REVIEWS

Neural interfaces for the brain and spinal cord—restoring motor function

Andrew Jackson and Jonas B. Zimmermann

Abstract | Regaining motor function is of high priority to patients with spinal cord injury (SCI). A variety of electronic devices that interface with the brain or spinal cord, which have applications in neural prosthetics and neurorehabilitation, are in development. Owing to our advancing understanding of activity-dependent synaptic plasticity, new technologies to monitor, decode and manipulate neural activity are being translated to patient populations, and have demonstrated clinical efficacy. Brain–machine interfaces that decode motor intentions from cortical signals are enabling patient-driven control of assistive devices such as computers and robotic prostheses, whereas electrical stimulation of the spinal cord and muscles can aid in retraining of motor circuits and improve residual capabilities in patients with SCI. Next-generation interfaces that combine recording and stimulating capabilities in so-called closed-loop devices will further extend the potential for neuroelectronic augmentation of injured motor circuits. Emerging evidence suggests that integration of closed-loop interfaces into intentional motor behaviours has therapeutic benefits that outlast the use of these devices as prostheses. In this Review, we summarize this evidence and propose that several known plasticity mechanisms, operating in a complementary manner, might underlie the therapeutic effects that are achieved by closing the loop between electronic devices and the nervous system.

Introduction

Spinal cord injury (SCI) affects over 130,000 individuals each year, and an estimated 2–3 million people worldwide are living with SCI-related disability.[1] SCI is a complex and multifaceted condition, but regaining the use of paralysed limbs is consistently rated as a high priority by patients with paraplegia or tetraplegia.[2] Current treatment options after acute management include physiotherapy and occupational therapy, but recovery of motor function is often limited and plateaus within the first year.[3] Although regeneration of descending pathways through the use of pharmacological agents, stem cells or other transplantation techniques remains the goal of much research,[4–6] the challenges facing such efforts have, in recent years, led to an increased focus on new technologies to improve the quality of life of patients with SCI.

Neural prosthetics is a field of SCI research that has seen rapid progress, two examples of which are the development of brain–machine interfaces (BMIs) that enable patients to control assistive devices—such as robotic limbs—by using neural signals recorded directly from the brain, and the use of functional electrical stimulation (FES) to reanimate paralysed limbs. Another promising approach to SCI is neurorehabilitation, which comprises techniques to maximize the efficacy of neural structures that are preserved following injury and could support functional recovery. At present, just over half of all new SCIs are incomplete—that is, some sensory or motor function persists below the level of injury —and surviving, but functionally silent, descending axons can remain even following clinically complete SCI.[7] Remodelling of such surviving pathways and their spinal targets to support some functional recovery could, therefore, prove easier in the short term compared with attempts to regenerate entirely new fibre tracts through injured areas.[4] New technologies such as implanted neurostimulators may find applications in modulating the excitability of spinal networks and guiding the activity-dependent processes that govern the formation of new motor circuits.

In this Review, we examine recent progress in the use of neuroelectronic devices to interface directly with the CNS and PNS, with a particular focus on techniques that have applications in SCI treatment and fall into three broad categories: BMIs, FES and neuromodulatory stimulation (Figure 1). As all three techniques involve manipulation of neural activity within the motor system either above or below the level of injury, we argue that these interventions will invoke activity-dependent plasticity mechanisms that might have lasting therapeutic benefits. Such benefits could accrue when the nervous system and neuroelectronics are bidirectionally coupled to enable the travel of information in a 'closed loop' (Figure 2). This broad term is applied to devices that decode brain signals and relay the output back to the user in the form of sensory feedback (as in closed-loop BMI), as well as devices that sense a motor act and augment it

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with electrical stimulation (as in closed-loop FES). We speculate that the convergence of recording and stimulating capabilities in closed-loop neural prostheses (Box 1) will provide effective tools to promote Hebbian synaptic plasticity for the functional rehabilitation of injured motor networks in patients with SCI.

Brain–machine interfaces
Decoding motor intent
Invasive techniques

The concept of inferring, or decoding, parameters of movement from the action potential discharges (known as 'spikes') of cortical neurons arose in the 1970s.[8] Improvements in chronic electrode arrays and computational techniques in recent years have enabled increasingly impressive demonstrations of 'brain control' in monkeys[9–13] and humans.[14,15]

One brain control system, called BrainGate, uses an array of 96 silicon electrodes that penetrate 1.5 mm in to the upper-limb representation of the primary motor cortex to record firing from 50 or more neurons. The spiking rates of these neurons are processed to provide control signals for various artificial effectors. The first patient (an individual who was tetraplegic owing to an injury at the C3–C4 spinal level) implanted with the BrainGate system was able to operate a 2D computer cursor as well as control grasping movements of a hand prosthesis.[14] In 2012, the same research group reported that the BrainGate system enabled control of 3D reaching and grasping of robotic arms in two patients who were paralysed after experiencing a brainstem stroke.[15] One participant in this study was able to use the robotic arm to drink though a straw from a bottle, demonstrating the practicality of such systems for activities of daily living. Notably, the electrodes in this patient had been implanted for over 5 years. The long-term performance of intracortical implants remains a source of concern, as mechanical and biological incompatibility of electrodes cause recording instabilities, tissue damage and formation of glial scars, all of which can progressively reduce the amplitude of recorded signals. That useful control could be achieved 5 years after implantation is encouraging, but efforts to improve long-term stability of electrodes remains a priority if devices are to be of practical use to patients who often live for many decades with their disabilities.[16–18]

Noninvasive techniques

Noninvasive recording techniques such as EEG are an alternative method to obtain signals for neural interfacing.[19] Real or imagined movements of the limbs are associated with desynchronization of 10–20-Hz rhythms recorded over sensorimotor cortical areas. The detection of power changes at these frequencies has enabled impressive control of 1D,[20–22] 2D[23] and 3D[24] computer cursors, and this approach might enable patients with tetraplegia to control robotic arm prostheses.[25] Unfortunately, as any imagined movement of a given limb produces the same general pattern of desynchronization over a wide area of cortex, the independent control

Key points

- Brain–machine interfaces (BMIs) that record and decode signals from the brain enable volitional control of assistive devices, and modify patterns of cortical activity through the process of neurofeedback
- The translation of invasive BMIs from animal studies to patients suggests that these technologies could control functional electrical stimulation for the restoration of movement to paralysed limbs
- Epidural and intraspinal stimulation generates functional limb movements involving the coordinated activity of multiple muscles, and the activation of spinal circuitry in combination with volitional intent could have therapeutic benefits
- Correlated patterns of spiking activity drive synaptic and structural plasticity, and experimental protocols that involve stimulation of the CNS and PNS have been used to artificially induce specific changes in neural connectivity
- Neural prostheses that combine recording and stimulation capabilities within wearable or implantable closed-loop devices could replace or augment injured pathways from the cortex to the spinal cord
- Long-term operation of closed-loop devices may have further therapeutic benefits through several complementary mechanisms of activity-dependent plasticity
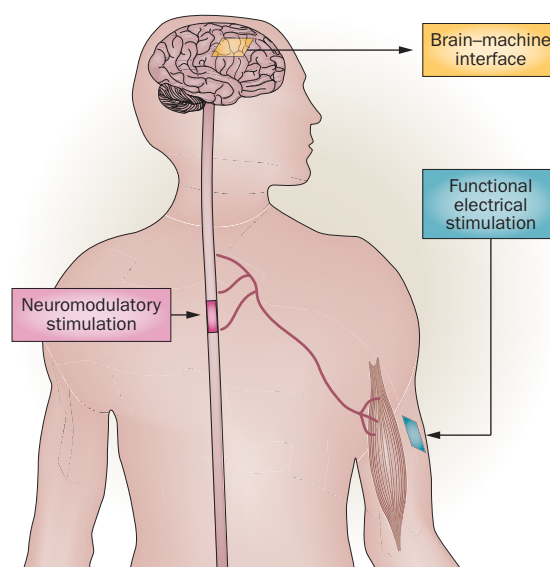
Figure 1 | Interfacing with the central and peripheral motor system for prosthetic and rehabilitation applications. Brain–machine interfaces that decode cortical signals are currently used to control computers or robotic prostheses. Neuromodulatory stimulation is usually delivered according to pre-programmed protocols adjusted by clinicians. Functional electrical stimulation delivered to muscles, peripheral nerves or the spinal cord often relies on proxies for motor commands, such as switches controlled by residual movements.

of movements in multiple dimensions requires the patient to learn nonintuitive combinations of left-hand, right-hand and foot movements.

Intracortical field potentials recorded in monkeys showed that the greatest amount of information about movement direction is contained in low-frequency (<4 Hz) and high-frequency (>60 Hz) bands.[26] Noninvasive techniques are generally poor at capturing the high-frequency bands, possibly owing to the spatiotemporal filtering that is inherent in scalp recordings.[27] Low-frequency EEG signals may be confounded by eye movements and other artefacts, although slow cortical potentials have been used to enable communication by
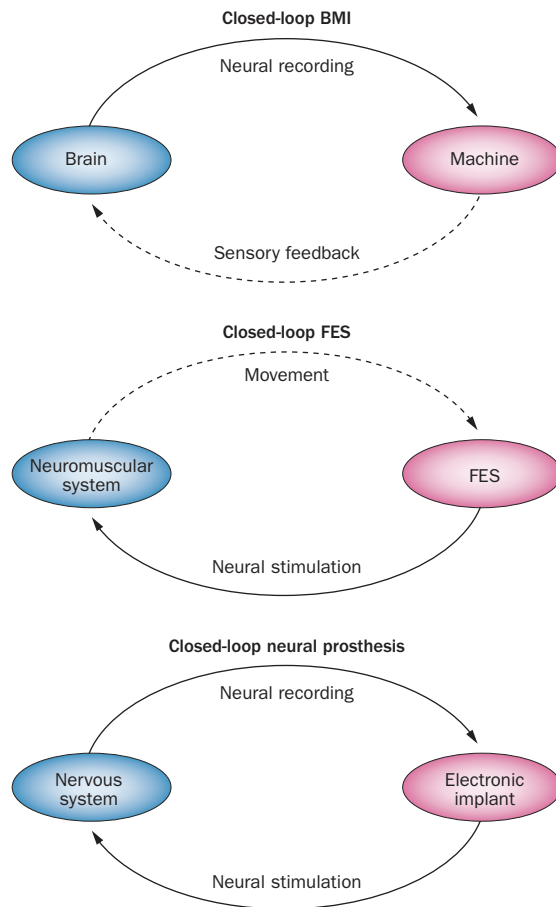
Figure 2 | Examples of 'closed-loop' connections between the nervous system and electronic devices. Closed-loop BMIs use neural signals recorded directly from the nervous system, but feedback to the user is typically provided by visual (sensory) feedback. Closed-loop FES systems typically sense movements using switches or tilt sensors and deliver electrical stimulation to the neuromuscular system. A general closed-loop neural prosthesis combines recording and stimulation capabilities, such that stimulation delivered to one site in the nervous system is contingent on activity recorded at another site. Abbreviations: BMI, brain–machine interface; FES, functional electrical stimulation.

patients with locked-in syndrome.[28] Robust single-trial decoding of movement direction has, however, been achieved with low-frequency magnetoencephalography (MEG).[29,30] Recently, electrocorticography (ECoG) has emerged as a promising recording modality to decode movement direction, yielding good spatiotemporal resolution of both low-frequency and high-frequency components through the use of subdural or epidural grids that are less invasive than penetrating arrays.[31,32] Although most studies in humans have been performed with grids that were implanted over a short time period to localize seizures, evidence from studies in monkeys suggests that movement-related ECoG signals could be stable for many months.[33]

Neurofeedback

The common principle of BMIs is that decoded motor intentions of the patient are used in real time to control an effector such as a computer cursor or robotic arm. Typically, the decoding algorithm is calibrated using neural signals collected during performance of an instructed set of real or imagined arm movements. Parameters are tuned such that the output of the algorithm best predicts the direction of the training movements. This approach is often termed open-loop decoding, as the output of the algorithm during this phase does not influence the user's behaviour. Once calibrated, the decoder may be used for real-time 'brain control', during which the user receives some form of feedback from the effector. This mode of operation, therefore, is termed closed-loop control. In most cases, feedback is provided only through vision of the effector. Evidence suggests, however, that (as for natural movements) proprioceptive information can improve the accuracy of BMI-mediated movement.[34] Indeed, several groups are now working to provide artificial afferent feedback using intracortical microstimulation of somatosensory areas.[35–37]

Irrespective of whether feedback is provided through a natural or artificial sensory modality, once the brain is 'in the loop', the patterns of neural activity change as the user masters the interface.[11,12,37–39] This fact had been anticipated in previous operant-conditioning studies, which showed that monkeys could increase the firing rates of individual cells to operate a device that controlled reward delivery.[40] This change in neural firing rate is an example of neurofeedback training, through which individuals learn volitional control of a feedback signal that relays real-time information about specific brain activity.[19] Subsequent BMI experiments have found that practice of brain control is accompanied by profound reorganization of cortical activity, involving changes in the directional tuning of neurons used by the decoder,[11,12] as well as reduced modulation of neighbouring neurons.[41]

Learning to control noninvasive BMIs also entails changes in the underlying brain signals, such as an increase in the amplitude of slow cortical potentials[28] or a sharpening of sensorimotor-rhythm topographies.[24,42] BMI-based neurofeedback can be used after injury to alter functional connectivity[43] and normalize patterns of cortical activity,[44] and could thus have therapeutic benefit by enhancing the volitional recruitment of surviving motor pathways.[19,45,46]

Functional electrical stimulation
Stimulation of the muscles

FES involves the stimulation of muscular contractions by electrical activation of motor nerves via surface or implanted electrodes. FES systems for the lower limbs can facilitate standing, walking or cycling,[47–49] whereas upper-limb systems can enable functional grasping as well as limited proximal arm movements.[50–52] Many FES systems use simple switches to trigger a small number of pre-programmed movements that can be controlled by an unaffected body part or incorporated into residual movements of the affected limb. For example, foot-drop stimulators often use heel switches or tilt sensors to control stimulation of the common peroneal nerve that assists dorsiflexion during the swing phase of gait.

Interestingly, such devices can have lasting therapeutic benefit after stimulation is turned off, resulting not only from increased muscle strength and fitness, but also via effects on the CNS such as increased efficacy of cortico-spinal transmission.[53] Functional electrical therapy of the upper limb, in which FES of distal muscles is coupled to voluntary control of proximal movements, can also produce these beneficial carry-over effects.[54]

The therapeutic effect of FES on the CNS is probably mediated by afferent fibres that are activated either during evoked movements or by direct electrical excitation. The benefits are suggested to be maximized when FES is integrated with surviving intentional control mechanisms, such that stimulus-evoked peripheral activity is associated with central motor commands.[55] The use of BMI technologies to enable direct control of FES by brain signals, therefore, offers a promising opportunity to couple patterns of activity above and below the level of injury. Interest in an 'artificial motor pathway' to bypass injured connections from the cortex to muscles —a concept first proposed in the 1970s by Brindley and colleagues[56]—has been revived in recent years after two studies in monkeys demonstrated the feasibility of brain-controlled FES to restore wrist movements after a temporary peripheral nerve block.[57,58] Subsequently, this approach was extended to involve independent stimulation of three muscles to restore volitional grasping movements.[59] The feasibility of FES-mediated brain control of reaching movements has also been tested in a patient implanted with the BrainGate system using a simulated FES controller.[60] An attractive feature of an invasive approach is that the link from brain to muscles could, in principle, be realized using a subcutaneous implant that operates autonomously without the need to communicate with external devices through percutaneous connectors or power-hungry wireless transmission. Brain control of FES has been implemented using a battery-powered 'neurochip' circuit that enables long-term neural recording and stimulating in primates,[57,61] and brain control of surface and implanted FES systems has also been demonstrated using EEG-based methods.[62–64]

Surface FES has the advantage over implanted FES of being noninvasive, but electrodes can take time to put on and remove, and only a limited number of muscles can be independently stimulated. Implanted FES systems for multiple muscles could be more convenient for patients, but require extensive surgery and have proved difficult to commercialize.[65] A promising alternative may be the more proximal stimulation of peripheral nerves, in which the use of multi-contact arrays enables the activation of multiple muscles from a single implant site.[66] Moreover, delivery of interleaved stimuli to different electrodes that activate the same muscle reduces the rate at which individual motor units must be stimulated for tetanic contraction, leading to greater fatigue resistance.[67] Sacral root stimulation has proved successful for restoration of bladder control in patients with SCI,[68] and a multichannel lumbosacral stimulator has been proposed to restore bladder and leg function from a single implant site within the vertebral column.[69]

Box 1 | Implementation and applications of neural interfaces

The pace of technology development has led to proliferation of terminology to describe the possible interfaces between nervous systems and devices. In our opinion, the most useful distinction is based on the direction that information travels across the interface:

Output devices

Output devices transduce signals directly from the nervous system to the outside world, bypassing movements of the limbs. If recording from the brain, the device can be called a brain–machine interface (BMI), brain–computer interface, neural interface system or neuromotor prosthesis, although signals can also be recorded by peripheral nerve interfaces and myoelectric interfaces. When invasive electrodes are used, the skin can be breached by physical leads, or signals can be transmitted wirelessly from battery-powered implants to an external receiver.

Input devices

Input devices deliver signals to the nervous system and can relay information (as in sensory prostheses such as cochlear implants) or modulate neural processes (as in deep brain stimulation and neuromodulatory stimulation). Stimuli may be delivered by implantable pulse generators similar to the heart pacemaker, or by noninvasive transcutaneous or transcranial electrical stimulation, transcranial magnetic stimulation or transcranial direct current stimulation. Functional electrical stimulation refers specifically to the generation of motor actions and is, therefore, distinct from therapeutic electrical stimulation, which maintains the strength and health of muscles, and transcutaneous electrical nerve stimulation for pain relief.

Closed-loop devices

Closed-loop devices combine input and output capabilities. In the context of BMIs, 'closed-loop' often refers to provision of feedback to the user through vision or other sensory modalities, but can more generally include feedback through any of the artificial input channels described above. Closed-loop interfaces involve implanted or wearable devices that operate as autonomous neural prostheses, continuously relaying information from one site in the nervous system to another.

Stimulation of the spinal cord

An alternative to peripheral FES is direct stimulation of the motor circuitry of the spinal cord (Figure 3a). Spinal stimulation through epidural electrodes is already in widespread clinical use, and is well established as a safe and effective treatment for chronic pain[70,71] and spasticity.[72] Such electrodes provide diffuse excitation of spinal circuits, which is probably mediated by activation of the dorsal roots. By contrast, intraspinal microstimulation uses fine microwires or microelectrode arrays that penetrate the spinal cord for focal stimulation of motor networks in the intermediate and ventral regions of the grey matter. Intraspinal microstimulation has been used for many years in animal experiments to explore intrinsic motor capacities of the spinal cord (Figure 3b). In the frog lumbar spinal cord, this form of stimulation evokes swiping or kicking movements of the legs, with the direction and amplitude of evoked forces being dependent on limb position, often converging at an equilibrium point.[73,74] Similarly, in rats and cats, lumbar intraspinal microstimulation tends to recruit naturalistic activity patterns in multiple leg muscles, presumably through excitation of spinal circuits that coordinate these muscles during natural movement.[75–78] Moreover, tonic stimulation of central pattern generator (CPG) networks can generate rhythmic stepping behaviours.[79,80] Lumbar intraspinal microstimulation could, therefore, provide an attractive alternative to peripheral FES for restoration of the ability to stand and walk in individuals with paraplegia.[81]
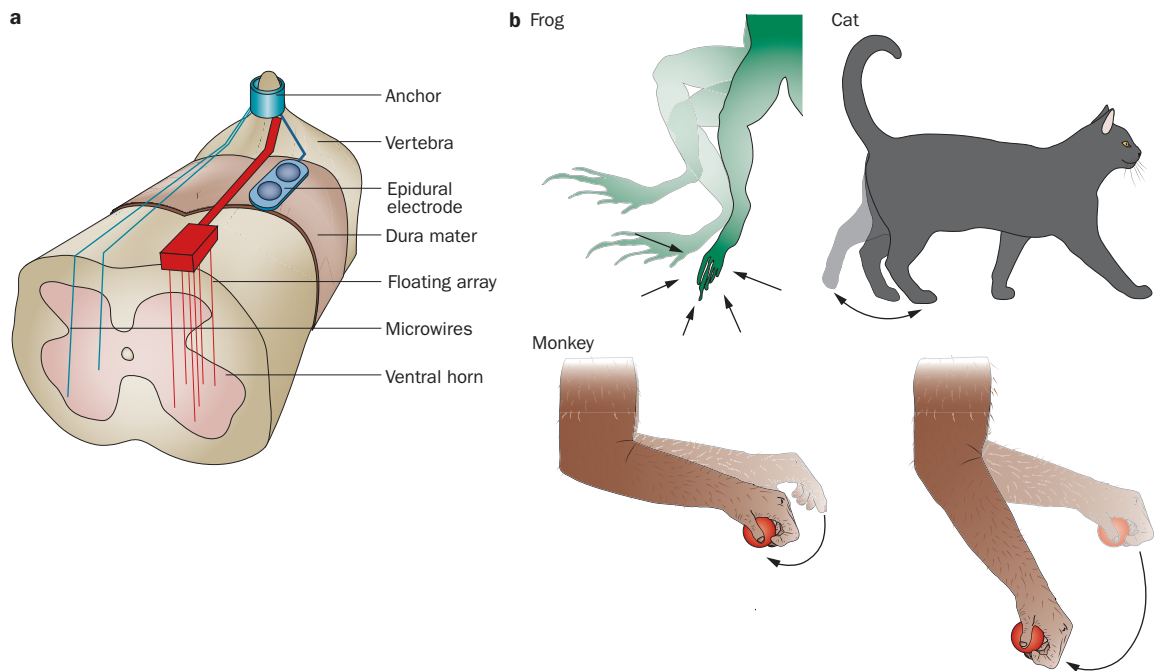
Figure 3 | Spinal cord stimulation—electrode designs and experimental outcomes. **a** | Microwires and floating microelectrode arrays target motor neuron pools in the ventral horn or interneuron circuits in the intermediate zone. Epidural electrodes are placed on the dorsal surface and activate predominantly afferent roots and dorsal horn circuits. **b** | Stimulation of the frog lumbar spinal cord elicits leg movements that converge to an equilibrium position, indicated by the arrows.[74,75] Stimulation of central pattern generators in the cat lumbar spinal cord produces stepping movements on a treadmill.[79,80] Stimulation of two microwires in the monkey cervical spinal cord independently activates finger flexion and elbow extension to grasp, transport, and release a ball.[83]

Intraspinal microstimulation of single sites in the cervical enlargement of monkeys activates multiple upper-limb muscles even at motor threshold (that is, the lowest intensity that will reliably elicit a response),[82] and stimulation using only two electrodes is sufficient to produce functional reach-to-grasp movements.[83] The lack of somatotopic organization of evoked movements implies that stimulation activates motor neurons indirectly through networks that coordinate diverse groups of upper-limb muscles. The difficulty in predicting where in the cervical cord a single electrode should be placed to produce a specific movement could prove problematic for neuroprosthetic applications. However, a small array of chronically implanted electrodes can yield a wide variety of movements involving several muscle groups (Figure 4).

Spinal stimulation and rehabilitation

Although intraspinal microstimulation has yet to be tested in humans, less-invasive epidural stimulation of the lumbar cord can, at high intensities, generate rhythmic electromyogram responses and weak stepping-like movements in patients with SCI.[84] Epidural stimulation is generally insufficient to produce functional behaviour in isolation, but may assist locomotor training by increasing the excitability of CPGs that are deprived of supraspinal input. Following successful trials in rats with complete spinal cord transection,[85] epidural stimulation electrodes were implanted over the lumbosacral enlargement of a patient with SCI who did not have detectable voluntary movement below the T1 spinal cord level.[86] Tonic stimulation delivered at low frequency (15 Hz) enabled weight-bearing standing for several minutes, whereas higher frequencies (30–40 Hz) enabled stepping behaviour in conjunction with manual assistance. Remarkably, after 7 months of stimulation combined with motor training, the patient also recovered some supraspinal control of the lower limbs, such as the ability to volitionally raise the legs while lying supine when the spinal stimulation was turned on. The implication is that spared but functionally silent descending pathways were reawakened by the rehabilitation programme and could drive specific movements when spinal circuits were brought close to motor threshold by diffuse stimulation. The authors further speculated that remodelling of surviving descending pathways was possible, but were unable to assess this within the clinical setting.[86]

The influence of epidural stimulation on supraspinal control in an animal model of incomplete injury has been studied using a body-weight-supporting robotic postural interface to encourage active movement of hind limbs.[87] Electrochemical therapy, which combines tonic epidural stimulation and pharmacological excitation with active rehabilitation, was tested in rats following bilateral hemisections at two thoracic levels—an injury that interrupted all descending white matter tracts but spared an intervening gap of grey matter. After 2–3 weeks of daily training, voluntary initiation of stepping behaviour was observed, and at 5–6 weeks the animals were capable of full weight-bearing bipedal locomotion during periods of electrochemical stimulation.[88] Further testing

in obstacle-avoidance tasks confirmed the supraspinal contribution to these behaviours, and postmortem histology revealed extensive remodelling of spinal circuitry, including sprouting of corticospinal tract fibres into the grey matter between the two thoracic hemisections, as well as increased projections from interneurons in this area to the lumbar level. Of particular interest, the anatomical remodelling and associated functional improvements were observed only when active stepping was encouraged by the postural interface: treadmill training alone was insufficient to produce these effects. In agreement with studies of functional electrical therapy, this finding reflects the importance of combining peripheral stimulation with volitional brain activity, and reinforces the long-recognized importance of active participation of patients in locomotor rehabilitation programmes.[89]

Hebbian plasticity in the CNS

A comprehensive review of the cellular and molecular mechanisms of activity-dependent plasticity is beyond the scope of this article, but can be found elsewhere.[90–93] Several themes of plasticity that are emerging from neuroscience, however, are of relevance to the clinical approaches described above. The conceptual framework of activity-dependent plasticity arose from studies of memory and skill-learning that focused initially on the hippocampus and cortex, but that similar principles also apply within the spinal cord is becoming increasingly clear.[94] An important mechanism by which neuronal activity drives plasticity is credited to Donald Hebb[95] who proposed that "some growth process or metabolic change" occurs to strengthen the connectivity between two neurons when their activities exhibit a persistent causal relationship with one another. This mechanism, popularly summarized by the phrase "cells that fire together wire together", is now understood to involve synaptic potentiation as well as structural changes such as axon sprouting and the formation and stabilization of new dendritic spines. Although the signalling pathways that regulate such changes are complex, many depend critically on correlated presynaptic and postsynaptic activity to activate N-methyl-D-aspartate (NMDA) receptors that allow calcium entry and trigger intracellular signalling cascades and exocytosis of neurotrophic factors. In addition, this basic mechanism for associative plasticity is influenced by neuromodulators including noradrenaline and serotonin.[96–98] The Hebbian condition of consistent presynaptic and postsynaptic coactivation can be imposed artificially using three stimulation paradigms: repetitive stimulation, paired stimulation, and closed-loop stimulation (Figure 5).

Repetitive stimulation

Tetanic activation of a single presynaptic input at sufficient strength to drive correlated postsynaptic activity is commonly used to induce long-term potentiation (LTP). Although LTP was first described for hippocampal connections, similar potentiation of spinal synapses can be induced by repetitive stimulation of descending[99] or afferent[100] fibres. As the stimulation rates used in these spinal
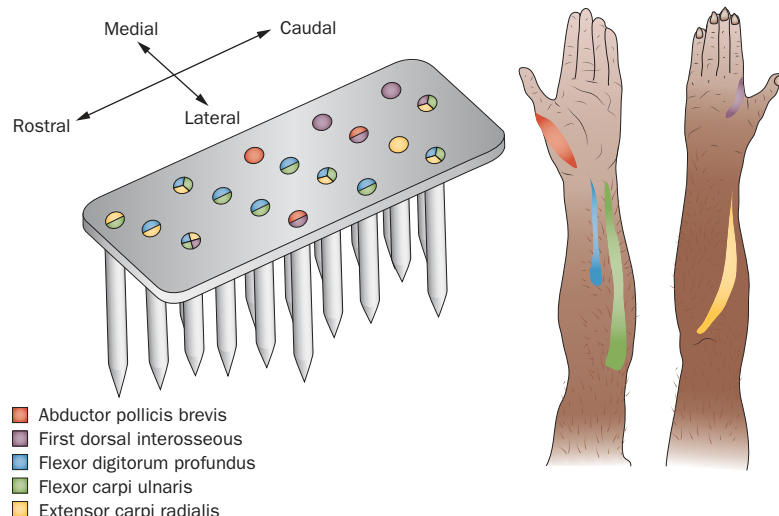

Figure 4 | Microelectrode arrays stimulate many muscle groups. Distribution of responses in hand and forearm muscles to stimulation of different electrodes in a floating microelectrode array (area 4 mm × 1.8 mm; depth 3–5 mm) chronically implanted into the macaque cervical spinal cord at the C7 level. Colour-coded circles indicate the muscles that were activated at motor threshold by each individual electrode.
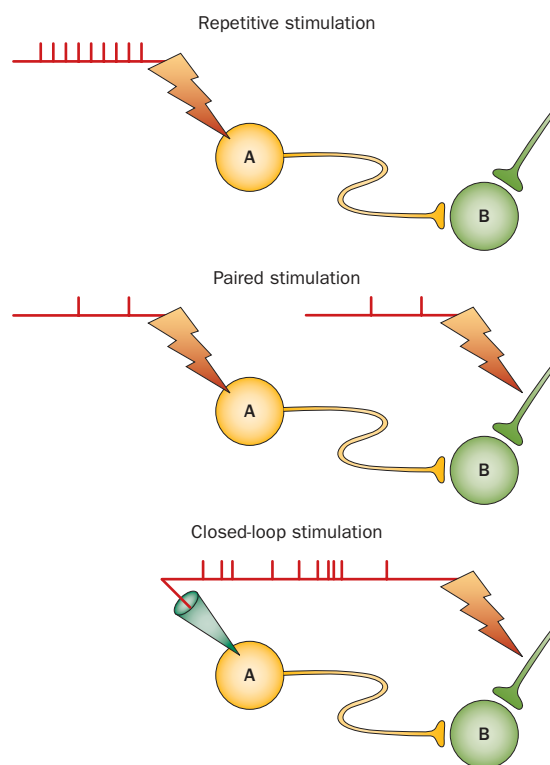
- Abductor pollicis brevis
- First dorsal interosseous
- Flexor digitorum profundus
- Flexor carpi ulnaris
- Extensor carpi radialis

Figure 5 | Protocols for inducing plasticity according to Hebb's rule. Repetitive stimulation of neuron A generates correlated presynaptic and postsynaptic activity by strong activation of a single pathway. Single stimuli that activate neuron A can be paired with stimulation of a strong input to neuron B. Closed-loop stimulation uses endogenous activity recorded from neuron A to trigger stimulation of neuron B.

LTP studies (around 100 Hz) are not dissimilar to those used for epidural spinal stimulation (30–40 Hz), potentiation of afferent and/or interneuronal synapses may have
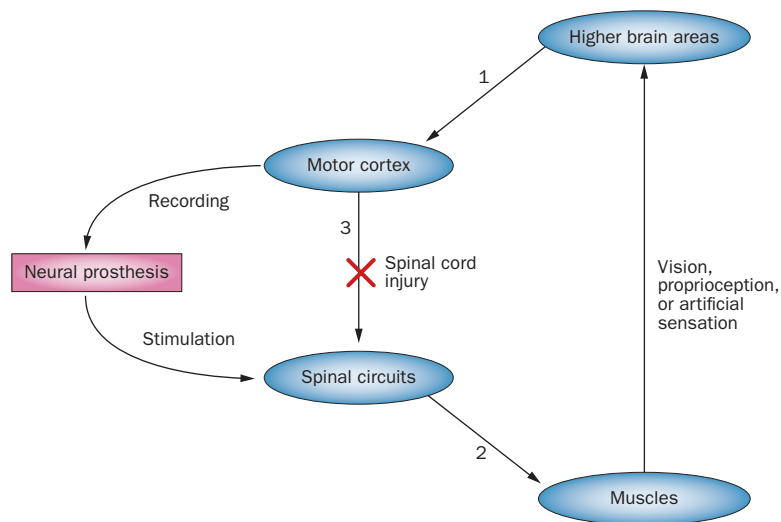
Figure 6 | Possible therapeutic effects of closed-loop neural prostheses. The normal sensorimotor loop is disrupted in patients with spinal cord injury. A neural prosthesis could replace injured descending connections by recording brain activity and stimulating spinal circuits below the injury level. Long-term use of such a prosthesis might induce plasticity at three sites: volitional drive to the motor cortex may be enhanced through neurofeedback mechanisms (1); repetitive stimulation might modulate spinal circuits to increase their excitability and facilitate movement (2); association of neural activity in the cortex and spinal cord could potentiate surviving, functionally silent connections (3). In this way, operation of a neural prosthesis could increase the efficacy of the augmented connection from the brain to the spinal cord.

contributed to the increased excitability of CPGs that was observed in human and animal studies.[85,86,88]

Repetitive stimulation can also promote structural changes in the spinal cord. After unilateral pyramidotomy in rats, long-term stimulation of the contralesional (intact) motor cortex promoted axon outgrowth into the denervated side of the spinal cord, which supported the process of functional recovery.[101] Noninvasive, repetitive transcranial magnetic stimulation (rTMS) can produce lasting increases or decreases in motor cortical excitability, depending on the stimulation protocol.[102] The mechanisms of action of rTMS remain a subject of debate, but evidence indicates their dependence on NMDA receptors,[103] implying that LTP-like processes are involved. Reports suggest that rTMS of motor areas can have beneficial effects on upper-limb function after incomplete SCI,[104,105] although whether these effects result from plasticity at the cortical or spinal level is currently unclear.

Paired stimulation
Most studies of spike-timing-dependent plasticity have focused on cortical and hippocampal synapses,[91] but emerging evidence suggests that similar associative mechanisms operate in the spinal cord. In able-bodied humans, repeated pairing of single TMS pulses with peripheral afferent stimulation, such that the volleys converge at the spinal level, produced lasting facilitation of corticospinal transmission.[106–108] These protocols could be adapted for therapeutic benefit in patients with incomplete SCI but, to our knowledge, no results of such attempts have yet been reported.

Closed-loop stimulation
A persistent causal relationship between presynaptic and postsynaptic activity can be imposed by timing stimulation at one site relative to endogenous neural activity recorded at a second site. This protocol is of relevance to closed-loop BMIs, as feedback through either sensory modalities or electrical stimulation will have a consistent timing relative to efferent brain signals. Direct evidence for Hebbian plasticity induced by closed-loop stimulation was obtained in the primary motor cortex of monkeys.[109] Neurochip electronics detected the spontaneous activity of individual neurons during several days of unrestrained behaviour and sleep, and subsequently triggered single-pulse stimulation of a second cortical site. Use of this protocol led to lasting changes in the upper-limb representation in the motor cortex that were consistent with potentiation of specific direct connections from the recording site to the stimulation site. A similar phenomenon has been reported in rodent sensorimotor cortex,[110] and preliminary evidence indicates that closed-loop intraspinal microstimulation triggered by cortical activity can potentiate corticomotor neuronal connections.[111]

Closing the loop
Many of the neural-interface technologies described above are in an early stage of development. Some, such as intraspinal microstimulation, are only being tested in animal models. Others, such as invasive BMIs and epidural stimulation, are beginning to be trialled in small numbers of patients. Which devices will be of practical use to patients, who have a diverse range of clinical needs, and whether any can become commercially viable propositions, remains to be determined. Nevertheless, the technological and scientific advances of recent years encourage us to speculate about promising directions for future research.

A common theme that emerges from studies described above[53–55,86,88] is the importance of encouraging volitional supraspinal activity in combination with electrical stimulation below the level of injury. After incomplete injuries, residual movements or myoelectrical signals can be used as a surrogate marker of activity to drive closed-loop stimulation.[112,113] For more-extensive injuries that result in complete paralysis, emerging BMI technologies will provide new ways to monitor central motor intent and relay this to spinal circuits, either directly through intraspinal or epidural stimulation,[46] or indirectly via afferents that are activated during movements generated by FES[57–60,62,63] or motorized orthoses.[42,114] In all cases, a key feature of closed-loop neural prostheses is restoration of coordinated activity on either side of the injury. By incorporating recording and stimulation capabilities into wearable or implantable devices, continuous operation outside the laboratory or the rehabilitation-clinic setting could provide day-to-day assistance to the user. We speculate, however, that continued operation of such devices could have additional long-term therapeutic benefits as a result of three plasticity mechanisms (Figure 6). First, neurofeedback will shape patterns of

volitional brain activity as users learn how to exploit the prosthesis more efficiently. Feedback could involve residual sensory modalities such as vision, or perhaps include artificial sensory pathways provided by electrical stimulation.[35–37] Second, repetitive stimulation might induce long-term changes that increase the excitability of spinal circuitry and enhance the efficacy with which movements can be evoked. Third, co-activation of the brain and spinal cord may strengthen surviving connections between the two sites through Hebbian mechanisms. Importantly, these three changes are complementary in acting to potentiate precisely the same sensorimotor loop that is augmented by the prosthesis.

Plasticity is not universally beneficial following injury, and depriving the spinal cord of descending input can lead to spasticity, hyperreflexia and chronic pain. Nevertheless, an advantage of using neural interfaces to manipulate plasticity is that they might allow targeted restoration of endogenous supraspinal inputs to spinal circuitry. A given closed-loop device could, therefore, have synergistic roles as both a neural prosthesis to replace function and a tool to rehabilitate function. Although speculative, such a hypothesis is supported by the experiences of patients using foot-drop stimulators[53] and myoelectrically controlled FES systems for the upper-limb,[112] with therapeutic outcomes that indicate a general convergence between neural prosthesis and neurorehabilitation.

Conclusions

Substantial challenges remain for the development of neural interfaces that can be of practical use in the day-to-day lives of patients with SCI, who have complex and varied disabilities. Nevertheless, that several technologies are now moving from laboratory demonstrations in animals to preliminary trials in a clinical setting is encouraging.[14,15,86] Continued progress in the development of technologies for monitoring and manipulation of neural activity will, hopefully, lead to a new generation of devices to augment injured neural circuits. In this Review we have focussed on upper-limb and lower-limb movements after SCI, but the mechanisms of activity-dependent plasticity seem to be ubiquitous throughout the nervous system. Closed-loop neural prostheses as tools to promote neurorehabilitation could, therefore, have more-general applications in restoration of function after any form of nervous system injury.

Review criteria

PubMed was searched for articles published in English from January 1990 to July 2012. Search terms included "brain–machine interface", "brain–computer interface", "functional electrical stimulation" and "spinal cord stimulation". Abstracts were reviewed, and papers with a focus on applications in spinal cord injury were further analysed in detail.

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