology. Rather, we aim to stimulate restricted neural populations of the facial nerve in an effort to elicit contractions of specific facial muscles.

Currently, scientific and clinical efforts to restore neuromuscular function are broadly grouped into one of three categories: 1) nerve regeneration, 2) reinnervation and muscle transfer, and 3) bioelectric technologies. Techniques to regenerate nerve tissue, including motor and Schwann cells, have shown great promise with in vitro experiments and have provided insight into potential methods to optimize neuromuscular communication.[10–13] Although experiments in animals have also been described, the translation to clinical use still awaits the results of these animal studies.[14] In contrast, nerve reinnervation and muscle transfer is already a mature and routine clinical intervention. In the setting of a compromised facial nerve, facial paralysis patients can undergo a hypoglossal-facial nerve anastomosis, which surgically connects the proximal end of the hypoglossal motor nerve to the distal end of the facial nerve trunk. This allows new axons extending from the hypoglossal neuronal cell bodies in the brainstem to grow into the facial nerve and provide the facial muscles with a tonic level of stimulation.[15]

Alternatively, free tissue microvascular transfer of an isolated muscle, such as the gracilis, to the face, and connecting its nerve to a motor nerve in the head and neck area (e.g., masseter or hypoglossal nerve, or nerve graft originating from the contralateral and functional facial nerve), among other dynamic facial reanimation surgeries, is routinely performed in a number of large volume facial nerve centers around the world. Although such procedures often provide patients with a meaningful smile, the surgeries are lengthy and at times multistaged, involving multiple neurovascular microanastamoses and requiring surgeons with highly specialized training and familiarity with anatomy outside the head and neck. Accordingly, access to these procedures can be limited by patient health, distance to tertiary care centers, and cost.

Similarly, bioelectric and direct nerve–electrode interface technology has already made its way into routine clinical practice. Vagal nerve[16] and deep brain stimulators[17] are frequently implanted into patients to effectively treat a variety of common neurologic and psychiatric pathologies. Chronic spinal cord stimulators are likewise in routine use for patients with severe neuropathic pain recalcitrant to conservative, noninvasive therapy.[18] A surgically implanted

device to electrically stimulate the hypoglossal nerve in patients with severe obstructive sleep apnea has been shown in clinical trials to effectively improve subjective and objective measures of sleep apnea.[19,20] Lower extremity nerves have also been the target of direct electrical stimulation to improve bladder, bowel, and sexual function in both animal and human trials.[21] Finally, the CI, arguably the most successful present-day neural prosthesis, consistently brings useful hearing and speech recognition to profoundly deaf people. Our results suggest that these successful bioelectric neuroprosthetic technologies could also be applied to the facial nerve.

However, many issues with this approach to facial reanimation remain to be addressed. Improving selectivity of desired muscle stimulation will require further work on the materials, design, and dimensions of electrodes and arrays. For instance, highly selective stimulation of neural fibers innervating only the palpebral portion of the orbicularis oculi could provide patients with a natural-appearing, gentle blink and tremendous functional and cosmetic benefit. Results from intraneural stimulation would have to be compared to those elegantly reported by Frigerio et al., who examined transcutaneous stimulation of one branch of the facial nerve to elicit a blink.[22] In addition, the ability of an intraneural electrode array chronically implanted into the facial nerve to steadily maintain function over a period of months to years, and to provide the face with muscular tone, remains to be demonstrated. Moreover, the function of intraneural electrode arrays in the context of validated animal models of facial injury and paresis[23] will need to be examined, including the study of fully neurotmetic facial nerves that are reinnervated following surgical anastomosis to an adjacent motor nerve (e.g., hypoglossal nerve). These studies and others are currently being investigated at our institution.

Ultimately, we envision the creation of a CI-like programmable device with one (or more) multichannel penetrating electrode arrays that can be surgically and securely inserted into the mastoid segment of an injured and poorly functioning facial nerve. Intraoperative electromyographic testing could confirm that all functionally and cosmetically critical muscles of the face can be adequately stimulated by the array. Postoperatively, graded stimulation levels for individual facial muscles could be evaluated. Notably, detection of patient-initiated electrical neural or myogenic signals that subsequently deliver messages to and activate a secondary device has been an area of recent and considerable interest, particularly in military research laboratories to address the needs of veteran amputees and improve the functionality of prosthetic limbs.[24] We aim to combine these advances with established CI technology to create a wired or wireless system that provides for transcutaneous or intramuscular detection of individual muscle contraction on the contralateral (normal/functional) side and consequent, simultaneous, and effort-matched stimulation of the same muscles on the paralyzed side. This hypothetical system could reconcile the shortcomings of current surgical interventions for facial paralysis by providing volitional and spontaneous function of a paretic face with a single, brief, technically simple, outpatient surgery. However, we acknowledge that the potential clinical applicability of this proposed approach to facial rehabilitation is yet to be determined and may be restricted to a select subset of facial palsy patients. Many limitations, including the need to further refine the precision and selectivity of facial muscle activation and establish chronic implantation parameters, among others, must be more fully addressed prior to contemplating the advancement of this technology toward translational and clinical applications.

CONCLUSION

We have established in the animal model the ability of a penetrating electrode array to selectively stimulate restricted fiber populations within the facial nerve and to selectively elicit contractions in specific muscles and regions of the face. Despite the coarse nature and limitations of this study, as well as a need to refine our stimulating and recording systems, these descriptive results show promise for the development of a facial nerve implant system. If a CI-like device with a multichannel penetrating electrode implanted into the facial nerve could selectively drive independent and current-graded contraction of facial muscles, including the *frontalis*, *orbicularis oculi*, *zygomaticus major*, *orbicularis oris*, and *depressor anguli oris* muscles, among others, both therapeutic and cosmetic goals could be accomplished in a single, short outpatient surgery and without any incisions in the face.

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These authors contributed equally to the manuscript: R.S., J.B.

BIBLIOGRAPHY

1. May M, Schaitkin B, Shapiro A. The Facial Nerve. New York, NY: Thieme; 2001.
2. Bleicher JN, Hamiel S, Gengler JS, Antimarino J. A survey of facial paralysis: etiology and incidence. *Ear Nose Throat* 1996;75:355–358.
3. Bhama PK, Weinberg JS, Lindsay RW, Hohman MH, Cheney ML, Hadlock TA. Objective outcomes analysis following microvascular gracilis transfer for facial reanimation: a review of 10 years' experience. *JAMA Facial Plast Surg* 2014;16:85–92.
4. Adams JE, Kircher MF, Spinner RJ, Torchia ME, Bishop AT, Shin AY. Complications and outcomes of functional free gracilis transfer in brachial plexus palsy. *Acta Orthopedic Belgica* 2009;75:8–13.
5. Lindsay RW, Bhama P, Hadlock TA. Quality-of-life improvement after free gracilis muscle transfer for smile restoration in patients with facial paralysis. *JAMA Facial Plast Surg* 2014;16:419–424.
6. Middlebrooks JC, Snyder RL. Auditory prosthesis with a penetrating nerve array. *J Assoc Res Otolaryngol* 2007;8:258–279.
7. Middlebrooks JC, Snyder RL. Intraneural stimulation for auditory prosthesis: modiolar trunk and intracranial stimulation sites. *Hear Res* 2008;242: 52–63.
8. Middlebrooks JC, Snyder RL. Selective electrical stimulation of the auditory nerve activates a pathway specialized for high temporal acuity. *Neuroscience* 2010;30:1937–1946.
9. Tomo S, Tomo I, Nakajima K, Townsend GC, Hirata K. Comparative anatomy of the buccinator muscle in cat (Felis domestica). *Anat Rec* 2002; 267:78–86.
10. Sachanandani NF, Pothula A, Tung TH. Nerve gaps. *Plast Reconstr Surg* 2014;133:313–319.
11. Xu H, Holzwarth JM, Yan Y, et al. Conductive PPY/PDLLA conduit for peripheral nerve regeneration. *Biomaterials* 2014;35:225–235.
12. Jesuraj NJ, Santosa KB, Macewan MR, et al. Schwann cells seeded in acellular nerve grafts improve functional recovery. *Muscle Nerve* 2014; 49:267–276.
13. Faravelli I, Bucchia M, Rinchetti P, et al. Motor neuron derivation from human embryonic and induced pluripotent stem cells: experimental approaches and clinical perspectives. *Stem Cell Res Ther* 2014;5:87.

14. Langhals NB, Urbanchek MG, Ray A, Brenner MJ. Update in facial nerve paralysis: tissue engineering and new technologies. *Curr Opin Otolaryngol Head Neck Surg* 2014;22:291–299.
15. Brudny J, Hammerschlag PE, Cohen NL, Ransohoff J. Electromyographic rehabilitation of facial function and introduction of a facial paralysis grading scale for hypoglossal-facial nerve anastomosis. *Laryngoscope* 1988;98: 405–410.
16. Hays SA, Rennaker RL, Kilgard MP. Targeting plasticity with vagus nerve stimulation to treat neurological disease. *Prog Brain Res* 2013;207: 275–299.
17. Karas PJ, Mikell CB, Christian E, Liker MA, Sheth SA. Deep brain stimulation: a mechanistic and clinical update. *Neurosurg Focus* 2013; 35:E1.
18. Wolter T. Spinal cord stimulation for neuropathic pain: current perspectives. *Pain Res* 2014;7:651–663.
19. Strollo PJ, Soose RJ, Maurer JT, et al. Upper-airway stimulation for obstructive sleep apnea. *N Engl J Med* 2014;370:139–149.
20. Kezirian EJ, Goding GS, Malhotra A, et al. Hypoglossal nerve stimulation improves obstructive sleep apnea: 12-month outcomes. *Sleep Res* 2014; 23:77–83.
21. Creasey GH, Craggs MD. Functional electrical stimulation for bladder, bowel, and sexual function. *Handb Clin Neurol* 2012;109:247–257.
22. Frigerio A, Heaton JT, Cavallari P, Knox C, Hohman MH, Hadlock TA. Electrical stimulation of eye blink in individuals with acute facial palsy: progress toward a bionic blink. *Plast Reconstr Surg* 2015;136:515e–523e.
23. Bridge PM, Ball DJ, Mackinnon SE, et al. Nerve crush injuries—a model for axonotmesis. *Exp Neurol* 1994;127:284–290.
24. Kung TA, Bueno RA, Alkhalefah GK, Langhals NB, Urbanchek MG, Cederna PS. Innovations in prosthetic interfaces for the upper extremity. *Plast Reconstr Surg* 2013;132:1515–1523.