REVIEW

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Technology Insight: future neuroprosthetic therapies for disorders of the nervous system

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SUMMARY

Most disorders of the nervous system result from localized sensory or motor pathologies attributable to disease or trauma. The emerging field of neuroprosthetics is focused on the development of therapeutic interventions that will be able to restore some of this lost neural function by selective electrical stimulation of sensory or motor pathways, or by harnessing activity recorded from remnant neural pathways. A key element in this restoration of function has been the development of a new generation of penetrating microelectrode arrays that provide unprecedented selective access to the neurons of the CNS and PNS. The active tips of these microelectrode arrays penetrate the nervous tissues and abut against small populations of neurons or nerve fibers, thereby providing selective access to these cells. These electrode arrays are not only beginning to provide researchers with the ability to better study the spatiotemporal information processing performed by the nervous system, they can also form the basis for new therapies for disorders of the nervous system. In this Review, three examples of this new generation of microelectrode arrays are described, as are potential therapeutic applications in blindness and spinal cord injury, and for the control of prosthetic limbs.

KEYWORDS artificial vision, electrode arrays, neural control, neuroprosthetics, spinal cord injury

REVIEW CRITERIA

PubMed was searched for articles published up to 2007. Search terms included "electrode arrays" and "microelectrode arrays". The abstracts of retrieved citations were reviewed, and full articles were obtained and references checked for additional material when appropriate. Some as yet unpublished findings by colleagues have been included in the manuscript.

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INTRODUCTION

Until recently, the concept of helping the deaf to hear, the blind to see, and the paralyzed to walk was more the province of science fiction or theology than of clinical medicine. Today, however, individuals with profound deafness who have been fitted with cochlear prostheses are able to hear, and to enjoy relatively normal conversations with family, friends and fellow workers. This approach to hearing restoration is rapidly becoming a widely accepted therapy.[1] In a similar vein, researchers in the US and Germany have implanted electrode arrays in the visual cortices[2] or on the retinas[3–5] of individuals who have lost all vision, and although these individuals have yet to experience useful patterned vision, they have once again been able to perceive points of light. Researchers in the US have also implanted electrodes into the motor regions of the brain in paralyzed patients, and have been able to use recorded neural activity to infer the desires of these patients, enabling them to control the cursor on a computer screen simply through volitional thought.[6] These attempts to restore lost sensory and motor function are the result of new neuroprosthesis-based therapy, a field that is still in its infancy. Although the restored functions fall far short of natural sensory and motor capabilities, these successes offer a tantalizing glimpse of what the future of neuroprosthetics might hold for individuals with profound sensory or motor dysfunction.

The neuroprosthetic approach to restoring these lost functions is based on arrays of microelectrodes implanted into neural tissues, which can 'talk' and 'listen' to large numbers of small groups of neurons in the CNS and PNS. These implanted electrode arrays enable direct communication with still-functioning parts of the sensory and motor neural pathways. By stimulating and recording from these neurons, it is possible to bypass, to a limited degree, regions of the nervous system that have been damaged by inherited or acquired disease, or

by traumatic injury. This approach is, however, made difficult by the complexity of the CNS and PNS. Even the simplest musculoskeletal movements or the most basic sensory perceptions are the result of the coordinated activity of hundreds of neurons. Complex and graceful movements and complex sensory perceptions require the activation of hundreds of thousands of synapses between thousands of sensory and motor neurons. Given this architectural complexity, one might conclude that it would be impossible to interact selectively with sufficient numbers of sensory or motor neurons to evoke any useful sensory percepts or motor behaviors. The success of the cochlear neuroprosthesis, however, highlights two important features of our nervous system: first, the brain has a remarkable capacity to make use of even the most limited amount of sensory stimulation, and second, the plasticity of these neural circuits is such that the brain can interpret somewhat inappropriate but systematic stimulation of sensory pathways, and can use this information to make useful judgments about the world.

The emergence of the neuroprosthetic approach to treating nervous system dysfunction is directly tied in with the development of a new generation of microelectrode arrays. Much ongoing work aims to develop various electrode array designs,[7–10] but this Review will focus on two contemporary examples of neural interface devices that were developed in the author's laboratory and have been evaluated in scores of animal experiments. Research and commercial versions of these electrode arrays have also been implanted in a small number of human subjects.[6,11] This Review also describes several possible applications of this technology in sensory and motor disorders, and concludes with a brief description of some of the remaining hurdles that must be overcome before neural interface devices can become clinical tools.

THE NEURAL INTERFACE: THE UTAH ELECTRODE ARRAYS

External devices that can stimulate and record from the cells of the nervous system date back to Galvani's experiments on the animation of frog muscle. These early neural interfaces—like some still in use today—consisted of relatively large metal electrodes that were placed over the skin, scalp or muscles, and they could not provide selective access to individual cells of the nervous system. Our understanding of the nervous system has improved as a result of the efforts of researchers who experimented with new generations of electrodes with better neural selectivity. Needle-shaped microelectrodes that could be safely inserted directly into the brain or PNS were developed. With the exception of their very tips, these needles were insulated, so they could selectively stimulate and record from individual neurons, or from very small numbers of neurons located around the tip of the electrode.

Sensory percepts and motor behaviors are associated with spatial and temporal patterns of electrical activity localized to specific regions of the CNS and PNS. An effective neural interface for a neuroprosthetic application must be able to record these spatially distributed neural activity patterns, recreate such patterns by passing temporal patterns of electrical currents through selected electrodes in the interface, or both. An ideal neural interface would, therefore, consist of an array of many microneedles, which could be inserted into the nervous tissues. The tip of each microneedle would either record the electrical activity in a small population of neurons surrounding the tip, or, when electrical current was passed though the electrode, activate small populations of neurons around the electrode tip. Workers at the University of Utah, Salt Lake City, UT, and the University of Michigan, Ann Arbor, MI, have devised methods by which such complex three-dimensional microelectrode arrays can be built. The Utah Electrode Array (UEA)[12] and the Utah Slanted Electrode Array (USEA)[13] are two examples of such neural interfaces (Figure 1A,B). A three-dimensional electrode array developed by researchers at the University of Michigan was built using more-conventional integrated circuit technologies.[14] It has multiple electrode sites that are distributed along a number of electrode shanks. The planes of the electrode shanks are integrated into a single electrode array (Figure 1C).

The UEA consists of one hundred 1.5 mm-long microneedles that were designed to be inserted into the cerebral cortex to a depth of 1.5 mm, the level of normal neural input to the cerebral cortex. The electrodes of the UEA and USEA are built on a square grid with 400 μm spacing. One hundred gold bond pads are deposited on the back surface of these arrays, and one hundred 1.25 mil insulated gold wires

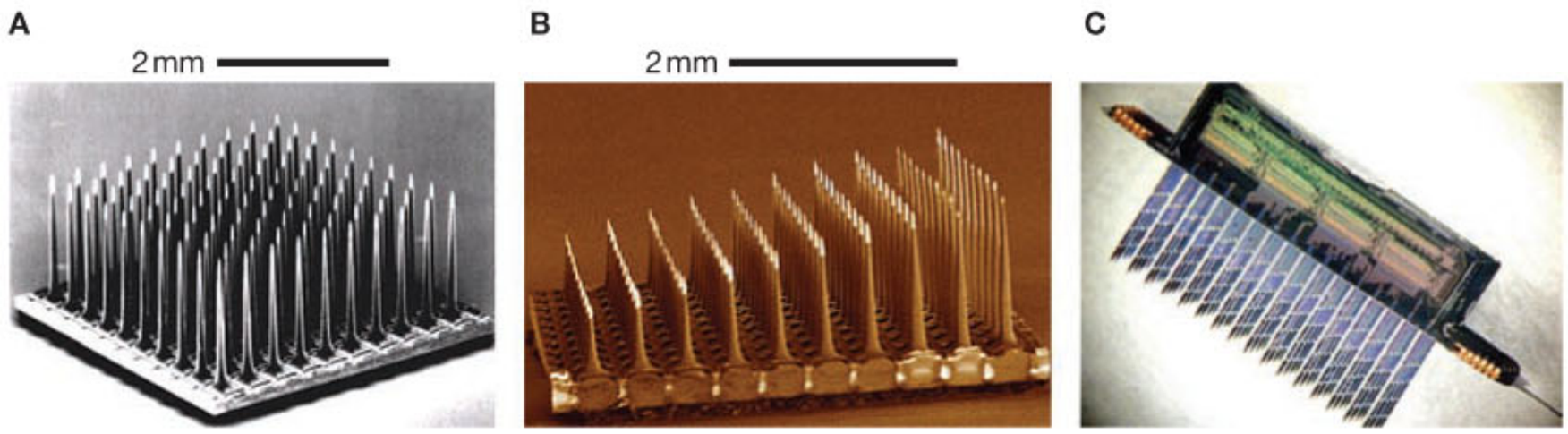

Figure 1 Neural interfaces. (**A**) The Utah Electrode Array (UEA). (**B**) The Utah Slanted Electrode Array (USEA). These electrode arrays are built of silicon and are designed to be implanted in cerebral cortex (UEA) or peripheral nerves (USEA). Both electrode arrays contain 100 microneedle-shaped electrodes that project out from a 4 mm × 4 mm substrate. (**C**) The Michigan three-dimensional electrode array contains active electronics integrated into the array.

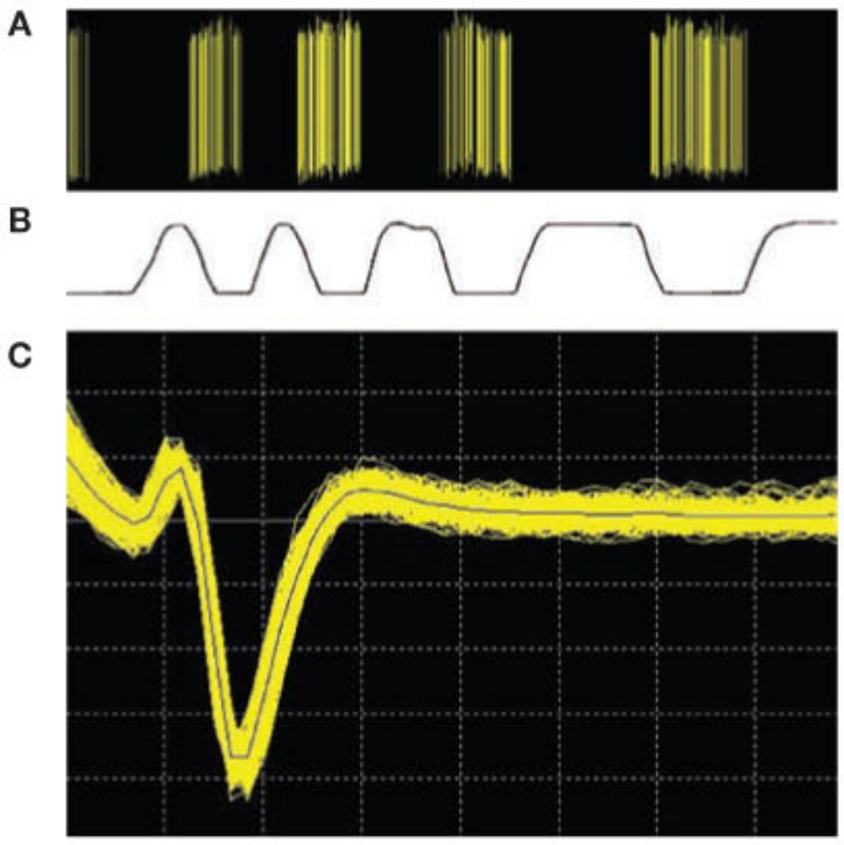

Figure 2 Single-unit responses from sciatic nerve recorded with a Utah Slanted Electrode Array. (**A**) Responses as the ankle was flexed and extended five times over a 30 s period. (**B**) Ankle position with upward direction representing ankle flexion. The unit fires on ankle extension. (**C**) Kinetics of 285 superimposed responses from the time series in (A). Lengths of axes in panel C: x-axis, 1.6 ms; y-axis, 263 μvolts.

are bonded to these pads and to a percutaneous connector for connection to external electronics. The tip of each microneedle is metalized with iridium oxide to facilitate electronic to ionic transduction, and the entire array, with the exception of the tip of each microneedle, is insulated with a biocompatible polymer.

The USEA also consists of up to 100 microneedles, but their lengths are graded from 0.5 mm to 1.5 mm along the length of the array. The graded lengths of the USEA ensure that when it is inserted into a peripheral nerve, the electrode tips uniformly populate the nerve, with most nerve fibers being no more than 200 μm away from an active electrode tip.

An example of action potentials recorded with a UEA implanted in feline sciatic nerve is shown in Figure 2. In this experiment, the cat's ankle was flexed and extended five times over a 30-second period, and large-amplitude single-unit responses were recorded on one of the implanted electrodes (Figure 2A). With each extension (Figure 2B), a burst of action potentials was evoked (Figure 2A). Figure 2C shows the kinetics of 285 superimposed recordings of these action potentials. Typically, only about one-third of the electrodes in the implanted arrays record such large-amplitude, stimulus-driven responses, one-third record multi-unit responses, and about one-third record only local field potentials. All forms of recorded neural activity provide good indices of the neural activity in the immediate vicinity of the implanted electrode array, however. A recent study conducted in cat and monkey cortices compared conventional single microelectrode neural recordings with those of Utah-type electrode arrays.[15] The study reported that the amplitudes of the neural recordings were somewhat smaller for implanted Utah type arrays, but that about 100 single units were typically recorded, with no signs of deterioration for the 30-hour duration of the experiments. Other studies have assessed the longevity of the recordings,[16–18] and high-quality single-unit recordings were observed at least up to 1.5 years after implantation of the array.[18]

CONTROL OF EXTERNAL DEVICES BY VOLITIONAL THOUGHT

The neural activity recorded on each electrode of an array reports the temporal sequence of action potentials of the neurons in the immediate vicinity of the electrode tip, and this local activity differs from the activity recorded by the other electrodes in the array. The spatiotemporal patterns of neural activity in the different regions of the brain are uniquely associated with sensory inputs, motor outputs or cognitive processes. These activity patterns can be correlated with the sensory stimulus or cognitive thoughts that evoked the patterns (e.g. a moving light bar if recordings are made in the visual cortex, a sound of a particular frequency and loudness if recordings are made in auditory cortex, the desire to move the arm or leg if recordings are made in motor cortex, or the consequences of limb motion if recordings are made in the dorsal root ganglia or peripheral nerves [Figure 2]). The desire or intent to move different parts of the body is also associated with specific activity patterns in the motor regions of the brain,[19–22] even in individuals with complete tetraplegia.[23] Recorded activity patterns evoked by volitional thought can be used to control external devices, such as the cursor on a computer monitor[24] and perhaps, in the future, a wheelchair. The neural activity pattern associated with the intent to move the fingers in a sequence, for example, can be used to construct a simple linear regression model that correlates this desire to move the fingers with a unique activity pattern in motor cortex.[25,26] Once constructed, the model can be used to predict future movements from recorded stimulus patterns. Such predictions have been used to control external devices simply on the basis of recordings evoked by the volitional thoughts of an experimental animal,[22,27] or to control the position of a paralyzed limb on the basis of recordings of sensory signals from the dorsal root ganglia.[28] A commercial version of the UEA (Neuroport®; Cyberkinetics Neurotechnology Systems Inc., Foxborough, MA) has been used in a number of paralyzed patients as a means of recording volitionally evoked motor activity. Predictive models use such activity to directly control the position of a cursor on a computer monitor, and thereby to enable a patient to control room lights and a television, play video games, and read email.[6] Although the construction and use of these predictive models might seem complex, they are easily realized with a conventional personal computer.

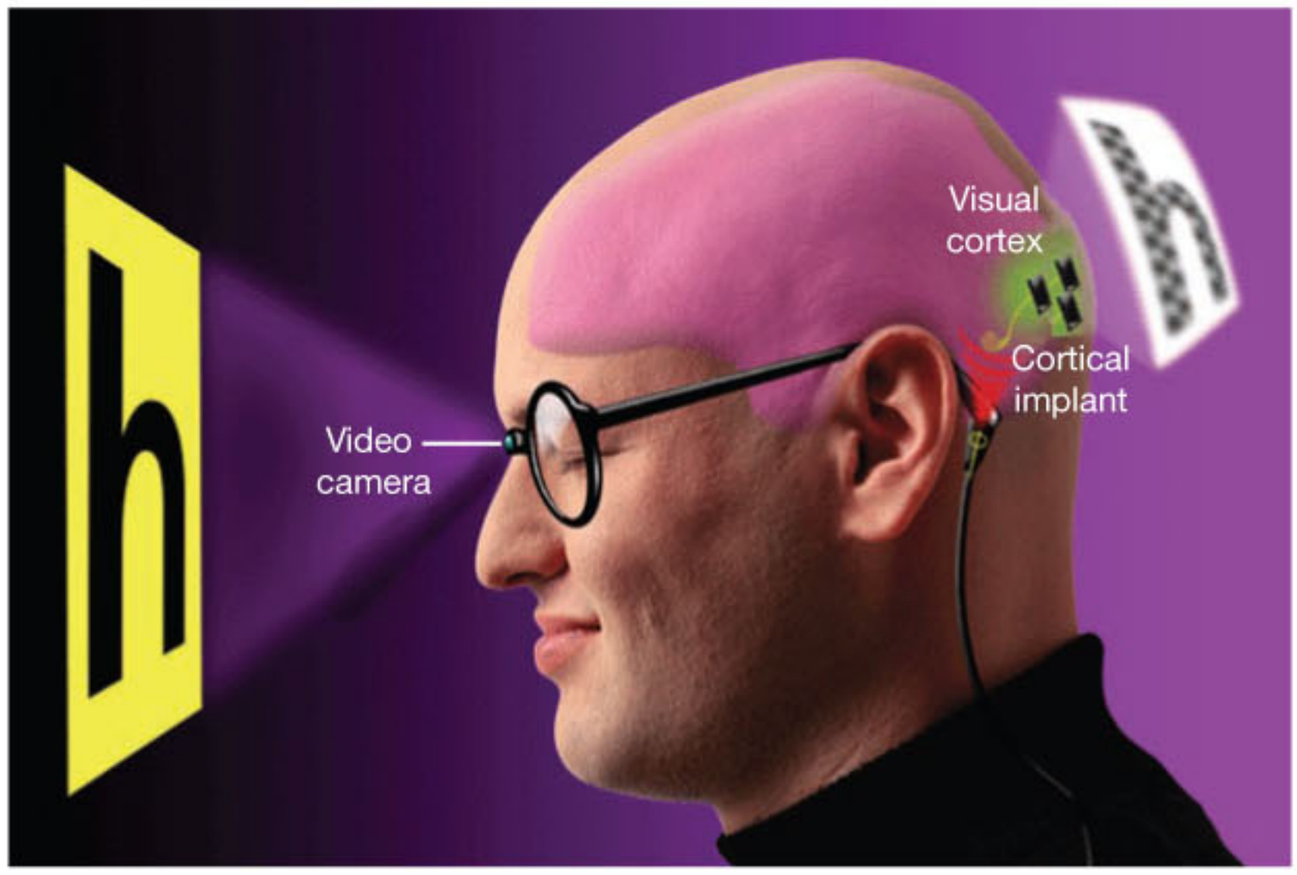

Figure 3 Drawing of a cortex-based artificial vision system. The system consists of a miniature video camera built into the nosepiece of the glasses, signal-processing electronics (carried in a pocket), and arrays of microelectrodes implanted in the primary visual cortex.

SIGHT RESTORATION

One of the primary motivations for developing the UEA was the possibility of restoring limited but useful sight to individuals with profound blindness. This goal could be achieved by using localized spatiotemporal patterns of electrical currents to activate the neurons of the visual cortex that had once been activated by input from the retina (via the lateral geniculate nucleus). It has long been known that electrical stimulation of the visual cortex of both sighted and blind subjects evokes percepts of spatially distinct points of light (called phosphenes).[29–32] By passing electrical currents through an array of electrodes inserted into the primary visual cortex, it should be possible to evoke spatiotemporal patterns of phosphenes. If the pattern of electrical stimulation of the visual cortex were to be derived from a video camera directed in front of a blind subject, this approach could be used to restore limited vision.

Figure 3 depicts a subject with complete blindness wearing spectacles that contain a miniaturized video camera in the nosepiece. Such 'video glasses' are already commercially available. The camera digitizes the scene in front of the subject, and this signal is sent to

signal-processing electronics carried in a shirt pocket. The signal-processing electronics transform the video signal into sets of stimulation levels that are sent wirelessly to a set of UEAs implanted in the subject's visual cortex. In this example, if the camera encodes the letter 'h' in front of the subject, an appropriate stimulation pattern is sent to the implanted UEAs and the subject experiences a phosphene percept in the general shape of the letter 'h'. The electronics that send video signals to the implanted array also wirelessly send power to the device. The wireless approach allows complete implantation of the UEAs, with no 'hard-wired' connections to the outside world, so an individual with an implanted array would look completely normal, an important consideration in patient acceptance of any new technology.

We have performed a number of experiments designed to estimate the number of electrodes that would be required in a cortical vision prosthesis to restore useful vision. We have used a portable pixelated image simulator to mimic what a blind subject would see if they had electrode arrays containing 100, 256, 625 or 1024 electrodes.[33] We found that subjects could read out loud at two-thirds the normal rate with as few as 625 pixels,[34] and that they could confidently navigate through normal environments with this number of electrodes.[35] On the basis of these observations, we feel that useful vision could be restored with six to ten UEAs implanted in the primary visual cortex. We have also conducted a series of behavioral experiments designed to determine how much electrical current needs to be applied to sensory cortex to evoke behavioral responses. These experiments were conducted in the auditory cortex, where currents in the 1–10 μA range evoked reactions in cats trained to lever-press in response to acoustic stimuli. Levels of current in this range are expected to produce little adverse tissue response.

Although the underlying concept is easily understood, there are a number of basic questions that must be answered before the neuroprosthetic approach to sight restoration can move to clinical studies. The most important question concerns the manner in which the brain processes spatiotemporal patterns of neural activity to form complex visual perceptions. A few simple experiments have been performed in a human subject, focusing on the nature of the perceptions evoked by stimulation of the visual cortex via multiple penetrating electrodes.[36] The results indicate that patterned electrical stimulation evokes distinguishable patterned percepts, an important requirement for 'artificial vision', but more work with human volunteers must be done to confirm this suggestion.

PARAPLEGIC STANCE

Getting patients with profound spinal cord injury to be able to adopt a standing posture would have many beneficial consequences, such as reducing muscle wasting and spasticity, reducing ulcer formation, and enabling transfers between a wheelchair and a car or bed. Researchers at Case Western Reserve University, Cleveland, OH, have been successful in stimulating the muscles of the legs to produce walker-assisted stance in a number of paraplegic patients.[37] In view of the fact that both cuff-type and epimysial electrodes stimulate the muscles maximally, however, these subjects are unable to stand for more than a few minutes before muscle fatigue increases the risk of falling.[38] Researchers at the University of Utah have been working on this problem in an animal model, in which they used USEAs implanted in peripheral nerves to produce fatigue-resistant muscle forces over extended periods.[39] The Utah researchers have utilized the stimulation selectivity of the USEA to recruit muscle force in much the same way that it is recruited in individuals without motor impairment. Such individuals produce small forces in their skeletal muscles by activating only a small number of the motor neurons that target a particular muscle. When they want to produce a large force, they activate a large number of the motor neurons targeting the muscle. A USEA, implanted in a peripheral nerve, can selectively activate small subpopulations of motor neurons.[40] The Utah researchers can produce small muscle forces by passing currents though only one or two electrodes that target a particular muscle, or larger forces by passing currents through many electrodes that selectively excite independent motor units in the target muscle. They have produced fatigue-resistant muscle forces by taking advantage of the observation that very low frequency stimulation of motor units in a muscle produces a sequence of muscle twitches that manifest little or no fatigue (RA Normann *et al.*, unpublished data). By interleaving stimulation via a number of electrodes that excite independent motor units in a targeted muscle, fatigue-resistant, tremor-free muscle forces can be produced. An additional

benefit of intrafascicular microelectrode stimulation via the USEA results from the abutment of the electrode tips against the axons of individual motor neurons; threshold stimulation of muscle is achieved with 100 μs duration pulses in the 1–10 μA range—currents that are unlikely to cause an adverse tissue response.

USEAs have yet to be used in patients with spinal cord injuries, but researchers have provided a proof of concept in anesthetized cats (RA Normann *et al.*, unpublished data). It was possible to produce sit-to-stand maneuvers through intrafascicular stimulation of the nerves innervating the extensor muscles of the knee and ankle joints. Figure 4 shows the results of one such experiment, in which an anesthetized cat was placed in a pivoted-trough supporting apparatus. A weight at the opposite end of the trough counterbalanced three-quarters of the animal's weight. When the trough was released, the unbalanced weight of the cat resulted in a motion similar to sitting. When electrical currents were passed through selected electrodes in a USEA implanted in the cat's femoral nerve, the animal manifested a normal-appearing knee extension, and when currents were then passed through selected electrodes in a USEA implanted in the sciatic nerve, the animal manifested ankle extension. The net result was a normal-appearing sit-to-stand maneuver as illustrated in the sequence of photographs in Figure 4.

DIRECT NEURAL CONTROL OF PROSTHETIC LIMBS

Another promising application of neuroprosthetic technology is the direct neural control of prosthetic limbs for individuals with limb amputations; for example, the movement of a prosthetic arm by subjects with elbow or midhumeral amputations. Such an arm could provide an individual with the strength and dexterity that he or she enjoyed before amputation. This degree of control would only be achieved by some form of direct connection of the prosthetic arm to the nervous system. An interesting approach to obtaining neuron-based control signals for a prosthetic arm has been achieved by Kuiken's group.[41–43] They used the severed nerves of the brachial plexus to reinnervate the pectoral muscles of a subject with a bilateral shoulder disarticulation. The electromyographic signals evoked in the reinnervated pectoral muscles by the intention of the subject to move the prosthetic arm were amplified and used as control signals for the actuators in the prosthetic arm.

As described earlier, another possible source of neural signals for control of a prosthetic arm is the neural activity patterns in the motor cortex that can be recorded with an implanted electrode array. A more direct site for neural control signals is the severed peripheral nerves above the level of the amputation, and this site has been used for neural control of external devices.[44,45] Although some of the peripheral motor and sensory nerves degenerate following amputation, many nerve fibers retain their function.[46] USEAs implanted in these severed nerves can selectively record neural activity from the motor nerve fibers that previously targeted the extensor and flexor muscles of the elbow, wrist and fingers. In view of the fact that the tips of implanted USEAs are distributed throughout the fascicles of the implanted nerves, certain electrodes would record activity evoked by the desire of the amputee to flex his or her elbow, other electrodes would be expected to record neural activity associated with the desire to flex the wrist, and yet other electrodes would record activity evoked by the desire to extend the wrist. This selective recording of volitionally evoked neural activity would extend to electrodes selective for individual digit extension and flexion, and these recorded motor signals could be used to directly control actuators in the prosthetic arm that extend and flex individual fingers, rotate the wrist, or bend or extend the elbow. This concept of direct peripheral nerve control of a prosthetic arm is illustrated in Figure 5.

Another requirement for dexterous control of a biological or prosthetic arm and hand is sensory feedback. Graceful, intuitive control of a hand cannot be achieved unless the subject knows when his or her digits are touching an object and what force the fingers are exerting when grasping an object. The 'next generation' prosthetic arm and hand will incorporate a network of sensors in the fingers and joints, and this sensory information will need to be fed back to the amputee, preferably via a neural pathway that is as close to the natural, pre-amputation pathway as possible. This goal might be achieved by using a USEA implanted in the severed nerve above the amputated limb to stimulate sensory fibers that previously conveyed sensory inputs to the brain. The large number of electrodes in a USEA, and the selective stimulation of nerve fibers that is possible with the implanted array,

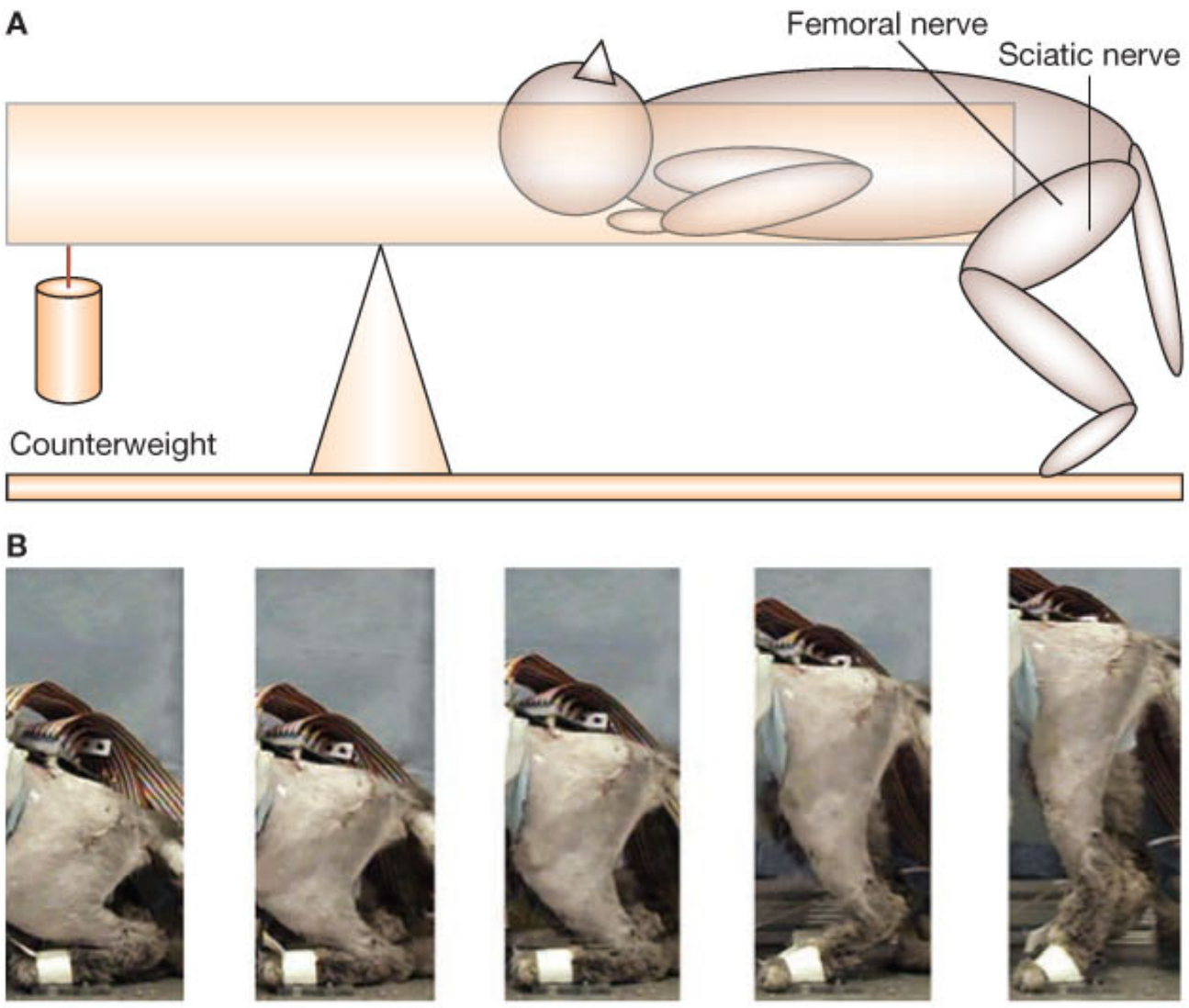

Figure 4 Generating a sit-to-stand maneuver in an anesthetized cat. (**A**) Apparatus for producing sit-to-stand maneuver. (**B**) Photographs taken at approximately 1-second intervals showing a slow sit-to-stand maneuver evoked by stimulation of selected electrodes in two Utah Slanted Electrode Arrays, one implanted in the femoral nerve (knee extension), and the other in the sciatic nerve (ankle extension). Extraneous objects have been removed from photographs.

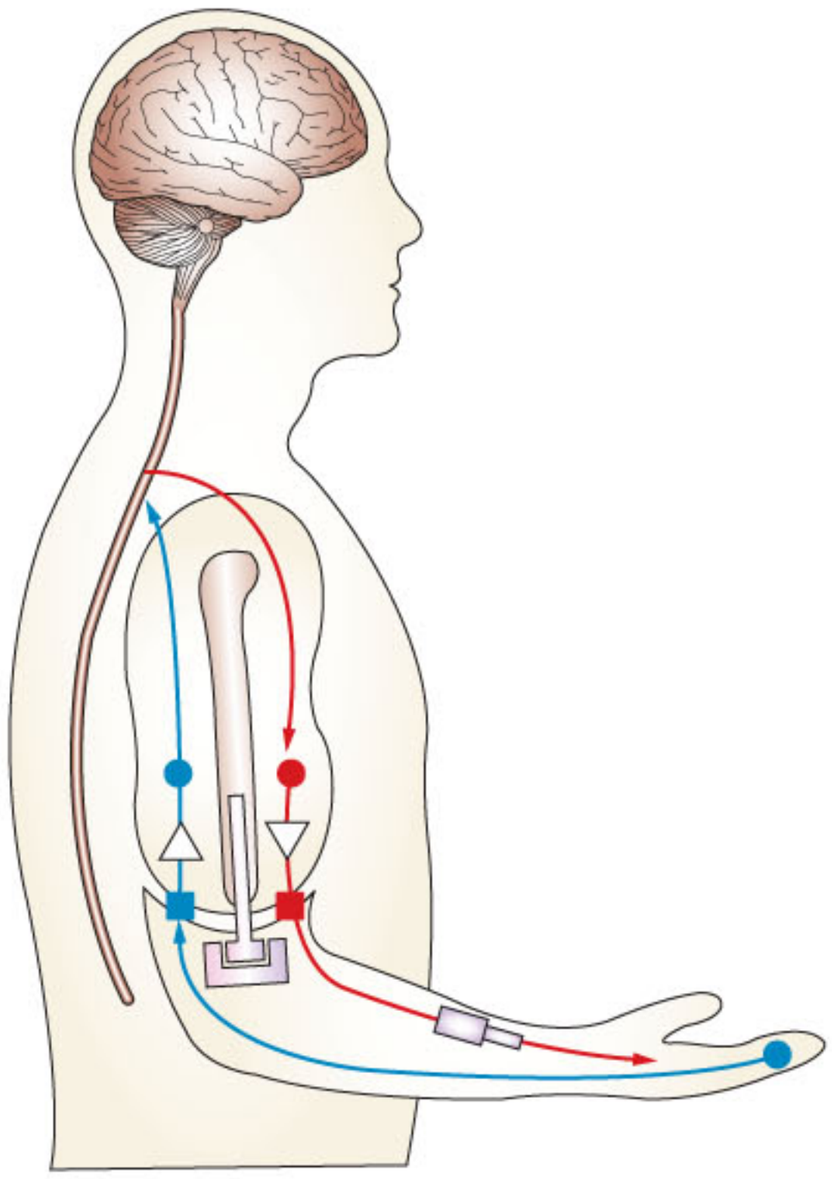

Figure 5 Illustration of neural interfaces that might control the 'next generation' of prosthetic arms. The arm contains actuators for elbow, wrist and fingers that are controlled by neural signals recorded from Utah Slanted Electrode Arrays (USEAs) implanted in radial and median nerves. Sensory signals from sensors in the hand and joints are fed back to the brain via implanted USEA electrodes. Illustration courtesy of GA Clark.

should provide access to many sensory channels. These sensory channels, when stimulated appropriately, should provide the amputee with a large range of sensory percepts (e.g. touch, heat, force, position and pain).[46]

The implantation of arrays of penetrating electrodes, such as the USEA, in the severed nerves of an amputee could mediate direct neural control of a prosthetic arm in a very natural fashion. The desire to move the arm in a particular trajectory would be recorded as a spatiotemporal firing pattern by specific electrodes of the USEA. These volitionally evoked firing patterns would be processed and used to control mechanical actuators in the prosthetic arm that bend or extend the elbow, rotate the wrist, or open or close the fingers. The result of the intended movement would be encoded by the network of sensors in the hand and arm, and these signals would modulate electrical currents passed though specific electrodes in the implanted USEA that target specific sensory nerve fibers. Activation of these fibers would provide feedback to the somatosensory parts of the brain, providing a natural sense of the consequences of the intended movements. Proof of concept for this approach has been achieved in a series of experiments with human volunteers.[44,47]

CONCLUSIONS AND FUTURE PROSPECTS

The achievements that have been made to date in restoration of function in the sensory and motor systems reflect a technology still in its infancy. Researchers in this emerging field have provided proof of concept in animal and human experimentation, demonstrating that it is possible to intervene in the CNS and PNS to restore limited sensation to individuals with profound deafness and blindness, or to produce simple movements in the motor system. Clearly, much work needs to be done before these systems can be considered as standard therapeutic approaches in clinical medicine.

The UEA and USEA are prototype examples of neural interfaces that can begin to selectively

communicate with large numbers of individual neurons, or with small groups of neurons and nerve fibers. Importantly, the electrodes in these neural interfaces are, in fact, foreign bodies that tend to be rejected by the host's immune system. Future-generation electrode arrays must be designed to deal with this immunological challenge in a way that allows the implanted devices to function for decades. Such solutions might involve new array architectures or new coatings that present a more biocompatible interface to the neural tissues.[48,49]

Work is ongoing to develop wireless versions of neuroprosthetic devices, an essential requirement for clinical systems.[50] It will be necessary to create miniaturized signal-processing electronics and computer algorithms that can take advantage of the high-electrode-count microelectrode arrays that have already been developed or will be developed over the next decade. The design of fault-tolerant active electronics also represents a challenge: circuits must consume very little power and produce very little heat. The electronic circuitry must be hermetically sealed so that it can function flawlessly for decades in the corrosive environment of the cerebrospinal fluid. New application-specific electrode array architectures need to be developed that will be tailor-made for different implant sites throughout the entire nervous system. Improved surgical techniques need to be developed that will allow neurosurgeons to implant these devices rapidly and safely in the CNS and PNS. Although work has begun on these and many other fundamental areas, the field of neuroprosthetics is in its infancy and much remains to be done.

In the next decade, it is anticipated that neuroprosthetic technology will be applied to a variety of targets in the nervous system, including bladder and bowel control, pacing of the diaphragm, stimulation of the vagus nerve for control of epilepsy and chronic depression, stimulation of the auditory nerve and cochlear nucleus for an improved auditory prosthesis, recording from and stimulation of epileptic foci to control seizures, and recording from the motor cortex to control external devices (wheelchairs or computers) or to control electrode arrays implanted in the PNS. This emerging technology is expected to provide the neurosurgeon with entirely new sets of tools to deal with the many nervous system dysfunctions that afflict mankind.

KEY POINTS

- Neuroprosthetic devices are therapeutic interventions that restore lost neural function by electrical stimulation of sensory or motor pathways, or by harnessing activity recorded from remnant neural pathways
- Research teams at the Universities of Utah and Michigan have developed high-electrode-count, penetrating microelectrode arrays that interface with the CNS and PNS
- The Utah Electrode Array was originally developed as a means of restoring limited but useful sight to individuals with profound blindness
- The Utah Slanted Electrode Array can produce a sit-to-stand maneuver in an animal model; similar approaches might eventually be applied to patients with spinal cord injury
- Another promising application of neuroprosthetic technology is the control of prosthetic limbs via recording and stimulation of severed peripheral nerves
- In the future, neuroprosthetic technology might also be applied to bladder and bowel control, pacing of the diaphragm, and control of epilepsy and chronic depression

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Competing interests
The author declared an association with Cybernetics Neurotechnology Systems. See the article online for full details of the relationship.

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