Neural Prostheses

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Introductory article

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A neural prosthesis is a device that aims to restore or replace the functions of the nervous system that are lost to disease or injury. Examples include devices to improve hearing, vision, motor and cognitive functions. Neural prostheses artificially stimulate the nervous system to convey sensory information, activate paralysed muscles or modulate the excitability of neural circuits to improve conditions such as chronic pain, epilepsy or tremor. Some neuroprostheses also record activity from the nervous system, which can be useful for patients who have difficulty moving or communicating. These devices can decipher the intention of the user or detect ongoing brain events such as seizures by recording neural signals directly from the brain. Emerging neuroprostheses aim to 'close the loop' using recorded neural activity to control stimulation delivered elsewhere in the nervous system with the goal of improving function.

Introduction

Similar to a prosthetic limb, a neural prosthesis is a device that aims to restore or replace the function of a damaged part of the nervous system. Some neuroprostheses restore sensory input through stimulation of the nervous system. An example is the cochlear implant, which restores a sense of hearing to individuals with certain types of deafness. This device works by transducing sounds recorded by a microphone into stimulation delivered directly to the auditory nerve, bypassing the damaged middle ear. The retinal implant is another sensory neuroprosthesis that aims to restore vision for individuals with some types of blindness. Images captured by a camera can be transduced into stimulation of the retina or other visual pathway structures to convey a rudimentary sense of vision. Both of these examples involve transducing sensory information from the outside world into stimulation of the nervous system. The nervous system itself can also be a source of useful signals for neural prostheses. In the case of paralysis, information from motor areas of the brain can be used to control external devices such as robotic arms or routed around an injury and used to drive stimulation to restore movement to paralysed limbs. A final group of neuroprosthetic devices are used for modulation of the nervous system. Deep brain stimulation (DBS) improves function for individuals with Parkinson's disease and essential tremor and is currently being investigated as a treatment for a range of psychiatric conditions. Here, we briefly review the state of the art in auditory and visual neuroprostheses, followed by more in-depth coverage of devices to improve motor function.

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Auditory Neuroprostheses

The auditory system utilises a set of 16 000 individual hair cells in the cochlea; each is tuned to a specific frequency of sound and releases neurotransmitters that are detected by synaptic processes of the auditory nerve. Auditory implants are an ideal application of a neural prosthesis. The nature of auditory information is relatively simple and the structures involved are easily accessed and organised by the frequencies they perceive (tonotopically organised); thus, a large amount of information can be conveyed with only a few well-placed electrodes.

The first neural prosthesis approved for use in human patients was the cochlear implant, a device that substitutes for the middle ear by transducing sounds into electrical stimulation of the auditory nerve (Wilson and Dorman, 2008; **Figure 1**). This device consists of an external microphone, speech processor (designed to filter and process audible speech) and transmitter coil, along with a surgically placed receiver, stimulator and electrode array. Auditory information from the external microphone is broken down into discrete frequency components to determine stimulation patterns delivered to the microelectrode array placed over the tonotopic map of auditory nerves in the cochlea (**Figure 1**). Insertion of this device often result in loss of residual hearing, thus the cochlear implant is most useful for patients with profound deafness. Many patients develop the ability to distinguish speech and music. New models have some ability to combine a smaller,

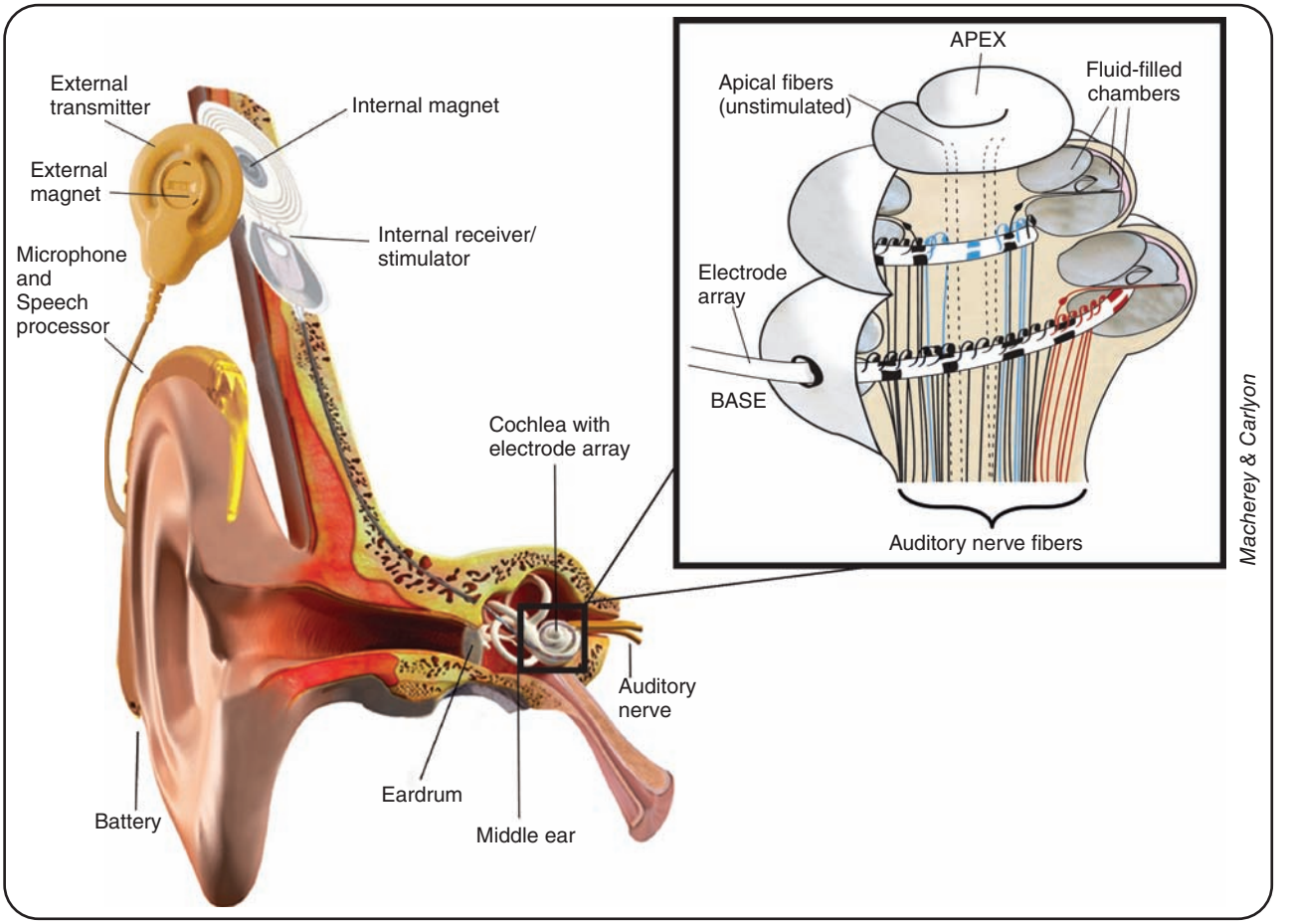

Figure 1 *Cochlear implant*. An external microphone and speech processor relay sound information to an external transmitter, which transmits it to the internal receiver. Here, it is converted to a stimulation pattern that is delivered to the cochlea via the implanted electrode array. Inset images detail the electrode array with multiple contacts ascending the spiral anatomy of the cochlea to activate the auditory nerves sensitive to different wavelengths of sound. Figure Copyright MRC Cognition and Brain Sciences Unit, used by kind permission.

less damaging implant with a hearing aid for patients with residual low-frequency hearing but complete deafness to middle- to high-frequency sounds (electric acoustic stimulation; Gstoettner *et al.*, 2006).

Cochlear implants require a functional auditory nerve and will not benefit patients with damage or dysfunction of their auditory nerve, such as patients with neurofibromatosis type II (NF2). A new type of neural prosthesis, the auditory brainstem implant, has been devised for patients lacking a functional auditory nerve. The design of the microphone and processor for this device is similar to that of the cochlear implant, but rather than stimulating the auditory nerve at the cochlea, electrodes stimulate the surface of the auditory brainstem. Current devices utilise 12–21 electrodes and patients generally develop the ability to recognise certain sets of sounds. The quality of input is far below that of the cochlear implant, and patients generally do not develop the ability to discern speech or music; however, a majority of patients claim the implant greatly aides in lip-reading. **See also**: **Hearing: Cochlear and Auditory Brainstem Implants**

Visual Neuroprostheses

Compared to hearing, vision is a more challenging sensory modality to restore using a neural prosthetic device. With 150 million photoreceptors (Shepherd *et al.*, 2013), the visual system contains over 10 000 times more sensory transduction cells than the auditory system, as well as a complex system of synapses in the retina processing the input from these transduction cells. This transformed information is sent through the optic nerve to multiple brain structures, primarily the thalamus (lateral geniculate nucleus) and the superior colliculus. Visual information is then sent to the visual cortex, where as many as 13 separate cortical areas process different components of the visual input, extracting details as simple as directional movement or colour and enabling processes as complex as recognising individual faces. **See also**: **Visual System**

Owing to the complexity of this system, researchers have developed various strategies in an attempt to build a visual neuroprosthesis. Visual prostheses consist of a sensing component (e.g. a

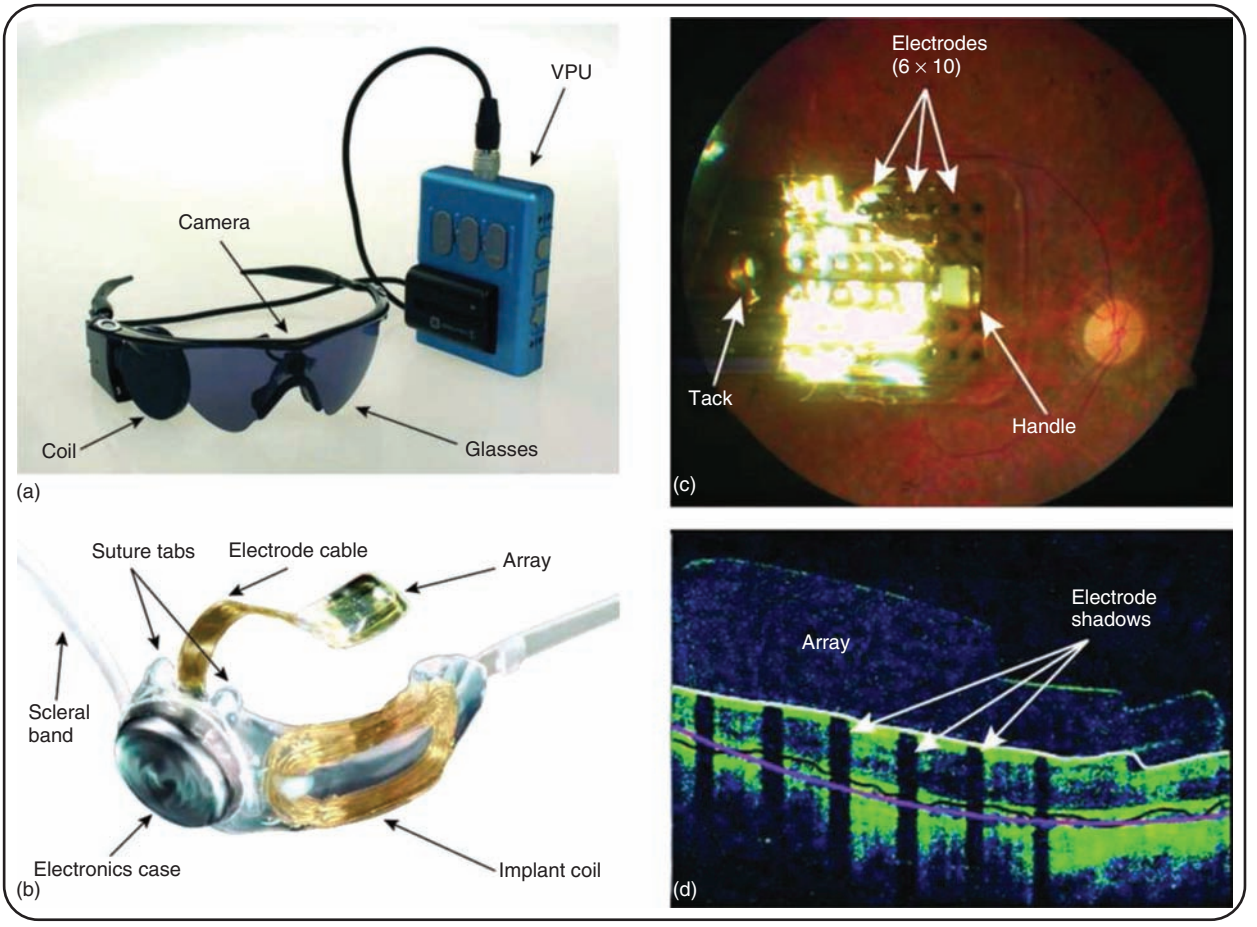

Figure 2 *Visual prostheses*. An example visual prosthesis system and its implantation. The Argus II (Second Sight Medical Products) consists of (a) a camera mounted on glasses and a video processing unit (VPU). The implanted components (b) include the electrode array and a coil for wireless communication and stimulation. In this design, the retinal stimulation is delivered through a 6 × 10 electrode array (c), visualised with optical coherence tomography in (d). Reproduced with permission from Humayun *et al.* (2012) © Elsevier.

camera), a processor and a set of stimulating electrodes implanted at relevant sites within the visual system (**Figure 2**). Visual system stimulation targets include multiple areas within the retinal, as well as the optic nerve, lateral geniculate nucleus and visual cortex (Lorach *et al.*, 2013). The choice of stimulation targets depends on the type of blindness affecting the person; for example, retinal stimulators that target the ganglion cell layer would be useful for people with photoreceptor loss resulting from retinitis pigmentosa or age-related macular degeneration, whereas stimulators targeting the thalamus or cortex are required for those with optic nerve injury, for whom retinal stimulation would otherwise not reach these brain structures.

While most research in visual prostheses is focused on retinal stimulators (Shepherd *et al.*, 2013), this approach is not useful for the many causes of blindness resulting from the destruction of the retina, necessitating other approaches further downstream in the visual system. In 1968, it was discovered that surface electrical stimulation of visual cortex in a blind patient resulted in the perception of visual sensation or 'phosphene' (Brindley and Lewin, 1968). Unfortunately, electrical stimulation of the surface of visual cortex produced variable responses and the effects of co-activation of multiple, spatially separated electrodes was unpredictable, with relatively poor spatial resolution (Dobelle and Mladejovsky, 1974). This led to the testing and development of penetrating electrode arrays, with recent work in non-human primates demonstrating responses to stimulation within visual cortex (Torab *et al.*, 2011). Future work is needed to test the effects of stimulating multiple electrodes simultaneously, as this will be needed to communicate information about complex visual scenes directly to the brain.

Motor Neuroprostheses

Injury or degeneration of the motor neurons, spinal cord or brainstem can lead to paralysis despite relatively normal function of other motor areas of the brain. In order to restore conscious or volitional control to paralysed limbs, efforts are underway to record activity from the brain to determine the movement intention of the user. A device that determines the user's intention

by recording directly from the brain is termed a brain computer interface (BCI) or a brain–machine interface (BMI). These brain recordings can be obtained from several types of electrodes either on the surface of the scalp or implanted within the body as described later.

Neural recording techniques

A number of different types of recording systems have been devised to gather information from the brain (**Figure 3**). Most methods take advantage of the small potentials created by neurons when they discharge action potentials, either individually or in concert, whereas others take advantage of global changes in neural activity.

Recordings of brain activity can be obtained from electrodes placed on the surface of the scalp, termed electroencephalography (EEG). These recordings register the average neural activity from a large area of the cortical surface (Whittingstall and Logothetis, 2009). Typically, neural signals at a number of electrodes (from 16 to 256) are recorded simultaneously, and information from these is decoded to identify signals relevant to a specific motor task. Human volunteers are able to achieve conscious (i.e. volitional) control of one or two EEG signals at a time. EEG can also be used to determine whether a subject is paying attention to an object, leading to the application of EEG recording to enable communication through a method known as the P300 speller. This system sequentially highlights the characters presented in a matrix of letters and numbers, determining the character that the user intends via a positive-going wave recorded in the EEG approximately 300 ms after the character is highlighted (P300 response). This P300 recognition signal can be used to sequentially identify letters and numbers that the user is trying to communicate when that person is otherwise unable to speak or write, for example, in the later stages of amyotrophic lateral sclerosis (ALS, or Lou Gehrig's disease). While the only option for these patients, the amount of information and data transfer rate via EEG-based recording tends to be low (0.1–0.3 bits/s) (Ryan *et al.*, 2011), making communication through these methods quite slow.

By surgically placing recording electrodes beneath the skull, recordings of smaller groups of neurons can be made using electrocorticography (ECoG) (Leuthardt *et al.*, 2004). Placing the electrodes inside the skull reduces noise and allows for recording of a smaller volume of cortical tissue (~1 mm). ECoG electrodes can be place either above or below the dura – a protective membrane surrounding the brain and spinal cord. More densely spaced arrays of ECoG electrodes (micro-ECoG) placed under the dura can record from smaller amounts of cortical tissue and may provide more precise control of the BCI (Rouse *et al.*, 2013). Signals from closely placed surface electrodes, however, tend to correlate strongly and the amount of information that can be extracted is not greatly improved with less than 1 mm electrode spacing. Recent studies utilising a subdural ECoG array in human motor cortex

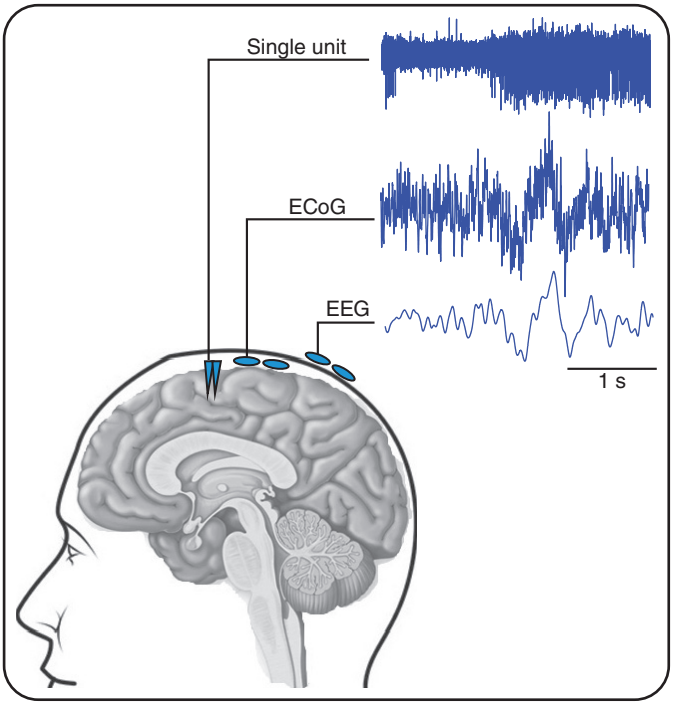

Figure 3 *Signals used for brain–computer interfaces*. High-frequency brain signals are recorded from micro-electrodes that penetrate the cortex of the brain to resolve the timing of individual neuron action potentials. Moderate frequency signals representing the activity of many thousands of neurons are recorded with electrocortigraphic (ECoG) electrodes on the brain surface. Low-frequency activity representing the average activity of hundreds of thousands of neurons is recorded from electroencephalography (EEG) electrodes on the surface of the scalp. These signals are then processed to extract information about the intent of the user and control a brain–computer interface, such as the movement of a robotic arm, control of a computer cursor or for written communication.

have allowed sufficient decoding to control a three-dimensional robotic arm in an eight-choice task with a high degree of success (Wang *et al.*, 2013).

Placing arrays of fine electrodes within the brain itself allows for recording from single or small numbers of individual neurons. Often these individual neurons and populations can be controlled by the subject with reasonably high fidelity (Fetz, 1969; Hochberg *et al.*, 2006). This recorded activity has been used by paralysed human subjects to control computer cursors or robotic arms and achieve movements such as grasping or self-feeding (Collinger *et al.*, 2013; Hochberg *et al.*, 2012). While recording of individual and multiunit neuronal activity may provide the highest bandwidth signal for control, the small microelectrode arrays currently used are quite sensitive to tissue reaction and encapsulation by glial cells, which contribute to scar formation. The immune reaction, encapsulation by glial cells (i.e. gliosis), and motion of the electrode relative to the brain can make long-term recordings challenging to obtain (Shain *et al.*, 2003; Prasad *et al.*, 2012). Although signal degradation occurs over time, some remaining neural signals have been recorded from microelectrode arrays for over 5 years in recent human studies (Hochberg *et al.*, 2012).

Recorded brain activity can be used not only to control robotic limbs but also to control stimulation of sites within the nervous system that can cause movements of an otherwise paralysed limb. Monkeys learned to control the activity of individual neurons (Moritz *et al.*, 2008) or populations of brain cells (Ethier *et al.*, 2012; Pohlmeyer *et al.*, 2009) to deliver stimulation to the nerves and muscles of their paralysed forearm and produce movements of their arms despite temporary paralysis (**Figure 4**). Several studies have also demonstrated that brain signals can be used to control stimulation delivered to the spinal cord below an injury (Zimmermann and Jackson, 2014; Nishimura *et al.*, 2013). Stimulation of the spinal cord has several advantages over direct stimulation of peripheral nerves and muscles, as described in the following section.

Functional stimulation

Paralysed muscles can be made to contract by the application of electrical stimulation to the muscles, nerves or spinal cord. When applied to the peripheral nerves or muscles, this is termed functional electrical stimulation (FES) and is accomplished by delivering current via electrodes placed on the skin surface, implanted within or near the muscle or wrapped around the peripheral nerve to form a cuff. FES can restore limb movements such as hand grasp (Peckham *et al.*, 2002) and walking gait (Kobetic *et al.*, 1997). Although advanced stimulation techniques partially mitigate this problem (Fang and Mortimer, 1991), FES applied to muscles or peripheral nerves often results in poor grading of force and rapid muscle fatigue due to early activation of the largest and most fatigable muscle fibres (Feiereisen *et al.*, 1997).

Stimulation within the spinal cord, termed intraspinal microstimulation (ISMS; **Figure 5**) has the advantage of activating muscle fibres in a more natural, fatigue-resistant manner (Mushahwar and Horch, 1998). Placing fine wires within the spinal cord circuitry also facilitates activation of complex movement synergies from single stimulating locations such as stepping and grasping movements (Moritz *et al.*, 2007; Mushahwar *et al.*, 2002). The ability to evoke coordinated, fatigue-resistant movements from

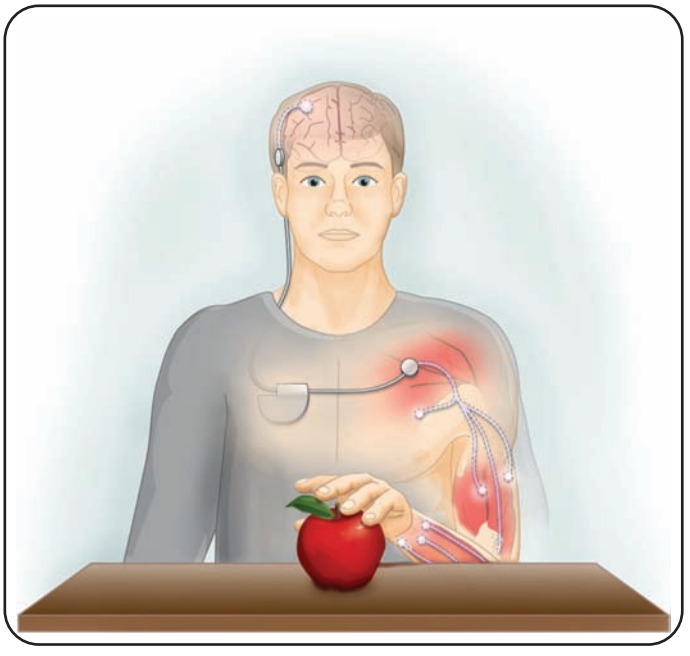

Figure 4 *Brain-controlled FES system.* Electrodes implanted on the surface of the brain (electrocorticography – ECoG) or penetrating within the cortex of the brain record neural activity that can be translated into stimulation of muscles to enable functional movements after paralysis. Reproduced from Scott SH (2008) © Nature Publishing Group.

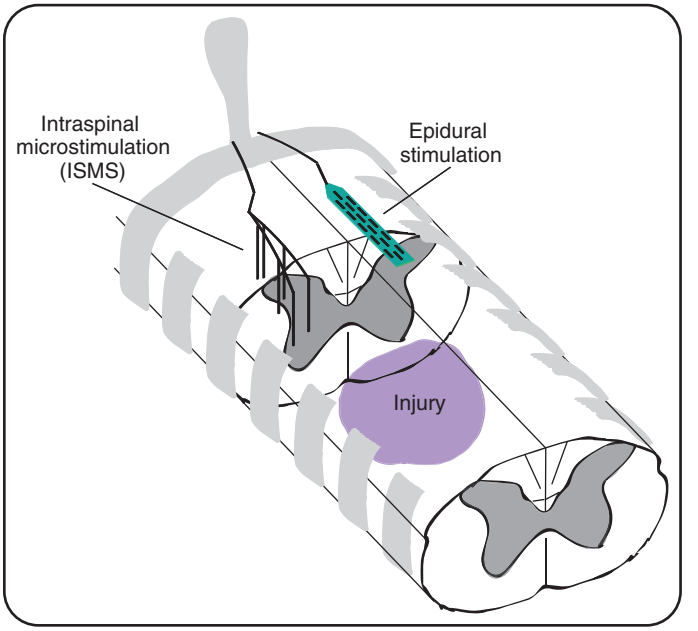

Figure 5 *Approaches to spinal stimulation.* Intraspinal microstimulation (ISMS) utilises electrodes placed within the spinal cord to activate specific neural circuits within the gray matter or area of spinal cord cell bodies. Epidural stimulation utilises electrodes placed on the dorsal surface of the spinal cord, above the dura or protective covering of the spinal cord. In most cases, stimulation is delivered below a site of injury to restore functional activity to the areas disconnected from descending brain input after injury. Epidural stimulation preferentially targets sensory fibres near the dorsal surface of the cord, whereas penetrating stimulation can reach the motor neuron cell bodies in the ventral horn. Reproduced with permission from Mondello SE, Kasten MR, Horner PJ and Moritz CT (2014) Creative Commons Attribution License.

within the spinal cord may simplify the control signals needed for an eventual system using brain activity to re-animate paralysed limbs.

In addition to restoration of limb movement, electrical stimulation may be used to improve respiratory function such as the ability to breathe and cough. Individuals with cervical spinal cord injury, ALS (or Lou Gehrig's disease) and other neuromuscular disease are sometimes unable to breathe when central respiratory centres and/or spinal motor neurons no longer control the diaphragm and intercostal muscles that generate respiratory contractions. The surface of the spinal cord can be stimulated to assist coughing and the clearance of secretions (DiMarco *et al.*, 2009). Respiration can also be promoted via phrenic nerve pacing (PNP), in which electrodes placed in or around the phrenic nerve are utilised to contract the diaphragm (DiMarco, 2009).

Following spinal cord injury or degenerative loss of spinal function, the loss of bladder and bowel control present substantial quality of life issues. As bladder function is controlled by identifiable nerves leaving the spinal cord, several neuroprosthetic approaches to restore function have been explored (Prochazka *et al.*, 2001). Stimulation of sacral roots or nerves innervating the bladder results in activation of the smooth muscle of the bladder, leading to increased bladder pressure and urination, whereas stimulation of nerves innervating the urethra results in activation of the smooth muscle of the urethra, closing the sphincter and eliminating incontinence. While bladder control appears deceptively simple, electrical stimulation of nerves innervating the bladder does not elicit a full range of function, as fully voiding the bladder requires simultaneous stimulation of bladder wall muscles for contraction and simultaneous stimulation of the pudental nerves for relaxation of the urethral sphincter (Creasey *et al.*, 2001).

Neuromodulatory stimulation

In addition to directly restoring function using electrical stimulation, the excitability of neural circuits can be changed or modulated using stimulation. For example, stimulation of the dorsal spinal surface preferentially activates the dorsal columns, which consist of sensory fibres carrying information to the brain (**Figure 5**). High-frequency stimulation of these fibres generally causes parathesia (numbness) that is used to alleviate certain types of chronic pain. This stimulation can be delivered via epidural electrodes placed on the spinal surface, which are currently approved for multiple types of regional pain syndromes. Recently, stimulation of the lower thoracic spinal cord has been tested in patients with complete motor loss following spinal cord injury (Angeli *et al.*, 2014; Harkema *et al.*, 2011). Stimulation via these electrodes below the level of the spinal injury resulted in the patient being able to move the lower extremities during periods of stimulation. In addition to the ability to generate volitional movements, patients have been reported to have improved bladder function, sexual function and temperature regulation that persist even after epidural stimulation (Angeli *et al.*, 2014; Harkema *et al.*, 2011).

The most common clinical neural modulation procedure is DBS, originally approved to treat essential tremor by stimulating

the ventral intermediate nucleus of the thalamus in 1997. DBS was later approved in 2003 as a treatment for Parkinson's disease via stimulation of the ventral intermediate nucleus of the thalamus or the subthalamic nucleus (Putzke *et al.*, 2003). The neural portion of a DBS device consists of a flexible tube electrode with multiple insulated wires each connected to separate platinum-iridium leads near the tip of the electrode. The end of the electrode is placed at or near the target and stimulation is applied via an implanted pulse generator, resulting in activation of fibres and neurons near the chosen electrodes. The exact mechanism by which DBS reduces tremor and improves motor function and whether the device works by activating or impeding neurons or fibres of passage is still a matter of some debate, but DBS has been demonstrated to reduce tremor, improve motor function and reduce dependency on medication.

Individuals with certain types of epilepsy also benefit from neuromodulatory stimulation delivered to the brain or vagus nerve. Approximately one third of epileptic patients have seizures that are not stopped by the current range of pharmacological treatment and are candidates for a neuroprosthetic device that could reduce seizure frequency, such as a vagal nerve stimulator. Stimulation of the vagal nerve (also known as cranial nerve 10 or CN X) causes release of norepinephrine in cortex and is believed to inhibit seizure initiation and propagation. While currently an open-loop stimulation device, research is underway to trigger vagal nerve stimulation in response to signs of a seizure such as altered cardiac rhythms. Electrical recordings from the brain can also provide information about impending or ongoing seizures. One recently approved device by the company NeuroPace provides closed-loop control of neurostimulation by recording from electrodes placed within or on the surface of the brain (e.g. ECoG) to detect ongoing seizures and then triggering stimulation within the brain to halt or reduce the severity of these seizures (Fridley *et al.*, 2012).

Future Neural Prostheses

In addition to effectively treating Parkinson's disease and essential tremor, DBS is also being explored for the treatment of depression and obsessive–compulsive disorder. In contrast to the pre-programmed, open-loop stimulation used to treat movement disorders, patients with psychiatric conditions may benefit from the ability to modulate stimulation in real time as symptoms flare or remit. Patient-controlled stimulation of the lateral hypothalamus, a likely passageway of the medial forebrain bundle (MFB) (Schlaepfer *et al.*, 2013), has been demonstrated to alleviate depression in human patients (reviewed in Widge *et al.*, 2014). Development of implanted, closed-loop DBS systems is underway. These devices use recorded neural signals to control the delivery of symptom-relieving stimulation. Proof-of-concept studies demonstrate that animal subjects can learn to modulate their brain activity in real time to deliver rewarding stimulation to the MFB (Widge and Moritz, 2014). Eventually, it may be possible for patients to intentionally or volitionally control the application of stimulation using their own brain activity, similar to the operation of a brain–computer interface, but with the output used to alleviate psychiatric symptoms (Widge *et al.*, 2014).

Research has begun on a neuroprosthesis designed to mimic neuronal connections lost in Alzheimer's disease and other illnesses that cause hippocampal degeneration and associated memory loss. Simultaneous recording from ensembles of CA1 and CA3 hippocampal neurons in rats during a memory task provided functional information about the task, and microstimulation delivered to the same electrodes was able to improve functional behaviour after pharmacological disruption of natural connections (Berger *et al.*, 2011).

In addition to being useful for medical imaging, ultrasound has also been shown to activate neuronal circuits from outside the body (i.e. non-invasively). The frequency and intensity of the acoustic signal required to activate neural tissue is variable in different tissues (Tufail *et al.*, 2011). Ultrasound energy tends to be fairly unfocused and not ideal for stimulating small regions, but recent work with modulated frequency-focused ultrasound has resulted in stimulation areas as small as 1 mm^2 (Mehic *et al.*, 2014). When compared with electromagnetic techniques, ultrasound stimulation has the unique advantage of effectively stimulating non-invasively at substantial depth through neural tissue. While current ultrasound devices are quite large, new developments in miniaturised ultrasound arrays may allow future ultrasound-based neuroprosthetic devices to be implanted within the body for long-term use.

Another novel technique for stimulation is optogenetics, in which light-sensitive ion channels or pump proteins (originally discovered in photosensitive algae) are introduced to neurons. Activity of these neurons can then be modified by exposure to light of the proper wavelength (Zhang *et al.*, 2010). Optogenetics allows temporally precise control of neural activity and the ability to localise to specific cell types. Multiple light-sensitive proteins now available permit either excitation or inhibition of neuronal activity (Han *et al.*, 2009). Optical stimulation has also been utilised in animal models of spinal cord injury with the goal of restoring respiratory rhythms after injury (Alilain *et al.*, 2008).

More recently, the Tonegawa lab used a targeted optogenetic approach to implant a false memory in hippocampal cells, demonstrating that manipulation of memory-encoding cells elicited clear behaviour (Ramirez *et al.*, 2013). While the technologies required to restore functional memory formation are beyond the current state of the art, these studies demonstrate the potential for a future memory neuroprosthesis. Expression of non-native ion channels and pumps in human neurons will require use of viral vectors or other expression systems to enable these cells to become light sensitive. Additionally, while applying light to the cortical surface is relatively straightforward, photons in the visual range scatter greatly within neural tissue, thus applying light sufficient to activate optogenetic ion channels and pumps to neurons deep within the brain in humans may require penetrating implants (Anikeeva *et al.*, 2012).

Optogenetics may be an ideal means by which to selectively activate the cortical surface to convey somatosensory information for individuals with sensory loss. Current efforts to develop a somatosensory neural prosthesis utilise electrical stimulation of the brain via surface or penetrating electrodes. Animals can be trained to discriminate different frequencies of electrical stimulation to either navigate toward or select specific targets (Thomson *et al.*, 2013; O'Doherty *et al.*, 2011). Initial experiments in human

subjects have utilised surface stimulation via ECoG electrodes positioned over the sensory cortex to convey sensory information (Johnson *et al.*, 2013). Sensations were somewhat non-specific, likely due to the fact that stimulation of the cortical surface results in a complicated response, as fibres near the cortical surface are preferentially stimulated (layer I fibres), generally resulting in activation of a broad region of cortex.

Conclusion

Neural prostheses have already demonstrated substantial benefits for individuals with certain types of sensory and motor challenges and have substantial potential to improve quality of life for patients with a broad range of diagnoses in the future. Current devices are capable of restoring limited auditory and visual sensation to individuals with specific types of hearing loss and blindness. Functional stimulation can also promote limb movements and respiration, although muscle fatigue is a challenge that requires advanced stimulation techniques. Neuromodulatory stimulation can improve chronic pain, enable some movements after spinal cord injury and reduce the occurrence of epileptic seizures. Stimulation delivered within the brain improves symptoms for individuals with Parkinson's disease and essential tremor and is currently being investigated for a variety of psychiatric conditions. The ongoing development of closed-loop devices for treatment of motor and sensory loss will benefit from both an improved understanding of the central nervous system and advances in computer electronics and implantable medical devices.

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